ECONOMICS OF AIDS AND ACCESS TO HIV/AIDS CARE IN DEVELOPING COUNTRIES. ISSUES AND CHALLENGES

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ECONOMICS OF AIDS AND ACCESS TO HIV/AIDS CARE IN DEVELOPING COUNTRIES. ISSUES AND CHALLENGES

Edited by

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Contents

Second part: *Impacts of AIDS and Expansion of Effective Therapeutic Strategies*

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ANRS : Agence nationale de recherches sur le sida.

CNRS : Centre national de recherche scientifique.

INSERM : Institut national de la santé et de la recherche médicale.

IRD : Institut de recherche pour le développement.

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Introduction

This book is a contribution to the debate on expanding access to HIV/AIDS treatment in developing countries. It presents an important and innovative aspect of the work of the ANRS (*Agence Nationale de Recherches sur le Sida*), one of the few agencies to have initiated research in this field.

The ANRS is a multi-disciplinary research agency. It finances projects in all scientific areas concerning HIV/AIDS and hepatitis. In last few years, the Agency has increased its commitment to research programmes in developing countries, with the specific aim of developing knowledge which will improve the care and treatment of people living with HIV/AIDS. For example, in the field of biological and clinical research, the ANRS is involved in exploring lower cost techniques for biological monitoring. The intention is that these should be adapted to conditions in resource poor environments. ANRS' funds are also flowing to evaluation of therapeutic trials which test protocols for use of highly active antiretroviral therapies within the health systems of these countries.

The ANRS began evaluation of the first pilot programmes to introduce antiretroviral treatment in the framework of the Drug Access Initiative backed by UNAIDS in 1998. This was done in partnership with the authorities of four countries [1]: Chile, Côte d'Ivoire, Uganda and Vietnam. In addition to the clinical and medical regimen, the ANRS recognised the need to consider context and has emphasised the economic and socio-behavioural part of the evaluation of the Ivorian initiative[2] (in association with Centers for Disease Control programme which assesses the biomedical aspects) and has been

involved in the evaluation of the Chilean programme. At the same time, a multidisciplinary research programme funded by the ANRS evaluated the Senegalese Initiative for Antiretroviral Access (ISAARV) [3]. The work carried out in Côte d'Ivoire and Senegal, together with that in other countries such as Uganda [4], has demonstrated the feasibility of introducing antiretrovirals in African circumstances

The launch of the ETAPSUD (Economic Evaluation of Access to HIV/AIDS Care in Developing Countries) programme at the beginning of 2001, saw the ANRS adopt a two pronged strategy:

1) to increase the contribution of economists to this important public health issue in the hope of facilitating wider access to HIV/AIDS treatment for patients in poor countries. This was very innovative at a time when most of the international literature on this aspect of health economics concluded that such a strategy was impossible;

2) to mobilise skills additional to those of health specialists, and particularly to draw experts from other fields who had not previously engaged with the AIDS epidemic. This programme was innovative and unique because it recognised that many specialists not usually involved in this field could make important contributions to understanding how access could be improved or facilitated. In this way the ETAPSUD initiative has encouraged and benefited from work by industrial and business economists, specialists in industrial innovation and intellectual property rights, development economists, anthropologists and econometricians.

The ETAPSUD research programme, which currently brings together 18 research teams including 7 from the South, is organised around two foci which in turn form the two parts of this book.

The first aspect concerns the accessibility and affordability of the drugs and other medical goods necessary for the care of HIV/AIDS patients in developing countries. This has involved in particular the empirical study of the international drugs and medical goods market. It has attempted to answer the following questions: What determine the price of antiretroviral drugs in developing countries? What are the rational economic mechanisms which can help lower the cost of these treatments?

Work on these topics relates to current international debates, particularly within the framework of the World Trade Organisation (WTO), on industrial property rights and patents (TRIPS agreements). It has been particularly helped by the official partnership between the Brazilian Ministry of Health and the ANRS since 2001.

Research performed in this domain overlaps with other approaches. An initial phase, carried out in collaboration with the Brazilian National STD/AIDS Programme (*cf.* article by Teixeira, Vitória and Barcarolo), is organised around an econometric analysis of factors determining the price of anti-HIV/AIDS drugs, particularly antiretrovirals (*cf.* article by Luchini *et al.*). A retrospective database of drugs-purchasing transactions in 14 developing countries was created to identify the most important factors associated with price variations. The question was not restricted only to product and quantity purchased but was extended to issues of care systems in importing countries, national legislation on patents and the procedures for purchasing the drugs. This database is now used as a model by UNAIDS and the Economic Community of West African States (ECOWAS) which are working in partnership with the ANRS to try to set up a body to monitor drugs prices. This procedure should encourage transparency in price information and help countries to build up their drugs purchasing policy on the basis of shared information. This is an example of where economic and industry research can assist in evening out market imbalances in a very practical manner.

This large-scale quantitative research initiative is complemented by several projects based on combined qualitative and quantitative methods. Thus examination of the ways that major actors in the drugs market behave provides important clues about the development of current pricing strategies and indicates possible trends in pricing policy, in particular price differentials between Southern and Northern countries (*cf.* article by Dumoulin *et al.*).

Several projects have studied the conditions under which generic drugs are produced. This is of utmost importance because generics constitute an essential competitive factor in reducing drug prices. These studies are being carried out as part of research centred around those southern countries which produce generics: Brazil (*cf.* articles by Cassier and Loyola and by Orsi *et al.*) and Thailand (*cf.* article by Guennif and Mfuka). These studies will identify political, technical and legal factors which have enabled these countries to build up the capacity to produce generic drugs, and the obstacles to greater use of these capacities and to distribution of generics both inside and outside these countries. Active engagement with current negotiations within the WTO to limit the constraints resulting from expansion of industrial property rights for drugs in poor countries lie at the heart of this work.

Finally, the link between industrial protection and R&D activity by multinational firms is tackled in a current project studying data banks of patents (*cf.* article by Combe, Pfister and Zuniga). This analysis will give a new

perspective on traditional assertions about the possible impact of a widespread drop in drug prices in developing countries on the pace of therapy innovation with regard to anti-HIV/AIDS treatments and vaccines.

The second aspect of the ETAPSUD programme deals with assessing the economic impact of AIDS in developing countries and the possible role of developing effective therapeutic strategies using antiretrovirals to reduce this impact.

Here economic procedures are used to optimise therapeutic strategies with antiretrovirals in resource constrained HIV/AIDS care, as well as to examine ways of funding these interventions. The following questions have arisen: is it possible to consider such strategies in cost effective terms in the resource-scarce context of these countries? How can the economic perspective contribute to adapting different prevention and care strategies to the different contexts of developing countries (*cf.* article by Freedberg and Yazdanpanah)? What operational methods of financing the supply and demand of treatment can be considered to provide "acceptable" compromises between the demands of efficiency and those of equitable access, as well as for the distribution of the financial burden between the public and private sectors. This part of the ETAPSUD programme is based on clinical and epidemiological research procedures funded by the ANRS and on support for assessing national programmes in a number of countries countries, particularly Côte d'Ivoire (*cf.* article by Laguide *et al.* and by Eholié *et al.*), Chile (*cf.* article by Moralès, Cid and Souteyrand) and Senegal (*cf.* article by Vinard *et al.*). It also involves reporting the impact of the epidemic on society and economy. How can the real long-term economic impact be measured other than by existing over-reductionist models? With this in mind, the impact on human capital and the transmission mechanisms in time and social space have been studied at the macro-economic (*cf.* article by Drouhin, Touzé and Ventelou) and micro-economic (*cf.* article by Freire) levels.

While this book constitutes an initial report of the research funded by the ANRS as part of the ETAPSUD Programme, it also includes many other contributions. The procedure adopted by the ANRS forms part of a broad international discussion and has provided the opportunity for an exchange and convergence of ideas between researchers from different countries, particularly in the fields of economic and social sciences and law. It has also begun an important dialogue on these issues between the francophone and anglophone research communities, a welcome development which will hopefully now move ahead more rapidly. The articles by Barnett, by Boulle, Kenyon and Abdullah, by McGreevey, Alkenbrack and Stover and by 't Hoen all provide

evidence of this "intellectual partnership". More generally, many articles in this book have benefited directly from the cooperation between the ANRS and the International AIDS Economics Network (IAEN) which co-ordinates discussion at an international level on the economics of AIDS. On the occasion of the 13th International AIDS Conference (Barcelona, July 2002), the IAEN and the ANRS jointly organised an international meeting of economists on the topic: "State of the Art: AIDS and Economics" [5].

This book, like the ETAPSUD programme as a whole, is both reflectively academic and extremely practical. Naturally the two approaches complement each other. Its aim is to increase the engagement of the economic and social science perspective so as to clarify international and national discussions about the best way to overcome the scandalous inequality in access to HIV/AIDS treatment between poor and rich region of the world. The chapters of this book should thus be read as attempts to influence the decisions of public and private actors in the fight against the epidemic. It was in this spirit that the authors contributed to discussions at the Workshop on "Economic Issues related to Access to HIV/AIDS care in Developing Countries" organised in Marseilles on May 27th 2003 by the ANRS and the Marseille Institut d'Economie Publique in the presence of Economic Nobel Prize Winners Kenneth Arrow and Joseph Stiglitz. It is in this spirit of co-operation and innovation that we hope readers of this book will use its ideas in their own activities in the fight against AIDS.

THE EDITORS.

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Patents, Generic Drugs and the Markets for Antiretrovirals

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After long years of negotiation, the Uruguay Round finally culminated in 1994 with the signing in Marrakesh of the controversial TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement, aimed at extending world-wide the type of intellectual property protection that had up until that point been granted to firms established in the most developed countries.

All the while, the AIDS virus, which had infected an ever-greater number of victims throughout the 80s, was spreading across the world, hitting the poorest and least protected regions the hardest – and Sub-Saharan Africa worst of all.

The coexistence of these two series of events is obviously coincidental. Yet, they have become closely intertwined - to such an extent that the fight against the AIDS epidemic is in fact largely predicated on the totally different issue of the new global intellectual property rights regime. Extended so that it now covers drugs, this regime has raised a number of barriers impeding poorer nations' access to treatment These conflicting interests have become more critical with the HAART therapies that began to develop in the mid-90s. Such treatments may not offer a definitive solution but they do represent real progress, giving hope to millions of AIDS victims across the world by extending their life expectancy by several years.

The chapters making up this section of the book focus on the conflictual interactions between drugs-related intellectual property rights and access to treatment. As we will see, each of these chapters deals in depth with one of the issues at stake. As such, the current introduction is no substitute for reading

these chapters, nor does it provide a summary of them. The aim here is different; it is to highlight the significance of some of the largely transversal themes running through the various chapters on offer. It is also to attract the reader's attention to what seems to be a growing tension between the dimension of the collective good of public health and profit-seeking by private firms involved in that domain. In this book we address this central issue and see how it affects the differential life chances of millions of HIV-infected persons.

Three themes will be emphasised. The first relates to the nature of the new legal framework that has governed drugs and healthcare access ever since TRIPS was first adopted. The second relates to the rich and varied lessons we can learn from different national generic drugs production experiences. This involves presenting and analysing the policies being pursued in Thailand, and especially in Brazil with its pre-eminent role in international issues pertaining to these topics. The third theme, which to a certain extent encompasses the first two, relates to actors' behaviour and to pricing mechanisms that have been observed in the world market for ARVs. As we will see, this theme is closely connected to the institutional conditions determining the trading of ARVs (whether generic or not) between the countries of the North and the South.

The new constraints that TRIPS has generated

To measure the significance of the Public Health changes that TRIPS has introduced, one has to remember that before the TRIPS Agreement was signed in 1994 the various Treaties that used to oversee Intellectual Property agreements at an international level authorised multiple protection systems [1-3]. In particular, it was acceptable that countries marked by weaker levels of economic and technological development could adapt systems that were much more conducive to the diffusion of technology than to incentives to innovate [4]. For example, it was perfectly legal to copy existing molecules (even ones that had been patented in the countries of the North). This enabled many countries to build up a local pharmaceutical industry based on copying molecules that had been developed elsewhere – making it possible to offer such products in the local market at much lower costs, a necessary albeit insufficient precondition for providing the poorest members of society with access to healthcare.

The old system may come as a surprise to many people today, but less so if we recall that these very same principles (free copying enabled by an absence

of patents on pharmaceutical molecules[1]) had originally been a key driving forces behind the growth of the pharmaceutical industry in the countries of the North. It was only from the 60s onwards, and sometimes much later (*i.e.*, 1977 in Switzerland) that patents were introduced for pharmaceutical molecules. Until these late dates, law-makers throughout the world were unanimous in affirming that the public nature of health necessitated a special treatment for all of the products and services comprising this good.

One may observe that the absence of patents on pharmaceutical molecules in no way hindered innovation-driven progress. Quite the contrary, reciprocal imitation and free copying fostered waves of innovation for several decades. Nor was this earlier regime damaging to companies: in addition to the market growth enabled by the low cost production of an increasing number of molecules, firms had a whole range of tools and instruments they could use to optimise their investments. These included "first mover advantages" plus the development of brands[2] and reputation effects – all of which usually allowed innovative firms to make a return on their investments [5].

There is little question therefore that the TRIPS agreement constituted a real break with the past – a shift that was all the more pronounced since not only did it align the least developed countries' IPR regimes with those found in the more developed ones (withdrawing the copying rights that the latter had used to build up their own base) but also because this alignment was only implemented once the North's own protection regime had been strengthened and extended [6][3].

The change was so sudden that TRIPS' initiators, aware of the problems such agreements could cause, made sure that the Treaty incorporated and encompassed a variety of exemptions and exceptions, including certain stipulations (often drawn from the Basel and Paris agreements that had historically been viewed as the world's leading Intellectual Property Rights treaties)[4]. These stipulations specifically authorised copying, notably in the event of a health emergency.

1. One particularity of the pharmaceutical industry is that until recently process-related patents were the only ones to be accepted. Since in chemistry many different pathways can usually be used to synthesise a given molecule, process patents were no obstacle to the production of identical molecules obtained via other pathways.

2. In a study of the decline of the Italian pharmaceutical industry, Scherer [5] shows that this coincided in fact with the advent of a patenting system.

3. For example, patent protection coverage rose on average from 16 to 20 years in recent times, first in the United States and then in Europe.

4. See Zhang [3], for details on this point.

The implementation of so-called "compulsory licensing" clauses were designed specifically to deal with these kinds of situations. Introduced into the system as a kind of cushion or shock absorber, this clause would nevertheless generate enormous problems for those countries that lacked research capabilities. States have supposedly retained room to manœuvre that will provide them with the means to ensure the primacy of public interests over those of patent-holders in the event of health crises; or else the means to regulate competition, thereby preventing pharmaceutical companies from abusing their dominant positions. However, much greater room to manœuvre has been granted to the countries of the North than to those of the South, specifically to Southern nations lacking in industrial production capabilities. Indeed, TRIPS Article 31f de facto prohibits countries of the South lacking in the requisite technological capacities from importing any drug which they cannot produce themselves. To some extent, this stipulation runs contrary to the spirit of the TRIPS agreement, which was intended to reduce barriers to international trade. Moreover it clearly emphasises monopoly protection as opposed to free trade and levies harsh penalties on the countries of the South. It is no surprise then that this issue is currently the subject of major international disputes. The chapter by 't Hoen that opens this section of the book retraces the history of these conflicts in detail.

As for the present article, it is enough for us to indicate that when faced with the AIDS pandemic and the needs arising from the fight against this disease, TRIPS has in many circumstances been used by the pharmaceutical multinationals (and/or their representatives) to erect a panoply of barriers undermining any attempts by actors from the countries of the South (NGOs, State organisations, etc.) to develop anti-AIDS policies based on the use of generic ARV-based treatments. There is little doubt but that TRIPS, if maintained in its current form, constitutes a major institutional hurdle that the fight against the pandemic will have to overcome[5].

Thailand, Brazil: what we can learn from Southern generics producers

Both Thailand and Brazil in their own way exemplify the preceding conclusion. They also provide matter for further reflection, involving an exploration of other dimensions and areas involved in the fight against AIDS.

5. For a different view on this issue see [7] which expresses the pro-patent arguments.

A key observation to begin with is that the successful generic ARV production in both countries has only concerned ARVs that are not protected under TRIPS, *i.e.* that were already being traded when the two countries first introduced legislation to ensure that their domestic intellectual property rights laws complied with TRIPS-introduced stipulations protecting patented molecules[6]. It is essential to note here that the production of ARVs in both countries was not being de facto limited to the oldest generation of ARVs due to some lack of technological competency. On the contrary, both Thailand and Brazil possess skills that could allow them to produce the whole range of the ARVs used today against the disease. The obstacles are definitely of a legal, as well as political nature. In particular, the United States has made it clear that it is prepared to use a variety of instruments to pressurize countries (including reprisals, if need be) if post-TRIPS ARVs were to be produced locally in a generic form. For instance, Thailand and Brazil have been named in US article 301 Special procedures, threatening them with serious reprisals because the US Trade Representative has deemed their national laws to be a threat to American corporate interests[7]. Worse still, local producers are being increasingly squeezed. In the case of Thailand for example, a sort of "Super-Trips" is being applied under the aegis of the *Safety Monitoring Program*[8] adopted in the country to satisfy some US demands (*cf.* the chapter by Guennif and Mfuka).

This is only one of the lessons we can learn from these countries' experiences. Others, some of which are more optimistic in outlook, are just as important.

First of all, copying molecules may not be all that easy, but it is quite possible for a large number of countries. Better still, since outright copying is apparently difficult (because patents reveal little about a product), the fact that something must be created if the same molecules are to be produced (*cf.* note 1 on the many different pathways that can be followed in manufacturing a particular

6. Those trading before 1996 for Brazil and before 1994 for Thailand, respectively the years when new TRIPS compliance-ensuring patent legislation was first introduced in each country.

7. The "301 Special" section is a whole set of U.S. trade law stipulations specifically devoted to the defence of intellectual property rights and used to justify the unilateral actions this country takes (*i.e.* not recognising the authority of the WTO dispute resolution mechanism) whenever its national firms' interests are deemed to be under threat. To study these stipulations, which have been a main driver behind the adoption of TRIPS, see [3] and [8]. For a criticism thereof, see Baghwati [9].

8. SMP consists of a whole set of stipulations introduced in Thailand under pressure from the U.S. It has resulted in 2-year "exclusive market rights" being granted to multinational companies, covering new chemical entities, new combinations plus new recommendations and delivery systems.

molecule) could engender drugs featuring a number of improved properties over the patented drugs' characteristics (*cf.* the chapter by Cassier and Correa).

Above all, it has been shown that production costs on generics thus obtained allow for significantly lower treatment prices (from $10-12,000 per person/year to about $300-350). A dollar a day: thanks to generic drugs, this is what the life of an AIDS sufferer costs; a figure that the international community could easily pay, if it decided to do so; and a figure that allowed Brazil to set up its remarkable universal and free public healthcare access programme, the effects of which have been spectacular (see the chapter by Texeira et al. for details of this programme).

Other less optimistic lessons can also be learned from these experiences, particularly from the fact that the provision of generic ARVs, the only ones whose price allows them to be used effectively to stem the pandemic, is still very dependent on the provision of low-priced active principles. For the moment, these continue to be mainly manufactured by Asian (notably Indian and Chinese) generics producers. It should be remembered that active principles amount to 90% of the cost of an ARV. Inasmuch as India and China have largely postponed their compliance with TRIPS until the year 2005, the active principles currently being used in ARV production are those being freely traded internationally between countries where they do not come under the aegis of patent protection. What will happen tomorrow if this trade is rendered impossible because of a restrictive application of TRIPS? If Brazil cannot develop its domestic active principles production capabilities, its remarkable universal and free healthcare access programme will be under threat and might have to be curtailed (*cf.* the chapter by Orsi *et al.*).

This is a crucial issue. Without the preservation of free trade in active principles, low-cost generics production could be threatened, even in those countries that have acquired the greatest experience and expertise in this domain (*i.e.* Brazil, Thailand).

Another key issue is generics provision in countries lacking in technological capabilities. In this crucial area, American intransigence (the U.S. being the only country to reject the intricate but successful compromise accepted by the 143 other participants in the 2002 Geneva Conference (*cf.* the chapter by 't Hoen) has hindered implementation of the advances achieved in the 2001 Doha protocol. Clearly the intransigence manifested until now by the US representative poses a grave threat to the fight against the pandemic.

Pricing and markets

The paragraphs above offer a sufficient reminder that ARV production and delivery pricing issues will be a key factor in the fight against AIDS. But how are these prices determined? How have the main protagonists in this field been behaving? What can we expect for the future? The final chapters focus on these questions.

The first observation is that the market for ARVs is complex and atypical in nature, being one of those markets which is described in economic analysis as based on forms of "imperfect competition". There are at least two reasons why this market can be termed atypical. Firstly, the products traded there (ARVs) are covered by patents that are tantamount to monopolies being granted to the firms owning such goods. Secondly, and partially as a consequence of the preceding fact, there are very few participants in this market. Seven firms deliver the 17 ARVs being used today, clearly indicative of an oligopolistic situation. These characteristics explain why we are so far from any of the "equilibrium prices" formed in competitive markets as a result of supply and demand mechanisms.

The main issue here is that the existence of patents is what guarantees monopoly pricing. The legitimacy of such patents has long been discussed in the literature on this subject (*cf.* the chapter by Combes, Pfister and Zuniga summarising some of the main arguments). Economic theory states that, due to some uncertainties attached to production of the good "knowledge", a number of transfers will have to be made in order to aid the actors ready to take on the risk of entering into research activities. There is an agreement (among theorists) that there must be incentives to reward firms taking on such risks. It is extremely difficult, however, to ascertain the form that such incentives should take, and previous responses have not been particularly conclusive [10][9]. For example, even if the solution chosen involves a patent (paving the way for a monopoly rent to reward the research investments that have been made), questions still remain as to the level at which this patent-generated rent should be fixed. Although it should be large enough to incentivize and reward the inventor, it should not be too heavy a burden for the consumer and/or (if s/he belongs to a

9. Since the seminal paper by Arrow [11], many studies have discussed the relevancy of patents as a way of creating incentives for research. The merits of other forms (subsidies, paying "bonuses" to inventors, etc.) have been thrown into the equation as well. However, theoretical literature has not been able to come up with any definite conclusions on this subject.

State health scheme) for the taxpayer. Between incentives to innovate and the cost of well-being, any equilibrium (if indeed one does exist) will be difficult to identify, especially since people's ability to pay (the factor that should define the "reservation price" beyond which consumers will no longer purchase a good) varies greatly from one part of the world to the next.

In addition to these theoretical questions, there are others that come from observing the market's actual modus operandi. At least three phenomena have helped to make this a particularly complex situation:

1) the market for patented drugs and the market for generic products are not completely cut off from one another. To a certain extent, the two types of products compete (this is the case for ARVs not covered by patents in Brazil and Thailand, and also certain Indian generics that might be in competition with some of the patented drugs on offer);

2) the market possesses a "political" dimension. A number of pharmaceutical firms have got together with international organisations and worked under the auspices of specific programmes to deliver patented ARVs at negotiated prices. The latter are much lower than current prices in countries of the North guaranteeing full compliance with patent laws. The so-called Accelerated Access Initiative (AAI) which brings together 5 organisations from the United Nations and 6 large pharmaceutical companies into programmes targeting the countries of the South is of special importance here. Lucchini *et al.* (*cf.* chapter in this book) have called this practice "political philanthropy". It is one that raises serious questions about the future of the ARV market;

3) the coexistence of these "negotiated" price programmes with bilateral forms of transactions (the purchasing country, operating in general via its "central pharmacy", develops a sourcing relationship with one or several firms which it forces to compete with one another) means that we are dealing with different market configurations and structures in which "suppliers" and "demanders" negotiate in very different ways, influencing the price of the transactions.

The chapter by Lucchini et al. (based on an exceptionally large and representative database), centred on the analysis of price mechanisms, provides valuable lessons. Three of them deserve special attention.

a) Up until now, North/South transactions have involved very small quantities of ARVs compared with the needs that have been identified. This fact attests in its own way, and irrespective of the underlying causes, to the weak commitment of national State authorities and international donors to the fight against the pandemic. This observation is particularly true for the African continent as a whole.

b) The second is the sharp fall in the constant market price of internationally traded ARVs over the past few years.

There are two explanatory elements:

i) the generic producers' massive entry into this market. Brazilian generics production, starting with the 1997 implementation of the country's national treatment access programme, has clearly driven prices down – as have the widely-reported proposals of Indian generics producers;

ii) the launch of the AAI programme. Prices negotiated as part of such programmes since 2001/2002 have had a major impact on world prices.

c) The prices of the different types of ARVs have tended to converge towards the prices of their generic equivalents and/or towards AAI programme prices. This means that we are moving towards a sort of "dual market" for ARVs, characterised by high prices in the North and lower prices in the South. It should be remembered, however, that the programmes currently being run in the South treat an extremely small number of patients compared to the needs that have been identified.

The preceding observations stress the fact that in this field, as in many others, the main instruments moderating and controlling prices are the forms of competition that have been introduced (however diluted and often indirect they might be in the case of ARV markets). Hence, the authors' conclusion that what we need to ensure is the ability of such principles to fulfil their role more completely in the future in order to encourage the transition from "politically philanthropic" behaviour (whose opportunistic dimension constitutes an undoubted problem) to clearly regulated markets guaranteeing a long-term downward pressure on the market prices of ARVs destined for the countries of the South – as well as access to treatment for insolvent patients in these countries. This sort of regulatory presence, even if it is insufficient to cope with the epidemic, is at least a prerequisite for this to happen.

For the moment we face a situation in which the absence of any clear willpower on the part of regulators and legislators (compounded by the weak bargaining power of the poorest countries) keeps the needs of developing countries from becoming the focal point of international dealings. The market for ARVs will probably remain imperfect for quite a while, being largely subject to the strategic behaviour of the different actors, and notably to the actions of the world's large pharmaceutical companies, still the main actors in this field.

Given this situation, by highlighting three possible development scenarios, the final chapter (Dumoulin *et al.*) provides some useful keys for the future.

A brief presentation of these scenarios will help us to identify some of the key elements characterising the complex dynamics running through the issue of access to HIV/AIDS care.

1) The first scenario extrapolates the "status quo". If unamended, TRIPS would guarantee multinationals considerable control over the pharmaceuticals sector, leaving generics producers with little room to work in. This scenario maintains and extends the great inequalities in access to treatment that we are experiencing today, and for this very reason would lead to a great deal of tension.

2) The second scenario is similar to the first, differing only in that it is predicated on the formation of a wider and more extensive market for ARVs. This would specifically result from the pharmaceutical multinationals undertaking a clear and confirmed price differentiation and market segmentation strategy, leaving some room for Southern market generics producers to operate in. This scenario, which extrapolates the current "market-orientation" of treatment, is unsustainable due to the same kinds of limitations as those mentioned above. At best, it extends healthcare access whose needs can at least partly be afforded, slightly broadening the target populations without providing any overall solution to the spread of the epidemic.

3) The third scenario differs in two respects. First of all, international organisations play a key role here, given their ability to regulate markets by redefining IPRs and authorising the international copying, distribution and circulation of low-priced generic ARVs, at least between countries of the South. In addition, funds can be collected and reallocated (again via international organisations) to allow patients without financial resources to access healthcare. This is an ideal scenario of course, but the only realistic one if the real aim is to eradicate the epidemic completely. This sort of scenario clearly infers the success of initiatives like those being implemented by the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Finally, as regards the overall scene, marked by the confrontation of, and cooperation between, actors with conflicting interests and goals, the future depends on two questions:

– the status of ARV (*i.e.* the nature and scope of the intellectual protection they are granted) vs. the right to produce generic drugs and to trade them freely between the countries of the South;

– the role attributed to markets vs. allocation and transfer mechanisms guaranteeing healthcare access to patients without financial means, (currently the vast majority of recorded cases).

It is undeniable that these issues are interrelated, and that no sustainable solutions can be found if regulators and legislators do not enforce the type of measures able to provide the legal instruments required to tackle the situation. Nearly 20 years after the epidemic first broke out, the contributions made in the first section of this book, constituting the current state of knowledge, show that pathways do exist. It is up to the policy makers to flesh them out.

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TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond

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KEY WORDS: TRIPS; patents; generic drugs; Research and Development; intellectual property; HIV/AIDS drugs.

Abstract

The reasons for the lack of access to essential medicines are manifold, but in many cases the high prices of drugs are a barrier to needed treatments. Prohibitive drug prices are often the result of strong intellectual property protection. Governments in developing countries that attempt to bring the price of medicines down have come under pressure from industrialized countries and the multinational pharmaceutical industry.

The World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS) sets out the minimum standards for the protection of intellectual property, including patents for pharmaceuticals. While TRIPS does offer safeguards to remedy negative effects of patent protection or patent abuse, in practice it is unclear whether and how countries can make use of these safeguards when patents increasingly present barriers to medicine access.

Public health advocates welcomed the Doha Declaration as an important achievement because it gave primacy to public health over private intellectual property, and clarified WTO Members' rights to use TRIPS safeguards. But the Doha Declaration did not solve all of the problems associated with intellectual property protection and public health. The recent failure at the WTO to resolve the outstanding issue to ensure production and export of generic

medicines to countries that do not produce may even indicate that the optimism felt at Doha was premature.

Résumé

Parmi les différentes raisons de l'absence d'accès aux médicaments essentiels dans les pays en développement, leur prix élevé constitue un obstacle majeur. Ces prix prohibitifs sont souvent le résultat de la protection très forte de la propriété intellectuelle. Les gouvernements des pays en développement qui tentent de réduire ces prix sont l'objet de fortes pressions de la part des pays industrialisés et de l'industrie pharmaceutique multinationale. Les accords ADPIC (Accords sur les Droits de Propriété Intellectuelle qui touchent au Commerce) de l'Organisation Mondiale du Commerce (OMC) définissent des normes minimales pour la protection de la protection de la propriété intellectuelle, incluant les brevets pour les médicaments. Si ces accords offrent des mécanismes de sauvegarde pour compenser les effets négatifs de la protection ou des abus liés aux brevets, en pratique, l'utilisation appropriée de ces mécanismes, lorsque les brevets constituent des obstacles majeurs à l'accès aux médicaments, n'est pas claire.

Les défenseurs de la santé publique ont considéré la Déclaration de Doha comme une étape importante parce qu'elle donnait la primauté aux considérations de santé publique sur celles de propriété privée intellectuelle et clarifiait les modalités d'utilisation des clauses de sauvegarde des ADPIC pour les membres de l'OMC. Mais la Déclaration de Doha n'a pas résolu les problèmes associés à la protection de la propriété intellectuelle et à la santé publique. L'échec récent à l'OMC des tentatives pour résoudre la question relative à la production et à l'exportation de médicaments génériques vers les pays qui n'en produisent pas confirme que l'optimisme post-Doha était prématuré.

Introduction

Infectious diseases kill over 10 million people each year, more than 90% of whom are in the developing world [1]. The leading causes of illness and death in Africa, Asia, and South America-regions that account for four-fifths of the world's population – are HIV/AIDS, respiratory infections, malaria, and tuberculosis.

In particular, the magnitude of the AIDS crisis has drawn attention to the fact that millions of people in the developing world do not have access to the medicines that are needed to treat disease or alleviate suffering. Each day,

close to eight thousand people die of AIDS in the developing world [2]. The reasons for the lack of access to essential medicines are manifold, but in many cases the high prices of drugs are a barrier to needed treatments. Prohibitive drug prices are often the result of strong intellectual property protection. Governments in developing countries that attempt to bring the price of medicines down have come under pressure from industrialized countries and the multinational pharmaceutical industry.

The World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS or "Agreement"), which sets out the minimum standards for the protection of intellectual property, including patents for pharmaceuticals, has come under fierce criticism because of the effects that increased levels of patent protection will have on drug prices. While TRIPS does offer safeguards to remedy negative effects of patent protection or patent abuse, in practice it is unclear whether and how countries can make use of these safeguards when patents increasingly present barriers to medicine access.

The Fourth WTO Ministerial Conference, held in 2001 in Doha, Qatar, adopted a Declaration on TRIPS and Public Health ("Doha Declaration" or "Declaration") which affirmed the sovereign right of governments to take measures to protect public health. Public health advocates welcomed the Doha Declaration as an important achievement because it gave primacy to public health over private intellectual property, and clarified WTO Members' rights to use TRIPS safeguards. Although the Doha Declaration broke new ground in guaranteeing Members' access to medical products, it did not solve all of the problems associated with intellectual property protection and public health. The recent failure at the WTO to resolve the outstanding issue to ensure production and export of generic medicines to countries that do not produce may even indicate that the optimism felt at Doha was premature.

I
THE ACCESS PROBLEM AND INTELLECTUAL PROPERTY

A number of new medicines that are vital for the survival of millions are already too costly for the vast majority of people in poor countries. In addition, investment in Research and Development (R&D) towards the health needs of people in developing countries has almost come to a standstill. Developing countries, where three-quarters of the world population lives, account for less than 10% of the global pharmaceutical market. The implementation of TRIPS is

expected to have a further upward effect on drug prices, while increased R&D investment that aims at addressing health needs in developing countries, despite higher levels of intellectual property protection, is not expected [3].

One-third of the world population lacks access to the most basic essential drugs and, in the poorest parts of Africa and Asia, this figure climbs to one half. Access to treatment for diseases in developing countries is problematic either because the medicines are unaffordable, have become ineffective due to resistance, or are not sufficiently adapted to specific local conditions and constraints.

Many factors contribute to the problem of limited access to essential medicines. Unavailability can be caused by logistical supply and storage problems, substandard drug quality, inappropriate selection of drugs, wasteful prescription and inappropriate use, inadequate production, and prohibitive prices. Despite the enormous burden of disease, drug discovery and development targeted at infectious and parasitic diseases in poor countries has virtually ground to a standstill because drug companies in developed and developing nations simply cannot recoup the cost of R&D for products to treat diseases that abound in developing countries [4]. Of the 1,223 new drugs approved between 1975 and 1997, approximately 1% (13 drugs) specifically treat tropical diseases [5].

TRIPS sets out minimum standards and requirements for the protection of intellectual property rights, including trademarks, copyrights, and patents. The implementation of TRIPS, initially scheduled for 2006 by all WTO Members, is expected to impact the possibility of obtaining new essential medicines at affordable prices.

Médecins sans Frontières (MSF), together with other non-governmental organizations (NGOs), formulated the following concerns related to TRIPS:

– Increased patent protection leads to higher drug prices [6]. The number of new essential drugs under patent protection will increase, but the drugs will remain out of reach to people in developing countries because of high prices. As a result, the access gap between developed and developing countries will widen.

– Enforcement of WTO rules will have a negative effect on local manufacturing capacity and will remove a source of generic, innovative, quality drugs on which developing countries depend.

It is unlikely that TRIPS will encourage adequate R&D in developing countries for diseases such as malaria and tuberculosis, because poor countries often do not provide sufficient profit potential to motivate R&D investment by the pharmaceutical industry.

Developing countries are under pressure from industrialized countries and the pharmaceutical industry to implement patent legislation that goes beyond

the obligations of TRIPS. This is often referred to as "TRIPS plus." TRIPS plus is a non-technical term which refers to efforts to extend patent life beyond the twenty-year TRIPS minimum, to tighten patent protection, to limit compulsory licensing in ways not required by TRIPS, or to limit exceptions which facilitate prompt introduction of generics [7].

Industrialized countries and World Intellectual Property Organization (WIPO) offer expert assistance to help countries become TRIPS-compliant. This technical assistance, however, does not take into account the health needs of the populations of developing countries. Both of these institutions are under strong pressure to advance the interests of large companies that own patents and other intellectual property rights.

II
IMPORTANT DEVELOPMENTS IN THE DEBATE ON ACCESS TO DRUGS AND INTELLECTUAL PROPERTY

A number of factors have shaped the debate on TRIPS and access to medicines, directly or indirectly impacting the content of the Doha Declaration.

Big Pharma vs. Nelson Mandela: trade dispute in South Africa

In February 1998, the South African Pharmaceutical Manufacturers Association and 40 (later 39, as a result of a merger) mostly multinational pharmaceutical manufacturers brought a suit against the government of South Africa, alleging that the Medicines and Related Substances Control Amendment Act No. 90 of 1997 ("Amendment Act") violated TRIPS and the South African constitution [8].

The Amendment Act introduces a legal framework to increase the availability of affordable medicines in South Africa. Provisions included in the Amendment Act are generic substitution of off-patent medicines, transparent pricing for all medicines, and the parallel importation of patented medicines[1] [9].

At the start of the litigation, the drug companies could rely on the support of their home governments. For its part, the United States had put pressure on

1. Parallel imports are cross-border trade in a patented product, without the permission of the manufacturer or publisher. Parallel imports take place when there are significant price differences for the same good in different markets.

South Africa by withholding trade benefits and threatening further trade sanctions, aiming to force the South African government to repeal the Amendment Act [10]. In 1998, the European Commission joined the United States in pressuring South Africa to repeal the legislation [11]. AIDS activists effectively highlighted these policies, profoundly embarrassing then-presidential candidate Al Gore. Confronted at election campaign rallies about his personal involvement in the dispute, demonstrators accused him of killing babies in Africa [12]. As a result of increasing public pressure, the United States changed its policies at the end of 1999. By the time the case finally reached the courtroom in May 2000, the drug companies could no longer count on the support of their home governments.

Demonstrators in major cities asked the companies to drop the case; several governments and parliaments around the world, including the European Parliament, demanded that the companies withdraw from the case. The legal action turned into a public relations disaster for the drug companies [13].

During the course of the trial it became clear that the most contentious section of the Amendment Act was based on a draft legal text produced by the WIPO Committee of Experts [14], a fact that made it difficult for the drug companies to maintain the position that the Amendment Act violated South Africa's obligations under international law. Eventually, the strong international public outrage over the companies' legal challenge of a developing country's medicines law and the companies' weak legal position caused the companies to unconditionally drop the case in April 2001.

The widely publicized South African court case brought two key issues out into the international arena. First, the interpretation of the flexibilities of TRIPS and their use for public health purposes needed clarification to ensure that developing countries could use its provisions without the threat of legal or political challenge. Second, it became clear that industrialized countries that exercised trade pressures to defend the interest of their multinational industries could no longer exert pressure without repercussions at home.

United States vs. Brazil: The Brazilian AIDS Programme

Since the mid-1990s, Brazil has offered comprehensive AIDS care, including universal access to antiretroviral (ARV) treatment. An estimated 536,000 people are infected with HIV in Brazil, with 203,353 cases of AIDS reported to the Ministry of Health from 1980 through December 2000. In 2001, 105,000 people with HIV/AIDS received ARV treatment. The Brazilian AIDS programme

reduced AIDS-related mortality by more than 50% between 1996 and 1999 [15]. In two years, Brazil saved US$472 million in hospital costs and treatment costs for AIDS-related infections.

At the core of the success of Brazil's AIDS programme is the ability to produce medicines locally. Brazil has also been able to negotiate lower prices for patented drugs by using the threat of production under a compulsory license [16]. Article 68 of the Brazilian patent law allows for compulsory licensing, which allows a patent to be used without the consent of the patent holder [17]. The Brazil AIDS programme serves as a model for some developing countries that are able to produce medicines locally, and Brazil has offered a cooperation agreement, including technology transfer, to developing countries for the production of generic ARV drugs [18]. In February 2001, the United States took action against Brazil at the WTO Dispute Settlement Body (DSB) over Article 68 of the Brazilian intellectual property law. Under that provision, Brazil requires holders of Brazilian patents to manufacture the product in question within Brazil – a so-called "local working" requirement. If the company does not fulfil this requirement, the patent shall be subject to compulsory licensing after three years, unless the patent holder can show that it is not economically feasible to produce in Brazil or can otherwise show that the requirement to produce locally is not reasonable. If the company is allowed to work its patent by importation instead of manufacturing in Brazil, parallel import by others will be permitted.

The United States argued that the Brazilian law discriminated against United States owners of Brazilian patents and that it curtailed patent holders' rights. The United States claimed that the Brazilian law violated Article 27.1 and Article 28.1 of TRIPS [19]. Brazil argued that Article 68 was in line with the text and the spirit of TRIPS, including Article 5.4 of the Paris Convention, which allows for compulsory licensing if there is a failure to work a patent. Article 2.1 of TRIPS incorporates relevant articles of the Paris Convention.

The United States action came under fierce pressure from the international NGO community, which feared it would have a detrimental effect on Brazil's successful AIDS programme [20]. Brazil has been vocal internationally in the debates on access to medicines, and on several occasions, including the G-8, the Roundtable of the European Commission, and WHO meetings, Brazil has offered support to developing countries to help them increase manufacturing capacity by transferring technology and know-how. NGOs feared that the United States action could have a negative effect on other countries' ability to accept Brazil's offer of assistance. On June 25, 2001, in a joint statement with

Brazil, the United States announced that it would withdraw the WTO panel against Brazil [21].

The role of NGOs

NGOs have played a key role in drawing attention to provisions of TRIPS that can be used to increase access to medicines. One such provision pertains to compulsory licensing, which enables a competent government authority to license the use of an invention to a third-party or government agency without the consent of the patent-holder. The patent holder, however, according to Article 31 of TRIPS, retains intellectual property rights and "shall be paid adequate remuneration" according to the circumstances of the case. The first international meeting specifically on the use of compulsory licensing to increase access to AIDS medicines took place in March 1999 at the Palais des Nations in Geneva and was organized by Consumer Project on Technology, Health Action International, and MSF. Later that year, the same group of NGOs organized the Amsterdam Conference on Increasing Access to Essential Drugs in a Globalized Economy, which brought together 350 participants from 50 countries on the eve of the Seattle WTO ministerial conference. The statement drawn up at this conference ("Amsterdam Statement") focused on establishing a working group in the WTO on TRIPS and access to medicines, considering the impact of trade policies on people in developing and least-developed countries, and providing a public health framework for the interpretation of key features of WTO agreements. The working group was to address questions related to the use of compulsory licensing to increase access to medicines, mechanisms to allow production of medicines for export markets to a country with no or insufficient production capacity, patent barriers to research, and overly restrictive and anti-competitive interpretations of TRIPS rules regarding protection of health registration data. In addition, the working group was to examine "burden sharing" approaches for R&D that permit countries to consider a wider range of policy instruments to promote R&D and to consider the practical burdens on poor countries of administrating patent systems. The Amsterdam Statement also urged national governments to develop new and innovative mechanisms to ensure funding for R&D for neglected diseases.

The Amsterdam Statement has served as a guide for the work of NGOs and other advocates on TRIPS and public health. Many international and national NGOs, such as the OXFAM campaign, "Cut the Cost," the South African Treatment Action Campaign, Act Up Paris, and the Health Gap

Coalition in the United States, are now involved in campaigning for access to medicines.

The WTO Ministerial 1999 in Seattle

Though public health and access to medicines did not form part of the official agenda in Seattle in the way it would two years later in Doha, the issue did receive attention for a number of reasons. First, in Seattle a Common Working Paper section on TRIPS contained the following proposal: "to issue… compulsory licenses for drugs appearing on the list of essential drugs of the World Health Organization." [22] Since only about 11 of the 306 products on the WHO Model List of Essential Drugs are patented drugs in certain countries[2] this proposal could have limited the use of compulsory licensing, rather than making sure it became a useful tool to overcome access barriers, such as prohibitive pricing, caused by patent abuse.

Then-United States President Clinton chose Seattle as the venue to declare a change in United States policy with regard to intellectual property rights and access to medicines. The United States government had come under fierce attack from AIDS activists because of its policies in South Africa. Under the new policy, the United States Trade Representative and the Department of Health and Human Services would together establish a process to analyse health issues that arise in the application of United States trade-related intellectual property law and policy. In his speech, President Clinton referred specifically to the situation in South Africa and the HIV/AIDS crisis, saying that "the United States will henceforward implement its health care and trade policies in a manner that ensures that people in the poorest countries won't have to go without medicine they so desperately need." [23]

In May 2000, President Clinton confirmed the change in United States policy by issuing an Executive Order on Access to HIV/AIDS Pharmaceuticals and Medical Technologies, supporting the use of compulsory licenses to increase access to HIV/AIDS medication in sub-Saharan Africa [24]. Although this policy change contributed to breaking the taboo on the use of compulsory licensing in the health field, attention to TRIPS and medicines at the WTO was diverted by the collapse of the WTO conference in Seattle [25]. However, outside the WTO, the debate on access to medicines, TRIPS, and compulsory licensing became more intense.

2. High cost or price of a drug in general used to exclude a drug from the WHO Essential Drug List.

Changing attitudes among global players

A number of international institutions and UN agencies contributed to the debate on access to medicines and looked into the consequences of stronger intellectual property protection as a result of TRIPS for developing countries.

The World Health Organization

The public health community first raised concerns about the consequences of globalization and international trade agreements with respect to drug access during the 1996 World Health Assembly. A resolution on the Revised Drug Strategy (RDS) set out the WHO's medicines policy [26]. The WHO resolution on the RDS requested the WHO in paragraph 2 (10) "to report on the impact of the work of the World Trade Organization (WTO) with respect to national drug policies and essential drugs and make recommendations for collaboration between WTO and WHO, as appropriate." This resolution gave the WHO the mandate to publish, in 1998, the first guide with recommendations to Member States for implementing TRIPS while limiting the negative effects of higher levels of patent protection on drug availability [27]. The United States and a number of European countries unsuccessfully pressured the WHO in an attempt to prevent publication of the guide [28].

At that time, the WHO's involvement in trade issues was highly controversial. The emphasis on public health needs versus trade interest was seen as a threat to the commercial sector of the industrialized world. For example, in 1998, in response to the draft World Health Assembly's resolution on the RDS and in reference to "considerable concern among the pharmaceutical industry," the European Directorate General for Trade (DG Trade) of the European Commission concluded: "No priority should be given to health over intellectual property considerations." [29]

However, subsequent resolutions of the World Health Assembly have strengthened the WHO's mandate in the trade arena. In 2001, the World Health Assembly adopted two resolutions in particular that had a bearing on the debate over TRIPS [30]. The resolutions addressed:

– the need to strengthen policies to increase the availability of generic drugs;

– and the need to evaluate the impact of TRIPS on access to drugs, local manufacturing capacity, and the development of new drugs.

As a result, the WHO's work programme on pharmaceuticals and trade now includes the provision of policy guidance and information on intellectual

property and health to countries for monitoring and analyzing the effects of TRIPS on access to medicines [31].

The European Union

In February 2001, the EU adopted the Programme for Action, a programme which accelerates action on HIV/AIDS, malaria, and tuberculosis in the context of poverty reduction. The EU programme recognized the potential problems of TRIPS and the need to rebalance its priorities. In addition, several European Parliament resolutions reflected a shift in support of a pro-public health approach to TRIPS [32]. As part of this approach, DG Trade changed its policy to acknowledge the concerns of developing countries. Reflecting this change, DG Trade dropped its objections to the use of compulsory licensing to overcome patent barriers to medicine access and became an advocate for a global tiered pricing system for pharmaceuticals [33]. These policy changes are in stark contrast to previous European Commission policies, which closely track the pharmaceutical industry's agenda.

Other Organizations

Other organizations, such as UNAIDS, the World Bank, the Group of 77, and regional organizations such as the Organization of African Unity, added their voice to the debate on TRIPS and access to medicines. The UN Sub-Commission for the Protection and Promotion of Human Rights passed a resolution, pointing out the negative consequences for human rights to food, health, and self-determination if TRIPS is implemented in its current form. Referring specifically to pharmaceutical patents, the resolution stresses the need for intellectual property rights to serve social welfare needs [34]. In 1999, the United Nations Development Programme's (UNDP's) Human Development Report made a plea for re-writing the rules of globalization to make them work "for people – not just profits." [35]

Unable to turn a deaf ear to the growing chorus of critics of TRIPS and its effects on access to medicines, the WTO changed course. In April 2001, when proposing a special TRIPS Council session on access to medicines, Zimbabwe – chair of TRIPS Council – said that the WTO could no longer ignore the access to medicines issue, an issue that was being actively debated outside the WTO but not within it [36]. The voices had been heard; public health would be featured as a key subject at the Doha Conference.

III
A BRIEF HISTORY OF THE DOHA DECLARATION ON TRIPS AND PUBLIC HEALTH

The Fourth Ministerial Conference of the WTO took place in Doha in 2001 and was a breakthrough in international discussions on TRIPS and access to medicines. The WTO Ministerial adopted a Declaration on TRIPS and Public Health, which put public health before commercial interests and offered much needed clarification in the field of TRIPS and public health.

The African proposal for a special TRIPS Council meeting in June

The "African Group" statement to the TRIPS Council about the need to confront the access to medicines issue initiated preparations for the Declaration. Just two months later, in June 2001, the TRIPS Council held its first session devoted to TRIPS and access to medicines. It was the first time that the TRIPS Council discussed intellectual property issues in the context of public health. At that meeting, the African Group proposed issuing separate declarations on access to medicines [37]. Referring to the devastating AIDS crisis in Africa and mounting public concern, Zimbabwe as head of the Africa Group stated: "We propose that Members issue a special declaration on the TRIPS Agreement and access to medicines at the Ministerial Conference in Qatar, affirming that nothing in the TRIPS Agreement should prevent Members from taking measures to protect public health." [38]

In September 2001, the TRIPS Council devoted another full day of discussion to the topic of access to medicines. At this meeting, the African Group, joined by nineteen other countries, presented a draft text for a ministerial declaration on TRIPS and Public Health. A comprehensive text, this proposal addressed political principles to ensure that TRIPS did not undermine the legitimate right of WTO Members to formulate their own public health policies. The text also provided practical clarifications for provisions related to compulsory licensing, parallel import, data protection, and production for export to a country with insufficient production capacity. In addition, the draft included a proposal for evaluating the effects of TRIPS on public health, with particular emphasis on access to medicines and R&D for the prevention and treatment of diseases predominantly affecting people in developing and least-developed countries.

At the meeting, the United States, Japan, Switzerland, Australia, and Canada circulated an alternate draft, stressing the importance of intellectual property protection for R&D, arguing that intellectual property contributes to public health objectives globally. The text was aimed at limiting the flexibilities of TRIPS during crisis and emergency situations. The EU circulated its own draft, which proposed a solution to the problem of production for exports to fulfil a compulsory license in a country with insufficient or no production capacity by allowing production under the TRIPS Article 30 exception.

From the onset of the pre-Doha negotiations, the main point of contention was the text proposed by the developing countries: "Nothing in the TRIPS Agreement shall prevent Members from taking measures to protect public health." [39] Some developed countries saw this wording as a new rule that would override the present rules of TRIPS, which do not allow for health exceptions that are inconsistent with TRIPS [40].

The text drafted by the chair of the WTO General Council, Mr. Stuart Harbinson, that was the basis for the negotiations in Doha, left the issue unresolved and instead offered two options for Paragraph 4. The first option read:

> *Nothing in the TRIPS Agreement shall prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement shall be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to ensure access to medicines for all. In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement which provide flexibility for this purpose.*

Whereas the second option offered was:

> *We affirm a Member's ability to use, to the full, the provisions in the TRIPS Agreement which provide flexibility to address public health crises such as HIV/AIDS and other pandemics, and to that end, that a Member is able to take measures necessary to address these public health crises, in particular to secure affordable access to medicines.*
>
> *Further, we agree that this Declaration does not add to or diminish the rights and obligations of Members provided in the TRIPS Agreement. With a view to facilitating the use of this flexibility by providing greater certainty, we agree on the following clarifications.*

Negotiations in Doha

In Doha, for three days the discussions on TRIPS and public health dominated the trade talks. Early on in the meeting it became clear that a majority of Members preferred the first option of the Harbinson draft, making it the basis for further negotiation. The reason for this was that option one recognises that measures can be taken for health in general and not only in cases of health crisis. Furthermore the text in option 2 implies that the Declaration would not create new rights or alter existing rights. This would have weakened the significance of the Declaration for example in WTO dispute settlement procedures. The core supporters of the second option included the United States, Japan, Australia, Switzerland, Canada, and Korea. The EU, at this stage, did not take a clear position and claimed it was playing the role of "honest broker." After three days of negotiation among the participating Members, a compromise was reached. The compromise text, which resulted from negotiations primarily between Brazil and the US, read:

> *We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitments to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all* [41].

This text acknowledges the unmitigated right of countries to take measures to protect public health. Thus, if intellectual property rules should stand in the way of doing so (for example, in the case of high prices associated with patented medicines), countries are allowed to override the patent.

In Paragraph 5, the Declaration lays out the key measures and flexibilities within TRIPS that can be used to overcome intellectual property barriers to access to medicines. The discussions at Doha and the Doha Declaration itself make it unambiguously clear that the use of compulsory licenses is in no way confined to cases of emergency or urgency; in fact, the grounds for issuing a compulsory license are unlimited. Members who proposed language that would have limited measures like compulsory licensing to emergency situations, pandemics, or specified diseases such as HIV/AIDS were unsuccessful. In addition, the Declaration leaves Members free to determine for themselves what constitutes a national emergency or urgency, in which cases the procedure for issuing a compulsory license becomes easier and faster. The Declaration

also resolves the question of whether TRIPS authorizes parallel trade once and for all by noting: "The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge." [42]

In addition, the Declaration grants Least Developed Country (LDC) Members an extra ten-year extension – until 2016, instead of 2006 – to the implementation deadline for pharmaceutical product patent protection. The negotiating history illustrates that this outcome was not predetermined. Pre-Doha, the United States proposed two operative paragraphs, which included this extension of transition periods until 2016 for patents on pharmaceutical products, as well as offering a moratorium on dispute settlement action to sub-Saharan African countries, which do not fall within the LDC grouping. The moratorium covered laws, regulations and other measures that improve access to patented medicines for HIV/AIDS and other pandemics. These proposals were viewed as a "divide and conquer" strategy employed by the United States to break the cohesion of the developing countries [43] and the proposal for a moratorium on dispute settlement actions was rejected at Doha. The proposal to extend the deadlines for LDCs were accepted. The extended deadlines are important because they extend the timeframe (until 2016) in which countries may rethink the kind of pharmaceutical intellectual property law they want while still being able to import and produce generic medicines.

The Declaration also refers to the as-yet unfulfilled commitment of developed-country Members to provide incentives to their enterprises and institutions to promote technology transfer to LDCs pursuant to Article 66.2. The ten-year extension might be of limited value because only LDCs will be able to benefit from this provision. Of the 143 WTO members, only 30 are LDCs, representing 10% of the world's population. The ten-year extension is limited to Sections 5 (patents) and 7 (undisclosed information) of TRIPS; the extension does not apply to other provisions of the Agreement relevant to pharmaceuticals, notably Article 70 ("exclusive marketing rights"). Though there seemed to be an understanding among the negotiators in Doha that Paragraph 7 implied that LDCs are not required to provide "mail box" protection or "exclusive marketing rights," this is not clear from the text of the declaration. Paragraph 7 of the declaration refers to pharmaceutical products, which means that LDCs are still under the obligation to provide process patents.

A key issue that remained unresolved in Doha is how to ensure that production for export to a country that has issued a compulsory license, but does not have manufacturing capacity, can take place within a country that provides

pharmaceutical patents. Since Article 31 (f) of TRIPS limits compulsory licensing to uses which are predominantly for the supply of the domestic market, countries agreed that further action was necessary to ensure that countries without production capacity can make use of compulsory licensing provisions to the same extent that countries with manufacturing capacity can use these provisions. The Doha Declaration acknowledges the problem in Paragraph 6:

> *We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.*

However to date no progress has been made to resolve this issue.

Other areas of debate in Doha

Public Health

Most of the language aimed at narrowing the scope of the Declaration to health crisis and pandemics[3] was replaced with language that referred generally to public health. Indeed, the title itself – Doha Declaration on Public Health – reflects this shift.

Access for All

Some countries objected to the text that countries have the right "to ensure access to medicines for all" [44]. In particular, Switzerland objected to the wording, but had difficulty defending a position that advocated access to medicines for some but not for others.

Scope

A point of strong contention was how far-reaching the Declaration would be. Some WTO Members feared that the negotiations could lead to changes in TRIPS and wanted to include a confirmation that the Declaration was purely a clarifying exercise. They borrowed language from the WTO Dispute Settlement Process Rules to indicate that the Ministerial Declaration would have no formal legal effect to change the rights and obligations TRIPS established.

3. Pandemics refer to diseases, mostly of infectious nature, that travel across borders.

The text did not, however, make it into the final version of the Declaration. As a result, one could argue that the Declaration actually does go beyond clarifying the already existing rules. A Member can appeal to the Declaration and its negotiating history in the event that a Member's legislation, particularly relating to patents in the health field, is challenged on the grounds that it is incompatible with TRIPS.

Why Doha came to pass

Why was it possible to achieve a declaration on such a contentious issue considering that public health hardly played a part in the trade talks two years ago? Mike Moore, WTO Director-General, made it clear on the opening day of the conference that the TRIPS and health issue could be the deal-breaker for a new trade round. Observers point to a number of factors that contributed to the success of the negotiations [45]. First, the developing country Members were extremely well prepared and operated as one bloc. Second, the uncompromising positions of western countries such as the United States and Canada were hard to maintain in light of the anthrax crisis and the threat that a shortage of ciprofloxacine (Cipro™) might occur. Both the United States and Canada rapidly expressed their willingness to set aside the patent held by the German company Bayer if other solutions could not be found [46]. The anthrax scare and the threatened shortage of Ciproâ forced all WTO Members to ask how much of a prisoner they wanted to be of their own patent systems. Third, a growing and active international NGO movement ensured the issue would be high profile, and that NGOs would monitor different countries' positions.

IV
DRUG INDUSTRY RESPONSE TO THE WTO DECLARATION ON TRIPS AND PUBLIC HEALTH

The multinational pharmaceutical industry argued from the beginning that a declaration was not necessary because:

a) patents are not a problem [47];

b) weakening patent protection would have devastating effects on the R&D capabilities of the research-based industry.

Although the International Federation of Pharmaceutical Manufacturers (IFPMA) officially welcomed the Declaration on TRIPS and Public Health,

individuals in the industry expressed their concerns. Indeed, the United States pharmaceutical companies asked the United States Trade Representation (USTR) to re-open the negotiations even after an agreement on the text of the Declaration was reached.

For more than two years, IFPMA has warned against the dangers of compulsory licensing-ever since NGOs started to propose compulsory licensing systems to overcome patent barriers. IFPMA's position has not changed. "Compulsory licensing is a threat to good public health by denying patients around the world the future benefits of R&D capabilities of the research-based industry from which new therapies come." [48]

The generic drug industry welcomed the Declaration, in particular the freedom of countries to decide the grounds for compulsory licensing. It did however express concern about possible unilateral pressure to influence countries not to make full use of the Declaration. The industry suggested that the advanced WTO Members should commit themselves to the Declaration in practice by refraining from exerting unilateral pressure. The generic drug contingent expressed disappointment that there was no resolution of the issue that arises when a country with limited production capacity that issues a compulsory license for a medicine cannot find an efficient, affordable, and reliable source of medicines, due to TRIPS restrictions on production and export of medicines. After 2005, production of affordable medicine will increasingly become dependent on compulsory licensing. However production under a compulsory license is restricted to production "predominantly for the supply of the domestic market." [49] The problem is not the compulsory license itself, but the need to allow exports from a country where the drug is under patent to a country that has issued the compulsory license.

The generic drug industry expressed further disappointment that the Declaration did not offer an interpretation of the data protection issue addressed in Article 39.3 of TRIPS. The concern here is that an overly restrictive interpretation of Article 39.3 will lead to delays in introduction of generic medicines, may provide exclusive marketing rights beyond the patent protection term and increase barriers to the registration of generic medicines including those produced under a compulsory license.

V
THE POST-DOHA AGENDA

It is crucial that the Doha declaration "paragraph 6" issue of production for export be resolved. Implementation deadlines for some important producing countries are quickly approaching, thus further limiting the possibilities of producing generic versions of medicines that are protected by patent elsewhere.

Another flaw of the Doha Declaration is that it does not resolve the problem of production for export from markets that provide patents to countries that do not grant pharmaceutical patents (and subsequently do not grant compulsory licenses). This is of particular importance now that the least-developed WTO Members can delay the granting of pharmaceutical product patents until 2016. These countries need to have access to sources of affordable medicines, which threaten to dry up as the 2005 deadline for TRIPS implementation is nearing for producing countries.

It will also be a challenge to find ways to make the Doha Declaration on TRIPS and Public Health operational at the regional and national levels. A classic example is the Bangui Agreement, the regional intellectual property agreement for francophone Africa, which was adopted in 1977 and revised in 1999 to ensure TRIPS compatibility, but includes typical TRIPS plus provisions that are not in line with the Doha Declaration.

At the national level, countries should be encouraged to make full use of the Doha Declaration in the process of adjusting national intellectual property laws to become compliant with TRIPS. This will require substantial advice and technical assistance from institutions like WIPO and WTO. While the spirit of the Doha Declaration is to tailor intellectual property laws to national needs, the practice has been to encourage developing countries to go beyond the minimum requirements and speed up the process to become TRIPS-compliant. It will require a "culture change" at WIPO and WTO to adjust the type of technical assistance to developing countries' needs. In addition to increasing their interaction with countries, WIPO and WTO will have to increase their level of collaboration with the public health community, including the WHO, which has become heavily involved in trade discussions as a result of the process that led to the Doha Declaration.

A key requisite for the success of the Doha Declaration will be the political will of countries to take measures to offer access to medicines to their population. There is no excuse for the South African government's lack of action at the moment.

VI
PRODUCTION AND EXPORT OF MEDICINES –IS THE DOHA SPIRIT DWINDLING?

In grim contrast to the optimistic spirit in Doha in 2001, the WTO in the months that followed the Doha conference failed completely to deliver on the promise that a solution to allow production of medicines for export to countries that do not have production capacity would be found before the end of 2002.

The TRIPS Council discussed different proposals. The opening moves of the key players, the European Union, the United States, Africa group, India, Brazil and the WHO in the TRIPS Council were the following: the EC and their members submitted two possible options to address the paragraph 6 problem: an amendment to Article 31(f) of the TRIPS Agreement that would create an exception to the requirement that a compulsory license is predominantly for the domestic market, and the option of allowing production for export as a limited exception under Article 30 [51]. Both options would be subject to conditions with regard to eligible countries and scope of diseases. The United States proposed a dispute settlement moratorium whereby the Members would agree not to bring a WTO complaint against countries that export some drugs to countries in need. The United States insisted that any solution should apply to epidemics mentioned in the Doha declaration, namely HIV/AIDS, TB and Malaria. The Africa Group, joined by Brazil, Cuba, Dominican Republic, Ecuador, Honduras, India, Indonesia, Jamaica, Malaysia, Sri Lanka and Thailand, suggested as possible options an amendment to Article 31 in order to delete the paragraph that limits compulsory licensing to "predominantly for the domestic market", or to develop an authoritative interpretation that would recognize the right of Members to allow the production for export without the consent of the patent holder to address public health needs in another country under Article 30 of the TRIPS Agreement.

The WHO favoured a solution that is based on Article 30 of TRIPS. In its statement to the TRIPS Council on September 17, 2002, the WHO set out the features of a solution to the Doha declaration "paragraph 6 problem" which are desirable from a public health perspective as follows: "a stable international legal framework; transparency and predictability of the applicable rules in the exporting and importing countries; simple and speedy legal procedures in the exporting and importing countries; equality of opportunities for countries in need of medicines, even for products not patented in the importing country;

facilitation of a multiplicity of potential suppliers of the required medicines, both from developed and developing countries; and broad coverage in terms of health problems and the range of medicines". The WHO concluded: "Thus, the basic public health principle is clear: the people of a country which does not have the capacity for domestic production of a needed product should be no less protected by compulsory licensing provisions (or indeed other TRIPS safeguards), nor should they face any greater procedural hurdles, compared to people who happen to live in countries capable of producing the product.

"Among the solutions being proposed, the limited exception under Article 30 is the most consistent with this public health principle. This solution will give WTO Members expeditious authorization, as requested by the Doha Declaration, to permit third parties to make, sell and export patented medicines and other health technologies to address public health needs." [52]

A coalition of NGOs (Consumer Project on Technology, Essential Action, Médecins Sans Frontières, Oxfam International, Health GAP Coalition, and the Third World Network) wrote on December 19, 2002 to the WTO members calling for a solution that is based on Article 30. They made the following proposal:

> *Under Article 30 of the TRIPS agreement, Members may provide an exception to the exclusive rights conferred by a relevant patent to permit all acts associated with the production for export to a third country of a patented product or a product produced by a patented process; where the export addresses health needs in the third country; and the product and/or process is either (a) not patented; or (b) a compulsory license has been granted or government use made of the relevant patent in the third country.*

They pointed out that the Article 30 approach to addressing the issue of exports of medicines passes the test of being administratively simple, workable and economically viable. They urged the WTO to reject proposals to tie Article 30 export exemptions to overly restrictive or complex conditions and procedures.

While negotiations went on in the TRIPS Council, the European Parliament on October 23, 2002 adopted Amendment 196 to the EU Directive 2001/83/EC relating to medicinal products for human use. This Amendment reads as follows:

> *Manufacturing shall be allowed if the medicinal product is intended for export to a third country that has issued a compulsory license for that product, or where a patent is not in force and if there is a request to that effect of the competent public health authorities of that country.*

The approach taken by the European Parliament is consistent with the position of the WHO in the TRIPS Council. The revision of the EU rules on medicines is still under discussion and it is unclear at this stage whether the EP amendment will be maintained. The Parliament's amendment had no impact on the EU's position in the TRIPS Council which by then was advocating a solution solely based on Article 31f of TRIPS. However, the Parliament's move is significant for the discussions at the TRIPS Council because it can serve as a model for a paragraph 6 solution, and it shows that countries can formulate exceptions under Article 30 of the TRIPS Agreement without prior consent of the WTO.

The Motta Text

Unfortunately, the WTO negotiations took an entirely different direction. Months of discussions in the TRIPS Council showed a deep divide between the developing countries that were seeking a workable solution and the industrialised world that tried to limit the scope of any solution as much as possible. In an attempt to meet the 2002 deadline, most delegations were prepared to accept a far from ideal compromise text that became known as "the December 16 Motta text" named after the chair of the TRIPS Council. The Motta text is ambiguous on the scope of diseases through its reference to paragraph 1 of the Doha Declaration which mentions AIDS, TB and Malaria. A more appropriate basis for the scope of disease would have been paragraph 4 of the Doha declaration which refers to public health problems in general. On the eligibility for countries, the Motta text seems to be at odds with the Doha Declaration which requires implementing the TRIPS in a manner to "promote access to medicines for all". The Motta text provides for cumbersome procedures to determine eligibility of countries, and for measures to prevent diversion of medicines to rich country markets.

Even though the Motta text was seen as far from ideal, all countries were ready to agree to it. NGOs called upon the negotiators to reject the text [53]. In the end it was the United States that vetoed the proposal. The lobby of the drug companies to restrict the scope of diseases and eligible countries of any solution to paragraph 6 has been very fierce in particular in the United States. The United States considered the scope of diseases too broadly defined, rejected the proposal and announced a unilateral moratorium on disputes. In an attempt to break the deadlock, the European Commission followed up on an earlier United States proposal and listed diseases for which the solution could apply, and introduced an advisory role for the WHO in case a Member requested

this[4] [54]. This proposal was rejected by the developing countries as backtracking on the Doha declaration and was met with a wave of objections from all over the world. In numerous letters, professional medical organizations, individual medical doctors, NGOs, consumer groups and human rights groups rejected any further narrowing of the scope of the Doha declaration [55]. Apart from HIV/AIDS, the list included only diseases for which there is either no treatment or where virtually all the recommended treatments are so old as to be off-patent [56]. The negotiations in the WTO became quite bizarre with trade negotiations trying to determine public health priorities for countries. The latest attempt to make the Motta text palatable for the United States came from the Chair of the TRIPS Council who proposed in January 2003 to adopt a statement that there is an understanding that the solution "under paragraph 6 of that Declaration as being essentially designed to address national emergencies or other circumstances of extreme urgency." Again this proposal was rejected by the developing countries. MSF reacted fiercely in an open letter to the WTO members and called upon the Members to reject the proposal. The use of compulsory licensing was never meant to address only emergency situations and it would certainly be unacceptable to limit the use of compulsory licensing for countries without production capacity even further, while the entire purpose of the paragraph 6 discussions was to lift the barriers to use compulsory licensing non-producing countries face [57].

At this point it had become clear that there was little left of the spirit that led to the Doha declaration on TRIPS and Public Health. In particular the United States seemed to want to turn the clock back to the pre-Doha era.

Conclusion

The very fact that public health and access to medicines have been singled out as major issues needing special attention in TRIPS implementation indicates that health care and health care products need to be treated differently from other products. By giving countries broad discretion in deciding how to counter the negative effects of TRIPS, the Doha Declaration may stand for the proposition that public health concerns outweigh full protection of intellectual property.

4. The EC proposal read: "This covers at least HIV/AIDS, malaria, tuberculosis, yellow fever, plague, cholera, meningococcal disease, African trypanosomiasis, dengue, influenza, leishmaniasis, hepatitis, leptospirosis, pertussis, poliomyelitis, schistosomiasis, typhoid fever, typhus, measles, shigellosis, hemorrhagic fevers, and arboviruses. When requested by a Member, the World Heath Organization shall give its advice as to the occurrence on an importing Member, or the likelihood thereof, of any other public health problem."

In fact, the Doha Declaration takes a large step toward ensuring that intellectual property protection actually serves the public interest, an interest broader than that of the commercial sector. In the years to come, it will be important to scrutinize closely whether the results of intellectual property protection serve the poor as well as the rich. The Doha Declaration lays out the options countries have available when prices of existing patented drugs are too high for their populations. But Doha did not solve every problem: the lack of R&D investment in new drugs for the particular health needs of the poor remains to be addressed [58].

In the Doha process, developing countries and NGOs pointed to commercial and public sector neglect of the R&D needs of developing countries.

Recent studies claim that the R&D cost of a commercial drug company per new pharmaceutical product is US$802 million [59]. The Global Alliance for Tuberculosis Drug Development, a non-profit entity for R&D of tuberculosis drugs, estimated that the total R&D cost for a new tuberculosis drug, including the cost of failure, is between US$115 million and US$240 million [60]. These high R&D costs claimed by the commercial pharmaceutical sector pose some key questions that need to be resolved. Is the present system for funding R&D the most efficient, and is it sufficient to rely on the present intellectual property systems to fuel innovation? Clearly, in the area of neglected diseases, the answer is no.

In an increasingly globalized economy, additional international mechanisms need to be developed to address health needs in developing countries. MSF and others have proposed a radical shift in the way health R&D is financed, in particular for drugs for neglected diseases. For example, health R&D could be financed based on burden-sharing between countries, or obligating companies to complete essential medical research. Such a proposal might be incorporated into an international treaty on essential health R&D. In the end, the challenge for the coming years will be to encourage essential health R&D not only for the benefit of some, but for the benefit of all.

A major concern is the backtracking of rich countries on the promises made in Doha as was seen during the discussions on paragraph 6. The failure to reach an agreement to allow the production and export of generic medicines in the face of current health needs in developing countries gives little reason for optimism about the full implementation of the Doha Declaration. The implementation of the Doha declaration is a test for the TRIPS Agreement. Ultimately the following question will have to be answered: Is there a future for the TRIPS Agreement if in practice the flexibility to ensure that "the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health" does not exist?

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The Brazilian Experience in Providing Universal Access to Antiretroviral Therapy

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Key words: Brazil; HIV/AIDS care; health system.

Abstract

Brazil is the first developing country to have implemented a large-scale universal antiretroviral distribution program. Initiated in the early 90s with the distribution of AZT, it now provides free antiretroviral medication to about 125,000 patients, which reflects a coverage of virtually all people living with HIV/AIDS with some form of treatment indication. The results achieved are telling: from 1996 to 2002, more than 60,000 AIDS cases, 90,000 deaths and 358,000 AIDS-related hospital admissions were averted. Financially, the balance is also positive: the savings in out-patient and hospital costs outrun the costs of implementation by more than US$ 200 million. These results demonstrate that it is feasible to extend the availability of ARV treatment to the millions of people in need, even in a resource-poor setting where the ideal infrastructure might not be in place. It is clear that the broad political and sociological context in which the Brazilian response evolved cannot be underestimated, but it is fair to say that the Brazilian experience is based on a concerted early government response, the strong and effective participation of civil society, a multisectoral mobilization, a balanced prevention and treatment approach and the advocacy of human rights in all strategies and actions.

Résumé

Le Brésil est le premier pays en développement à avoir mis en œuvre un programme de distribution d'antirétroviraux universel sur une large échelle. Initié au début des années 90, avec la distribution d'AZT, ce programme procure aujourd'hui des traitements antirétroviraux gratuits à environ 125 000 patients, c'est-à-dire à tous les individus vivant avec le VIH qui ont besoin de traitement. Entre 1996 et 2002, plus de 60 000 cas de sida, 90 000 décès et 358 000 admissions hospitalières liées au sida, ont été évitées. Au plan financier, le bilan est également positif : les économies en termes de coût hospitalier et ambulatoire dépassent le coût du programme de plus de 200 millions de dollars US. Ces résultats démontrent qu'il est possible d'élargir l'accès aux traitements antirétroviraux aux millions de personnes qui en ont besoin, même dans les lieux les plus démunis où l'infrastructure idéale n'est pas disponible. À l'évidence, le contexte sociologique et politique global dans lequel s'est organisée la réponse brésilienne, ne peut être sous-estimé ; il est important de rappeler que l'expérience brésilienne repose sur une réponse gouvernementale concertée précoce, sur une participation forte et effective de la société civile, sur une mobilisation multisectorielle, sur une approche équilibrée en termes de prévention et de traitement, et sur un plaidoyer en matière de droits de l'homme dans toutes les stratégies et les actions.

Introduction

Scaling up the fight against the HIV/AIDS epidemic has gained unprecedented momentum. It is now possible, finally, to say that an agreed minimum body of policies exists among scientists, activists and policymakers on how to intervene effectively to curb the spread of the epidemic. In few areas such a consensus is more impressive than in the field of access to life-saving medicines, particularly regarding the need – as well as the feasibility – to expand dramatically the availability of antiretroviral drugs (ARVs) to the millions of HIV/AIDS patients living in the developing world who are currently unable to purchase them. The year 2002 witnessed the launch of several related initiatives, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the International HIV Treatment Access Coalition.

Brazil is the first developing country to have implemented a large-scale universal ARV distribution program. About 125,000 patients receive ARVs freely through the official Public Health System. This number means that more than a third of the estimated total number of ARV treated patients in the entire

developing world at the end of 2002 live in Brazil. This context has attracted growing attention to the successes and challenges experienced in Brazil, and this paper intends to describe and discuss them in brief, notably in the field of treatment and care. As a conclusion, a few recommendations to other countries and to the international community in general will be explored.

I
THE BRAZILIAN SOCIAL AND EPIDEMIOLOGICAL CONTEXT

Brazil is a federal republic with approximately 172 million inhabitants, making it the fifth most populous country on the planet. At the end of the year 2002, it had an estimated Gross Domestic Product per capita of roughly US$3,000. Such numbers, however, hide the persistence of huge income inequalities as well as the deep regional disparities that exist within Brazil. Nevertheless, such an outlook did not prevent the Brazilian Government from adopting a pro-active and aggressive stance against the epidemic, a collective response that gradually involved various sectors of the Brazilian society such as the government, universities, churches and civil society in general.

Of course, the evolution of the Brazilian response was strongly influenced by its broad political and sociological context, particularly the structure and role of its public health system. Actually, this public health system, developed throughout the last decades but consolidated as free and universal under the new Constitution of 1988, took its current form following a movement for reform that was initiated in the late 60s and was called the sanitarist movement (from "movimento sanitarista"). Conducted under the strong leadership of public health activists, it already established as a cornerstone feature of public policy-making a constant dialogue with communities and civil society, especially as a means to enhance social control over governmental policies. This would later on be particularly important to shape the current care and treatment policies toward HIV/AIDS. In the mid 80s, the emergence of the AIDS epidemic in Brazil coincided with profound changes in the sociopolitical arena, with the end of military government, return to democracy, and concomitant reforms in the roles and responsibilities of the State, including in the health sector. The advent of the 8th National Health Conference in 1986 involved a wide range of social representatives and was fundamental in the establishment of the current Public Health System.

This public and universal health model, launched in 1988 as a constitutional right, is therefore the final outcome of fundamental changes in the national

socio-political scenario, and it can be considered the structural "backbone" around which the Brazilian AIDS policy emerged. The fight against the disease set the stage for a new kind of interaction between the state and civil society, one that has contributed to substantially strengthen the new democratic institutions, to greater recognition of all Brazilians as citizens and to open the debate on the ethics of national healthcare, a consideration that spilled over to other public health concerns as well. On the face of scarce financial resources, a vocal and active civil society, coupled with a professional community committed to ensuring access to integral public health care, were instrumental in moving the State machinery to appropriately confront the AIDS epidemic.

As of March 2002, close to 240,000 AIDS cases (Table 1) have been reported to the Ministry of Health (MOH) since the beginning of the epidemic, with approximately 107,000 cumulative deaths. Brazil's epidemic profile has been changing fast in recent years. Despite a clear temporal trend of deceleration in all regions (Figure 1), HIV infection has spread in smaller towns, among heterosexual men and women and among low-income individuals. Moreover, evidence indicates that the AIDS epidemic has basically remained an urban disease in Brazil, with limited spread in rural areas.

Table 1: Brazil epidemic profile

– CUMULATIVE AIDS CASES (March 2002): 237,588
– CUMULATIVE AIDS DEATHS (March 2002): 110,651
– ESTIMATED NUMBER OF HIV+ INDIVIDUALS (2000): 597,000
– INCIDENCE RATE OF AIDS (2000): 12.4/100,000
– PREVALENCE RATE OF HIV (2000): 0.6%

The numbers in Table 1 may seem quite low from the epidemiological point of view, but the World Bank anticipated in 1992 that Brazil would reach the year 2000 with much worse numbers. According to this earlier estimate, approximately 1.2 million people would have been infected by the year 2000 in Brazil. However, recent estimates have in fact placed that figure close to 600,000 people living with HIV/AIDS (PLWAs) or, in other words, half the number predicted.

II
MAKING IT POSSIBLE

The Brazilian response is based on a concerted early government response, a strong and effective participation of the civil society, a multisectoral mobilization, a balanced approach between prevention and treatment and a systematic advocacy of human rights in all strategies and actions. It is worth mentioning that these principles are an integral part of the Declaration of Commitment on HIV/AIDS adopted in July 2001 at the Special Session on AIDS promoted by the United Nations General Assembly (UNGASS).

In particular, guidelines for prevention policies have emphasized the need to:

– direct special attention to more vulnerable populations, such as men who have sex with men, injecting drug users and commercial sex workers;

– ensure access to prevention supplies, especially condoms, syringes and needles;

– introduce preventive actions in health care services.

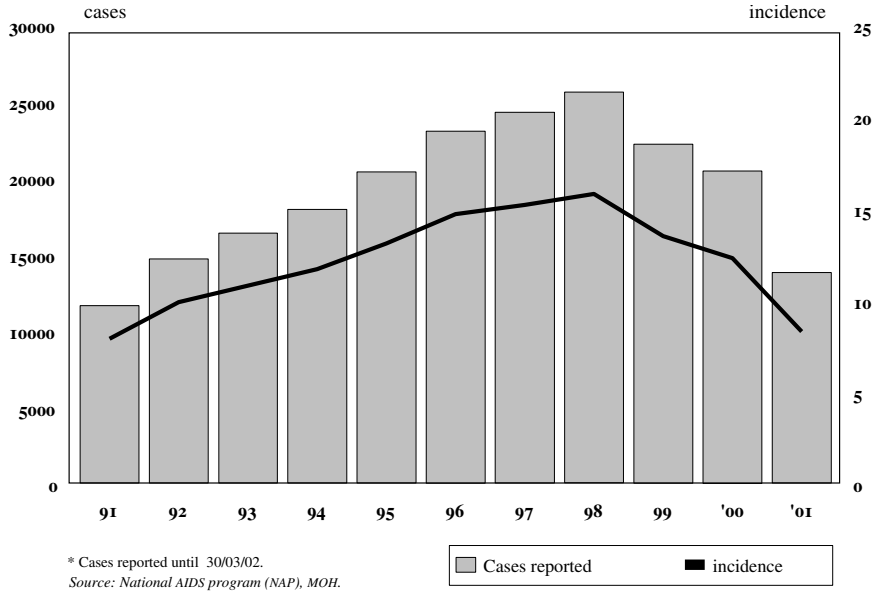
As a result of this strategy, the consistent use of condoms has been brought to new grounds. Research undertaken in 1999 in the general adult population showed that from a low 4% in 1986 at the beginning of the epidemic, we have managed to boost this number to 48% in 1999, a ten-fold increase [1, 2]. This increase has brought Brazil to the same level of condom use as significantly wealthier developed countries. For example, the rate of condom use at first sexual intercourse in those segments with higher education (71%) is very similar to that observed in France or even in the United Kingdom [2]. Using combined strategies, the Ministry of Health (MOH) is planning to promote an additional 100% increase in condom use by the general population together with a 45% price reduction in the next five years.

Another important intervention was the implementation of syringe and needle exchange programs as a public health policy. Between 1994 and 2002, 160 harm reduction projects were implemented with a population coverage of approximately

65,000 injecting drug users (IDU). As examples of the impact of this policy, an analysis of two major Brazilian cities covered by this kind of program has shown a sharp reduction in the incidence of HIV among IDUs, from 63% to 42% in one city in 7 years, and from 50% to 7% in the other over a period of 4 years [3]. These findings have stimulated the MOH to increase the number of cities covered by this type of intervention.

As already mentioned above, the number of new AIDS cases has also been dramatically lowered. Down from its peak of nearly 25,000 cases in 1998, we expect the year 2003 to close with a number between 10,000 to 15,000 new cases.

Figure 1: AIDS cases (notified and estimated) and incidence rate by year of diagnosis



* Cases reported until 30/03/02.
Source: National AIDS program (NAP), MOH.

Considerable results have also been achieved in strategic segments of the population, especially among the most vulnerable groups. Sentinel studies conducted with thousands of parturients between 1997 and late 2000 indicate that the estimated prevalence rate among 13 to 49 years-old has nearly halved in this period, coming down from 1.2 to 0.6%. Brazil has also managed to achieve a significant reduction in the rate of incidence among men who have sex with men, sex workers and, as previously mentioned, IDUs.

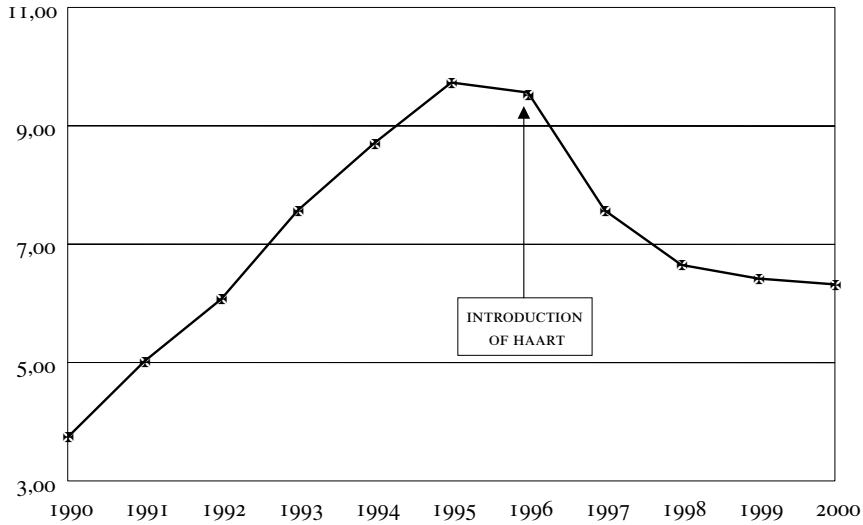
Table 2: Estimates (%) of HIV infection in selected populations

Pregnant women	1.2 (1997)	0.6 (2001)
commercial sex workers	17.8 (1996)	6.1 (2000)
injecting drug users (Rio de Janeiro)	25.0 (1996)	8.0 (2000)
men who have sex with men	10.8 (1999)	4.7 (2001)

Source: MOH, 2002.

The mortality rate and number of deaths from AIDS have also fallen dramatically, especially since 1996, with the free and universal distribution of Highly Active Antiretroviral Therapy (HAART) through the Brazilian public health system.

Figure 2: Annual rate and mortality trend of AIDS Brazil 1990-2000



Source: Mortality Information System – National Health Foundation.

III
CARE AND TREATMENT IN BRAZIL

In order to improve quality of life for people living with HIV and AIDS, the Brazilian MOH has implemented a policy of free and universal access to antiretroviral therapy and drugs for opportunistic infections since 1991. This effort was initiated with the distribution of zidovudine (ZDV) capsules, and was institutionalized by a 1996 presidential decree that guaranteed that all patients would have free access to essential medications to combat HIV, including protease inhibitors, whose distribution began at the end of that same year.

The criteria for dispensing HIV treatment is established by the MOH, which now has three technical groups working on the problem, one focusing on HIV therapy for adults and adolescents, one for children and one for pregnant women. These technical groups come together at least once a year to review the medical criteria for eligibility and to discuss changes made necessary by medical breakthroughs and the availability of new treatments.

Table 3: Initial therapy – protocol of the Brazilian Ministry of Health, 2002-2003

SYMPTOMATIC OR ASYMPTOMATIC with CD4 < 200/mm^3	2 NRTI* + NNRTI** or 2 NRTI + PI***
ASYMPTOMATIC with CD4 between 200 and 350/mm^3	2 NRTI + NNRTI or 3 NRTI
ASYMPTOMATIC with CD4 > 350/mm^3	NO TREATMENT

* Nucleoside Analogue Reverse Transcriptase Inhibitors.
** Non-nucleoside Reverse Transcriptase Inhibitors.
*** Protease Inhibitors.

Table 4: ARV class; 1st and 2nd choice

ARV CLASS	1st CHOICE	2nd CHOICE
2 NRTI	ZDV + 3TC or d4T + 3TC	AZT + ddI or ddI + 3TC or ddI + d4T
NNRTI	EFZ	NVP
PI	NFV or LPV/R	SQV/R or IDV/R

Additionally, a network of more than 1,000 public alternative care and HIV testing services has been established to provide the necessary infrastructure to support this policy. Spread on a regional and administrative basis according to the complexities associated with care services, it is aimed at improving the diagnosis and monitoring of HIV infection, as well as diagnosis and medical observation of opportunistic diseases. Such an extensive network builds, wherever possible, on the organizational and functional structure of the Public Health System, where both responsibilities and costs are split among the Federal Government, the States and the Municipalities. Since the Federal Government structurally possesses the largest financial capacity among the different associated entities, it is entrusted with complex and costly interventions, and is therefore expected to cover the lion's share of the budget allocated to AIDS. Nevertheless, as previously mentioned, the national response to the AIDS threat was responsible for creating positive externalities which impacted several other health areas, including the infrastructure provided for by the Public Health System itself.

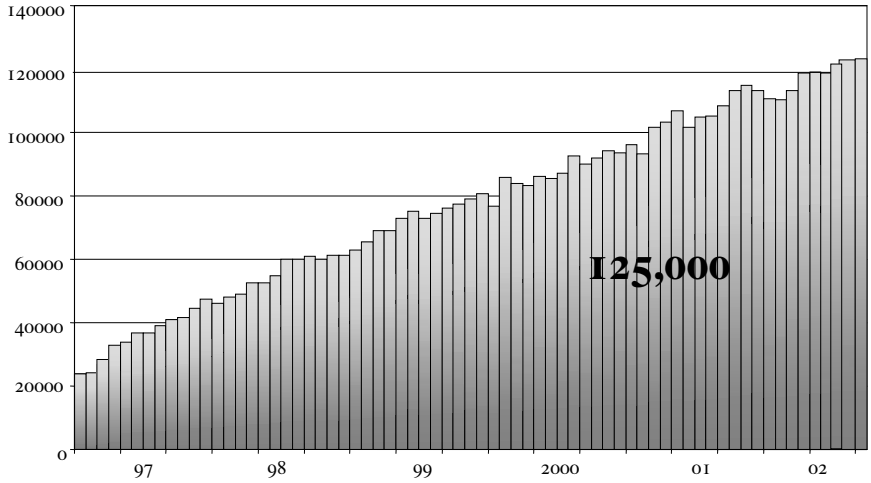
In order to adequately monitor the patients, the Brazilian Ministry of Health has established a National Network of Viral Load Laboratories and a network of CD4 + CD8 + lymphocyte counting laboratories, with 80 and 65 units, respectively. Moreover, considering the overall impact and probabilities involved in ARV delivery, the MOH decided to establish a national genotyping network (named RENAGENO), able to perform and interpret the results of HIV-1 resistance tests using adequate and rational criteria. At this first phase, 14 laboratories have been accredited and 60 reference genotyping expert physicians from different parts of the country have been trained to assist the demand on a regional basis. The process of building such an elaborate infrastructure was long, especially in the poorest parts of the country. However, vital to its success was the political decision to offer treatment and start related activities even before the ideal structure was in place.

The Brazilian MOH has also put in place a specific computer-based system for logistic management of ARVs (named SICLOM) in order to ensure rational supply and consumption throughout all 480 dispensary units. The major objectives of this logistic control system are:

1) to control drug stocks at national, state and municipality levels;
2) to ensure efficiency and safety of drug supply;
3) to adequately plan for drug purchases;
4) to assure optimal drug management.

At this moment, more than 125,000 people receive free antiretroviral treatment.

*Figure 3: Patients on ARV therapy in the public health system. Brazil, 1997-2002**



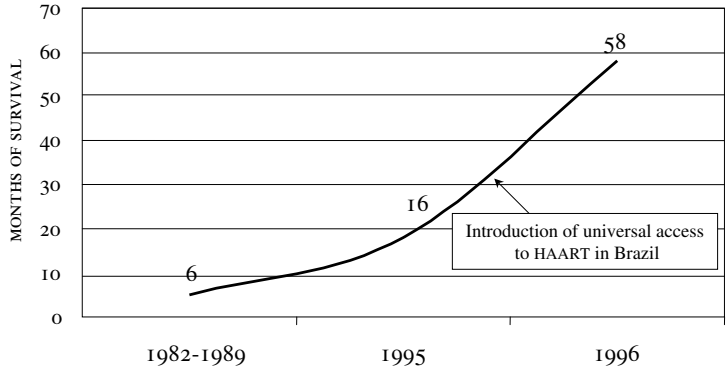
* september/02 - estimated data.

Source: MOH.

IV
RESULTS

A study presented at the XIV[th] International AIDS Conference [4] has shown that the survival rate has increased substantially with ARV therapy in Brazil. In this study, the average survival time before availability of combined therapy was less than 6 months and now is close to 5 years. This 12-fold increase is not only quantitatively important: quality of life has also improved significantly. Patients go on working normally and interacting with their friends and families, which in the long run represents the most powerful weapon against the very foundations of stigma and discrimination. It is also an active anti-poverty and development policy. As the latest UNAIDS Epidemiological Update recognizes, "by robbing communities and nations of their greatest asset – their people – AIDS drains the human and institutional capacities that drive sustainable development. This, in turn, distorts labor markets, disrupts production and consumption, erodes productive and public sectors and ultimately diminishes national wealth. As HIV prevalence rises, poverty deepens, and in combination with other setbacks, AIDS can trigger social crises. Some of the countries worst affected by AIDS face the prospect of 'un-developing' – seeing their development achievements dissolve in the wake of the epidemic [5]."

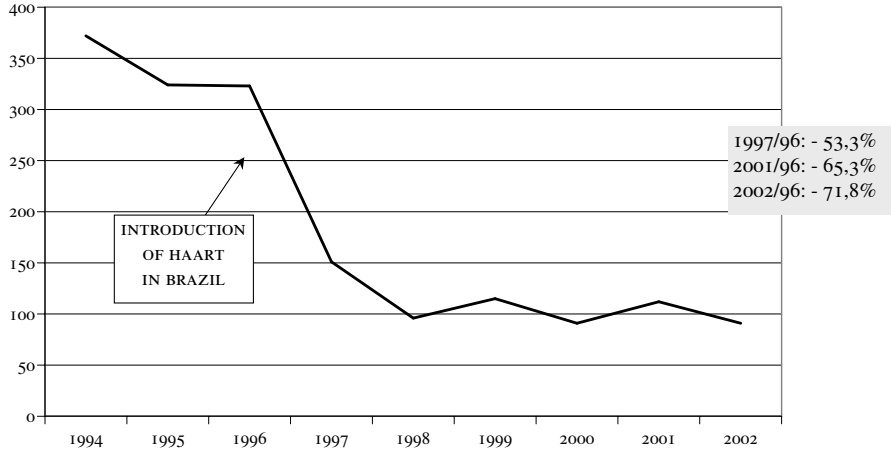
Figure 4: Impact of universal access to HAART on average survival after AIDS diagnosis in Brazil



Sources: [6, 7].

As a result, the occurrence of common HIV-related opportunistic infections has declined by 60 to 80%. The number of tuberculosis cases, for instance, has dropped by 75% in the last four years in the State of Sao Paulo, which carries roughly fifty per cent of all AIDS cases reported in Brazil. Moreover, a change in the profile of HIV health care services has been observed, with a significant increase in the demand for outpatient services, home care and day-hospital services.

Figure 5: Tuberculosis in PLWAs CRT - DST/AIDS, São Paulo, Brazil (1994-2002)*



Source: Epidemiological Surveillance of the Training and Reference Centers in STD/AIDS (V.E. CRT DST/AIDS) (Data until 31/12/2002).

* Centro de Referencio e tretamento DST/AIDS.

It is clear, therefore, that providing treatment to the millions in need is a basic feature of intervening effectively against the global destabilizing power of the AIDS epidemic. Though costly, it is by any comparison a relatively low amount when compared to the potential loss of national stability caused by underdevelopment and poverty.

Moreover, we have learned that waging war against HIV/AIDS is good business. Millions spent in the short term can save billions in the long run. After six years, an evaluation of the results of the Brazilian AIDS policy shows pretty impressive numbers. Since 1996 until now we have observed a striking reduction in mortality (40-70%), morbidity (60-80%) and hospitalization rates of HIV + patients, with more than 90,000 avoided deaths. Near 60,000 AIDS cases were prevented. At the same time, we have observed a significant reduction in the number of hospitalizations of AIDS patients during this time. In the last five years, a seven-fold reduction has been observed, with more than 358,000 AIDS-related hospital admissions avoided. This resulted in savings to the Government of more than US$1.1 billion from 1997 to 2001. However, when we take into consideration the additional US$1.2 billion saved on ambulatory care, including drugs for opportunistic infections, the total amount rises to approximately US$2 billion. In the meanwhile, US$1.8 billion were invested in carrying out this policy, suggesting total net savings of circa US$ 200 million. It should be noted, however, that such figures underestimate the total net social benefit of providing treatment and care for people living with HIV/AIDS, given that they do not take into account elements that are more complex to quantify (*e.g.* associated cost savings with tutors who continue to teach, children who remain with their families, etc).

Furthermore, a study soon to be published demonstrates that the relative number of permanent public pensions requested in Brazil due to AIDS-related disabilities has fallen consistently since 1996, while the number of temporary illness-related benefits has increased, suggesting that AIDS is slowly becoming a chronic and controllable disease.

The actions of the Ministry of Health have resulted in important changes in the epidemic evolution in Brazil. Striking reductions in the occurrence of new AIDS cases and AIDS deaths, a 70 % drop in big cities like Sao Paulo and Rio de Janeiro, are evident five years after introduction of universal access to HAART. All these aspects are consequences of a reduction in the number, in the time of duration and in the complexity of the treatment in hospital admission episodes, suggesting a significant welfare profit for these patients after a more disseminated use of combined antiretroviral therapy.

In 2002, the Brazilian MOH distributed 15 antiretroviral drugs of 3 different pharmacological classes to all HIV-infected patients that meet the criteria spelled out in national guidelines. Of these, seven are locally produced formulations, with pharmacological specifications for generic versions.

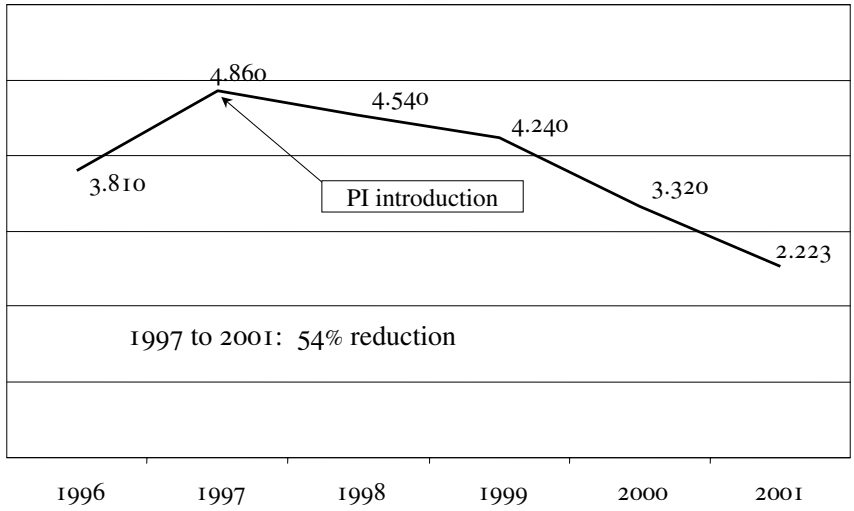
Table 5: ARVs distributed by MOH (2002)

- Zidovudine (ZDV)*
- Didanosine (ddI) *
- Zalcitabine (ddC) *
- Lamivudine (3Tc) *
- Stavudine (d4T) *
- Abacavir
- Indinavir *
- Ritonavir
- Saquinavir
- Nelfinavir
- Amprenavir
- Nevirapine *
- Delavirdine
- Efavirenz
- Lopinavir/r

* generic version available.

Public policymakers cannot lose sight, however, of the relevance of adopting strong strategies to lower the prices of these drugs as a prerequisite for the long-term sustainability of any ARV delivery program. In Brazil, the average cost per ARV-treated patient per year has decreased by more than half in the last few years (Figure 6), in spite of the proportional increase in the number of patients needing more expensive and complex treatments. Also worthy to say that these expenditures with antiretrovirals represents only 1.6% of the total budget of Ministry of Health and less than 0.05% of Brazilian GDP in 2001. This reduction in costs of care occurred due to a combination of two concomitant strategies.

Figure 6: Median cost (US$) of ARV therapy by patient/year. Brazil 1996 to 2001



Source: MOH, 2002.

Table 6: Antiretroviral drugs: MOH expenditures (1996-2002)

Year	US$ millions	Average number of Patients	% MOH Budget
1996	34	-	0.2
1997	224	35,900	1.2
1998	305	55,600	1.8
1999	336	73,000	3.2
2000	303	87,500	2.9
2001	235	105,150	1.6
2002*	167	119,500	1.8

* Preliminary data. *Source: NAP/MOH, 2003.*

First, investments were made by the MOH to set up domestic national laboratories with the capacity to manufacture large quantities of ARV drugs. Local production has worked remarkably well to regulate the market and to favor a decreasing trend in the average prices of drugs paid by the MOH. Interestingly, the prices of ARVs produced within Brazil fell on average by 82% between 1996 and 2001, while the decrease was only 40% for imported ARVs during the same period. Second, effective negotiation of drug prices was carried out with those pharmaceutical drug companies that are exclusive producers. The Brazilian MOH has used a negotiation strategy with some exclusive producers based on tiered prices. As a consequence, deals were made with Abbott, Merck and Roche, cutting the prices of 4 drugs by more than 50%. Although desirable, these recent decreases must be taken only as an initial step towards much greater cuts.

Table 7: Brazilian MOH & Merck, Roche and Abbott agreements on ARV price reduction (2001/2002)

64,8% Price Reduction on Indinavir
US$1.33/capsule → US$0.47/capsule

59,0% Price Reduction on Efavirenz
US$2.05/capsule → US$0.84/capsule

40,0% Price Reduction on Nelfinavir
US$1.075/capsule → US$0.64/capsule

46,0% Price Reduction on Lopinavir/r
US$2.97/capsule → US$1.60/capsule

Experience suggests, however, that the efficacy of this strategy rests upon the possibility of credibly using the mechanism of compulsory licensing. Thus, domestic production capacity is a crucial element that strengthens the bargaining power of government agencies.

Until this moment, the prevalence and profile of drug resistance mutations in Brazilian patients under HAART has been very similar to what have been found in other international studies [2, 8]. However, the prevalence of primary resistance in drug naive patients is significantly lower than what we have seen in Western Europe and the US [9, 10]. This reinforces the quality, safety and

efficacy of generic antiretroviral drugs and the policy of universal access to ARV therapy adopted by the Brazilian Ministry of Health in the last decade.

One of the most interesting lessons from our experience with treatment and care is that the adherence rate of patients to ARV therapy in developing countries can be exactly the same as in developed countries. Studies carried out in Brazil have shown that the main factor linked to adherence is the quality of medical service, regardless of the mode of transmission [5]. Therefore, IDUs, for instance, when properly reached, adopt all measures recommended[1].

Finally, the role of a solid and constructive partnership with civil society as a powerful force towards greater social control and participation must be emphasized. NGOs play a major role in advocating the rights of people living with HIV/AIDS, speeding up government processes, and providing vital additional efforts to official agencies so as to strengthen implementation capacity and outreach. In Brazil, from 1994 until 2002, more than US$ 40 million have been invested in 2,300 projects implemented by civil society organizations, including communities and NGOs of people living with HIV/AIDS.

This is, in rather brief and general terms, the Brazilian experience in scaling up a program of continental proportions. It provides fruitful ground from where important lessons can be learned. What follows is an agenda, based on this on-going experience, for future consideration at both national and international levels.

V
MOVING FORWARD: NATIONAL AND INTERNATIONAL LEVEL

At the national level, countries must do more to mobilize the necessary political commitment to put together national financial resources and to decisively confront cultural, religious and legal barriers to prevention. Despite the low costs involved, minority groups are still discriminated against and excluded from national responses, as is the case of homosexuals, commercial sex workers and injecting drug users. The latter have even been repeatedly denied access to treatment. In this regard, openness and courage to speak out and break the silence are equally cornerstone features of any successful program.

1. For example, consistent condom use within this population has risen to 65% [3].

No time can be spent with ambiguous prevention messages. HIV transmission happens primarily through sexual contact, and prevention is made through condom use. Other alternatives, such as postponement and abstinence are indubitably incompatible with our global reality, particularly eroticized and based on sex promotion. The alleged ethical character of such initiatives is today one of the main enemies of effective prevention.

In what concerns treatment availability, countries must be more resolute. It is quite emblematic to see so many people debating how to solve the dilemma caused by the death of teachers due to AIDS and ways to train others to replace them. This is a false dilemma. Although training may be an adequate measure, the first step obviously needs to be a decision to treat the teachers already infected to avoid their death.

The importance of community participation, of transparency and multisectoral mobilization in the elaboration and implementation of national responses goes without saying. Governments cannot exclude or choose the organizations they intend to work with.

At the international level, the current level of international funding directed to fight AIDS in the developing world is simply not sufficient to face the various needs of these countries, particularly when we take into account the efforts that will have to be made towards strengthening and capacity building of health systems. Revised figures from the Joint United Nations Program on HIV/AIDS indicate that by the year 2005 an annual 10.5 billion dollars will be needed for prevention, care and support programs in low- and middle-income countries. The current level, although growing, remains at less than a fourth of this amount.

What the world is facing is a catastrophe of the proportions seen at the end of World War II. Back then it was absolutely unthinkable to suppose that countries in Western Europe would ever recover from the massive economic and social destruction inflicted upon them and that their peoples would ever rise up to enjoy, fifty years later, the highest levels of social development and quality of life known to human kind. Crucial to such accomplishment was the mobilization of hundreds of billions of dollars in today's terms by the United States under what came to be known as the Marshall Plan. Today we need a new "Marshall Plan" to scale up national responses in poor countries. Developed societies, such as the United States, Japan and Western Europe, finally need to assume their responsibility in changing this dramatic situation. After all, the vast majority of infected people worldwide, especially in Sub-Saharan Africa

and in the Caribbean, simply lack the minimum financial resources necessary to intervene in the field. No matter how much the prices of antiretrovirals are reduced, for instance, they will still be out of reach to these peoples.

United Nations Agencies and Programs have no other choice but to enormously scale up their programs of international assistance. They have various areas of expertise as is the case with the WHO and UNAIDS regarding treatment and care, and the World Bank and UNDP in the areas of development and technical capacity building. We cannot ignore the fact that the international community unanimously agreed at the Millennium Assembly in September 2000 to halt and begin to reverse the spread of HIV/AIDS by 2015. Clearly, this is not the best that we can do; on the contrary, it is simply the minimum we must do.

At the same time, this agenda must be equally pushed forward in international forums. Although the Doha Declaration on TRIPS and Public Health re-established the preeminence of health over profit, attempts have been made at nullifying recent advances. It is imperative that countries lacking sufficient manufacturing capacity be able to make use of all possible means, particularly compulsory licenses, to procure drugs internationally for the public health problems they deem appropriate. Equally, developed countries must also commit themselves to improve access to pharmaceutical products in the developing world, drastically supporting aggressive differential pricing strategies, and allowing, when needed, the production of medicines by third parties for export purposes.

Successful experiences based on interventions linking prevention and treatment, as implemented in Brazil and Thailand, prove that it will be impossible to control the epidemic in the long run without an effective vaccine. Here, once again, the commitment of the developed world is paramount, since the development of a vaccine is a costly endeavor. In this aspect results are rather disappointing. In the last two years, more vaccine candidates have entered human trials around the world, but the pipeline of promising vaccines is still woefully inadequate.

Winning the fight against HIV/AIDS is not easy, cheap or quick. However, much more difficult, expensive and longer will be to redeem our world from the scourge of poverty, instability and war that comes with the epidemic. We have the knowledge; we know the proven strategies, the right policies. Time has come to act.

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Patents, Innovation and Public Health: Brazilian Public-Sector Laboratories' Experience in Copying AIDS Drugs

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Key words: anti-AIDS drugs; patents;
reverse engineering; technological learning.

Abstract

The Brazilian experience in producing HIV/AIDS drugs is based on the lawful copying of medicines patented abroad, on a health policy of universal access to antiretrovirals (ARV), and on technological learning, especially in public-sector laboratories through reverse engineering. The information contained in patents has proved to be incomplete and the chemical standards of these molecules are not available in the pharmacopoeias. Chemists at the Rio health ministry's laboratory have had to partially rediscover the qualitative and quantitative composition of these drugs. They have thus acquired knowledge on the synthesis processes of the active principles of drugs, which they are now able to transfer to pharmaceutical companies. Apart from copying existing drugs, the laboratory also develops research both in-house and in partnership with universities, to create new molecules. The learning process initiated through copying is thus combined with a research policy.

Résumé

L'expérience brésilienne de production des médicaments anti-VIH/sida repose sur la copie licite des médicaments brevetés à l'étranger, sur une politique de santé publique visant l'accès universel aux ARV, sur un processus

d'apprentissage technologique, notamment au sein des laboratoires publics, grâce à des méthodologies d'ingénierie inverse. L'information contenue dans les brevets s'est révélée incomplète et les standards chimiques de ces molécules ne sont pas disponibles dans les pharmacopées. Les chimistes du laboratoire pharmaceutique du ministère de la Santé à Rio ont dû redécouvrir partiellement la composition qualitative et quantitative de ces médicaments. Ils ont acquis des connaissances sur les procédés de synthèse des principes actifs qu'ils sont aujourd'hui en mesure de transférer à des firmes de chimie pharmaceutique. Au-delà de la copie de médicaments existants, le laboratoire public développe des recherches internes et externes, en coopération avec les universités, pour créer de nouvelles molécules. L'apprentissage initié par la copie se double d'une politique de recherche.

Introduction

In 1997 the Far Manguinhos state-owned pharmaceutical laboratory was mobilized by the Brazilian health ministry to launch production of copies of medicinal drugs used to treat HIV/AIDS. The main objective was to obtain price reductions so that the Health Ministry's AIDS programme could be supplied with these drugs at a lower cost. Between 1997 and 2002 the volume of Far Manguinhos' drug production increased sevenfold, notably through development of antiretroviral (ARV) production[1]. The laboratory premises were totally rearranged. The surface area devoted to drug manufacturing was tripled, separate production lines were created for ARV in order to comply with ANVISA[2] health safety standards, and construction of a large building is currently underway, to house the chemical analysis and Research and Development (R&D) departments.

This original experience, in which industrial economics and public health policy are closely combined, can be explained in terms of three main factors:

– first, the particular configuration of industrial property rights in Brazil where, until 1996, pharmaceutical inventions were public goods that could lawfully be copied;

– second, the impetus of the Health Ministry which, in a context of health emergency and demands of civil society for care, embarked on a policy of

1. During the same period Far Manguihnos' financial resources were multiplied by twenty.

2. Agencia de Vigilancia Sanitaria. In September 2002 Far Manguinhos received the ANVISA Certificate of approval for Good Manufacturing Practices. This was one of the conditions on which authorization was granted to produce generic drugs.

universal access to medicinal drugs (promulgation of the law on universal access to AIDS drugs in November 1996). Far Manguinhos, a pharmaceutical laboratory belonging to the Health Ministry, plays a key part in the implementation of this policy, alongside other state-owned laboratories and Brazilian private-sector laboratories;

– third, this experience is based on a process of acquisition of knowledge on copied drugs, primarily through reverse engineering.

The Health Ministry's pharmaceutical laboratory plays an essential part not only in Brazil's ARV production (accounting for 40% of Brazilian production of ARV, the remaining 60% being shared between other state-owned laboratories and private-sector industry). In our opinion, it also has a key role in the acquisition of knowledge on these drugs, which it can then transfer either to Brazilian public-sector laboratories or to private-sector pharmaceutical laboratories in Brazil and, in the future, in other countries of the South. It is this gradual acquisition of knowledge that we wish to consider here.

Theories on the economics of knowledge often compare two strategies: one based on the imitation of knowledge created elsewhere, and the other on the local production of research and development that generates new knowledge in situ [1]. The Brazilian experience of AIDS drug production has shown that reverse engineering is a source of acquisition of knowledge for a laboratory. In so far as imitators do not have the complete recipe for the drugs they wish to reproduce, nor the relevant know-how and synthesis processes, they are forced to rediscover basic knowledge on the drug. This reverse identification of the components and formulae of drugs, synthesis processes, and standards concerning active principles. Moreover, during this reverse engineering, chemists identify variants of molecules and diverse synthesis processes, and sometimes even propose improvements. Reverse engineering is therefore basically a process of technological learning, that is, of local knowledge production. The Far Manguinhos laboratory uses accumulated knowledge to develop systematic applied research on these molecules, and especially on processes for synthesizing active principles – which can be transferred to the Brazilian pharmaceutical industry – on combinations of molecules, and on polymorphic variants of those same molecules, likely to produce new technical effects. The laboratory is also working on the identification of new ARV in partnership with university researchers. The challenge is therefore not only to rediscover basic knowledge on molecules created elsewhere, but also to create new knowledge on new pharmaceutical products.

This technological learning process has important implications in terms of industrial economics and the economics of industrial property rights. First, there

is a real process of knowledge acquisition based on the imitation of inventions. Second, this example shows the advantages of the right to free use of knowledge – in this case the non-patentability of medicinal drugs that Brazil enjoyed from 1945 to 1996 and which allowed the lawful reproduction of protected pharmaceutical inventions. The adoption of patentability of drugs in Brazil in 1996, ahead of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement schedule, complicated the task of Brazilian public-sector laboratories as regards the copying of new patented molecules. The different actors involved in this experiment – public laboratories, patients associations and Non Governemental Organizations (NGOs) – therefore now wish to demand the application of compulsory licensing in Brazil in order to be able to produce ARV patented since 1996[3].

I
EVOLUTION OF THE ECONOMIC STATUS OF DRUGS IN BRAZIL: FROM PUBLIC GOODS TO PRIVATE GOODS PROTECTED BY PATENT

From 1945 to 1996, in Brazil like many other countries, drugs were considered to be public goods that could be copied freely for industrial purposes[4]. The first stage of the exclusion of drugs from patenting was during the presidency of Getulio Vargas in 1945. Already at that time the idea was to encourage the transfer of inventions patented abroad and local production of medicinal drugs. This policy was reaffirmed in the early 70s. The 1971 industrial property act excluded pharmaceutical patents on both processes and products. This political exclusion of pharmaceutical inventions from patenting had two objectives: first, public health – the law highlighted the importance of the pharmaceutical sector for the population – and second, industrial policy – to

3. Our research consisted of a laboratory study based on the principles of the socio-economics of innovation, aimed at revealing the pharmaceutical laboratory's technological learning process. Twenty three in-depth interviews were hold with the far Manguinhos laboratory management, the individuals responsible for industrial property rights, and chemists in the different departments of the laboratory. We also recorded a meeting with synthesis chemists responsible for ARV, and interviews were held with the patients associations and NGOs involved.

4. In France, medicinal drugs were excluded from patentability from 1833 to 1959; and in Germany from 1877 to 1969 (only chemical processes were patentable in Germany). They only became patentable in 1976 in Japan, in 1977 in Switzerland, in 1978 in Italy and Sweden, and in 1992 in Spain.

boost technology transfer and local laboratories. In May 1970 a new Drug Production Institute was created by presidential decree within the Oswaldo Cruz Foundation. During the 80s, the Health Ministry ran a chemical synthesis laboratory for copying and transferring formulae to Brazilian industry. In the mid-90s a private-sector laboratory, Microbiologica, took advantage of this opening to undertake the copying of AZT. Finally, since 1997 Far Manguinhos has used the possibility of lawfully copying drugs patented abroad to start producing ARV in Brazil.

The 1996 patent law, which allows patenting of pharmaceutical products and processes, finally put an end to the public goods status of pharmaceutical inventions. It nevertheless contains limits to patent rights in the form of compulsory licensing in cases where the patented product is not produced locally (the aim being to curb the wave of closures of international manufacturing plants) and in cases of national emergency and public interest. These exceptions were stipulated in 1999 in a decree based on the TRIPS agreement which provides for exceptional measures to protect public health. The decree was drafted in a context of controversy with the United States over Brazilian law, in which the US challenged the obligation for pharmaceutical companies to manufacture patented drugs in Brazil within three years [2].

These compulsory licences were the subject of a tug of war with international pharmaceutical laboratories, and the Brazilian Health Ministry used them in negotiations on the purchase price of molecules patented after 1996. In the summer of 2001 it challenged Roche with a threat to produce Nelfinavir in Brazil from 2002, until the company agreed to a substantial price reduction. Another example is Merck, which accepted a 60% cut in its prices in exchange for a commitment by the Health Ministry not to produce patented molecules locally. Chemists in Brazilian public-sector laboratories are demanding application of compulsory licences to be able to continue reproducing new generations of ARV. To date, no compulsory licence measure has been taken. Government laboratory lawyers also complain about very restrictive conditions for application of these licences, and are calling for amendments to Brazilian law[5].

5. Brazilian law is more restrictive than the TRIPS agreement as regards compensation for patentability in cases of compulsory licensing. Article 31 of the TRIPS agreement stipulates that the patentee will receive adequate remuneration, depending on the case, in view of the economic value of the authorization. Article 71 of the Brazilian law states that a compulsory licence must be granted "without prejudice to the rights of the respective patentee". This condition is judged contradictory to the very notion of a compulsory license which naturally entails loss of a market for the patentee. It increases the possibilities of lawsuits in which the patentee wins.

II
THE PROCESS OF COPYING AND ACQUIRING KNOWLEDGE ON DRUGS (1997-2002)

Brazilian public-sector laboratories are not in a position to incorporate the entire drug manufacturing process. Their capacities are too limited to produce the active principles of the drugs, which have to be obtained from Indian, Chinese, Korean and, to a lesser extent, Brazilian companies. Consequently, the Far Manguinhos laboratory has specialized in the final production phase: purchasing raw material, formulation, and production and packaging of drugs. It may seem that such narrow specialization would have limited the laboratory's expertise on these drugs. Yet as we are about to see, that is by no means the case, for several reasons.

First, when it decides to manufacture a drug, Far Manguinhos has to develop expertise and tools for controlling the quality of the raw material it buys. Second, in order to meet ANVISA standards for approval of generic drugs, it has to establish standards of purity and quality of the various molecules it uses. Note that in the case of most ARV these standards are currently not available in international pharmacopoeia since patent holders refuse to disclose them. Far Manguinhos has therefore had no alternative but to reformulate them in order to be allowed to produce generic drugs. Third, Far Manguinhos has developed a strategy of systematic acquisition of knowledge on these molecules, particularly their synthesis, in order to be able to transfer it to Brazilian private-sector laboratories that either are, or might be, able to develop production of the active principles of the relevant drugs. The laboratory's aim here is to organize technology transfer towards Brazilian private-sector industry. Fourth, acquisition of knowledge on drugs, that is, on their formulae, on molecule standards and on synthesis processes, is a key element in Health Ministry negotiations with international laboratories. The Ministry can use this knowledge, and the potential ability to manufacture drugs locally, as a real threat when bargaining to obtain price reductions. Fifth, Far Manguinhos does not intend to limit itself to reproduction of existing drugs. Apart from reverse engineering on existing products, the laboratory is developing research on combinations of molecules, on the polymorphic molecules of ARV and on new molecules for treating AIDS.

To acquire this knowledge base on AIDS molecules and drugs, Far Manguinhos has developed a proven reverse engineering methodology now formalized in computerized management of projects. We shall now examine

the different areas of expertise and the reverse engineering methods used by Far Manguinhos chemists.

We first consider the three areas of expertise directly related to local drug production, *i.e.* characterization of raw materials bought elsewhere, formulation of drugs, and development of standards to be added to the pharmacopoeia. We then look at research on molecule synthesis processes. The results of this research exceed the needs of Far Manguinhos itself; they are transferred to Brazilian pharmaceutical firms and used by the Health Ministry in negotiating price reductions with the pharmaceutical laboratories that own the patent rights. Finally, we consider research on the design of new combinations of existing molecules and the identification of new ARV.

The first kind of knowledge that the laboratory needs to acquire on the drugs it wishes to manufacture concerns the characterization and quality control of the raw material it buys, primarily from foreign suppliers – Indian, Chinese and Korean – and secondarily (about 20%) from Brazilian suppliers. Quality control is a matter of strategy. The idea is to guarantee the reputation of drugs manufactured in the public sector, on which the Health Ministry's AIDS programme relies. To this end, Far Manguinhos recruited a chemist who previously worked in the federal food and drug agency laboratory, and entrusted him with the task of setting up a testing department. The number of staff employed in this analytical chemistry department has risen from 8 to 20 in the past five years. The department has also acquired new equipment – especially two sets of Nuclear Magnetic Resonance apparatus used to identify chemical substances – and is recruiting young chemists with a PhD to develop new analysis techniques. It has simultaneously formed partnerships with university laboratories which perform complementary analyses.

Chemists in the analytical department use several knowledge acquisition techniques in characterizing raw material purchased elsewhere and in formulating quality standards. They start off by analysing available information on the drugs in question: patents and publications. They then acquire samples of raw material to test, and draw comparisons with the proprietary drug. When the programme was launched in 1998 the director of the analytical department went on two trips to India. He wrote follow-up reports containing technical information gathered during visits to several pharmaceutical factories. The aim was to get to know suppliers, to assess their competencies, to inquire into certain problems of quality encountered – which sometimes helped to solve irregularities in batches of raw material, as in the case of Indinavir – and to obtain information on the synthesis processes used.

The analytical department's work has resulted in the development of quality standards and of methods for analysing the structure of molecules and the purity of material. These are used routinely to check batches of raw material used in manufacturing the drug on site. This knowledge is thus applied directly in the production process[6]. Characterization of raw material also produces knowledge for research. For example, by means of reverse engineering, contaminants found in raw material can be used to find the synthesis process of a particular supplier. This information is transmitted to the relevant research laboratory which thus enhances its expertise on the synthesis processes used. These results also serve in negotiating or cooperating with suppliers. On several occasions the analytical department established that the synthesis routes stated by Indian suppliers did not correspond to the ones they actually used, for the contaminants identified differed from the process disclosed by the suppliers. The department has sometimes even informed suppliers about contaminants of which they were unaware. In such cases Far Manguinhos asked the suppliers to change their synthesis processes in order to avoid the production of dangerous contaminants. Thus, the analytical department produces data that are useful to suppliers, to Far Manguinhos production managers, and to researchers in the synthesis department.

Local production of drugs also entails working on their formulation, and Far Manguinhos has a group of chemists devoted to the task. The laboratory director is herself a chemist specialized in formulation, who for many years worked in a large international laboratory. Her team consists of twelve chemists and pharmacists, and a PhD student. It is about to employ a further three pharmacists. This team has developed the formulae of 50 drugs since 1996 and is currently working on 35 projects. It also developed the project management software that is now used in the other departments. The formulation of molecules used in AIDS drugs is also based on reverse engineering from information and proprietary drugs, to identify the excipients used. Formulation furthermore involves frequent interactions with the synthesis and analytical chemistry departments to select the appropriate raw material. Chemists working on formulation ask for a particular raw material or synthesis: "we want that product in that way; our aim is to formulate and produce but we know which raw material we want and therefore which synthesis" (chemist, formulation group). This choice also incorporates financial parameters in so far as the aim of reducing

6. The analytical department's expertise has thus made it possible to detect batches with defects and unreliable suppliers.

prices is essential to the AIDS programme. Several formulae are tested (often four or five) in order to evaluate their performance in the production stage. The final product is compared to the reference drug during bio-equivalence tests undertaken by outside laboratories.

One of the most remarkable results of the formulation group is their discovery of a ddI formula that was more effective than the one invented by the original manufacturer Bristol Myers Squibb (BMS). During bio-equivalence tests on ddI at Sao Paulo University, researchers discovered that the Far Manguinhos product was not bio-equivalent to the original product. Its bio-equivalence curve was substantially better! BMS congratulated the Far Manguinhos chemists who did not patent their result since the new formula had been disclosed in a conference. The Far Manguinhos officials in charge of industrial property rights are now more careful and will ensure that any new improvements are patented.

The third area in which reverse engineering is practised concerns the creation of molecule references to be added to the pharmacopoeia. The creation of these standards became a necessity when Far Manguinhos embarked on the production of generic drugs[7]. Purity standards for chemical substances listed in the pharmacopoeia are a compulsory reference for any generic drug manufacturer wanting to reproduce the molecule. As soon as they are recorded in a pharmacopoeia, for example the European one, these references are accessible to any potential user. In the framework of the AIDS programme, Brazilian government laboratories were, however, faced with a major problem. The substances that they decided to reproduce were patented abroad and their purity standards were not available in international pharmacopoeias – with the exception of the standards and samples of two molecules, including AZT, that Far Manguinhos was able to obtain from pharmacopoeias. With the other molecules, when the Health Ministry's laboratory wanted to obtain authorization to produce generic drugs, it had to recreate these references by reverse engineering. After being approved, such standards are added to the Brazilian pharmacopoeia.

For its standards production programme, Far Manguinhos was supplied with new equipment financed by the Brazilian Food Safety Agency, ANVISA. This programme has benefited from computerized management of reverse

7. ARV produced by Far Manguinhos are currently being registered with ANVISA as generic drugs. Until now Far Manguinhos has produced "similar" drugs that contain the same active principle and have the same pharmaceutical form and therapeutic result as the reference drug but do not necessarily have the same bio-equivalence.

engineering which sets out the steps in the creation of standards for each molecule. The first step consists in the collection of data from patents, scientific publications and other documents; the second concerns the choice of methodology: extracting the molecule from capsules of proprietary drugs, working from raw material bought on the market, especially from Indian generic drug producers, and reproducing the molecule by laboratory synthesis; the third step is that of extraction and purification of the molecule; the fourth consists in approval of the reference; and, lastly, the fifth consists in its registration in the pharmacopoeia. For each step the software records the time spent and the financial value of the work. Far Manguinhos has a small manual for each molecule listed, which recapitulates all the data produced.

Creation of standards is a particularly complex task, for the exact molecule used by the manufacturer has to be identified. Although it is possible to use a different synthesis pathway to that of the manufacturer, for example one that is more efficient and/or safer, when it comes to the original molecule it is essential to find the exact structure and standards of purity. The elaboration of standards must furthermore comply with guidelines established by the WHO which specify analyses to perform and purity thresholds to meet. The process of purification of substances is arduous. It involves extraction of the active principles from the manufacturer's capsules and from raw material purchased, and comparisons between the two: "And it's a huge job, complicated, we have to extract the substances from the capsules, purify, purify, purify, and buy raw material in India and purify that to compare it with the capsules." (Director of the Synthesis Department). Even when the active principle has been extracted from the original drug, there is no guarantee that the right structure has been isolated, for it can change during the extraction process. The second difficulty concerns the existence of several polymorphs for the same molecule[8]. It is essential to identify the right polymorph used by the patent-holding laboratory commercializing the substance: "Sometimes we discover that there are different polymorphs and it is difficult to know which is the right one, which is the company's polymorph; it's a challenge but we learn." (Director of Synthesis Department). Once the Far Manguinhos chemists have isolated the right substance it has to be tested externally by university laboratories, by the federal drug agency and by the pharmacopoeia. The average time taken to create a standard is around six months.

8. Differences of crystallisation can occur with the same molecule prepared according to the same synthesis processes. These differences can result in very different properties and effects in the final product.

The acquisition of knowledge on synthesis processes is also crucial in the laboratory's technical and economic strategy. First, knowledge on synthesis processes enables it to check the quality of raw material and, when necessary, to ask suppliers to adjust their processes. Second, acquisition of synthesis expertise by Brazilian public-sector laboratories, combined with the possibility of demanding a compulsory licence for public health reasons, carries a lot of weight in negotiations with international laboratories: "A way of exerting pressure is by doing synthesis ourselves and showing that we can do it, that we know how to." (researcher, Far Manguinhos). Third, the fact of mastering synthesis makes it possible to envisage technology transfer from the public laboratory to Brazilian industry, in keeping with an industrial policy of replacement of imported active principles by local production. This process can be introduced gradually: Brazilian laboratories can initially limit themselves to the last steps in the synthesis process, before integrating the entire cycle.

The reverse engineering policy regarding synthesis draws on several sources. Apart from the knowledge produced during the process of characterization of imported raw material, chemists collect information from available sources – patents, scientific and trade publications – which they then test in their laboratory. During this process the 35 chemists in the synthesis department frequently interact with the analytical department. In 1999 Far Manguinhos management requested a chemist to review available information on five molecules used in the treatment of HIV/AIDS: "I spent three months reading patents and the literature and giving my opinions on the difficulties involved in synthesis." Patent analysis alone enabled him to perform an initial assessment of synthesis processes and above all to show the difficulty of synthesizing anti-proteases. But conclusions drawn from descriptions contained in patents are not enough to reproduce laboratory synthesis. Despite the obligation to provide an adequate description of the invention, the knowledge described in patents is fundamentally incomplete: "A patent is supposed to say everything and experience has proved that everything is not said." It is therefore essential to perform laboratory tests on knowledge collected from patents: "If they are hiding something, it's something that's not going to be noticed in the patent but that will be missed if the reaction is to be achieved. So one has to actually test it to see if it works." The incompleteness of knowledge recorded in publications is not peculiar to invention patents. Researchers are confronted with the same problem when they wish to reproduce an experiment described in a scientific article. But control of disclosure in a patent reinforces the phenomenon. This gap between the description in the patent and the knowledge needed to reproduce the molecule obviously

complicates the task of chemists in the Brazilian laboratory. They lack access to know-how not disclosed by the inventor who owns the patent.

Chemists in the synthesis department emphasize this incompleteness of knowledge contained in patents. For example, the synthesis path described in a patent may be deficient, the addition of reagents may not be fully specified, reaction time may be defined very imprecisely, or contaminants from the synthesis reaction may simply not be mentioned. Such omissions can be particularly serious in the case of a molecule such as Indinavir, for at a certain temperature its synthesis produces a toxic molecule. It is therefore essential to validate knowledge drawn from patents, through laboratory tests: "Sometimes it is stated that reagents are added, but in fact that doesn't work: the quantity isn't right; it's necessary to analyse, to see the processes, to evaluate in detail, to see if it's necessary to heat it; the reaction is supposed to happen at that temperature, but it's not true; or in a very wide interval, so it's necessary to rediscover." (chemist, responsible for ARV).

Chemists in the synthesis department have undertaken laboratory scale development of the synthesis processes of several ARV copied by Far Manguinhos, as well as of two patented ARV not produced on site, Efavirenz and Nelfinavir. In the case of the latter two patented molecules this knowledge has been used in negotiations with manufacturers to obtain price reductions. During the summer of 2001 the Brazilian Health Ministry was able to threaten Roche that they would produce its molecule on site if the company did not reduce its price sufficiently. For every molecule studied, Far Manguinhos has a document setting out its synthesis path. This knowledge is likely to be transferred to Brazilian private-sector laboratories.

Reverse engineering on synthesis processes of AIDS molecules is described by our interlocutors as a learning process. The task of Far Manguinhos chemists was particularly difficult in the case of Indinavir: information contained in the patent was incomplete; Indian suppliers failed to disclose their synthesis processes; and Far Manguinhos chemists were discovering the chemistry of antiproteases whose synthesis is difficult to control. Gradually their knowledge base expanded, through the collection and systematic analysis of a growing number of publications (patents and articles), through information gathered during tests on raw material purchased, through experiments run in their laboratories, and through interaction with Brazilian universities. As a result, reverse engineering can now advance faster. It is often the time spent buying reagents that is the most constraining element in the process. Brazilian chemists have, in a sense, become "the consultants of Indian manufacturers" (chemist, responsible

for ARV)[9]. It was the Far Manguinhos synthesis department that showed that the last step in the synthesis of Indinavir could produce a dangerous contaminant. The laboratory's chemists gave their Indian supplier specifications for synthesis and: "Since then they've done it according to our specifications." (Far Manguinhos chemist). It has therefore become possible to draw on this knowledge base to fill in the gaps of incomplete descriptions of synthesis processes in patents, or to assess synthesis processes kept secret by a supplier: "one needs a theoretical base from the literature as a basis for discussion: it's not path X that they sent us, it's something else" (chemist, Synthesis Department).

To conclude on this process of knowledge acquisition by reverse engineering, we wish to underscore the following points.

First, this process requires reliable knowledge management, from trips to suppliers to consultation of patent data bases and scientific publications, testing of knowledge collected through laboratory experiments, and reverse engineering starting from capsules of reference drugs or raw material bought elsewhere. This learning process involves the combination and comparison of external and internal knowledge, as well as interactions between the laboratory's different specialized departments: analytical chemistry, synthesis, formulation and production.

Second, this learning process is gradual and cumulative. The knowledge base that has been built up currently serves for evaluations, comparisons, and the design of improvements to processes and products. Work on several copying projects undertaken simultaneously has also facilitated comparisons and added to experience. The Health Ministry now readily entrusts Far Manguinhos chemists with the evaluation of synthesis processes of a new molecule before negotiating its acquisition, including in fields other than AIDS. This is what happened recently with a very expensive drug used for treating leukaemia.

Third, knowledge acquired by Far Manguinhos is partly public – ARV standards are put into the Brazilian pharmacopoiea – and partly confidential – for instance the discovery of new polymorphs or elements not described in the literature. By publishing the latter type of result the government laboratory would be giving information to patent holders who refuse any technology transfer to the Brazilian laboratory. According to the head of organic synthesis, this is "internal knowledge".

9. Far Manguinhos chemists also highlight the contribution of their Indian counterparts: "The Indians have all studied in American universities and are excellent chemists. They publish a lot in order to optimize these steps, to reduce costs and to use less expensive reagents. I'm amazed by the literature they produce in this field" (researcher).

Fourth, drug copying projects incorporate more and more cost variables, for example for choosing between different possible synthesis routes.

Fifth, the reproduction of patented molecules is not simply an exercise in copying, in so far as the Brazilian chemists do not start off with a complete list of the knowledge that needs to be applied. Patents are fundamentally incomplete and the chemical references of ARV were not available in pharmacopoeias. Chemists therefore have to combine the copying of available knowledge with the rediscovery or reinvention of other data, such as standards for pharmaceutical molecules, that they have had to recreate, or synthesis procedures imperfectly described in publications, that they have had to rediscover or develop.

Sixth, this learning process extends beyond the copying of existing drugs. In the course of the reverse engineering process chemists discover new entities or introduce variations or improvements. During work on synthesis routes of a particular existing molecule they sometimes propose improvements: "How can we do the synthesis of this? We can find it in the literature, and we can do some innovation because we have some experience here; we can change certain things." (Head of Synthesis). The same applies to the new formulation proposed for ddI. New polymorphs discovered during reverse engineering are now systematically studied, and this research could lead to new patents. The formulation group has a research programme on combinations of existing molecules. Finally, Far Manguinhos chemists run research programmes on new molecules for AIDS drugs. For instance, the young head of the ARV programme has moved from copying to doing R&D on a new molecule. This chemist's individual progression illustrates possible passages between copying and creation of molecules[10]. The development of research activities, apart from copying, is a challenge for this government laboratory which is recruiting more and more young PhD students.

10. One chemist told us about someone whose career was the opposite. A young researcher who did his PhD in France and a post-doc in the US, during which he invented several patents, is currently copying patents at Far Manguinhos. The prospect of developing new molecules would be far more attractive to him.

III
AN R & D LABORATORY FOR BUILDING UP PHARMACEUTICAL INNOVATION NETWORKS IN BRAZIL

Whereas the Far Manguinhos government laboratory started out by copying existing drugs used to treat HIV/AIDS and manufacturing them in the final pharmaceutical production stage, from raw material bought primarily from Indian or Chinese companies, the technological learning process thus triggered off has now enabled it to plan industrial integration higher up in the process. The Health Ministry's laboratory is equipped to transfer knowledge acquired on molecule synthesis processes to Brazilian companies, thus enabling them progressively to produce intermediates and then active principles. In the future Far Manguinhos is expected to play a strategic part in this industrialization process, starting upstream with a policy of systematic acquisition of knowledge and R&D, right down to technology transfer.

This strategy is clearly apparent in the field of ARV. It explains the reverse engineering carried out by Far Manguinhos chemists on ARV synthesis processes even though the laboratory's mission does not include production of active principles. Far Manguinhos started to implement the strategy by signing a technology transfer agreement with the Brazilian laboratory Nortec, for the production of raw material according to a process specified by the government laboratory's chemists. The private company, with which the Far Manguinhos synthesis department maintains close ties, pays for the technology transfer in the form of raw material. More generally, Far Manguinhos has a policy of systematic technology transfer towards private industry. Processes developed on a laboratory scale – on a scale of one liter – are simultaneously sent to the companies concerned: "We have three molecules which are developed on a laboratory scale, afterwards they are sent back to the customer firms who want the technology." (Far Manguinhos chemist). Far Manguinhos has also transferred technology on the final stage of AIDS drug production to other Brazilian government laboratories.

At the same time, Far Manguinhos is developing its R&D activity, both inhouse and in collaboration with universities. The laboratory has used income from the sale of drugs to the Health Ministry to build new research premises designed to house research in partnership with universities (PhD research, research contracts). Academics thus have access to premises and equipment that is often unavailable at their university. One of the recent results of this

cooperation is a patent filed on an anti-protease, owned jointly by Far Manguinhos and the university.

Several engineers and one research chemist are responsible for intellectual property rights, research agreements with university, and technology transfer. The new accent on intellectual property relates to the laboratory's internal and external research programmes on polymorphs of existing molecules, combinations of ARV, and the discovery and development of new molecules for treating AIDS and other pathologies. For Far Manguinhos, patenting is a form of protection against opportunistic appropriation, a way of guaranteeing the transfer of innovations to outside partners, and a means for regulating prices and supply in the medicinal drug market[11]. The aim is also to develop different types of technology transfer contracts with industry, generally from Far Manguinhos towards industry (*cf.* the contract with Nortec). On two occasions Far Manguinhos has negotiated with Indian and Brazilian suppliers for access to their synthesis processes. In these cases the raw material purchase agreement was combined with a technology transfer contract from the seller (the Brazilian laboratory Cristalia) to the buyer (Far Manguinhos).

The Health Ministry laboratory is busy building technical-economic networks with multiple actors: Brazilian universities, for testing its products and searching for new molecules; other pharmaceutical laboratories in various Brazilian states – Far Manguinhos transfers to them the technology of final production stages of the drugs it develops; and Brazilian private-sector industry, regarding both the production of the drugs – the public laboratories purchase the raw material from the private companies and manufacture the final product – and the transfer and development of the synthesis processes of the active principles of these drugs – in the framework of Brazil's industrialization policy.

This industrialization process is nevertheless confronted with a major stumbling block: during the 90s the Brazilian pharmaceutical chemical industry declined considerably. The number of firms able to receive and implement Far Manguinhos technologies today is relatively limited[12].

11. Interview with the person in charge of Intellectual Property.

12. The head of technology transfer to industry knows of only nine Brazilian pharmaceutical chemicals firms.

Conclusion

The first encouraging results of the Brazilian Health Ministry's AIDS programme launched in 1996 are well-known, both in terms of medicinal drug prices and public health. The launching of Brazilian production has resulted in the plummeting of the cost of ARV per patient in Brazil and in a regulatory effect reducing prices in the world market. The originality of this experience is based on the combination of a favourable industrial property policy for drugs until 1996 (*i.e.* non-patentability of pharmaceutical products and processes), a public health policy (the 1996 decree on universal access to ARV), and an industrial policy that allows the copying of existing drugs. The Rio de Janeiro Health Ministry laboratory Far Manguinhos has played an essential part in this system, even though it was a small private laboratory that initiated the copying of AZT in 1993. Far Manguinhos is also part of the Oswaldo Cruz Foundation, the largest scientific and technological institution in Latin America in the health field. It has a long history, starting in 1938 on the Manguinhos site which mass-produced yellow fever vaccine [3].

In our opinion, the launching of the copying of ARV has had an essential effect in terms of economics of knowledge and industrial economics. It triggered a process of technological learning and acquisition of knowledge relative to the molecules copied, especially in the Health Ministry's laboratory in Rio, a process that is now being continued in the form of projects to discover new drugs. This can be explained primarily by the fact that the Brazilian chemists who embarked on copying the molecules from 1997 were forced to partially rediscover the quantitative and qualitative composition of the active principle of these drugs, as well as their pharmaceutical form. They did not have access to the knowledge that the owners of patented molecules held or transferred to their licensees. Nor could they rely on references in pharmacopoeia on the components of these drugs since they were not disclosed. These chemists therefore reinvented tests to identify drug components, consisting of reverse engineering to find their formulae and synthesis processes. The knowledge acquired exceeds the industrial capacities of the government laboratory which is equipped only to produce the pharmaceutical form of the drug. Yet Far Manguinhos has developed a strategy for the acquisition of knowledge on synthesis processes, by increasing its in-house and external research and by acquiring technology from its suppliers. The laboratory is therefore currently able to transfer the synthesis processes that it develops to Brazilian industry, provided it can solve the problem of switching from a laboratory to an industrial scale. The challenge is also to go

beyond copying, to develop new molecules, both in-house and in cooperation with Brazilian academics. During this experience, the copying process spawns the creation of a local knowledge base and an R&D dynamic. The two development strategies identified by Paul Romer, "Using ideas and Producing ideas" [1] are thus closely combined here. Yet, even though Far Manguinhos has started to launch research that goes further than simply copying existing molecules, the development of a new molecule, from initial research down to industrial production, is still a challenge in areas like AIDS and tuberculosis.

This process of acquisition and creation of knowledge around the copying of ARV has been facilitated by the non-patentable status of drugs in Brazil before 1996. The copying of new ARV patented since 1996 would require Brazil to use compulsory licensing provided for in its 1996 industrial property law and in the 1994 TRIPS agreement. This is what the Far Manguinhos chemists that we interviewed want – and they have already done the reverse engineering of these drugs. It is also what the patients' associations and NGOs (*e.g.* Médecins sans Frontières – Brazil) that support their work want. This experience provides an outline of some of the amendments that could be made to patent laws – especially free use of drug inventions in countries of the South – to solve public health and industrial development problems in those countries. How many of us remember that the French pharmaceutical industry enjoyed a non-patentable status of drugs in France from 1844 to 1959 and was therefore able to copy German patents freely?

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Intellectual Property Rights, Anti-AIDS Policy and Generic Drugs.

Lessons from the Brazilian Public Health Program

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Key words: TRIPS; pharmaceutical patents; generic drugs; public health policy; ARVs.

Abstract

The paper intends to get into Brazil's National anti-Aids Program's "black box" and unveil the elements that drive its dynamics. The focus is on the main choices that have governed the Program's preparation, the obstacles it has faced and how it has overcome them. By doing so, the paper also identifies some remaining limitations that may undermine the program's long-term sustainability in its current form. The paper specifically highlights the contradiction that exists between a public health goal of ensuring the lowest possible prices of ARVs for a maximum number of patients, and the way the means used to achieve this goal have made it harder to implement autonomous and competitive local production, notably in the field of active principles. The paper concludes with the key elements provided by the Brazilian experience for the debate on TRIPS.

Résumé

L'article se propose de pénétrer dans la « boîte noire » du programme de santé publique brésilien d'accès universel et gratuit aux traitements ARVs. Il met en évidence les grands choix qui ont rendu possible ce programme et les principes sur lesquels il est construit. Au-delà de ses remarquables succès, est mise en évidence une fragilité du programme qui tient au fait que

les politiques mises en œuvre pour assurer l'approvisionnement à bas coûts en ARVs (exigé par le caractère « universel » des soins dispensés), ont rendu difficile l'émergence d'une offre locale compétitive de principes actifs. L'article propose enfin quelques conclusions susceptibles d'enrichir le débat actuel sur les ADPIC (accords sur les aspects des droits de propriété intellectuelle qui touchent au commerce).

Introduction

At an international level, Brazil's National anti-Aids Program stands out as a unique experience. Guaranteeing free and universal access to HIV/AIDS care for all HIV-infected patients, it currently provides antiretroviral treatments (ART) to about 125,000 persons, by far the highest number of ART-treated patients in a developing country. Moreover, with its resolute focus on the local production of generic drugs, Brazilian policy has played a key role internationally by contributing to a sharp decrease in the source prices of the antiretroviral drugs (ARVs) being patented by multinational companies.

To understand better the reasons for this success, we present the main findings of an investigation aimed at analysing the strategies of the main actors involved in establishing and developing this policy [1]. Our research is mainly based on a series of field investigations and on interviews with Brazilian public institutions, including the Health Ministry's National DST/AIDS Coordination, the National Agency for Health Monitoring, the National Intellectual Property Institute, patient associations and Brazilian NGOs, as well as private Brazilian companies and public laboratories involved in ARV production. In addition, multinational firms importing ARVs into Brazil were also interviewed.

The goal of the present research project has been to get into the program's "black box" and unveil the elements that drive its dynamics. By presenting the conditions and constraints surrounding the program's implementation and development, we focus on the main choices and principles that have governed its preparation, the obstacles it has faced and how it has overcome them. By so doing, we will also identify some remaining limitations and weaknesses that may undermine the program's long-term sustainability in its current form. We will specifically look at the contradiction that exists between a

1. The present paper is based on an ongoing research project, managed under the Scientific Direction of B. Coriat, and sponsored by the ANRS. The authors wish to thank the ANRS warmly for its generous and efficient support at all stages of the research.

public health goal of ensuring the lowest possible prices for a maximum number of patients, and the way that the means used to achieve this goal have made it harder to implement autonomous and competitive local production, notably in the field of active principles.

Our conclusion will contain a few key lessons from the Brazilian experience. In our opinion, these lessons extend far beyond the Brazilian case alone. Just eight years after the adoption of the World Trade Organisation agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), what we can learn from the Brazilian practices will provide food for thought for all actors engaged in the battle against this pandemic.

I
THE POLICY OF "UNIVERSAL AND FREE ACCESS" TO ARVs AND ITS SIGNIFICANCE

In 1996 the Brazilian government, in a decision that would be crucial for the country (and on a wider level, for the "political economy" of access to HIV/AIDS drugs in developing countries), committed itself to the principle that its anti-AIDS public healthcare access program should become universal and free for all eligible patients.

This portentous choice was not made in just one day. To measure its impact, it must be remembered that just nine years before, in 1987, when the first effective ARV drug for treating HIV infection (Zidovudine [AZT]) was introduced in Brazil, only a small minority of patients could afford to buy imported AZT. The situation started to change in 1988 when non-governmental organizations (NGOs) and other organized pressure groups pushed the Ministry of Health[2] to introduce guidelines for Zidovudine use in HIV/AIDS treatment, establishing that such treatment could only be carried out in medical centers that had been accredited by the Ministry of Health (MoH). Through the public health system (SUS)[3], the MoH began to provide medicine for treating opportunistic infections (OIs) suffered by patients living with HIV/AIDS. In 1991 came the first deliveries of AZT through the public health system. However, before early 1990, there were many interruptions in this distribution of AZT and drugs for HIV-related OIs. Many factors contributed

2. Decree n. 483 (published at DOU de 8/23/1988).
3. Sistema Único de Saúde (SUS).

to this situation: the impecunious state of the municipal and state public health systems[4]; the high cost of AZT, concomitant with high inflation rates existing in Brazil through the early 1990s; and above all, the high import costs charged by multinational drug manufacturers[5].

In 1996, through federal Law 9.313[6], the Government decided to guarantee free and universal access to all HIV/AIDS treatments within the SUS, not only to OI drugs but also to the ARV drugs that are such a crucial part of the Highly Active Antiretroviral Therapies (HAART), whose effectiveness was just starting to be demonstrated in developed countries[7]. With this new law, a large-scale public treatment access policy began to take shape in Brazil. Its main impetus was the drive to set up a strategy for reducing drug prices (especially for ARVs).

II
THE POLICY OF ARV PROCUREMENT AT LOW PRICE

Once the commitment was made to deliver free care to patients, the key issue for Brazilian health authorities became the procurement of cheap ARV drugs. In itself, designing or implementing a policy for the procurement of low-price ARV drugs was no mean feat, given that the pharmaceutical industry had been operating under the protection of a strong intellectual property regime ever since the 1994 enactment of TRIPS [2], [3]. Moreover, since 1993 public procurement in Brazil has come under the auspices of a law requiring the organisation of international calls for tender. This created an environment that was highly unfavourable to the development of a local product offer. Vying with international traders operating on behalf of major non-Brazilian exporters (notably Indian and Chinese companies, frequently the large multinational pharmaceutical companies' main suppliers of active principles), it was highly unlikely that the much smaller local firms, which often lacked the strengths of the foreign firms (*i.e.* economies of scale and powerful

4. The decentralization of the public budget in Brazil for Municipalities began only in 1988 with the new Federal Constitution. Thus the organization of public health services was very incipient and precarious in the first half of the 90s.

5. For more details of this dimension of the Program see [1].

6. Law 9.313 (regulated by Decree 2.334/96).

7. It can be noted that the MoH bears the costs of ARV procurement and distribution while States and Municipalities share the costs of procuring medicine for opportunistic diseases.

networks), could put in a successful bid. These two series of constraints delineated the institutional framework within which the program would have to be developed, as we will describe below.

The 1996 Brazilian Patent laws and their implications

From 1971 to 1996 Brazilian law did not recognise any type of patents for pharmaceutical products or processes. Indeed, these provisions were perfectly consistent with the World Intellectual Property Organisation (WIPO) treaties that were in force at the time, and which guaranteed less developed countries the right to set up intellectual property rights (IPRs) regimes enabling a rapid and inexpensive local diffusion of developed country technologies [4], [5], [6]. The 1971 Patent Law suspended patent rights for pharmaceutical processes and reaffirmed that no patents would be granted for those pharmaceutical products that had been established since an earlier law of 1945. In May 1996, however, a new Patent Law was approved reintroducing the recognition of patents for pharmaceutical processes or products in order to comply with the TRIPS agreement. It is important to note that this change in the Brazilian legislation is largely due to US economic and political pressure to comply with TRIPS before the 2005 legal deadline. In addition, the new Brazilian Patent Law introduced a retroactive deposit application, the so-called "pipeline" protection. This powerful measure allows patents that are valid abroad or pending in Brazil to be applied, provided that the product was not being marketed anywhere when the Law was passed, and that third parties in the country had already prepared the exploitation of said patent claim [7].

The impact of the premature enforcement of the Brazilian Patent Law on the MoH procurement strategy for ARVs is reflected in the fact that only those molecules that had gone into circulation before 1996 (and which were not included in the "pipeline" protection) could be copied. The patent situation that emerged is presented in Table 1 below.

Table 1: Patent situation of ARVs provided by the Ministry of Health for HIV/AIDS treatment in Brazil

Active Principle (Brand Name/Marketing Company)	*USPTO* Patents Related to the active principle registered with the FDA*	*USPTO Patent Holder*	*USPTO Expiration (Year)***	*Patent in Brazil*	*Patent Holder in Brazil*	*Situation in Brazil*	*Year included in the DST/AIDS Program*
Nucleoside analogues reverse transcriptase inhibitors							
Zidovudine (Retrovir / Glaxo Smith Kline)	4724232, 4818538, 4828838, 4833130, 4837208	Glaxo Wellcome	2005	Not Filed	-	-	1991
Didanosine (Videx / Bristol Myers Squibb)	4861759, 5254539, 5616566	US Dept. of Health Services	2006	Not Filed	-	-	1998
	5880106	Bristol Myers Squibb	2011	Not Filed	-	-	
Estavudine (Zerit / Bristol Myers Squibb)	4978655	Yale University	2008	Not Filed	-	-	1997
Lamivudine (Epivir / Glaxo Smith Kline)	5047407	IAF Biochem	2009	Not Filed	-	-	1999
	5905082	Glaxo Group	2016	Not Filed	-	-	
	6004968	Glaxo Wellcome	2018	PI9808060	Wellcome Foundation	Pending	
	6180639	Biochem	2018	Not Filed	-	-	
Lamivudine + Zidovudine (Combivir / Glaxo Smith Kline)	5859021	Glaxo Group	2012	Not Filed	-	-	1999
	6113920	Glaxo Wellcome	2018	PI9712614	Glaxo Group	Pending	
Abacavir Sulfate (Ziagen / Glaxo Smith Kline)	5034394	Glaxo Wellcome	2009	Not Filed	-	-	2001
	5089500	Glaxo Wellcome	2009	PI1100288	Wellcome Foundation	Granted (1998)	
	6294540	Glaxo Wellcome	2018	PI9809126	Glaxo Group	Pending	
Non-nucleoside reverse transcriptase inhibitors							
Nevirapine (Viramune / Boehringer Ingelheim)	5366972	Boehringer Ingelheim	2011	Not Filed	-	-	2000
Delavirdine Mesylate (Rescriptor / Agouron)	5563142	Upjohn	2013	Not Filed	-	-	1998
	6177101	Pharmacia Upjohn	2018	PI9910481	Pharmacia & Upjohn	Pending	

*Efavirenz (Stocrin / Merck &Co.)****	5519021, 5663169, 5811423	Merck & Co.	a	Not Filed	-	-	1998
	6238695	Du Pont Pharmaceuticals	2019	PI9908810	Du Pont Pharmaceuticals	Pending	
Protease Inhibitors							
Saquinavir Mesylate (Invirase / Roche)	5196438	Roche	2019	PI9006264	Roche	Not Granted	1996
Ritonavir (Norvir / Abbott)	5484801	Abbott	2017	Not Filed	-	-	1996
	5541206	Abbott	b	PI1100661	Abbott	Pending	
	5635523, 5648497, 5674882, 5846987, 5886036, 6037157, 6232333	Abbott	c	Not Filed	-	-	
Indinavir Sulfate (Crixivan / Merck & Co.)	5413999	Merck & Co.	d	PI9406576	Merck & Co.	Not Granted	1997
Nelfinavir Mesylate (Viracept / Agouron)	5484926	Agouron	2012	PI110066	Agouron	Granted (1999)	1997
	5952343, 6162812	Agouron	e	PI110066	Agouron	Granted (1999)	
Amprenavir	5585397	Vertex	2016	PI1100824	Vertex	Granted (1999)	2001
Lopinavir + Ritonavir (Kaletra / Abbott)	5914332	Abbott	2016	PI1100397	Abbott	Granted (2000)	2002
	6232333, 6284767	Abbott	f	Not Filed	-	Not Granted	

Source: Primary Data based on FDA Electronic Orange Book, USPTO and Derwent Innovation Index, INPI.

Notes: *Us Patent and Trademark office. ** Patents also refer to formulae. Moreover, process pharmaceutical companies use different patenting strategies. Thus some active principles relate to one or more patents - in which case the expiry dates will differ for each patent. ***Efavirenz was developed by Du Pont Pharmaceuticals and is marketed by Bristol Meyers Squibb under the trade name Sustiva in UK, Ireland, France, Germany, Italy and Spain. In other European countries, Australia, Latin America, South Africa and other regions it is marketed under the trade name Stocrin by Merck Sharp Dohme. According to the FDA Electronic Orange Book, Merck & Co. and Du Pont Pharmaceuticals hold patents on efavirenz. Although Merkc & Co. USPTO patents have not been filed in Brazil, Du Pont Pharmaceuticals USPTO patent related to efavirenz has been filed in Brazil.
a – 2012, 2013 and 2014; b – 2010, 2014; c – 2014, 2014, 2014, 2012, 2012, 2016, 2017; d – 2012, 2016; e – 2012, 2013; f – 2017, 2016.

Out of the medicines currently being provided by the Brazilian Ministry of Health, four have had their patents granted by the National Industrial Property Institute[8] (Abacavir, Nelfinavir mesylate, Amprenavir, Lopinavir + Ritonavir) and two have a patent pending (Ritonavir and Efavirenz). The other 10 ARVs included in the program are not covered by patents (Zidovudine, Lamivudine, Zidovudine + Lamivudine, Didanosine, Estavudine, Nevirapine, Delavirdine mesylate, Saquinavir mesylate and Indinavir sulfate). It can also be observed from Table 1 that there are two patents pending related to Lamivudine and its association with Zidovudine. Nevertheless, these patents refer to formulae, and not to molecules. As will be discussed below, the establishment of patent protection has had some very significant consequences for the ARV price reduction strategies of the Brazilian public health authorities.

However, it must be noted that, in accordance with TRIPS, the new Brazilian Patent Law allows for compulsory licensing in the case of "national emergency" (Art.71) and if the patent holders "practice abuse of economic power", which, according to the Law, explicitly means that there is no local production for three years after the patent has been issued[9] (Art.68).

As many authors have pointed out, compulsory licensing may appear as a key tool of public heath policy in developing countries [8-10]. Nevertheless, due to the lack of consensus at the World Trade Organization (WTO) negotiations, developing countries have only made limited use of compulsory licensing, as TRIPS requires compulsory licensees to restrict the "predominant part" of their production to the domestic market. This means that TRIPS dramatically limits the export (or import) of drugs made under compulsory licensing arrangements. As a result, access to low-price medicines is restricted in developing countries which lack sufficient local manufacturing capacity to produce drugs under compulsory license.

As will be discussed later, even in the case of Brazil where a real technological capacity to produce drugs exists, there remains a great deal of uncertainty about the effective use of compulsory licensing in the near future.

8. The Brazilian Agency in charge of delivering patents.

9. It is important to note that at the end of the 90s, the USA asked a WTO panel to judge the Brazilian Patent Law's non-compliance with TRIPS. US representatives intended to exclude art.68 from the Brazilian Patent Law, arguing that this article was contrary to TRIPS principles of non-discrimination between local production and imports and also that compulsory licenses would discriminate against North American patent holders in Brazil, companies whose products are imported from their parent company but not produced locally. For more on this topic see for example [11,12]. Although the US government finally withdrew its complaint, Brazil is still on the so-called "Special 301 Watch list".

Norms for public procurement: the 1993 Call for Tender Law

The other major institutional constraint which the health authorities have had to contend with relates to a provision in the 1988 Constitution. In an attempt to clean up the administration's behaviour and fight against "corruption", this Constitution stated that the government's procurement of goods and services had to comply with the principles of legality, impartiality and transparency. As time went by (with the passing of a Law in 1993 and a Constitutional Amendment in 1995), provisions maintaining some form of protection for national products were eliminated and companies suffered from increased foreign competition. As we will show, competition became much fiercer between 1993 and 1995. Whereas the 1993 Law generalising the obligation to proceed via calls for tender still contained a number of stipulations that were beneficial to Brazilian companies or to firms with operations located in Brazil, the same no longer applied after the 1995 Constitutional Amendment, which introduced principles of competition that were much more rigid than before.

According to the 1993 Law, States and Municipalities – even if they had to comply with the requirement of passing through call for tenders – could create their own norms. In this framework, a call for tender is defined as an administrative act and must therefore:

I) be public and standardized;

II) follow a price registration system;

III) be based on the prices currently being practiced within public administration bodies;

IV) specify the goods to be acquired without explicitly referring to particular brands (art.4).

In addition, the successful bid should be decided upon under conditions of fair competition and be based on the following criteria:

I) goods produced or services supplied by domestic companies;

II) produced in the country;

III) goods produced or services provided by companies established in Brazil (art.3).

In other words, article 3 clearly announces the criterion of "national preference". Finally, the Law foresees exceptions which define cases where there is no need to invite for tenders, namely:

I) when the Government must intervene to regulate prices or normalize provision;

II) when proposals present prices that are clearly higher than those being observed in the domestic market, or are not compatible with those fixed by competent official bodies;

III) when the contract is between public administration bodies once the price is compatible with those observed in the national market (art.24). In addition, there is no need to invite for tenders if goods or services (irrespective of the brands) can be provided by a single company, as long as that company can prove that it has exclusive rights to them (art.25).

In addition, there is no need to call for tenders:

I) in emergency situations justifying this non-obligation;

II) if there is a justifiable reason to choose a single supplier;

III) if there is any reason relating to pricing (art.26).

As we can see, the 1993 Law opened up several possibilities that could be beneficial to national firms or to companies running local operations.

However, in the wake of the WTO agreements and as part of a new economic policy aimed at putting national firms under serious competitive pressure to force them to modernise, this "national preference" was revoked by a 1995 Constitutional amendment that forced Brazilian firms to compete with foreign companies. At the same time, and again as a result of the WTO agreements, customs tariffs on pharmaceutical products and fine chemicals (the main components in active principles) dropped sharply, on average from 65% to 20%.

As we will show by examining the local supply of HIV/AIDS drugs, this major constraint significantly restricts the ability of locally established firms to take part in the program or use it to strengthen their own position.

Local capabilities and supply of ARVs

To understand clearly the prevailing situation in the Brazilian ARV market, some details should be given about local regulations and about the types of actors operating in this market.

First, to have the right to commercialise drug products in Brazil, it is necessary to register with the National Agency for Health Monitoring (ANVISA). This registration, however, does not require the applicant firms to be engaged in local production. Secondly, registration criteria and conditions vary depending on whether an "Innovator Drug Product" (or "Reference Drug Product"), a "Similar Drug Product" or a "Generic Drug" is involved. Like most legislation in the Western world, according to Brazilian law an

"innovator drug product" is defined as "a drug product presenting in its composition at least one active drug that has already been covered by a patent (even if that patent has expired) that was taken out by the company responsible for its development and innovation in the market of its country of origin. If the innovator drug product is available on the national market, it is generally considered to be the drug product of reference" [13]. On the other hand, unlike legislation in the Western world, Brazilian law authorizes the marketing of two types of reference product copies: "similar drug products" and "generic drug products". Under Brazilian legislation a "similar drug product" is "a drug containing the same or more active principles, presenting the same concentration, dosage, means of administration, posology and therapeutic indication. Moreover, it has to be equivalent to the drug product registered at the ANVISA. It may only differ with regard to its size and shape, period of validity, packaging, labeling, excipients and vehicles".

Regarding "generic drug products", these are "drug products similar to a product of reference or to an innovator drug, and which are meant to be interchangeable with the said product. They are generally produced after the patent's expiration or after a rejection of the patent protection or of any other rights of exclusiveness". In other words, unlike similar drug products, registering generic drugs requires bioequivalency and bioavailability testing.

It should be specified that the distinction between "similar" and "generic drug products" was introduced in 1996 with the enactment of the law on generic medicine. Until that point, Brazilian regulations had not required any bioequivalency testing, nor had they envisaged any special status for the products being tested. Lastly, it should be noted that the Brazilian health authorities were planning to get rid of regulations on similar products in the medium term, in order to promote the development of a market for generic medicine.

Table 2: Private companies and public laboratories with ANVISA registered ARVs as of December 2002

Locally-owned companies	*Multinational Companies*	*Public Laboratories*
Cristália	Merck Sharp & Dohme	Fundação para o Remédio Popular (FURP)
Eurofarma	Boehringer Ingelheim	Instituto de Tecnologia em Fármacos (Far-Manguinhos)
Laob	Roche	Laboratório Farmacêutico da Marinha (LFM)
Microbiológica	Abbott	Laboratório Químico Farmacêutico da Aeronáutica (LQFA)
Sanval	Bristol Meyers Squibb	Instituto Vital Brazil (IVB)
Lab. Bioquimico	Prodotti	Fundação Ezequiel Dias (FUNED)
Itafarma – Imp. Exp.	Pharmacia	Laboratório Industrial Farmacêutico de Alagoas (LIFAL)
Cazi Química	IB Farma (acquired by the Apotex – Canada)	Lab. Farm. do Estado de Pernambuco S/A (LAFEPE)
Ativus	Ranbaxy	Indústria Química do Estado de Goiás S/A (IQUEGO)
Neo-Química	Glaxo Wellcome (GSK)	
Greenpharma Química e Pharmaceutica	Merck S.A. (AG)	
União Química	AstraZeneca	
EMS-SIGMA PHARMA		
Biolab Sanus		
Teuto		
Sintofarma		
UCI Farma–Indústria Farmacêutica Ltda.		
Virtus		
Blausiegel		
AB Farmoquimica		

Source: www.anvisa.gov.br

Regarding the state of HIV/AIDS drugs in December 2002, according to ANVISA's electronic data base, thirty-one private companies (domestic and multinational) have registered ARVs in Brazil (Table 2).

It should be noted that these are firms and ARVs whose distribution within Brazil has been authorised by the ANVISA. This does not necessarily mean that they have actually been distributed, since marketing is a matter of corporate policy. We are therefore faced with a complex situation. On the one hand, some multinational corporations holding patents of ARVs supply the market through imports. On the other hand, other foreign companies such as Ranbaxy, nineteen locally-owned private firms and nine public laboratories hold off-patent ARVs that have been registered at ANVISA[10]. It is noteworthy that despite the 1996 Brazilian Generic law, generic ARVs, as such, are almost non-existent on the local market. In fact, most off-patent ARVs are not registered as "generics" but as "similars". For the moment, only one private Brazilian company (AB Farmoquimica) and an Indian firm (Ranbaxy) have obtained a generic status for some of their products[11]. According to Brazilian firms that have been interviewed, the costs involved in registering generic medicines, together with frequent changes in public policy procurement (see below), make it too costly and risky to produce officially registered generic ARVs[12].

Focusing now on Brazil's national product offer, it can be argued that with nineteen local private firms and nine public laboratories involved in the production of ARVs, Brazil has considerable production capability for these drugs. Nevertheless, this capability does not involve the entire production process. Strongly specialized in active principle formulae – due to a historical policy of actively building up strong capabilities within this field in public laboratory networks - the Brazilian industry lacks the synthetics capabilities that would enable it to undertake industrial production of intermediates and raw materials.

10. These are ARVs in circulation before the 1996 law, or where the foreign patent holders had not initiated a patent registration procedure in Brazil.

11. Nevirapine for the Brazilian firm. Indinavir sulfate; Estavudine; Zidovudine + Lamivudine; Neviparine, Lamivudine for Ranbaxy.

12. The Brazilian standards for bioequivalency tests are similar to the FDA's. Nevertheless, the difficulties in obtaining the required availability levels established by the Brazilian standards do not mean that the medicine is not good or safe. It is believed that ANVISA has adopted such high generics standards so as to be able to guarantee the effective implementation of this segment, seeing as physicians were once very skeptical about prescribing generics, doubting their efficiency in comparison with reference medicines (for more on this topic see [14]).

The local development of ARV production capacities – chemical synthetics as a missing link

During the 70s and 80s, Brazil implemented an active import substitution policy aimed at enhancing both industrial capacities and technological capabilities in the pharmaceutical sector, including production of intermediates and active principles. Policy at the time included the development of an upstream petrochemical industry, on which the production of medicines is dependent. The production of basic fine chemical raw materials originates from the petroleum refining process through which naphtha is obtained, which will later be used for producing active principles (APIs) and medicines. In the 80s, with the creation of the public company Nordeste Química S.A. (Norquisa), the government began to plan investments in the production of synthetic intermediates as a downstream diversification for the petrochemical industry which was then facing declining internal demand. Significant among those initiatives was the creation of Carbonor for the production of salicylic acetyl.

Another key stimulus for the development of technological capabilities in the pharmaceutical sector was the suspension of IPRs covering pharmaceutical processes and products, in the wake of the aforementioned 1971 Law. This law, which suspended all forms of intellectual property rights relating to pharmaceutical products, made it possible (via "copying" and imitation effects) to engage in large-scale experimentation without any legal restriction, thus allowing a number of firms and laboratories to acquire synthetic capability formulae through reverse engineering. Another important initiative was the creation in 1976 of a company for technological development, named Companhia de Desenvolvimento Tecnológico (CODETEC). CODETEC involved a partnership between academic researchers and technicians from the Industrial Technology Department of the Ministry of Industry and Trade. Its main contribution was the development of diverse active principle production processes that were ultimately transferred to the private sector. Overall, these measures allowed Brazil to acquire during the 80s an adequate scientific, technological and industrial capacity for producing medicine.

Nevertheless, in the 90s, following trade liberalization and greater exposure to international competition, the country lost much of its industrial capability to produce synthetic intermediates and raw materials, falling far behind its Asian competitors in terms of marketing and price competitiveness. In particular, the sudden reduction of import tariffs, from 60% to 20% on average,

and the removal of non-tariff barriers created new challenges for the local production of fine chemicals. Privatization of petrochemical raw material firms reinforced the phasing out of the production of synthetics intermediates. In the first half of the 90s, 1,700 production lines of synthetic intermediates were shut down. Firms that remained in the market moved to less competitive areas, subsequently concentrating their production on low added value commodities. In the vast majority of cases, projects implemented in the 80s could not compete in scale and technology with imported drugs distributed locally by specialized international traders. This situation explains why the vast majority of the 400 or so Brazilian pharmaceutical firms have only mastered those active principles and intermediates formulae that have been supplied by other companies, generally through imports. Of the 19 domestic companies with ANVISA-registered ARVs, only 15 master the formulae for these drugs. Public laboratories also followed this trend by focusing on existing production capacities through imports of active principles.

Developmental potential for the future

Nevertheless, eight companies produce pharmaceutical active principles locally in Brazil (Labogen, Cristália, Microbiológica, Laob, Nortec, Formil, Quiral and Globe/Sanofi). Among these eight companies, five have industrial and technological synthetic ARV capabilities (Labogen, Cristália, Microbiológica, Laob, and Nortec). Amongst these five, three (Laob, Cristália and Microbiológica) can be considered as integrated firms (from synthetic APIs to formulae), whilst Nortec and Labogen focus on synthetics alone. In the early 90s, Microbiológica, a spin-off firm from the Federal University of Rio de Janeiro, developed the first local industrial ARV production line. It was successful in reverse engineering for AZT, but for economic reasons it gave up production in 2000, redirecting its strategy towards the search for new molecules for other diseases such as hepatitis C. Two other locally-owned firms – Laob and Cristália – have the technological capabilities to fulfill every step of the production process, from synthetics to formulae. However, Laob is currently changing its focus from ARVs to the production of anti-neoplasms. Only Cristália is still investing in ARV production and continues to be involved in a partnership with the public laboratory Far-Manguinhos, seeking new anti-HIV molecules and trying to improve the formulae for existing molecules. Nevertheless, Cristália does possess a diversified product line. The firm manufactures different kinds of active principles and finished products,

including some for anesthetics, pain management, psychiatry and hospital infection control. This diversification is a competitive advantage that has allowed the company to remain within the ARV sector.

Labogen is an example of a firm that is only involved in the production of active principles. It has a competitive disadvantage compared with the integrated companies, since most of the active principles used for pharmaceutical production in Brazil continue to be imported. There are considerable advantages associated with downstream integration in the pharmaceutical sector, due to the fact that a larger share of added value is appropriated through the marketing of finished products. Labogen was created in 1995 as a spin-off from the University of Campinas. Soon after its creation, the company entered the ARV segment as a result of the launching of the National AIDS ARV procurement program. It now produces active principles for eight ARVs and other active principles with lower added value. The company dominates the entire synthetics process and its industrial plant is ISO 9002 certified. Labogen has also enhanced quality control procedures in order to reduce synthetics process costs. However, when forced to compete with the product ranges being offered by the large international traders (firms sourcing specifically from Indian and Chinese active principles producers), Labogen's poor economies of scale mean that only a limited number of their tenders have been accepted by the Brazilian public laboratories. This situation has endangered Labogen's very existence in the market segment of active principles for ARVs.

IV
PATENTS AND PRICE CONTROLS: EFFICIENCY AND LIMITATIONS OF THE BRAZILIAN PROCUREMENT POLICY

Controlling prices via central purchasing and mobilizing local capacities constitute the main driving force behind governmental strategies for cutting ARV prices. The main success of the Brazilian MoH has been to obtain a lowering of prices on non-patented and locally-produced ARVs (-75.2% on average (1996-2001), [15]). This unprecedented fall in ARV prices is mainly due to the role of public laboratories in local production. Mobilisation of these laboratories' resources by the authorities has created an unprecedented situation characterised by a veritable breakthrough in procurement organisation.

As mentioned above, nine public laboratories are currently involved in the production of non-patented ARVs (Table 2). These are: LAFEPE, the first public laboratory to launch ARV production when it began manufacturing AZTs in 1994; the state-run Institute Far-Manguinhos, currently the main public ARV-producing laboratory; Fundação para o Remédio Popular (FURP); Fundação Ezequiel Dias (FUNED); Instituto Vital Brazil (IVB); Indústria Química de Goiás (IQUEGO); Laboratório Farmacêutico de Alagoas (LIFAL); Laboratório Farmacêutico da Marinha (LFM); and Laboratório Químico Farmacêutico da Aeronáutica (LQFA).

Since they do not come under the aegis of the law on tendering and because they operate through contracts with the MoH, these laboratories have in fact become the main suppliers of non-patented ARVs for the public program. That being so, local private sector input would appear to be little more than a supplement to public production. Both the discontinuing of tendering and the small quantities on auction attest to the fact that the authorities have scarcely made any use of the private sector (or, at a wider level, of local supplies of synthesized products). Fine chemical and pharmaceutical firms have therefore been unable to use the ARV public program as leverage in revitalising and developing their skills through investments in new equipment and technology. As shown in Table 3, the quantities of ARV involved in calls for tender have been much smaller than public sector supplies. In fact, in some years, certain ARVs have been supplied through public production alone. In addition, this limited reliance on supply from the private sector does not reflect any greater price competitiveness in the public sector, as the prices achieved via the call for tender procedures have usually been identical or lower than those agreed in contractual deals with public laboratories. Moreover, close examination of the different calls for tender reveal that:

i) no foreign generic seems to have won a bid up until now;

ii) some calls for tender have been won by multinationals who sell their patented products at highly discounted prices (for a comprehensive discussion on the issue of pricing, see [16]).

Table 3: The Brazilian procurement policy: public and private suppliers for non-patented ARVs (selected numbers, 1998-March, 2002)

Year	*Medicine*	*Public supplier*	*Unit Price (US$)*	*Quantity*	*Private supplier*	*Unit price (US$)*	*Quantity*
1998	Didanosine 100 mg	LAFEPE,FM, IGUEGO	1.02	18,647,742	-	-	-
1999		FM, IVB, FUNED	0.63	16,740,000	-	-	-
2000		LAFEPE, FM, IQUEGO IVB, FUNED	0.67	20,954,340	Bristol Myers Squibb	0.50	8,980,500
2001		LAFEPE, FM, IQUEGO IVB	0.37	36, 961,800	LAOB	0.27	5,280,420
2002		LAFEPE, FM, IQUEGO FUNED, LIFAL	0.39	20,000,100	-	-	-
2000	Indinavir 400 mg	FM	1.72	11, 103,885	Merck & Co.	1.91	7,309,620
2000					EUROFARMA	1.34	13,412,160
2000					NEO QUÍMICA	1.34	7,402,500
2001		FM, LIFAL	0.47	42,313,320	-	-	-
2002		FM, LIFAL	0.47	17,499,960	-	-	-
1998	Zidovudine 100 mg	FURP, LAFEPE, IQUEGO	0.45	32,074,000			
1999		FURP, LAFEPE, IQUEGO, FM	0,21	57,408,390	TEUTO	0.21	6,306,967
1999					CRISTÁLIA	0.21	5,000,000
1999					EUROFARMA	0.21	4,860,000
2000		FURP, LAFEPE, FM	0.18	50,271,800	-	-	-
2001		FURP, LAFEPE, IQUEGO, FM	0.13	41,892,680	-	-	-
2002		FURP, LAFEPE, IQUEGO, FM	0.13	24,000,000	-	-	-

Source: Brazilian Ministry of Health.

Going back to the Brazilian suppliers, it is noteworthy that whilst existing private ARV production capacities have been achieved in response to the establishment of a Brazilian program for the public procurement of these drugs, it can also be argued that by favoring public labs the current policy has not been able to create incentives to induce private companies to invest more in their manufacturing capacities. This may create an obstacle to the sustainability of the Aids Program, especially as public labs are confronted with a major problem: their access to imported active principles involves participation in calls for tender.

API Calls for tender: a market dominated by Chinese and Indian suppliers

Active principles account for 90% of ARV production costs. This means that further efforts to cut ARV prices should focus on manufacturing active principles, hence on controlling their production processes. As previously mentioned, a few private Brazilian companies have the requisite skills for this production, but the public laboratories, specialised as they are in formulae, are forced, in order to manufacture their finished product, to turn to third party API producers. In the absence of any public competence in this domain, relying on calls for tender from the private sector is the only way for Brazilian public laboratories to procure APIs for their production needs. Until now, the call for tender procedure has made it possible to acquire cheap active principles from foreign sources, but it also raises two key issues:

i) quality control on imported APIs;

ii) more fundamentally, the public ARV production sector's dependency on Asian active principle producers.

Since the 1993 Law and the 1995 Constitutional Amendment, tendering processes cannot be based on "technical and price" or just "technical" modalities, but must be given to the offer with the lowest price. Although public laboratories can establish technical requirements for tendering, these cannot a priori be considered to be eliminatory criteria. Samples cannot be used as an eliminatory criterion since there is no guarantee a priori that the samples correspond to the production batch that is to be delivered. Nevertheless, if the successful tenderer sends a product that does not correspond to the technical specifications, the public laboratory has two alternatives: to negotiate a new batch (whose acceptance will also depend upon its compliance with technical

specifications) or to cancel the call for tenders in question and invite new tenders. Before inviting new tenders, the laboratory can also ask the company which came second in the previous tender if it can supply the requisite medicines at the previously accepted price. However, in most cases, this firm cannot lower its price and there is a need to open a new call for tenders.

Although there is a learning curve from the experience of such tendering processes, and even though it is possible to know which suppliers possess the actual technical conditions that will allow them to deliver active principles with the technical specifications, this cannot also be used as a priori eliminatory criteria. Thus if a company that has proved itself incapable of supplying quality active principles submits the lowest offer, then the public laboratory is still obliged to accept it. Amongst the many implications of such a problem, there is the delay in the public laboratories' commitment to the previously established MoH demand[13].

Non-compliance with technical specifications occurs mainly in inputs acquired from Chinese and Indian laboratories. The reason is that ANVISA only requires foreign laboratories to respect basic storage and distribution conditions. There is no need to inspect the industrial plants from which the active principles are being imported. This is a de facto advantage that the Law bestows upon imported products, since ANVISA's demands on local manufacturers entail additional costs compared to Indian and Chinese suppliers. It is therefore no surprise that Asian suppliers are currently dominating the Brazilian active principles public market. Represented locally by traders, Indian and Chinese firms account for 90% of all tender submissions and the prices they are able to offer leave little room for Brazilian companies in their domestic active principles market. Despite the participation of Brazilian firms in these calls for tender, in most cases they are unable to compete with Chinese and India laboratories. According to Brazilian firms, this situation has created little incentive to continue to operate in the active principles market, and some of them are considering withdrawing from the ARV segment. Microbiologica for example, once the first local firm able to synthesize AZT (and for many years the only firm to provide the MoH with that drug) was forced to leave the market, due to the lower prices being offered by foreign competitors. This trend may progressively lead to a situation in which the

13. Another problem relating to the tendering process is that the time between the announced result of the "call for tender" and the required delivery date is too short. Domestic private companies do not have enough time to plan the production process and buy the required inputs. Consequently they need to keep expensive stocks without any sales guarantee.

AIDS Program is entirely dependent on imports – and it could also result in the phasing out of private laboratories' production of active principles. The negative effect of interrupting local production would be the loss of existing technological capabilities, hence of a key element for making the threat of compulsory licenses credible, and thus obtaining significant price reductions of ARVs that are still under patent.

The politics of lowering prices on patented ARV: how to maintain a credible threat through the use of compulsory licenses

Multinational firms currently account for nearly two-thirds of all Brazilian Government ARV procurement. Moreover, spending on imported ARVs that are still under patent represents around 62% of the total ARV procurement budget. In addition, imports are likely to grow rapidly in the future, with a new generation of on-patent drugs coming on line. As such, the threat posed to foreign firms by the use of compulsory licensing in local production constitutes a key issue in controlling the future costs involved in providing ARVs that are still under patent. In Brazil the government has recently adopted this strategy in its negotiations with multinational firms, trying to get them to lower their prices. Given the public Far-Manguinhos laboratory's ability to establish cost-based reference prices, this strategy was used in 2001 to negotiate reduced prices for Nelfinavir and Efavirenz. After Brazil threatened to break the patent and produce the drug itself, the patent holders agreed to price cuts of 40% for Nelfinavir and 59% for Efavirenz [15].

Nevertheless, despite these first successful results, the Brazilian strategy is a temporary window of opportunity that might be closed in the near future once the TRIPS agreement has been fully complied with by the main Asian (Chinese and Indian) suppliers of active principles.

In fact, by 2005 India will have to comply with the new international law being set up under TRIPS; and China, which has already started to front-run the implementation of TRIPS (revising its 1992 Patent Law in 2001), is already subject to certain regulations prohibiting copying and/or exporting some of the products for which a Chinese patent already exists. Hence the risk for Brazil is that its cheap active principles suppliers will dry up before it can develop local capabilities in this domain. Furthermore, as soon as it is no longer in a position to ensure local ARV production using imported APIs, Brazil could lose its ability to negotiate the price of new treatments with

multinational patent-owners via the only tool designed towards this end, *i.e.* the threat of compulsory licensing.

V
CONCLUSION: FINAL ASSESSMENT AND A FEW POLICY IMPLICATIONS

The Brazilian ARV Program offers some important lessons for other developing countries aiming to control the AIDS epidemic.

1. As mentioned above (and demonstrated in greater detail in the chapter by Teixera *et al.*[13], part 1), it has unquestionably been highly successful as a public health program.

2. To highlight the key factors underlying the spectacular success of this public healthcare program, it must be stressed that the main driving force for the AIDS program's expansion of access to ARVs has been the reduction in drug prices. The lesson taught by the Brazilian example is that acquiring technological capabilities in ARV formulae is essential for increasing the bargaining power of the national public authorities with patent holders. Once public laboratories began their own production of off-patent ARVs (and started to supply these drugs at much lower prices than those of the multinational firms), ARV prices fell dramatically in Brazil, which contributed to price decreases in other markets throughout the developing world. With respect to patented ARVs, threatening patent holders with compulsory licensing and demonstrating the technical ability to develop ARVs locally has been the key to obtaining this drastic reduction in drug prices. In addition to ensuring cuts in patented drug prices, local formula capabilities have also contributed to a decrease in the prices of off-patent ARVs.

3. At a more theoretical level, the Brazilian experience also provides us with a few key elements for the debate over TRIPS. Since its adoption, the agreement's supporters and opponents have argued bitterly over the subsequent tightening of IPR laws. These discussions have specifically revolved around the impact of TRIPS on the countries of the South, which have been forced to align themselves with prevailing protection standards in the world's most developed countries (in R&D terms). TRIPS supporters have argued

that by introducing tighter regimes, the countries of the South will attract multinationals, whilst creating an incentive for local firms to invest in R&D, since they can be sure that their discoveries will be protected (for a detailed and critical analysis of these arguments, see [17]). The evidence, after some 20 years of fight against the AIDS pandemic, has led to outcomes that seem totally different from the ones predicted by the proponents of strong protection. This is because the multinational companies, sitting on their monopolies and protected by international law, have not at all delocalised their activities to the South. On the contrary, after the clauses that used to be beneficial to the locally established firms were suspended, certain multinational companies began to abandon some of their facilities in the South, regrouping their worldwide manufacturing units in an attempt to achieve economies of scale [7], [17]. Furthermore, even before generics began to be produced and distributed locally, multinational drugs manufacturers did anything but lower their prices. In other words, they perpetuated a situation in which access to treatment remained totally out of reach for patients in the South. Lastly, local firms, the vast majority of whom lack sufficient R&D capabilities, have tended to regress rather than progress. As for the fine chemicals firms that used to produce active principles, Brazil witnessed a mass destruction of its stock of manufacturing facilities once the free-trade agreements that were signed in 1994 came into effect (remember that TRIPS are only one aspect of the general agreements signed under the WTO framework).

In addition, it was only once the Brazilian authorities made a commitment to local production that the multinational firms, for once under considerable pressure, began to lower prices visibly. In other words, aside from its remarkable effects in terms of Public Health, one of the main achievements of the Brazilian program is that it provided unambiguous elements for dealing with key issues in the country's political economy.

4. For all of these reasons, the ensuing phase (the 2001 Doha Declaration) has been crucial, with WTO members now openly admitting that it is essential that countries facing epidemic threats be able to use compulsory licenses of patented drugs. Depending on whether this statement of intent is followed by tangible after-effects and enacted in law, the circumstances surrounding the continuation of the battle against this epidemic could vary greatly[14]. The United States' recent opposition (the U.S. is the only country to refuse a compromise

14. This issue is discussed in detail in [18].

text accepted by the 143 other countries represented in Geneva) was a disastrous signal for the wealthy nations to send to the countries of the South. In any event, and even if "South-South" exports of ARVs and other active principles are finally authorised (something that was refused in Geneva in 2002), the Brazilian experience clearly shows that the use of a "compulsory licensing" clause (or the credible threat to use it) constitutes a key strategic tool for achieving the significantly lower prices of drugs that are needed to fight the epidemic.

5. However, in spite of its evident merits, the Brazilian program, when seen from the point of view of its long term sustainability, draws attention to some of its inherent limitations. These mainly stem from the fact that the program was implemented and developed without sufficient attention having been given to the development of local industrial and scientific API capabilities. Most of the fine chemical production capacity built up in the 70s and 80s was dismantled after market liberalization in the 90s. The shutting down of 1,700 production units of intermediates increased the dependence on imports. In this context, the ARV Program revealed that the preference for acquiring drugs from public laboratories might have detrimental impacts on the existing technological capabilities of locally-owned private companies. In fact, regarding the short-term public health goal of guaranteeing the lowest possible price for ARVs in order to maximize the number of ART-treated patients, public laboratories hold the lion's share of public demand. This policy has discouraged local production of active principles and local private involvement in ARV formulae. The larger share of private supply of active principles for public laboratories is now being dominated by trading firms representing Indian and Chinese pharmaceutical laboratories. This situation is further narrowing the limited space for Brazilian private domestic firms to participate in the supply of ARVs. Squeezed between Indian and Chinese active principles suppliers, multinationals and public local laboratories specialized in the development of finished medicines, private domestic firms are withdrawing from the ARV market segment. This situation poses future challenges for Brazil: how to guarantee the quality and low price of imported active principles and how to maintain the sustainability of their ARV procurement program in the light of a potential trend towards increasing API prices.

The complete enforcement of patent rights in India and China after 2005 may undermine the Brazilian government's ability to negotiate prices with multinationals. Without an alternative cheap source of active principles, the credibility of the compulsory license as a threat will be limited.

As such, what appears to be essential is that the new policies be designed in such a way as to maintain an AIDS program at affordable costs and encourage the development of technological capabilities in local firms, based on the production of intermediate inputs. This would seem to be all the more necessary insofar as, even if the Doha negotiation did open the door to the advent of a generics industry in the countries of the South (facilitating export in case of a national emergency), the Brazilian industry's real ability to compete with foreign generics firms will be a crucial factor in the price of the ARVs that the public program will be distributing.

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Impact of Intellectual Property Rights on Aids Public Health Policy in Thailand

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Key words: HIV/AIDS; TRIPS agreements; public health; industrial policy; intellectual property rights.

Abstract

After a committed policy to contain the spread of the HIV/AIDS epidemic in Thailand, another challenge must now be faced: that of providing accessible anti-AIDS treatment to those infected. This paper explores both the technical and legal aspects of a possible solution involving the provision of low-cost medicines by the Thai pharmaceutical industry. It shows that even if the efficient domestic drugs industry could participate in meeting this challenge, recent modifications in the intellectual property rights system hinder the large-scale local production of generic drugs. These institutional modifications can therefore be viewed as an obstacle to the continuation of public health policy as they impede the provision of affordable treatments.

Résumé

Après une politique volontaire menée pour infléchir le cours de l'épidémie du sida en Thaïlande, à présent un autre défi apparaît, celui de faciliter l'accès des personnes infectées aux antirétroviraux. Ce papier aborde les aspects techniques et juridiques de ce problème en examinant la possibilité de mobiliser l'industrie pharmaceutique domestique pour satisfaire cet objectif. Il montre que si l'industrie pharmaceutique locale est performante et peut aider à relever

ce défi, les modifications récentes intervenues dans le système de droit de propriété intellectuelle thaïlandais constituent un obstacle non négligeable. Ces modifications freinent la production large de traitements anti-sida et empêchent pour partie la poursuite d'une logique de santé publique en matière d'accès des patients à des antirétroviraux abordables.

Introduction

Since 1991, due to a strong political will, the public authorities have been active in controlling the epidemic. The public information program and the 100% condom campaign have brought about a significant increase in condom use among brothel-based sexual workers and their clients. For instance, condom use rose from 14% to 90% between 1988 and 1992 among brothel-based sexual workers[1]. An estimated 2 million infections were thus averted [5].

Yet much more preventive action must be taken if public authorities want to influence the future course of the epidemic [1]. Two population subgroups, street-walkers and Injected Drug Users (IDUs), who display high-risk behaviour, must be urgently included in the prevention program, as they represent an important reservoir for infection and transmission of HIV/AIDS to the whole population[2]. Likewise, the number of infected pregnant women and infected children obtaining the AZT treatment is still low, due to the prohibitive price of the drugs. It costs 500 dollars per year to treat a woman and her child. Out of a population of 62,000 pregnant women requiring treatment in 1999, the Thai Red Cross provided only 2,891 courses of treatment [6][3].

Up until now, the low number of people living with HIV/AIDS (PLWAs) entering the symptomatic phase of the disease justified the Ministry of Public Health's (MOPH) prevention policy[4]. However, out of 755,000 PLWAs, about 70,000 are now developing the first symptoms of the disease. So they urgently need HIV/AIDS treatment in order to live more comfortably with the disease, to be able to keep on working and avoid a decrease in the household's income [9]. Meanwhile, less than 5% of the population have access to anti-AIDS treatment.

Concerning the treatment issue, in 2000 the World Bank estimated the expenditure the MOPH may incur in facilitating people's access to palliative care,

1. For a comprehensive presentation of AIDS public policy in Thailand, see [1, 2, 3, 4].

2. For the future, a quarter of new adult infections will be due to IDUs.

3. As Prescott said, to treat all infected pregnant women would require spending the whole AIDS budget [7].

4. In 1998, 73% of public funds allocated to the fight against AIDS was devoted to prevention[8].

opportunistic disease treatment and anti-AIDS drugs[5]. Among other things, this report showed that the expenditure required to supply antiretroviral treatment ranged from a 66% share of the AIDS budget up to 27% of the health budget, according to the price level and number of patients to be treated. In particular, in order to treat 55,000 patients with the most expensive drug, the expenditure represents about 12 times the AIDS budget or 27% of the health budget. Using generic drugs would cost about 3.6 times the AIDS budget or 8.1% of the health budget[6]. As a consequence, Thailand could use generic treatment to alleviate the health burden.

So the question is: "Does Thailand have the technical and legal possibilities to address the generic drug issue in order to ease health expenditure constraints and to facilitate as far as possible people's access to anti-AIDS treatment?" In other words, can Thailand take advantage of an "industrial policy logic" to serve public health goals in a specific context, that of strengthening intellectual property rights (IPR)?

Due to a committed industrial policy, the domestic pharmaceutical industry has the formulation capabilities and equipment to produce generic drugs. The Government Pharmaceutical Organisation (GPO)[7] has obvious formulation capabilities to produce anti-AIDS treatment. Nevertheless, it provides only a limited range of treatments and faces some difficulties in providing people with access to treatment.

This paper aims to demonstrate that the explanation for this apparent paradox lies in the successive modifications of the Thai Patent Act (TPA). The implementation of patent on product, the introduction of the Safety Monitoring Program (SMP) in 1992 and the ratification of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreements in 1994 have brought about a new institutional environment. This environment prevents comprehensive mobilisation of the domestic pharmaceutical industry and especially reduces the GPO's capability to foster health objectives such as facilitating access to AIDS treatment.

We briefly describe how, thanks to a favourable legislation on IPR (patent on process), Thailand has promoted the creation of an effective pharmaceutical

5. Through HIV, some diseases are again rising. Since the early 80s, in the north of Thailand, tuberculosis, pneumonia and cryptococcal meningitis have been particularly common among individuals infected with HIV/AIDS: 43% have tuberculosis, 16% pneumonia and 15.9% cryptococcal meningitis [10].

6. Public authorities will have to spend about 70.8 bahts per year and per patient to provide low cost palliative care and treatment for opportunistic infections to only 10,000 individuals: 5% of the AIDS budget for the 2000 tax year or 0.1% of the health budget [8].

7. The organisation is in charge of the production of essential medicines for hospitals.

industry. We then list the successive IPR system modifications that have affected the current and future course of the Thai pharmaceutical industry. In relation to the production of anti-AIDS medicines, these modifications have provoked the withdrawal of domestic pharmaceutical firms (I). We describe the strategies the GPO has consequently implemented to circumvent IPR on products and provide anti-AIDS treatments at low cost. Recently, these strategies have permitted the formulation and production of the least expensive HIV/AIDS cocktail in the world. However, this treatment only partly solves the accessibility issue in Thailand (II).

I
THE EVOLUTION OF THAI REGULATION: A BRAKE TO GENERIC ANTIRETROVIRAL (ARV) PRODUCTION

From the 1992 Thai Patent Act to the Safety Monitoring Program

Up until the end of the 80s, drug patents were forbidden in some developing countries; only process patents were granted. To reinforce this position, during the Uruguay Round in 1989, developing countries put forward industrial considerations. India consistently asserted that developing countries (like developed ones)[8] have the right to follow an "Educational Protection"[9] model [12]. In this way, developing countries could ensure the technological development of domestic industry through imitation of brand name drugs, provide medicines at low cost and avoid dependence on supply from multinational companies[10].

8. For instance, in Europe, the first drug patent was implemented in the United Kingdom in 1949 followed by France in 1959 which introduced a "special drug patent". Switzerland, home of one of the largest pharmaceutical companies, allowed drug patents only in 1977 [11].

9. According to List, when there is an industrial divide between countries, the only solution for the least developed countries is to protect their infant industry by erecting barriers to ensure their development. Through a period of "Educational Protectionism", the country strengthens its competitiveness by promoting "learning-by-doing" [13] or "learning-by-copying" when there are no IPR. After that, international competition may be allowed. Empirical studies show that the lack of pharmaceutical IPR in Argentina, Costa Rica and Turkey enabled the local pharmaceutical industry to develop [14].

10. Thanks to process patents and a drug price control order, India has developed a powerful generic industry, which provides among the cheapest medicines in the world [15, 16]. In the same vein, due to their 14-year-old generic industry, Brazil is now implementing a research program promoted by the public laboratory Far-Manghuinos.

Following this argument, the first TPA was implemented in 1979 (Patent Act B.E. 2522) and only acknowledged patents on process. The lack of drug patents promoted "learning by copying". Appropriating knowledge and core skills through "reverse engineering", domestic firms achieved generic drug production such as Nucleoside Reverse Transcriptase Inhibitors. In 1997, the Thai pharmaceutical industry was composed of small and medium-sized enterprises (176 private companies) and a public firm (GPO)[11]. In summary, a positive correlation between regulation and industrial development was built up [18].

1992 was a turning point for the Thai pharmaceutical IPR system. The 1979 Patent Act was revised in order to introduce product patents. Henceforth, all drugs discovered after 1992 could be patented in Thailand. Patent life is fixed at 20 years from the date of filing for patent[12]. During this protection period, no generic version can be produced.

Moreover, with the support of their national government, American firms put pressure on the Thai public authorities and obtained the implementation of the Safety Monitoring Program (SMP) in 1992. Officially, the goal is to increase the safety and effectiveness of products on the domestic market. In fact, this program grants "exclusive market rights" for 2 years to multinational companies. SMP covers new chemical entities, new combinations, new recommendations and new delivery systems.

Again in 1993, Thailand was the subject of "special 301" provisions under the US trade Act of 1974[13]. The Thai government was constrained to amend the law to extend the market exclusivity period. Firms could then ask for two successive extensions of one year of SMP. At the end of these extensions, firms have to collect data about the safety and effectiveness of drugs. These data are submitted to the Thai Food and Drug Administration (FDA) which may grant a drug registration certificate after 6 months. The FDA will approve the registration provided that the submitted data and reports are scientifically correct and complete. The drug can then be distributed through the market channels. The period of market exclusivity is eventually extended to 5 years.

11. In 1997, these firms produced generic medicines with a market share of about 60% in volume and 30% in value [17]

12. In practice, due to the delay between patenting and marketing approval, the effective life of a patent is less than 20 years.

13. The "special 301" section is used as a market weapon against countries which don't respect the American market rules because this could be prejudicial to American interests.

After the Safety monitoring program expiration, generic drugs may be put on the market and can be imported or manufactured by local firms. Consequently, drug prices may decrease because of generic competition (Table 1).

Table1: Brand name and generic price comparison in Thailand (in US$, 2001)

Drugs	*Brand name price*	*Generic price*	*% reduction*
Fluconazole (200 mg caps)	6.20	0.26	95.8
Stavudine (40 mg caps)	2.60	0.10	96
Zidovudine (100 mg caps)	0.50	0.15	70
Didanosine (100mg tab/170 mg powder)	1.20	0.62	48

Source: Adapted from [19, 20, 21].

Until 1998, about 700 "new drugs" were controlled by the Safety monitoring program, including some ARVs. Patent owners' interests were thus furthered at the cost of national generic producers. In fact, by strengthening the patent system, SMP constitutes a real entry barrier to Thai generic production.

In addition to the introduction of drug patents in the Thai IPR system, parallel importation was forbidden by the Thai government in 1992 because of the American threat to limit Thai textile imports. One year later, the Thai government was once again under American pressure: compulsory licences provided by the TPA (Patent Act, section 46) were suppressed. In return, the American government promised low customs duties on Thai gems and wood products.

The SMP plays a negative role in the industrial response to the AIDS epidemic. By delaying or even preventing generic production of ARVs, it obstructs the population's access to vital medicines. For instance, didanosine (ddI, Videx™) was only released from the Safety Monitoring Program in 1998. Furthermore, discovered before 1992, stavudine (d4T, Zerit™) is out of patent in Thailand. Yet the implementation of the SMP allowed Bristol Myers Squibb (BMS) to obtain exclusive market rights for d4T. In 1999, d4T was released from the SMP. Upon expiry of exclusive market rights, generic production was implemented, enabling a substantial reduction in the price of the medicine (Table 1).

New strengthening of Intellectual Property Rights: Thailand ratifies TRIPS Agreements

The ratification of TRIPS means the introduction of IPR into international trade agreements. From now on, the signatory states must grant patents for 20 years (article 33, "Term of Protection")[14].

To convince developing countries to accept TRIPS agreements, developed countries argued that the lack of IPR is prejudicial to technology transfers and Foreign Direct Investments (FDI) in developing countries. On the contrary, TRIPS agreements favour technology transfers and local Research and Development (R&D), allowing developing countries to do their "catching-up" and provide people with the latest drugs.

The TPA was amended in 1999 (Patent Act n°3, B.E. 2542) to comply with the terms of TRIPS. Since 1992, Thailand had already been in compliance with the 20-year product patent. Now, parallel imports and compulsory licences have been reintroduced into the Thai patent system (articles 36 (7) and 51). Furthermore, in compliance with TRIPS (article 31), compulsory licences could be used not only in the event of a national emergency or other extreme circumstances such as public health emergencies (article 8.1), but also for public non-commercial use and to remedy anti-competitive practice. Therefore, according to articles 31 and 8 (paragraph 1), TRIPS provide for the exclusion of vital drugs from the patent system in order to allow generic production. Finally, the amendment of TRIPS in 1999 relaxes the law on IPR.

In spite of the public health emergency related to the AIDS epidemic, the compulsory licences measure has never been used in Thailand, as shown by the "GPO case". Before TRIPS ratification, GPO succeeded in developing a generic version of ddI[15]. When the new TPA came into effect in 1992, BMS patented an improved formulation of ddI. The company was granted exclusive market rights and fixed its prices freely in compliance with the Thai pharmaceutical

14. In 1994, World Trade Organization (WTO) agreements clearly introduced a strengthening of the monopoly of multinational firms. If GATT allowed members to protect intellectual creations (article XX (d)), there was no obligation to adopt protection measures. IPR were allowed only if they did not lead to a reduction of international trade or a discrimination between members. The emergence of a knowledge-based economy promotes the critical role of IPR for developed countries. IPR is a strategic instrument in their rent-seeking dynamic.

15. The National Institute of Health (NIH), the US public research institution has been the patent owner of ddI since 1987. It has granted a licence to operate (production and marketing) to BMS who pays royalties: 5-6% of sales. This first version of the ddI was not patented in Thailand.

pricing system. Consequently, ddI was unaffordable for most patients[16]. Yet the new ddI was not a real innovation. It only offered a slight improvement compared to the ddI patented by the NIH[17]. Because of the BMS patent and SMP, GPO's project for production of a generic ddI was stopped[18]. Nevertheless, in 1997, GPO made a request for a CL (for governmental use) to the Thai Patent Office under the cover of article 51 of TPA. According to this article, if GPO and BMS did not agree on a reasonable amount of royalties, the Thai Patent Office would take a decision. The GPO request led BMS to lobby for the intervention of the American government. The threat of commercial retaliation on Thai gems, wood and microprocessors dissolved the willingness of the Thai government to authorise national generic production of ddI. In the end, GPO was not allowed to market its generic version under cover of a compulsory licence. Finally, as the Thai government could not resort to TRIPS because of international pressure, part of the regulation was used as a barrier to generic and affordable production.

II
HOW TO RECONCILE PUBLIC HEALTH AND INDUSTRIAL LOGIC?

Regarding the modification of the TPA before 1994, with the implementation of SMP and the ratification of the TRIPS agreement in 1992 on one side, and the international commercial pressures the Thai government faced on the other, it clearly became difficult for Thailand to provide access to anti-AIDS treatments. However, thanks to GPO commitment, Thailand is trying hard to discover ways of reconciling public health logic and industrial logic through generic production that respects patents. Indeed, aware of the existing constraints of TPA, GPO has developed 3 strategies.

The first consists in identifying non-patented medicines or drugs discovered before 1992. At the present time, GPO produces many drugs at low prices (Table 2).

The second strategy is to produce a new formulation of patented drugs. Considered as an innovation, the medicine is covered by a "petty patent". Provided by the TPA, petty patents cover minor innovations and provide 10-year protection.

16. In spite of a "fair-pricing" clause provided by NIH in the licence.

17. The modification of the formulation consists of the addition of anti-acidity.

18. Based on a specific production process, GPO was about to market a generic version at a lower price in the country (25 bahts vs 45 bahts the tablet).

The last strategy is to combine non-patented molecules in a 3-in-1 tablet. Again, this kind of "invention" may be patented in Thailand under cover of a "petty patent".

For instance, faced with the impossibility of obtaining a compulsory licence for the production of ddI, patented by BMS in a tablet form, GPO developed a new formulation of ddI (in powder) and asked for a "petty patent". Likewise, developed in December 2001, GPO-VIR combines 3 ARVs not patented in Thailand: d4T, 3TC and Nevirapine. A two-dose daily treatment is prescribed for GPO-VIR, which means lower prices for PLHAs. Indeed, taken separately, the treatment costs $114 per month and per patient. Taken in a single pill, the cost falls to $27 per month and per patient, the lowest price in the world for this treatment[19].

Table 2: GPO ARV drugs list

List	Brand Name
Zidovudine (AZT)	ANTIVIR ™
Didanosine (ddI)	DIVIR ™
Stavudine (d4T)	STAVIR ™
Lamivudine (3TC)	LAMIVIR ™
Nevirapine	NERAVIR ™
AZT+3TC	
d4T + 3TC + Nevirapine	GPO-VIR ™

Source: [21].

With GPO-VIR, the government can hope to treat about 80% of people living with HIV/AIDS if the political commitment made in December 2001 to

19. The three ARV cocktail produced by CIPLA, an Indian generic firm, costs $350 per year (sale price for MSF).

provide ARVs to PLWAs is fullfilled[20]. Twenty percent of PLWAs display resistance to Nevirapine and have to switch to Efavirenz (Sustiva™). But the latter is patented in Thailand. It is still unaffordable. While one can be satisfied with GPO's results, which have broadened PLWAs' access to ARV treatments, new ARVs remain unaffordable for most Thai patients. In the event of a future radical innovation, *i.e.* the discovery by multinationals of a more efficient anti-HIV drug, local producers and especially the GPO will not be allowed to produce a generic version, even if they have the technological know-how.

Conclusion

This leads to the conclusion that there is a need to make the IPR system more favourable for domestic firms. New public policies seem to be moving in this direction. Currently, the liberation of drugs from SMP is accelerating, and an amendment of SMP in January 2001 restricts the scope of exclusivity rights. Henceforth, exclusivity rights are granted only for drugs patented abroad between 1968 and 1991. In the same way, the National Drugs Committee has allowed the production of generic versions of patented drugs in order to begin bio-equivalence studies. Known as the "Bolar provision", this measure allows their registration before the end of the exclusivity period and thus cuts the multinational exclusivity period by 2 to 3 years [22].

Furthermore, we can observe that Thailand has been severely disillusioned on the question of technology transfer. Article 7, "Objectives", of the TRIPS agreements stipulate that "The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations". Furthermore, Article 66-2, "Least-Developed Country Members", stipulates that "Developed Country Members shall provide incentives to enterprises and institutions in their territories for the purpose of promoting and encouraging technology transfer to Least-Developed Country Members in order to enable them to create a sound and viable technological base".

20. Under the pressure of Non Governmental Organizations (NGOs), the New Health Insurance Policy was implemented under the slogan "30 bahts for curing every disease". The objective was to extend cover to all Thai people and to decrease the burden on household expenditures. However, in practice, the introduction of ARVs is still problematic because of their price.

In fact, since the Thai Patent Act amendment in 1999, evidence of growth in technology transfer in the Thai pharmaceutical market is weak [23, 20]. According to Supakankunti *et al.* [24], 82% of directors in the R&D-based pharmaceutical industry believed that there was no technology transfer in the Thai pharmaceutical industry. From 1984 to 1998, the nationality of firms in the local market was Thai, leading to the conclusion that there were few foreign direct investments (FDIs) in the Thai pharmaceutical industry[21]. Furthermore, since "working patents" allow both local production and importation of medicines, multinationals continue to import instead of producing drugs locally. In 1999, imported products represented 60% of the Thai medicine market. When production units of multinationals are actually installed in Thailand, their activities are limited to manufacturing finished products. Ultimately, FDI numbers have not increased in Thailand, despite significant modifications of the TPA. It appears that the disadvantages of the new TPA are clearly obvious, whereas the advantages remain questionable.

21. Similarly, The Thai boards of many R&D-based multinationals moved to Singapore in spite of the strengthening of the Thai Patent Act. The chief executive of the Pharmaceutical Producers Association, Professor Chitman, argues that Singapore is more attractive than Thailand because of many advantages like abatements, faster registration procedures and work permits for expatriates [22].

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Pharmaceutical Patents, Developing Countries and HIV/AIDS Research

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Key words: patents; pharmaceutical innovation; Research and Development.

Abstract

Patents are one of the reasons why many patients from developing countries lack access to AIDS treatments. The usual justification for implementing patent systems in the third world economies is based on the increased incentives to innovate that patents should provide. In this paper, we argue that, for various reasons, developing countries'patent systems are unlikely to be a crucial determinant of access to innovation against AIDS. On the other hand, however, patents could act as a complement to public funds dedicated to buying back treatments and future vaccines from pharmaceutical firms.

Résumé

Les brevets d'invention sont une des raisons pour lesquelles les patients des pays en voie de développement n'ont pas accès aux traitements contre le sida. La justification traditionnellement donnée à la mise en place de systèmes de brevets dans ces pays réside dans les incitations à innover accrues des firmes pharmaceutiques. Dans cet article, nous discutons la pertinence de cet argument et concluons qu'en réalité, les brevets d'inventions délivrés par les pays en développement ne sont probablement pas suffisants pour accélérer la recherche contre le sida. En revanche, ils pourraient s'avérer un complément à la mise

en place de fonds publics destinés à racheter aux firmes pharmaceutiques les traitements et les futurs vaccins.

Introduction

The debate on whether developing countries should enforce pharmaceutical patents protecting treatments of deadly and widespread diseases such as AIDS confronts two distinct, opposing arguments. Governmental and non-governmental organisations argue that patents entail a significant increase in the price of medicines, thus restricting treatments to a minority of wealthy patients. On the other hand, pharmaceutical firms, as well as the United States'representatives, stress that these patents are needed to encourage research in areas that are already under-explored, such as the HIV/AIDS viral strains affecting developing countries.

This debate starkly reflects the dynamic trade-off between the static deadweight loss generated by the patent-induced monopoly and its incentive-enhancing effect on research. Ever since Nordhaus and Scherer wrote their seminal papers in the 70s, economists have tried to come up with an evaluation of the direction and extent of this trade-off.

For developed countries, it has often been pointed out that suppressing pharmaceutical patents would entail long-term, dynamic losses in terms of new medicines, which would be less than compensated by the downward pressure on drug prices [1]. Hence, despite having been initially very reluctant, most industrialised countries, such as the United Kingdom (in 1949), France (in 1959), Germany (in 1968), Italy and Sweden (in 1970), Japan (in 1976), have introduced patent protection for pharmaceutical innovations. Several trends, such as an increasing patent life or the application of patents to human genes, also seem to indicate that in the United States at least, this protection has even been strengthened.

But how should economists consider the implementation of the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement in disease-ridden, low-income, developing countries? This paper analyses the likely impacts of developing countries'patent systems in the case of the HIV/AIDS treatments. Patents are indeed likely to be crucial in the price-fixing strategies of pharmaceutical firms: for instance, a copy of the antiretroviral treatment Stavudine was retailed at a price of US$0.6 in India compared with a US$4.9 gross price in the

United States. If patents were to impose comparably high prices in developing countries, the cost in terms of access to treatments would be huge, since most patients could not afford such medical expenses, partly because of low individual incomes, partly because of the absence of any health care insurance system. Indeed, if all AIDS patients in Sub-Saharan Africa were to be treated through a combined therapy (using Crixivan™, AZT and 3TC) priced on the American standard, the resulting health expenses would by far exceed the total Gross Domestic Product (GDP) of these countries [2]. Current anecdotal evidence stresses that patents can result in large price increases for AIDS treatment. In South Africa, for instance, a daily treatment of the patent-protected Fluconazole (against AIDS-induced meningitis) is currently priced at US$17.84, twice as much as the daily local average wage [3]. More generally, countries that have built ambitious generic programs to provide treatments to their patients seem to fare much better than countries that bowed to the demands of patent protection from pharmaceutical firms and the United States.

To balance these static deadweight losses, stronger patents in developing economies should entail dynamic gains in the form of higher investments in research against AIDS. This paper discusses the intuitions and empirical evidence gathered so far on this matter.

In a first section, we acknowledge the role played by patents in the pharmaceutical industry. Still, we argue that the introduction/strengthening of the patent systems in developing countries is unlikely to be a necessary component of innovation if AIDS is considered as a "global" disease. Indeed, the bulk of market revenues is and will be made in industrialised countries. Therefore, innovation incentives in AIDS research would only be marginally affected by a strengthening of patent protection in developing economies.

In contrast, research incentives for those innovations concerning local diseases, such as the HIV strains affecting developing countries, may well be sensitive to the scope and effectiveness of patents (section II). Still, they are probably far from sufficient to ensure the socially desirable rate of innovation. Yet, patents could act as a complementary mechanism to other policy initiatives (for instance, to strengthen the credibility of funding programs for vaccine development).

We are therefore drawn to the conclusion that patents alone are very unlikely to provide much incentive to pharmaceutical firms while their social costs in terms of higher drug prices are certainly not marginal. On the other hand, patents could increase the effectiveness of other innovation programs like research and procurement funds. Such programs should however seek to reduce the adverse consequences of the patent systems.

I
PATENTS AND THE RESEARCH AGAINST "GLOBAL" DISEASES

Ever since they came into existence in 18th century industrialised countries, patents have stirred a controversial, if lively, debate on whether that reward system was effective and/or necessary. Note that, contrary to what is currently happening in the context of the TRIPS agreement, the discussion was not so much focused on the static dead-weight losses imposed on the economy, as to whether patents were really performing the function they were supposed to. Some of these arguments still carry great weight for today's economists.

Patents, imitation and innovation incentives

A patent is supposed to deter imitation, thus providing the innovator with a monopoly for a period of 10 to 20 years (depending on the lag between the patent grant and the market introduction of the innovation). The short-term distortion entailed by patent monopolies can only be justified by the boost given to research incentives. Theoretically, the optimal length of a patent is that which equals the marginal benefit of greater protection (in terms of innovation performance) with its marginal costs (in terms of deadweight losses). This basic principle falls prey to several criticisms, however:

– first, firms resort to other strategies than patent enforcement to protect their innovations. The study by Levin *et al.* [4] and its recent follow-up by Combe & Pfister [5] demonstrate that very often, patents are evaluated as less effective than alternative appropriation schemes, such as lead-time or secrecy. In that case, what is the point of maintaining costly and administrative patent systems?

– second, the patent system can act as a barrier to innovation: from a theoretical standpoint, they discourage cooperation and can be used to block rivals doing research in related fields (see Lerner [6] and Austin [7] for evidence of this sort in the biotechnology industry, and Shapiro [8] for a discussion on overlapping patent rights in high technology industries);

– third, effective patents can lead to an overall excessive level of Research and Development (R&D) as firms try to outpace each other to reach the patent office first [9]. Several theoretical models recommend that some of the rents earned by the patent owner be redistributed to rival companies in order to prevent excessive investment from emerging;

– finally, the patent mechanism bears sense only for those innovations that are generated through private (as opposed to public) R&D expenditures. Otherwise, the cost of public innovations would be imposed twice on the consumers, first through tax mechanisms, then through monopoly pricing. Note though that the United States have introduced patent protection for government-funded research institutions, as a way to promote cooperation between public and private organizations.

Let us take each of the above criticisms and see whether they are of any relevance to the pharmaceutical industry and to AIDS research in particular.

Consider first the "patents-are-ineffective" line. All empirical studies stress the economic importance of patents in the pharmaceutical industry. Corporate respondents to patent surveys judge them as more effective than any other appropriation tool at their disposal. This relative effectiveness stems from the ease with which pharmaceutical imitations can be detected: indeed, pharmaceutical research deals mainly with which compound to use against a given disease and how to use it, rather than how to produce that compound. Thus, once a chemical entity is discovered, a patent allows the innovator to have a market exclusivity on the new molecule and its therapeutic applications, regardless of the industrial process of production[1]. Copy-cat drugs or treatments, based on chemical compositions or molecules under patent protection, are therefore easy to detect. The intense lobbying by pharmaceutical firms to extend patents' geographical reach and duration is also a proof of the industry's commitment towards patent protection. Finally, the stock market value of biotechnology firms often increases when patents that are judged to be relevant for future developments are granted, while that of pharmaceutical firms routinely declines when their patents on blockbuster drugs expire [10].

Second, may patents deter inter-firm cooperation and slow down rival research projects? Economists are rather divided on this point. As Bessen and Maskin [11] point out, a firm that owns a patent may not be willing to license its innovation to a competitor as competition may significantly erode its innovation rent. The problem is compounded by what Heller and Eisenberg [12] term the "anti-commons tragedy": there are other already granted patents that will be needed to do research in the patented area, and the negotiation and transaction costs might deter any potential licensee. Hence, several economists

1. An innovator can patent different production methods to obtain the molecule and benefit from patent protection on the different therapeutic applications, if these are claimed in the original patent application (molecule).

have stressed that antitrust provisions regarding inter-firm cooperation and patent pools might have to be relaxed in order to diminish obstacles to patent licensing [13, 14].

On the other hand, however, the absence of patent protection can be an obstacle to cooperation: indeed, secrets remain hard to commercialise and the protection of intellectual assets reduces the risk of misappropriation by the partner. Empirical evidence tends to indicate that patents actually help firms to cooperate one with the other [15].

Consider for instance the patent issued to Human Genome Science (HGS) concerning the gene CCR5 (that controls how AIDS begins infecting its victim). This patent gives its owner a sweeping control over who gets to use the gene in commercial development of a new class of AIDS drugs. However, HGS plans to make the gene widely available to other drug companies in exchange for fees and future royalties (and to academic researchers at no cost). It should also be noted that the absence of patent protection might have prevented HGS from disclosing its knowledge altogether, thus incurring large R&D wastes as duplicative investment would have lingered on. Given the high cost of research and the relatively unpredictable results it could yield, patent-induced disclosure could be a great economic and social improvement over secrecy.

On the other hand, however, it was a Maryland university that found the AIDS-related chemical property of gene CCR5, after a broad patent had been granted to HGS for having discovered the gene itself (regardless of its use). Their research was in no way inspired by the HGS patent which was disclosed to the public only after the Maryland university found their results. Hence, the economic and technologic role played by the HGS patent has been very minor so far, and some argue that HGS did not deserve a patent so broad as to foreclose any research in this area. Yet, given that many a gene could turn out to have no function leading to marketable applications, HGS should reap a reward for its research on these "useless" genes too.

Now, take the "excessive R&D" argument. Pharmaceutical firms are often very secretive about their R&D investments on individual projects, so it is hard to evaluate whether they may be driven too high by the prospect of patent grants. Note though that Cockburn and Henderson [16] find no evidence of cross correlations in R&D project-level investments so that an increase in one's research investment has no impact on project competitors (contrary to the "excessive R&D" argument that predicts a positive relationship).

More generally, this type of argument may not be relevant for HIV/AIDS research. Indeed, patent race models usually assume that only one competitor

can win and be granted a patent. Yet, pharmaceutical patents rarely narrow the prospects of further patent on inventions (as the case of "me too drugs" patents tends to demonstrate). For instance, ten patented anti-retroviral drugs (ARVs) using nucleoside or nucleotide reverse-transcript inhibitors are currently available. Three non-nucleoside reverse transcripts inhibitors and six different protease inhibitors have also earned patent protection [17]. Further, each one of these drugs fights the HIV virus in a slightly different way. Since combining several different drugs yields more favourable results than using any single drug alone (HAART, highly active antiretroviral therapy for instance), and because genetic mutation enables the virus to develop into resistant strains, differentiated classes of drugs are particularly needed. The same logic applies to the research prospects in vaccines. The probable need for vaccines adapted to different strains – at least 11 genetic subtypes of HIV virus have been identified to date – will translate into a significant number of patenting opportunities.

Finally, innovation in public health matters is not only driven by patents. The public sector has been an irrefutably important element of pharmaceutical innovations [18][2]. As an illustration, around 70% of the drugs considered as having a therapeutic gain in the United States are produced with governmental support. Indeed, publicly funded research in that country has led to major drug discoveries for various diseases such as tuberculosis, cancer, and infectious illnesses. In the case of HIV/AIDS, publicly funded research has led to the discovery of an important number of therapeutic advances: AZT, 3TC, Saquinavir, Abacavir, Staduvine, Zerit™, Didanosine, Lamivudine, Nevirapine [21][3]. For instance, Didanosine [ddI] was originally synthesized by NIH scientists, and the United States holds the key use patent for ddI (Patent No. 4861759), which

2. In general, as confirmed by different studies, public sector involvement in pharmaceutical innovation has been more significant in determining private sector productivity than in any other industry (except defence) in the United States. Quantitative estimates suggest that the rate of return to publicly funded research (through different funding mechanisms such as tax-credits, subsidies, direct funding, cooperative R&D, etc.) as measured by its effect on the private sector, may be as high as 30% [19, 20].

3. D4T - one of the components of a dual therapy shown to slow the progression of the AIDS virus which Bristol-Myers Squibb (BMS) sells under the brand name Zerit™ - was synthesized by the Michigan Cancer Foundation in 1966 with the support of public funds. Its use to treat AIDS was discovered by Yale University, which holds a patent on D4T [21]. See also www.cptech.org/ip/health/aids/gov-role.html documents on Public Sector involvement on AIDS drugs.

has been exclusively licensed to Bristol-Myers Squibb (BMS) through the National Technical Information Service (NTIS)[4].

Thus, our discussion has highlighted four distinct points on whether and how patents can affect pharmaceutical research:

– patents are an important incentive to innovate in that industry;

– the insights developed by the theoretical literature on how strong patents can block pharmaceutical research disproportionately exceed the empirical evidence that has been gathered on that subject;

– it is very unlikely that stronger patent protection might result in excessive R&D investments in AIDS research for firms often pursue complementary rather than substitute objectives (as in the case for HAART);

– finally, the strong role of state intervention in this industry testifies that even in industrialised countries with strong patent systems, some sort of public support is needed to reconcile private incentives to innovate with social needs.

Developing countries'patent systems and innovation

In addition to the above arguments, the effectiveness of a pharmaceutical patent system for developing economies remains very uncertain too, for at least two reasons.

First, the incentive to innovate is mainly driven by those markets with a strong, creditworthy demand, and most developing countries are unlikely to fit in this group. Indeed, because of their low purchasing power, developing countries account for less than 20% of the global drug market, and Africa itself represents only 1.1% of the global sales of pharmaceuticals [23]. Thus, regardless of patent protection, these markets are unlikely to be of great importance in determining the level and direction of R&D spending. For instance, a recent study based on IMS data and the World Bank reports that countries with Gross Domestic Product (GDP) per capita lower than US$2500 together contributed less than one half of one percent to global spending on ARV drugs in 1999 [24]. Therefore, patent protection on antiretroviral drugs in developing countries should not greatly affect the research path for antiretroviral drugs primarily developed to be marketed in industrialised countries, even less so since

4. The recent case of the anti-retroviral AZT (Zidovudine) also illustrates the case of public involvement in HIV/AIDS treatments. Indeed, Zidovudine was initially synthesized through a National Cancer Institute (NIC) grant at the Michigan Cancer Foundation, and therefore several patent suits have challenged Glaxo, as NIH scientists claim they were the first to identify anti-HIV activity and clinical efficacy of AZT [22].

relatively strong patent laws in industrialised countries preceded the implementation of the TRIPS agreement in developing countries. Likewise, given the low level of South/North parallel imports, generics sold in developing countries should not affect prices in Northern markets, and neither should they reduce the incentives to innovate by pharmaceutical giants.

Second, many developing countries' local firms lack the technological capital to compete with industrialised companies, so that imitation does not represent a significant threat to the innovators' profits. Unsurprisingly, patent protection has been sought by pharmaceutical firms firstly in countries showing increasing imitative capabilities and some pharmaceutical expertise such as Chile, Turkey and Mexico (1991), Thailand, Taiwan, Romania, Russia and Ukraine (1992), and Brazil (1996).

Furthermore, as suggested by some recent studies by Harvard University and UNAIDS on the patent status of ARV drugs, patents are not systematically applied for in developing countries. Hence, very few patents for ARVs are reported in those African countries providing legal opportunities for patent protection, one exception being South Africa which has granted patents on most ARVs [25].

II
PATENTS AND THE RESEARCH AGAINST "LOCAL" DISEASES

Some diseases that were eradicated from industrialised countries decades ago still plague southern countries: according to the World Health Organization, 100% of the cases of malaria and tetanus and 99.9% of the cases of polio, syphilis and leprosy are found in low income countries. Besides, some diseases are common to industrialized and developing countries but present region-specific traits. Hence, the AIDS virus affecting the USA and Europe is not of the same type as that affecting South America and Africa. Finally, treating one particular disease in a given country may need existing treatments to be adapted to local conditions (for climatic reasons, for instance). What role may developing countries' patent systems play in this context?

Patents and innovation on tropical diseases

Relative to their effects on R&D for global diseases, patents might stimulate a stronger additional investment on diseases for which incentives are currently

weak, such as those specific to poor countries [26]. If the regional strains of HIV/AIDS affecting poor countries can be considered as tropical diseases, and consequently as neglected diseases, a strengthening of patent protection might potentially lead to increased R&D investment in this area.

Lanjouw and Cockburn [27] explored how R&D investment on neglected diseases evolved during the years surrounding the conclusion of bilateral and multilateral agreements on intellectual property rights. With much effort, a 10 to 15% increase in the number of patents on neglected diseases is discernible between 1985 and 1990, *i.e.* those years which correspond to the beginning of international efforts to ensure a better enforcement of patents in developing countries. Yet, the number of granted patents on tropical diseases remains very marginal (0.5% of the pharmaceutical patents). According to the US National Institutes of Health, a similar trend is observed for scientific articles related to tropical diseases (they represent 1.5% of the total) and for public funding (2% of which was devoted to research on tropical diseases in 1985 against 3.7% in 1995). Along with patents, other dimensions of profit incentives remain prime movers of R&D investment. For instance, there are more patents and scientific articles for those diseases likely to affect the third world upper class (like malaria and unlike leprosy).

One proposed interpretation of these trends is that the building-up of international (mainly American) efforts to promote patents in the third world encouraged more "tropical" research towards the end of the 80s, while the levelling-off corresponds to the period when opposition against patent laws began mounting. In any case, given that these reforms remain highly reversible, pharmaceutical firms are probably not too keen to invest in research areas where property rights and profitability remain so uncertain. At the other extreme, the slight increase in research output at the end of the eighties may rather be due to a small burst of technological opportunities in this scientific area, making research less costly and/or more productive. At the same time, it is worth noting that Indian pharmaceutical firms have also turned out to be more innovative, as the proportion of their patents (over all Indian patents) in Europe and in the USA increased from 15 to 25% between 1980 and 1998.

In any case, even though patent laws may influence research on tropical diseases, investment will not take off if the market demand remains uncreditworthy. One estimation puts the number of new "tropical compounds" developed between 1975 and 1997 at 13 out of a total of approximately 1400. In other

words, less than 1% of the total pharmaceutical innovations (new chemical entities) reported in the last twenty years represent new medical solutions for tropical diseases. For instance, less than 0.2% of world pharmaceutical investment is spent on diarrhoea, pneumonia and tuberculosis [28]. Moreover, while 50% of global health R&D in 1992 was undertaken by private industry, less than 5% of that was spent on diseases considered specific to less developed countries [29]. Likewise, a recent paper by Trouiller *et al.* [30] concludes that only 16 of the 1393 new chemical entities marketed between 1975 and 1999 in the United States and Europe targeted tropical diseases and tuberculosis; all were developed with public-sector involvement.

As far as AIDS is concerned, a disproportionate amount of investment is devoted to treatments as opposed to vaccine research, that if successful would offer an effective and cheaper tool for HIV prevention. But lack of investment in this area does not exclusively stem from the low levels of market incentives:

- searching for a treatment is less risky and less costly than pursuing future vaccines, which represents a scientific challenge and whose clinical tests are likely to be very costly too. Indeed, daunting scientific obstacles remain to date in HIV vaccine development: unknown correlates of immune protection, high variability and mutation of genetic clades, undemonstrated effectiveness in reducing transmission in large populations, etc. [31];

– for firms marketing drugs entering into HAART combinations, vaccine research falls prey to the "replacement effect" [32]. Indeed, treatments are more beneficial in terms of profits, given that they have to be administered for the whole life of a patient. The introduction of a vaccine may reduce this important flow of profits. Therefore, research against AIDS remains disproportionately focused on treatments (US$2 billion a year, against US$300 million on vaccines according to the World Bank);

– as stated by industry representatives, the threats of compulsory licensing (article 31 of the TRIPS agreement) and marginal-cost pricing following public debate on patents and access to ARV drugs, might lead to a reduced commitment to further private overall investment in R&D that would affect the discovery of both new drugs and vaccines for HIV/AIDS.

Figures in the pipeline of clinical stages of vaccines for sub-clades A, C, D, E, etc. also suggest a polarized strategy by private firms. First, investment in vaccine development remains still far from that in HIV/AIDS treatments. Second, research is concentrated on the B sub-clade, the one prevalent in

rich countries. Indeed, among the 60 phase I/II trials conducted since 1987, approximately 30 concern different HIV candidate vaccines for the sub-clade B in the United States and Europe.

Nonetheless, private and public research strategies are beginning to target the local needs of developing countries. Two clinical trials currently conducted in Thailand (and in the United States) target those clades affecting the local population. A first candidate vaccine against HIV (a gp120 product from VaxGen) has entered phase III efficacy evaluation and uses clades B/E depending on the transmission mode of the virus[5]. Even if most of the clinical testing against non-B strains done so far primarily targets strains of the virus that affect middle-income countries such as Brazil and Thailand, phase I and II trials are currently being implemented in Africa [33][6]. These are based on the so-called "canary pox", which is one of the first candidate HIV vaccines that has induced cross-clade functional CTL (cytotoxic T lymphocytes) responses. This testing should determine the extent to which Ugandan volunteers have CTL active against the subtypes of HIV prevalent in the region, sub-types A and D. It will also explore immunogenicity across clades, or subtypes, of HIV, thus answering questions about the possibility of designing a global vaccine[7]. Likewise, the above-mentioned Thai clinical trials are expected to be soon extended to Africa and tests on a hybrid vaccine candidate for sub-clades A/G conceived by the United States should be initiated in Côte d'Ivoire. These clinical experiments may indicate that vaccine development on traditionally neglected sub-clades is now increasing, thanks to stronger public-financing. Indeed, budgetary constraints have often prevented local governments from supporting clinical testing for regional clades. The lack of medical infrastructure in much of the less developed economies remains an important obstacle to the implementation of clinical trials there.

5. Testing began in Thailand in 1999 and involved 2,500 recovering injected drug users (IDU) in Bangkok. The interim efficacy analysis of the US and Thai trials is still underway. There are plans to initiate a second phase III trial in several countries, including Thailand, the Caribbean and South American countries, using a prime-boost strategy including two different subtype B products: a canarypox-HIV recombinant vector (Aventis Pasteur) followed by gp120 (VaxGen).

6. Aventis Pasteur in collaboration with WRAIR has initiated trials on clades E; phase I/II trials are under way in Thailand in combination with protein boosts [33].

7. This vaccine research strategy parallels that of the Agence Nationale de Recherches sur le Sida (ANRS) in France (lipopeptide program) in partnership with Aventis-Pasteur. Again, this program attempts to circumvent the problem of clades diversity by inducing cross-clade functional CTL responses.

How to strengthen incentives in AIDS research?

It seems clear that strengthening the developing countries' patent system is not, by itself, sufficient to accelerate AIDS research and development, as the number of vaccine candidates currently in the pipeline may suggest for instance. The main barriers are the non-profitability of these markets, the limited information concerning the exact market demand, as well as strong uncertainty about the appropriation of innovations ("the time inconsistency problem"; [34, 35]). In the case of vaccines, extremely high uncertainty about the best research avenues to explore among the scientific community, even for the development of vaccines on strain B, accentuates the reluctance of the private sector to invest in this domain. Since patents in poor countries are not sufficient to build the required investment, implementation of complementary incentives and funding are necessary.

Policy options to encourage R&D efforts can take different forms [36, 37]. Incentives to innovate can be enhanced from the supply side ("push" policy), and from the demand side ("pull" policy):

– push mechanisms such as subsidies for research input, R&D tax credits or grants to researchers, aim to reduce the costs of investment by providing direct funding for research. Other push instruments may focus on facilitating regulatory processes for the new pharmaceuticals (such as the fast regulatory approval of ARVs) [18]. Nevertheless, the effectiveness of these instruments to spur HIV/AIDS research for poor countries would be limited since market failure is not explained by the costs or the supply of R&D *per-se*;

– programs to increase investment must therefore seek to build market prospects in these research fields. By improving the likelihood of a return on investments, pull incentives reward the actual output of R&D efforts, such as vaccine development for HIV strains in poor countries.

Pull programs such as purchase pre-commitment may constitute a good alternative because of their attractive features over the traditional push-type incentive [34, 35]. Indeed, a pull system avoids the traditional moral hazard and information asymmetry problems that plague the push. To the extent that researchers overestimate the probabilities of discovering, and since monitoring of R&D efforts is difficult to implement, subsidies suffer from not delineating innovation outcomes. By rewarding actual outputs of R&D, pull instruments stimulate researchers to self-select the most promising projects, and therefore

to focus more precisely on developing marketable innovations (rather than other goals such as scientific publications, etc.). On the other hand, the diffusion of innovations will be ensured as the purchasing agencies should distribute the treatments/vaccines across affected countries.

Nonetheless, such an approach does present some shortcomings. In particular, sponsors are likely to downplay the value of the new treatments in order to favour a better deal. In order to reduce uncertainty, and therefore achieve a higher return on investments, private firms need clear and transparent rules concerning the property rights to prevail on innovations as well as the rules governing their exploitation. Patents could thus serve as a property right mechanism ensuring firms that they could still revert to a monopoly-based pricing strategy in the case of governmental proposals being judged unfair. Thus, patents can enhance the creditworthiness of purchasing mechanisms and ensure a better reward for innovators without imposing heavy deadweight losses on the patients.

Thus, patents have not been discarded from recent regulatory proposals. Some of these suggest, for instance, that international funding organizations should seek to acquire a patent-pool on essential medicines, which would then be put in the public domain under an international drug procurement policy [38,2]. This fund could be managed by UN agencies and payments to patent holders would be in the form of a fixed yearly lump-sum transfer that would guarantee innovators a net present value roughly equal to R&D costs and positively related to the social value of the innovation and the global share of patients in the licensed areas.

More specifically, Kremer [39] suggests that a patent buy-out program might be implemented through an auction system to determine the private value of patents and the sums that should be paid by the government. Finally, Lanjouw [24] argues for the international recognition of a discriminatory patent protection, depending on whether the drug targets global or neglected diseases.

Conclusion

There is hardly any doubt that patents are needed to promote pharmaceutical innovations and, although some concerns have recently been raised about whether strong patents might block pharmaceutical research rather than enhance it, they have so far proved to be very effective in industrialised countries. The dire state of pharmaceutical research on AIDS treatments and vaccines for developing countries might support the argument that these economies lack an effective,

well-enforced and credible patent system that could direct pharmaceutical firms'research towards their needs.

However, there are several reasons why reforms aimed at strengthening patent protection may turn out to be rather ineffective at promoting research into AIDS. First, regardless of patent protection, developing countries represent a minor market since low average income makes the strong potential demand largely unsolvable. Secondly, in many developing countries, there is no capability of developing copies of patented medicines, therefore strengthening patent laws would not have a great impact on the innovator's profit. Thirdly, in accordance with these two arguments, there is no convincing evidence so far that the TRIPS agreement has led to an increase in R&D investment in tropical disease. Fourthly, there are at least two other reasons than property right why vaccines remain under-developed in the case of AIDS: they are technically more costly and challenging, and the profits associated with them remain low compared to the revenues raised through the daily AIDS treatments.

We finally argue that patents can find a positive role in strengthening the creditworthiness of purchasing funds into which governmental organisations would pay in exchange for a license for the patented drug or vaccine. While treatments and vaccines would be sold to patients at low marginal cost price, the incentive to innovate relies on the pledge of the government to buy such drugs at pre-negotiated prices. In this context, patents would greatly reduce the risk of opportunism by governments and be a spur to innovation: indeed, knowing that they would retain the property of their inventions, pharmaceutical firms would be more willing to invest in HIV/AIDS research.

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Decrease in Prices of Antiretroviral Drugs for Developing Countries: from Political "Philanthropy" to Regulated Markets?

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Key words: HAART; drug prices; econometric analysis; generics; market competition.

Abstract

This paper gives some economic background about recent debates on the feasibility of introducing a "differential pricing" for HIV/AIDS drugs in favour of developing countries. It presents the methodology and the main results of research carried out for the ANRS ETAPSUD programme on determinants of source prices of antiretroviral (ARV) drugs in Brazil and 13 African countries (see page 207) during the period 1998-2002. Analysis of 1,030 observed transactions reveals a declining price trend for antiretroviral (ARV) drugs which is nearly linear between 1997-2000, with an accelerated decrease for the year 2001, followed by a more limited decrease in 2002. This trend corresponds to a significant reduction in price differences between brand drugs and generic substitutes and between countries. It also shows a relationship between higher volumes per transaction and lower prices that has, however, tended to diminish in the last few years.

Econometric analysis, using multiple linear regression, shows that the following factors were associated with price increases: ARV drugs belonging to the more recent classes, such as protease inhibitors (PIs), existence of patent protection for the drug at country level, higher HIV prevalence, national guidelines recommending PI drugs for first-intention treatment, and intervention of intermediary wholesalers in the transaction. On the other hand, transactions in

countries with organised public programmes for ARV delivery and in countries which participated in the Accelerated Access Initiative (AAI), the partnership that was launched in 2001 between UN organisations and six brand-name major pharmaceutical companies, were associated with lower prices. However, even after adjustment for these factors, the introduction of generic competition remains an essential factor for price decreases. Indeed, while countries like Brazil, Nigeria and Malawi have always carried out competitive negotiations with multiple suppliers including generic manufacturers, most African countries in our sample have evolved toward a "hybrid" mechanism of procurement that combines negotiations in the AAI international framework with national tenders or other procurement mechanisms introducing generic competition.

The main policy recommendation that emerges from the study is that excessive reliance on "corporate philanthropy" and international bargaining between UN organisations and the major brand-name manufacturers will not guarantee the long term sustainability of the lower differential pricing of ARV drugs that has de facto been established in some African countries since the year 2001, and its extension to a greater number of countries and to a greater number of drugs that are needed, in addition to ARVs, for HIV-infected patients. The buyer-size effect, that could be obtained through globalisation of purchases of HIV/AIDS drugs between several countries, will only translate into price decreases to the extent that buyers have the power to substitute between multiple suppliers. To achieve the recommendation recently adopted by the Global Fund to Fight AIDS, Tuberculosis and Malaria that countries should purchase quality-controlled HIV/AIDS drugs at the minimum cost, decentralised negotiations, extended market competition to all potential drug suppliers, and regulatory flexibility (in international agreements, and in national legislation) towards local production and imports of generic drugs are essential.

Résumé

Après avoir synthétisé la littérature économique récente sur la faisabilité d'un mécanisme de « prix différentiel » pour les médicaments du VIH/sida en faveur des pays en développement, ce chapitre présente la méthodologie et les principaux résultats d'une recherche conduite dans le cadre du programme ETAPSUD de l'ANRS sur les prix sources des antirétroviraux (ARVs) au Brésil et dans 13 pays africains dans la période 1998-2002. L'analyse de 1 030 transactions effectuées dans ces pays confirme la tendance à la baisse des prix des ARVs, qui s'est avérée quasi linéaire de 1997 à 2000 et s'est

accélérée fortement en 2001 pour se ralentir en 2002. Cette baisse s'est accompagnée d'une réduction de la variabilité des prix pour une même molécule entre pays, comme entre les médicaments de marque et leurs substituts génériques. Sur l'ensemble de la période, les prix sont d'autant plus bas que les quantités achetées par transaction sont élevées, quoique cette relation prix/quantités s'est estompée dans les deux dernières années.

Dans l'analyse économétrique multivariée, les facteurs suivants apparaissent reliés à une hausse des prix: le fait que le médicament appartienne à une classe thérapeutique plus récente comme les inhibiteurs de protéase (IPs) et que les recommandations cliniques officielles du pays recommandent ces molécules pour le traitement de première intention, le fait que la molécule soit protégée par un brevet dans le pays, une prévalence du VIH plus élevée, et l'intervention de grossistes comme intermédiaires dans la transaction. À l'inverse, l'existence de programmes publics organisés de distribution des ARVs, et la réalisation de la transaction dans le cadre du partenariat international introduit en 2001 entre six firmes pharmaceutiques et les Nations Unies (AAI – Accelerated Access Initiative), sont associées à des baisses de prix. Cependant, même après ajustement pour ces différents facteurs, l'introduction d'une concurrence générique demeure un facteur essentiel de la baisse des prix sur la période. Certains pays (Brésil, Malawi, Nigeria) ont d'emblée utilisé une stratégie de négociations avec les firmes productrices fondée sur des appels d'offres et sur la mise en concurrence avec les producteurs des médicaments génériques. La plupart des pays africains étudiés ont progressivement évolué vers une stratégie «hybride» qui associe une participation à l'initiative AAI pour bénéficier de tarifs préférentiels auprès des firmes de marque avec un recours croissant à la concurrence générique.

La principale recommandation qui ressort de cette recherche est que la pérennité à long terme du mécanisme de prix différentiel qui s'est instauré de fait pour les antirétroviraux dans certains pays africains, comme son extension à un plus grand nombre de pays et de médicaments nécessaires au traitement des patients infectés par le VIH, ne peut être garantie par le seul recours à la «philanthropie» (même politiquement intéressée) des principales firmes et à une négociation «fermée» entre celles-ci et les organisations internationales. De plus, l'obtention de baisses des prix par des achats groupés afin d'augmenter les quantités par transaction ne s'avère possible que dans la mesure où les acheteurs ont le pouvoir de substituer entre elles différentes sources d'approvisionnement. Une recommandation récente du Fonds Global de Lutte contre le Sida, la Tuberculose et la Malaria est d'inciter les pays à s'approvisionner

en médicaments du VIH/sida de qualité attestée et au moindre coût. La réalisation de cet objectif suppose la poursuite de négociations décentralisées, la mise en concurrence systématique entre producteurs et le maintien d'une souplesse réglementaire (au plan des accords internationaux comme des législations nationales) permettant la production et l'importation de médicaments génériques.

Introduction

In June 2001, the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS, the first session of the UN in history that has been totally devoted to the fight against a specific disease, unanimously adopted a Declaration of Commitment recognising the need for implementing "national strategies, supported by regional and international strategies […], to address factors affecting the provision of HIV-related drugs, including antiretroviral drugs"[1]. During 2002, significant progress was made in improving access of people living with HIV/AIDS in developing countries to antiretroviral treatment (ART). Following the recommendations of UNGASS, the Global Fund to Fight AIDS, Tuberculosis and Malaria became operational in January with initial pledges from donors of just over US$2 billion for 3 – 5 year programs, two thirds of these funds being planned for HIV/AIDS prevention and care activities[2]. In March and November, the Global Fund announced its first and second round of grants respectively committing US$616 million and an additional US$866 million over two years to enable 85 recipient countries to scale up national programs to fight these diseases, with about 60% of funds allocated to HIV/AIDS[3]. In March, eleven antiretroviral drugs (ARVs) were added to the World Health Organisation (WHO) list of essential medicines[4]. In April, WHO announced the first treatment guidelines for HIV/AIDS in

1. United Nations General Assembly Special Session on AIDS: *Declaration of Commitment on HIV/AIDS: global crisis-global action.* New York: June 27, 2001.

2. World Health Organization (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS) and United Nations Children's Fund (UNICEF). *Access to Quality HIV/AIDS Drugs and Diagnostics. Joint news release.* March 20, 2002. Available at: www.who.int/inf/en/pr-2002-19.htm

3. Total pledges to the Global Fund to Fight AIDS, Tuberculosis and Malaria amount to over US$3.2 billion. In 2001-2002, the Global Fund had pledges of US$944 million. For 2003, the Fund has pledges to date of US$647 million. Pledges and contributions as of February 6, 2003. Available at: www.globalfundatm.org

4. Global Fund to Fight AIDS Tuberculosis and Malaria. News release. January 31, 2003. Available at: www.globalfundatm.org

resource-poor settings, and added a twelfth ARV to this list[5]. The World Bank's Multi-Country AIDS Program (MAP) is expected to disburse around US$1 billion for Africa and US$155 million for the Caribbean over the next 3–5 years, and many supported projects explicitly include the provision of ARVs [1]. An analysis of the national HIV/AIDS plans of 90 developing countries conducted by WHO indicates that about 60% of these countries have now either incorporated ART into their national strategies to fight the epidemic or have defined specific ART coverage targets. Even governments which have been reluctant to involve the public health-care sector in the delivery of ARVs, as has been the case in South Africa, are revising their position and moving forward a more active policy concerning ART [2].

At both international and country levels, ambitious targets for scaling up access to ART in developing countries have been publicly set. In July 2002 at the XIVth International AIDS Conference in Barcelona, WHO and other UN organisations committed themselves to the goal of expanding access to ART to 3 million people in the developing world by 2005[6]. The Economic Community of West African States (ECOWAS) has committed itself to providing treatment access to 400,000 patients, representing at least one-third of the people in need of HIV treatment in the region, by the end of 2005[7]. At least five countries in Latin America and the Caribbean (Brazil, Costa Rica, Cuba, Mexico, Venezuela) are already implementing public policies for universal access to ART. Two others, Chile and Salvador, are actively preparing to do so.

However, practical accomplishments have, so far, remained modest. UN organisations estimate that 6 million people world-wide are in immediate need of ART, including 4 million in sub-Saharan Africa alone[8]. By contrast, ART was initiated for only an additional 70,000 patients during 2002, leading

5. World Health Organization: *Treatment guidelines and AIDS medicines list announced by WHO*. News release. April 22, 2002. Available at: www.who.int/mediacentre/releases/ release28 /en/ print.html

6. World Health Organization: *News release*. Barcelona, July 9, 2002. Available at: www.who.int/mediacentre/releases/who58/en/print.html

7. The Member States of ECOWAS are: Benin, Burkina Faso, Cape Verde, Côte d'Ivoire, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Mauritanie, Niger, Nigeria, Senegal, Sierra Leone and Togo. West African Health Organization. ECOWAS Initiative to Scale Up Access to HIV Treatment. Framework for Dialogue with Partners. Ouagadougou, November 2002.

8. World Health Organization (WHO): *International Action Plan on Scaling-Up Access to HIV Care. A Commitment to Universal Access and Action on HIV/AIDS Treatment*. Geneva: December 2002. Available at: www.who.int

to a maximum of 300,000 HIV-infected persons in developing countries currently receiving ARVs of any kind, nearly one half of them in Brazil alone[9]. According to the Global Fund, funding commitments made in 2002 will allow 490,000 HIV-infected patients to get access to treatment, a two-fold increase in the total number of individuals receiving ART in developing countries, and a six-fold increase in Africa [3].

A large gap obviously persists between the current level of funding for HIV care and treatment and the minimum needed to have an effective global impact against the pandemic. Recent estimates of the funding needs, which have taken into account the goal of increased access to ART, have been consistent in calling for an investment of US$8 billion –$10 billion per year to be provided jointly by the international community and national resources [4-6]. To respond to country proposals, the Global Fund alone has called for an additional US$6.3 billion in 2003 and 2004[10]. In January 2003, the US administration made promises to commit US$15 billion over five years – including nearly US$10 billion in new money – with the goal of providing ART to 2 million HIV-infected people in 14 of the most affected nations in Africa and the Caribbean[11]. The extent to which funding will be available for the scaling-up of ART in the next 3 – 5 years however remains a matter of uncertainty and still represents a major challenge for the international community.

When Highly Active Antiretroviral combination Therapies (HAART) were introduced in 1996, conventional wisdom held that it would remain financially beyond the reach of most HIV-infected patients in developing countries, the high price of these innovative drugs being the main obstacle to expanding access. Indeed, at current prices on the international drug market, whereas full coverage of medically eligible patients for HAART represents less than 0.1% of Gross Domestic Product (GDP) in high-income OECD countries, it would exhaust public health expenditures and account for a significant share of GDP in the 16 sub-Saharan countries where HIV prevalence is over 10% of

9. Ministry of Health of Brazil: *National Drug Policy*. Brasilia: February (2001).

10. Executive Director Richard Feachem at the opening of the 4th Board meeting of the Global Fund to Fight AIDS, Tuberculosis and Malaria. Geneva, January 29, 2003. Available at: www.globalfundatm.org

11. These 14 countries are: Botswana, Côte d'Ivoire, Ethiopia, Guyana, Haïti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda and Zambia. Available at: www.whitehouse.gov/news/releases/2003

the adult population [7]. As affordability of drugs is a fundamental starting point for increasing access to ART in low-resource settings, achieving lower prices for ARVs was, and remains, a prerequisite for scaling up HIV care programmes in developing countries. Between 1996 and 2002, there have been spectacular price decreases for ARV drugs in most developing countries, in some cases to 5%-20% of their price in developed countries. Such decreases, that could hardly have been expected five or six years ago, are the result of a complex process combining negotiations between the major pharmaceutical companies and the UN organisations as well as governments, intense controversies and international mobilisation of public opinion and Non-Governmental Organisations (NGOs), emerging competition of generic manufacturers and articulated strategies of some national governments of developing countries to guarantee supply of HIV/AIDS drugs at lower differential pricing.

The UN organisations initially gave the priority to a process of negotiation with the major pharmaceutical companies which own the patents of ARV drugs. This process of negotiations was mainly carried out at international level with limited margins for price bargaining at country level. In 1998, when the UNAIDS secretariat started the so-called Drug Access Initiative (DAI) to explore the feasibility of a "structured introduction of price-reduced ARV therapy in a range of developing countries", the recommended mechanism for procurement of ARV drugs was based on the introduction, in each country, of a private not-for-profit company (Medical Access) bringing together representatives of the five patent-holding pharmaceutical companies which internationally agreed to support this initiative[12]. In this initial phase, it was quite clear that the main rationale pursued by the UN organisations was to convince these multinational companies to adopt a "philanthropic" attitude towards the prices of ARV drugs in the developing countries most in need in exchange for the "political" gains that these companies could obtain from a close partnership with the UN system. In May 2000, five UN organisations[13] entered in a partnership offered by these same five pharmaceutical companies, joined later by a sixth one[14]. The stated goal of this new Accelerated Access Initiative (AAI) was to "make

12. UNAIDS. *Report of the meeting on the evaluation of the UNAIDS HIV Drug Access Initiative*. Geneva, May 30-31, 2000. Available at: www.unaids.org

13. These five organisations are the: United Nations Population Fund (UNFPA), United Nations Children's Fund (UNICEF), WHO, World Bank and UNAIDS Secretariat.

14. The five initial companies were Boehringer Ingelheim GmbH, Bristol-Myers Squibb, GlaxoSmithKline, F. Hoffmann-La Roche Ltd and Merck & Co. Inc while Abbott Laboratories Inc later joined.

HIV/AIDS drugs more affordable and accessible in developing countries" through a "preferential pricing" mechanism[15]. The AAI model was based on a priori international price negotiations that set a standard for procurement in all the countries that adhere to the Initiative. As of June 2002, the AAI has been "used as a framework for dialogue with pharmaceutical companies and has led to successful UN-brokered supply agreements for ARVs in 19 countries"[16]. In May 2002, two major regional groups of countries, ECOWAS and the Caribbean Community (CARICOM) coalesced to engage negotiations with these pharmaceutical companies through the AAI and a formal statement of intent was signed with fifteen Caribbean countries in July 2002. In parallel to the AAI, during 2001 and 2002, international manufacturers made selective offers of substantial discounts to governments and non-governmental organisations of the least-developed countries and sub-Saharan African countries [8][17].

Of course, the trend in price decrease of patented ARV-drugs in the context of the AAI cannot be separated from the numerous external events that have simultaneously occurred during the past three years. Pilot projects of the UNAIDS Drug Access Initiative itself, that were carried out in Côte d'Ivoire, Uganda, Chile and Vietnam, as well as community-based projects of ARV delivery supported by NGOs like *Médecins Sans Frontières* (MSF) [9], quickly highlighted how increased competition, including generic competition, could be a powerful mechanism to achieve the goal of decreasing prices in negotiations for drug procurement directly carried out at country level.

15. Accelerating Access Initiative. *Widening access to care and support for people living with HIV/AIDS*. Progress Report, June 2002. WHO/UNAIDS, 14th International AIDS Conference, Barcelona, July 2002.

16. The 19 countries are the following: Barbados, Benin, Burkina-Faso, Burundi, Cameroon, Chile, Republic of the Congo, Côte d'Ivoire, Gabon, Honduras, Jamaica, Mali, Morocco, Romania, Rwanda, Senegal, Trinidad and Tobago, Uganda and Ukraine. Although not formally mentioned as a member of the AAI, Botswana can be considered as having installed and developed its national ARV program in the AAI framework. Indeed, Botswana's strategy has even preceded the AAI with the establishment, as early as July 2000, of the Botswana Comprehensive HIV/AIDS Partnership, based on a joint collaboration with the Bill & Melinda Gates Foundation and Merck & Company, Inc. Procurement of ARV drugs for the country goes via this partnership and agreements with other drug companies such as Boehringer Ingelheim GmbH and Bristol-Myers Squibb have followed the AAI procedures.

17. During 2001, the US-based Bristol-Myers Squibb and Abbott Laboratories announced their aims to provide ARV drugs "below cost", with Merck offering their "at cost". In addition, UK-based GlaxoSmithKline, German-based Boehringer Ingelheim and Swiss-based F. Hoffmann-La Roche further reduced their prices and increased the provision of free ARVs for prevention of mother-to-child HIV transmission.

Between 1996 and 2000, prices of ARVs were lower in Côte d'Ivoire where the Public Health Pharmacy introduced a tendering mechanism open to all international suppliers, including generic producers, than in Uganda where procurement was restricted to Medical Access Uganda Ltd [10]. In 2001, soon after the Joint Clinical Research Centre in Kampala started using imported generic drugs, a 20% – 45% decrease in the cost of the most frequently prescribed combinations occurred in Uganda. Moreover, the significant impact of generic competition has been obvious in the case of locally produced ARVs in Brazil [11] and Thailand, and the 2001 offer by Indian generic manufacturers to provide some combination antiretroviral therapies at a price of around US$1 per day in developing countries attracted world-wide media attention. International mobilisation of public opinion in 2001 was also a key element in the price decrease process. It led the US government to retract the complaint it had made against Brazil at the World Trade Organization (WTO) for violation of its obligations under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the 1994 General Agreement on Tariffs and Trade (GATT) [12][18]. It forced the Pharmaceutical Manufacturers Association of South Africa, backed by 39 international drug companies, to drop their lawsuit against the newly introduced South-African legislation allowing the generic substitution of off-patent medicines (a policy already used in many developed countries to control drug expenditures) and the parallel importation of patented medicines [13]. Finally, in November 2001, it facilitated the adoption of the "Doha Declaration" which recognised that HIV/AIDS qualifies as a case of "national emergency" in developing countries and authorised the use of compulsory licensing allowing a third party to use a patent without the owner's consent under the current rules of WTO[19]. As persisting controversies on the practical interpretation of this Declaration have later shown, the extent to which developing countries will be allowed to import generic drugs produced through this mechanism of compulsory licensing in another country, as well as the precise international safeguards against the re-export of these

18. The US complaint was directed against Brazilian legislation, that came into force in 1997, establishing that in order to enjoy exclusive patent rights the holder of a patent on an invention must satisfy a "local working" requirement. In other words, the patent holder must "work" the patent in to enjoy full patent protection. If it fails to do this, the law says it shall be subject to the possibility of the government issuing a compulsory license, allowing someone else to use the invention and pay a royalty fee to the patent holder.

19. World Trade Organization (WTO): *The Doha Declaration on the TRIPS Agreement and Public Health.* Adopted by Ministerial Conference, Fourth Session, Doha, November 14, 2001.

drugs to developed countries[20], remain a matter of debate that has not yet been resolved by the TRIPS Council of the WTO.

According to some industry representatives, these developments and current price decreases have been sufficient to ensure that "drug price is off the table as an issue, thus transferring the focus in the battle against AIDS from lack of access to the drugs to poor infrastructure and ineffectual government measures" [14]. UNAIDS and the WHO also optimistically state that "as a result of the AAI and related efforts, with companies independently entering into discussions with countries and other purchasers, the prices of antiretroviral medicines have declined significantly in the past two years". It is however important for the future to make a clearer distinction between, on the one hand, the respective roles of the international "political bargaining" between the UN and other donor organisations and the "corporate philanthropy" of pharmaceutical companies eager to restore their image, and on the other hand the effective emergence of market mechanisms for HIV/AIDS drugs in developing countries. As suggested by the literature on other "emerging markets" [15-16], in order to secure long-term procurement of low-price ARV drugs in the low and middle-income countries that are the most severely hit by the epidemic, it is essential to establish efficient economic mechanisms of negotiation between buyers and suppliers that should be, at least partly, protected from "political volatility". A better understanding of the determinants of ARV price decreases in recent years is also essential to help define the most appropriate regulatory mechanisms at international and country levels for promoting "differential pricing" without jeopardising future progress in HIV therapies and its associated welfare gains [17][21].

In this chapter, we will first give some economic background about recent debates on drug prices. In the second section, we will focus on the methodology and results of research carried out for the ANRS ETAPSUD programme on determinants of source prices of ARV drugs in Brazil and 13 African countries.

20. Commission des Communautés Européennes. *Proposition de règlement du Conseil visant à éviter le détournement vers l'Union Européenne de certains médicaments essentiels.* 02557 ACCC, Bruxelles, 30 Octobre 2002.

21. WHO and WTO Secretariats: *Workshop on differential pricing and financing of essential medicines.* Norwegian Foreign Affairs Ministry, Global Health Council, April 8-11, 2001, Høsbjør, Norway. Geneva: World Health Organization, 2001. Available at: http://www.who.int/medicines/library/edm_general/who-wto-hosbjor/hosbjorexe-eng.pdf

In the last section, discussion of these preliminary results will serve as a basis for policy recommendations about HIV/AIDS drugs procurement strategies.

I
SOME BACKGROUND ON DRUG PRICES

Prices charged by pharmaceutical companies for patented drugs are commonly several orders of magnitude higher than their marginal cost (the cost of producing an additional unit of the drug). Low marginal costs explain why generic drug producers, provided that they do no have to pay royalties to patent holders, are able to offer substitutes to branded products at comparatively very cheap prices. Taking into account current production costs of generic suppliers and potential economies of scale, marginal costs of delivery of some triple drugs HAART combination can be expected to be lower than US$200 per patient/year. In a perfectly competitive market, in which consumers will automatically buy a substitute good if its price is lower, international drug prices would spontaneously tend to be based on such marginal cost.

Of course, in the case of innovative products like ARVs, private firms legitimately need to recover their high overhead costs for Research & Development (R&D) and for fulfilling the regulatory prerequisites of market approval in high income countries [18]. The pharmaceutical industry claims to have invested US$30·5 billion in R&D in 2001, which would make it the largest direct backer of medical research world-wide[22], and legitimately points to the time, risk, and costs associated with new drug development: on average, drugs take about 12 years to develop, and there is a high failure rate at the stage at which drugs enter clinical development. The most widely quoted estimate of the cost of bringing a new drug to market is that of US$500 million [19]. This figure was updated in 2000 to US$800 million [20]. A substantial proportion of the cost was the lost income that might have been earned had companies invested their assets rather than making drugs (the opportunity cost of the capital). Economic theory has long recognised that long term incentives for private risky investments in R&D of innovations are needed, and has extensively debated how guaranteeing the intellectual property rights

22. The Pharmaceutical Research and Manufacturers of America. Pharmaceutical industry profile 2001. Available at: http://www.phrma.org/publications/publications/profile01/

of the inventors, which, although it corresponds to the attribution of a "temporary monopoly power" to the patent owner, may correspond to such socially useful incentives [21]. Patents grant exclusive manufacturing rights for a period of 20 years from the date of filing for the patent. In practice, because of the time taken to get a new drug to the market, the monopoly selling power is usually around 12-14 years. Pharmaceutical companies rely heavily on patents and go to great lengths to maintain and extend them. The techniques they use are known as "evergreening" and include: introduction of new formulations (including fixed combinations), which are marketed heavily before the generic version of the drug is released; second-medical-use patents for products nearing the end of their basic patent life; repeated patent infringement suits, which trigger an automatic 24-30 month delay in processing the generic product in Canada and the USA; and collusion with generic manufacturers to keep products off the market [22].

In developed countries, competition from generic manufacturers who provide non-patented drugs has increased in recent years. In 1997, the top ten generic drug companies had world sales of around US$6 billion. Although the extent to which generic drugs are substituted for original branded drugs and their impact on prices vary widely from country to country and across therapeutic categories, generic suppliers have now a substantial effect on health-care delivery: their volume share (by countable units, *e.g.* tablets) of US prescription sales rose from 18.6% in 1984 to 44.3% in 1998 and is also above 40% in countries like Canada, Denmark, Germany or the UK [23]. Interestingly enough, generic competition in developed countries has not led average drug prices to fall but has rather provoked a "bifurcation of the market": while generics tend to enter the market at wholesale prices which are 40 to 70% of those prevailing before the original drug's patent expired and generic prices continue to decline through time, originators drug prices tend to increase following generic entry. This "generic paradox" is due to the dominant strategy of the branded drug suppliers which usually find it more profitable to serve a minority fraction of the market at high prices (the price-insensitive consumers willing to pay high prices for the security of a brand name) than to reduce their prices to the low levels required to match generic competition [24-27].

In any case, the current international market of branded ARV products remains characterised by imperfect competition: a limited number of firms (7) supplies a limited number of products (17); inside each of the three

classes of ARV drugs, nucleoside reverse transcriptase inhibitors (NRTIs), the oldest category, non nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), the number of suppliers is even smaller ($\leqslant 4$). In such oligopolistic markets, private firms are in a position to impose prices and rates of return that may capture an "excessive rent". An indirect indicator of such risk is that pharmaceutical companies tend to feature prominently in "antitrust" court actions in North America as well as the European Union[23]. Therefore, it is sometimes in the interest of society to associate patent rights with compulsory licensing obligations in order to guarantee an efficient public disclosure of innovative knowledge [28]. As already mentioned, existing WTO rules such as article 6 of TRIPS permit compulsory licensing[24].

In the context of imperfect competition, information asymmetries between suppliers and buyers are likely to be exacerbated [29]: in such markets, private firms have a priori no incentive to disclose information on their real production costs or on the lowest sales prices that they would rationally be ready to accept. Indeed, some of the evidence previously mentioned about the presumably high costs of R & D has to be balanced by taking into account additional factors. During the early 1980s in the US, 43% of "failures" in drug development were for "economic reasons" of limited expected profitability, compared with 31% for efficacy issues and 21% for safety problems [30]. Development time is shorter for some classes of drugs, for example, the first 14 ARVs took an average of only 4.4 years from the date of filing of key patents to approval by the US Food and Drug Administration [31]. Published estimations of high R&D costs often do not reflect the contributions made by public research institutions[25] and by tax credits from doing R&D, which can reduce totals costs by between 16% and 39%, or savings made by licensing drugs from other organisations. Alternative estimates of drug development costs have therefore sometimes been lower than the US$500-800million endorsed by the industry, between US$115 and $240 million including

23. US Department of Justice. *Four foreign executives of leading European vitamin firms agree to plead guilty to participating in international vitamin cartel*. Available at: http://www.usdoj.gov/opa/pr/2000/April/179at.htm

24. Correa C.: *Integrating Public Health Concerns into Patent Legislation in Developing Countries.* Geneva: South Centre, 2000.

25. A study of 21 drugs introduced in the USA between 1965 and 1992, and considered to have had the highest therapeutic effect on society, found that public funding of research was instrumental in the development of 15 of them.

adjustment for failures, according to a 1993 study of the Office of Technology Assessment of the US Congress[26].

Economic theory also emphasizes the fact that firms in a monopoly (or oligopoly) position can rationally practice price discrimination, *i.e.* they offer different prices for the same product according to the characteristics of each segment of the demand on markets. It would be rational for the firm to offer the highest prices to customers with the lowest price elasticity of demand (and the highest willingness to pay for the product) and vice versa. Price discrimination between markets in different countries and between various sectors in the same national market (especially for different therapeutic indications of the same drug) is a common practice. It sometimes translates into global price increase as was recently the case for pentamidine, a treatment for trypanosomiasis which used to cost $10 per course of treatment until it found a "new" market in the treatment of infections prevalent in AIDS patients making the price soar to US$300 [32]. Price discrimination explains why various "intermediary" agents may interfere with the process of retail price determination and share some fraction of the "rent" with the firm exercising monopoly power: a process that partly explains the sometimes huge differences between source and retail prices of drugs in developing countries. Because price discrimination for HIV/AIDS drugs between developed and developing countries is not per se an economic anomaly, it can be argued that differential pricing based on some measure of national wealth or "ability to pay" can be used as a regulatory tool for promoting access to low-cost ARV drugs in the developing countries most in need. It can even be argued that, to the extent that parallel imports of low-cost drugs to developed countries remain under control, the increased volume of drug sales that would be promoted by unit price decreases in developing countries with high HIV prevalence can contribute to the profitability of the drug industry at an international level.

In general, informed consumers (in the sense of consumers who have the most exhaustive information about available prices) produce a "positive externality" in favour of less informed consumers because they contribute to increased competitive pressure on suppliers which creates an incentive for firms to decrease prices and to improve quality of products. Logically, this

26. Office of Technology Assessment: *Pharmaceutical R&D: costs, risks and rewards.* Washington: US Government Printing Office, 1993.

leads to a positive impact of improved dissemination of price information on the collective efficiency of the market mechanism [33]. Theoretical as well as empirical research has already shown that "uninformed" consumers will tend to pay higher prices and that an increase in the proportion of such uninformed consumers favours an increase of the average price level, which also negatively affects better-informed consumers (the latter will ultimately obtain higher prices than those that would have been reached at equilibrium in the absence of uninformed consumers) [34-35]. Economic evidence clearly suggests that appropriate information would never be spontaneously revealed by market mechanisms characterised by imperfect competition. It strongly supports the usefulness for buyers to benefit from a mechanism of systematic information about drug prices and transactions on the different national markets. This kind of information can be considered as a "global public good" whose availability would increase public welfare in the different countries.

However, it should be recognised that the impact of increased price information may not always lead to price decreases. For instance, when consumers a priori discriminate between products belonging to a similar class of goods (for example, by exhibiting an a priori preference for brand rather than generic products), diffusion of information may paradoxically translate into price increase. In such a case, informed consumers may reveal their preferences by giving priority for seeking transactions concerning their a priori preferred products, and by stopping their market search as soon as they find a price below their maximum willingness to pay; this behaviour will render firms' demands more inelastic (informed consumers will not check out another firm's product if the preferred firm's price exceeds the anticipated price by less than the search cost) and will contribute to price increase at equilibrium [36]. It explains why perceptions of product characteristics may strongly influence the outcome of competition between brand-named and generic drugs [37], and how misperception of respective qualities may bias the emergence of market mechanisms [38-39]. It shows that, in the case of HIV/AIDS drugs any public effort to improve information on prices should be combined with quality control mechanisms in order to avoid undesirable effects on prices related to a priori consumer preferences which do not adequately reflect effective differences in quality of products. In 2002, WHO has therefore made an important contribution by publishing the first results of its new initiative to promote internationally guaranteed quality control for HIV-related

medicines on a voluntary basis by branded and generic manufacturers[27]. Compliance with quality standards set by this international initiative will automatically guarantee the eligibility of the product for purchase with Global Fund resources[28].

II
DETERMINANTS OF SOURCE PRICES FOR ARV DRUGS IN 13 AFRICAN COUNTRIES AND BRAZIL: AN ECONOMETRIC ANALYSIS

Debates about scaling up access to HIV/AIDS drugs have accelerated international efforts to collect and exchange information about prices of drugs in developing countries. These efforts were elaborated with quite different objectives, and collect data at various levels of the drug procurement and delivery channels in the countries.

The joint UNICEF/UNAIDS/WHO/MSF project on Sources and Prices of selected drugs and diagnostics for people living with HIV/AIDS is considered as a reference database for indicative manufacturers'prices for ARVs, drugs used for the treatment of HIV-related opportunistic infections, and for diagnostic tests[29]. This database contains a list of manufacturers who have the capacity to supply quality drugs at these indicative prices. The information system implemented by MSF called "Access to Essential Drugs Campaign" with the objective to improve access to equitable drug prices, is a database of lowest source prices obtained, by either public institutions or NGOs, within different countries, from manufacturers of brand or generic drugs[30]. It includes the patent status of the molecule in the country. The AFRO-Essential Drug Price Indicator project is an initiative focused on African countries, and constitutes an original example of south/south cooperation with an operational

27. World Health Organization: *Initiative to promote access to quality HIV medicines releases first batch of results today*. News release. March 20, 2002, Geneva. Available at: www.who.org The Global Fund will also allow purchases of products that "have been authorized by the national regulatory authority in the Recipient's country".

28. The Global Fund will also allow purchases of products that "have been authorized by the national regulatory authority in the Recipient's country".

29. UNAIDS/UNICEF/WHO-EDM: *Sources and prices of selected drugs and diagnostics for people living with HIV/AIDS*. Geneva: February 2000.30. Pérez-Casas C. (Ed.). *Accessing ARVs: untangling the web of price reductions for developing countries*. October 2001. MSF Access to Essential Medicines Campaign. Available at: www.accessmed-msf.org

institutional framework already approved by the 24 member states[31]. All these data bases offer operational information on indicative prices of HIV/AIDS drugs and are helpful tools for buyers at country level.

However, information available in these data bases is not fully appropriate for econometric analysis aimed at explaining the dynamic of HIV/AIDS drugs source prices on the markets: the recorded prices are indicative (mean price, minimum price), and rarely reflect the actual purchase price of the drug, or the effective conditions of transaction; price information is rarely associated with the quantity procured and is mainly collected from firms rather than at country level. For these methodological reasons, the ANRS ETAPSUD programme has supported a research project based on retrospective observation of effective transactions dealing with HIV/AIDS drugs in African countries between 1996 and 2002. The project was carried out in close collaboration with the Brazilian National AIDS Programme which gave the opportunity to compare African data with the Brazilian experience of universal coverage of HIV-infected patients for ART. The research goal of the project was focused on analysing the major determinants of inter-country and inter-temporal variations of prices of HIV/AIDS drugs (although in this chapter, we will only focus on ARVs). An associated operational goal was to contribute to the definition of the most appropriate format for establishing inter-country prospective observatories of HIV/AIDS drugs with the goal of optimising the process of procurement.

Data collection

In 2002, visits were carried out in 13 Sub-Saharan African countries to collect retrospective data describing the real transactions for procurement of ARVs that occurred in each country between 1996 and 2002. For each transaction, in each country, a standardised questionnaire was filled out with the help of representatives of the institution which was in charge of buying the drugs (either public pharmacies or Ministries of Health, private wholesalers, or private-not-for profit NGOs). All recorded prices were source prices, in US dollars at time of the transaction, when entering the country and were standardised using Cost-Insurance and Freight (CIF) prices that include the added costs of freight, insurance, import duties or taxes. Detailed data about each transaction

31. WHO/AFRO/EDP: *AFRO Essential Drugs Price Indicator*. Geneva: December 2000.

included the price, quantities, dosage pharmaceutical form and packaging of each individual drug as well as the supplying firm (which makes it possible to distinguish between brand and generic drugs). It also included precise characteristics of the buying institution and of the process of negotiation associated with the transaction: whether it was carried out through a tender mechanism (either "restricted" to some manufacturers or "open" to all international potential suppliers) or through bilateral mutual agreement with manufacturers (either supported by the AAI or not), and whether it was associated or not with donations of additional quantities from the manufacturer. Data about patent protection for each drug, in each country, were based on available information from the literature that relied on inquiries to the intellectual property divisions of major pharmaceutical companies [40].

In addition, interviews were carried out with representatives of National AIDS programmes and/or Ministries of Health, as well as representatives of international donor agencies to collect data about the institutional, economic and epidemiological context of procurement, including whether or not national guidelines and recommendations for use of ARVs existed and had been disseminated in the country as well as information about the national drug patent system and the regulatory procedures for drug market approval. Basic socio-economic indicators, such as the size of the population, GDP and heath expenditures per capita, percentage of GDP devoted to public expenditures for health and number of physicians per 100,000 inhabitants, as well as estimations of HIV seroprevalence in the adult population were obtained through UNAIDS, UNDP and World Bank data bases.

The 13 countries visited in Africa were quite different in size (varying from a population of less than 3 million in Botswana, Congo and Gabon to more than 100 million in Nigeria) and in prevalence of HIV infection in the adult population (from less than 2% in Mali and Senegal to more than 10% in Botswana, Cameroon and Malawi). Six of them (Benin, Burkina-Faso, Burundi, Malawi, Mali and Togo) are currently designated as one of the 49 least-developed countries while an additional five (Cameroon, Republic of the Congo, Côte d'Ivoire, Kenya and Nigeria) rank among the World Bank's low-income countries (GNP per capita < US$745). Only Botswana and Gabon are classified as middle-income countries. The percentage of government budget spent on health care is however low in all 13 countries always ranging under 5%.

For Brazil, we had access to the exhaustive data base on HIV/AIDS drugs procurement of the Brazilian STD/AIDS Program which allowed us to obtain

similar standardised data about transactions carried out in this country between 1998 and 2002. In addition to immediate availability of data, the choice of Brazil was obviously justified by the fact that it is the only developing country to date which has been able to successfully implement a public policy for universal ART coverage for medically eligible HIV-infected patients.

Statistical analysis

Evolution of drug prices per country and per year was described using price per unit. Prices per daily dose were also computed by multiplying the unit price by the number of units required for standard adult dosage[32]. The logarithm[33] of the price per daily dose was used as the dependent variable to conduct multiple linear regressions with characteristics of products and characteristics of the transaction (including year of transaction introduced as a dummy variable) and variables describing its context being the explanatory variables. This kind of econometric models, as applied to drug prices [41], basically consists of ordinary least squares (OLS) regressions where the observed price is the dependent variable and the different characteristics of the transaction the explanatory variables. Such regressions allow us to determine (statistical) relationships between prices and quantities but also to test the effects of additional characteristics on prices.

III
RESULTS

Emerging markets of ARV drugs in Africa

Table 1 shows that we were able to collect data about a total of 1030 transactions for ARV drugs in the 14 countries, with Brazil and Côte d'Ivoire being the two countries with the highest number of observations. Not surprisingly, Brazil accounts for the majority of total quantities purchased (respectively 94.3% of NRTIs, 91.0% of NNRTIs, 98.6% for PIs and 95.6% for multiple combination drugs).

32. Definition of daily doses (number of tablets, volumes for oral solutions or syrups) were based on adult posology defined in Dorosz Ph.: *Guide pratique des médicaments*. Paris: Éditions Maloine, 23e éd., 2003.

33. Since observed prices are always positive, one must use the logarithm of prices to avoid problems due to the left censoring of the dependent variable.

Although not exhaustive, data in Table 1 remind us of a trivial but major fact. At the end of 2002, not only was access to ART in African countries still totally inadequate in relation to estimated needs, ARV delivery had not even reached a sufficient level to start having a significant impact on public health. According to the countries'official estimations, only one out of the thirteen African countries in our sample (Nigeria) could already claim some large scale clinical experience with more than 10,000 ART-treated patients. To our knowledge, the only two other African countries, that were not included in our sample, with a similar level of experience with ART are South Africa and Uganda. In some other countries (Botswana, Cameroon, Côte d'Ivoire), experimental public programmes dealing with 2 to 3,000 ART-treated patients, already existed in 2002 and a similar figure had been reached in Kenya in the absence of any direct public involvement. All other countries studied had only pilot projects at early stages with less than 1,000 patients treated, although some of them, like Benin and Burundi, had already accumulated systematic experience of HIV/AIDS care including ART.

Table 1: Observed transactions for ARVs in 14 developing countries 1997-2002 (ANRS ETAPSUD-INSERM U379 project)

Country (purchase period)	*Number of transactions* *Total number of purchased daily doses* *% of generic drugs in total purchase of daily doses*				*Total Nb of transactions*
	NRTI	*NNRTI*	*PI or association of 2 PI*	*Multiple combination drug**	
Benin (2000-2001)	**17** 62,250 *0%*	**1** 6,000 *0%*	**7** 12,314 *0%*	**2** 1,050 *0%*	**27**
Botswana (2001-2002)	**47** 216,445 *0%*	**3** 42,165 *0%*	**2** 30,645 *0%*	**4** 198,000 *0%*	**56**
Brazil (1998-2002)	**137** 168,611,573 *93.5%*	**40** 40,119,845 *35.6%*	**39** 69,728,934 *21.9%*	**18** 47,891,340 *76.2%*	**222**
Burkina Faso (1999-2000)	**42** 364,459 *0%*	**5** 145,620 0%	**11** 81,060 *0%*	**8** 176,850 *0%*	**66**
Burundi (1999-2002)	**21** 293,540 23.8%	**6** 59,400 54.5%	**1** 18,000 0%	**5** 70,500 72.3%	**33**
Cameroon (2000-2002)	**34** 418,265 *20.9%*	**14** 235,564 *13.1%*	**12** 73,347 *0%*	**19** 597,420 *100%*	**79**
Congo (Rep) (2001-2002)	**13** 59,156 *0%*	**7** 31,668 *0%*	**3** 16,500 *0%*	**3** 2,400 *0%*	**26**

Côte d'Ivoire	**132**	**9**	**41**	**13**	**195**
(1996-2002)	2,391,456	372,780	619,130	750,480	
	10.2%	*0%*	*0%*	*0%*	
Gabon	**21**	**4**	**2**	**5**	**32**
(2001-2002)	190,202	39,720	45,120	64,800	
	0%	*0%*	*0%*	*0%*	
Kenya	**113**	**25**	**31**	**23**	**192**
(1997-2002)	86,770	37,104	10,200	33,540	
	21.2%	*0%*	*0%*	*0%*	
Malawi	**2**	**0**	**0**	**9**	**11**
(2000-2002)	32,933	0	0	127,800	
	0%			*92.0%*	
Mali	**32**	**6**	**6**	**2**	**46**
(2001-2002)	98,198	23,453	26,190	16,500	
	21.1%	*24.3%*	*0%*	*0%*	
Nigeria	**7**	**3**	**0**	**1**	**11**
(2001-2002)	5,927,040	2,981,520	0	115,200	
	100%	*100%*		*100%*	
Togo	**19**	**0**	**10**	**5**	**34**
(1997-2002)	67,778	0	35,280	55,256	
	0%		*0%*	*21.7%*	
Total	**637**	**111**	**165**	**117**	**1,030**
	178,820,064	44,094,839	70,696,720	50,114,640	
	91.7%	39.3%	21.6%	74.6%	

* Multiple combination drug corresponds to association of 2 NRTIs (Combivir™ or generic equivalent) or 2 NRTI + 1 NNRTI (Triomune™) or 3 NRTI (Trizivir™).
The term generic here includes real generic drugs and also "copies" which may not have established bioequivalence testing with the original brand medicine.

It must also be noted that the majority of transactions (64.7%) and more than 90% of the purchased quantities in the African countries of our sample were observed in the most recent period (2001-2002). This reflects the major change that has occurred since 2001. Before this date, only Côte d'Ivoire (and Uganda not included in our sample) had started experimental programmes as early as 1998 in the context of the UNAIDS sponsored Drug Access Initiative (DAI), while Senegal (also not included in our analysis) and Cameroon had also started pilot projects for ART in the public health care sector in 1998 and 2000 respectively. There was elsewhere no clear commitment of governments to facilitate delivery of ARV drugs, with the exception of their preventive use (either for prevention of mother to child transmission or post-exposure prophylaxis). Such a situation still prevails in Kenya which remains typical, as is also the case for South Africa, of exclusive diffusion of ARVs in the private and private-not-for profit health care sectors. In spite of the courageous efforts of some NGOs, these two countries remain archetypal of a priority given to pure market mechanisms for ARV procurement and delivery, that was dominant in the whole continent before 2001, and led to what some authors have called

"antiretroviral anarchy" [42-43]. It must however be noted that access through the private sector has led these countries to be in the upper range in Africa for the number of ART-treated patients (respectively 3,000 in Kenya and 20,000 in South Africa). By contrast, in the twelve African countries, other than Kenya, for which we were able to collect data, access to ART is now explicitly included in national strategic plans for the fight against AIDS (or in documents that express a similar level of endorsement by the government such as official country proposals to the Global Fund).

Since 2001, 9 out of the 13 African countries in our sample (Benin, Botswana, Burkina-Faso, Burundi, Cameroon, Republic of the Congo, Côte d'Ivoire, Gabon, Mali) have contracted agreements with brand-name pharmaceutical companies in the context of the AAI, and a majority of the total number of observed transactions in Table 1 is related to AAI in these countries with the exception of Burundi, Cameroon and Côte d'Ivoire. In Kenya, although there was no direct involvement of government, the majority of observed transactions also happened in reference to the AAI. As clearly suggested in Table 1, attitudes of countries toward purchasing generic drugs have however been quite contrasted in the period studied. On the one hand, some countries participating in the AAI (Benin, Botswana, Burkina-Faso, Congo, Gabon) have never introduced generic drugs and have strictly followed the "AAI model" that restricted procurement to bilateral negotiations with six brand pharmaceutical companies in the framework of the international agreement they have signed with the UN-organisations at international level. On the other hand, Nigeria and Malawi have systematically carried out negotiations with multiple suppliers ending up with purchases of drugs supplied by Indian generic manufacturers. Interestingly enough, as shown in table 1, countries with the oldest experience of UN-related ARV procurement, like Côte d'Ivoire, as well as countries which participate in the AAI with the most ambitious plans for scaling up access to ART (Burundi, Cameroon, Mali), have purchased various amounts of generic NRTIs, NNRTIs and multiple combination drugs [44]. Indeed, these countries have evolved toward a more "hybrid" mechanism of procurement that combines negotiations in the AAI international framework with national tenders or other procurement mechanisms introducing generic competition. A similar trend toward such a "hybrid model" of procurement has happened in other countries not included in our sample (Senegal, Uganda) and is in the process of happening in countries like Benin or Burkina-Faso.

In the majority of African countries (Benin, Botswana, Burkina-Faso, Cameroon, Côte d'Ivoire, Gabon, Malawi, Mali, Nigeria) all observed transactions were ARV purchases by public pharmacies or other public authorities in charge of national drug procurement policy. Indeed, in six of these countries (Benin, Botswana, Burkina-Faso, Cameroon, Côte d'Ivoire and Mali), these public agencies have a regulatory monopoly for importing ARV drugs into the country, whereas public purchasers only account for the majority of imports of ARVs in Gabon, Malawi and Nigeria. In Burundi and Togo, the majority of observed transactions were carried out by public pharmacies although some transactions (20-30%) concerned private buyers in accordance with the global situation of ARV delivery in the country. In Congo, the majority of transactions were actually purchased by the Red Cross (private-not-for-profit) but in close connection with the Ministry of Health. Finally, Kenya is the only example of ARV procurement directly carried out through private and public health centres as well as private wholesalers. Of course, the case of Brazil, whose policy is detailed in this book (*cf.* Teixera *et al.* article, chapter 1), is quite different: national production of ARV drugs has allowed the country not to depend on imports for the majority of transactions dealing with NRTIs and multiple combination drugs, and to supply a significant amount of NNRTIs and even of PIs.

The converging trend toward decrease of ARV prices

Figures 1 to 7 describe the evolution of average unit prices per year and per country of the 7 ARV drug dosages which accounted for the highest number of transactions in each of the three therapeutic categories: Lamivudine 150 mg (n=96), Didanosine 100 mg (n=90), combination Zidovudine 300mg + Lamivudine 150 mg (n=78), Stavudine 40 mg (n=73), for NRTIs; Efavirenz 200 mg (n=58) and Nevirapine 200 mg (n=36) for NNRTIs; Indinavir 400 mg (n=79) for PIs. The selected dosages correspond to usual dosages for adult care and are included in the most used HAART therapies indicated in WHO guidelines. Figures 1 to 7 confirm the declining trend of prices for all therapeutic categories as well as a trend for reduction in variability of prices across countries. This latter trend has to be partly related to the introduction of the AAI in transactions which occurred in 2001-2002, to the extent that the international framework of this initiative has tended to introduce a kind of reference pricing for bilateral negotiations with brand-name pharmaceutical companies at country level.

Figure 1: Evolution of average unit prices per year and per country of Lamivudine 150 mg (n = 96)

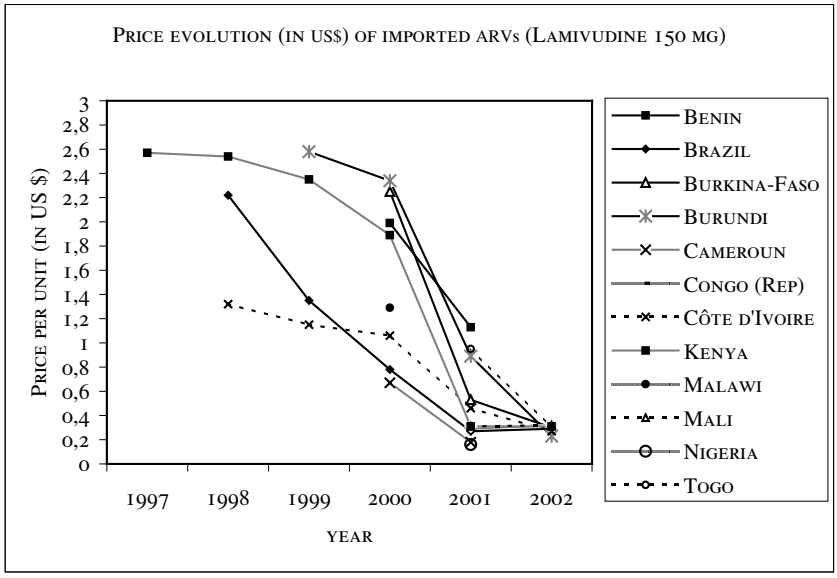


Figure 2: Evolution of average unit prices per year and per country of Didanosine 100 mg (n = 90)

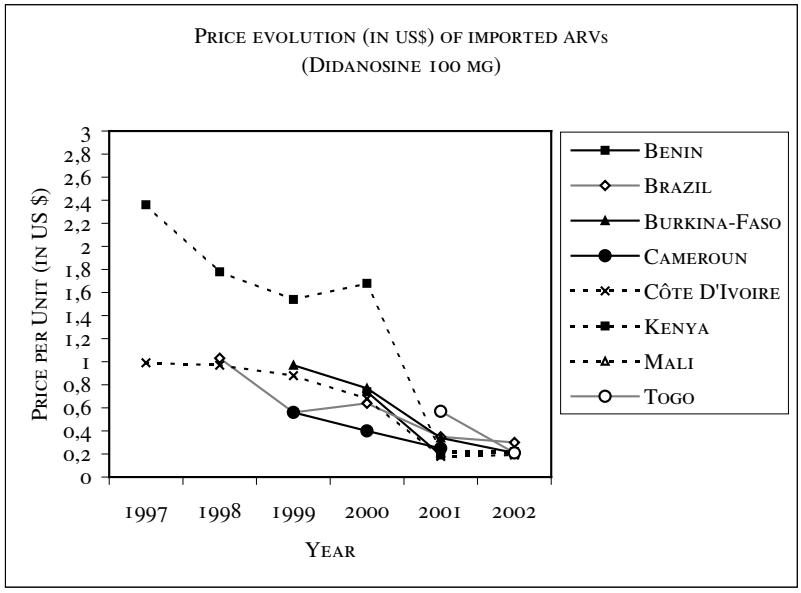


Figure 3: Evolution of average unit prices per year and per country of combination Zidovudine 300 mg + Lamivudine 150 mg (n = 78)

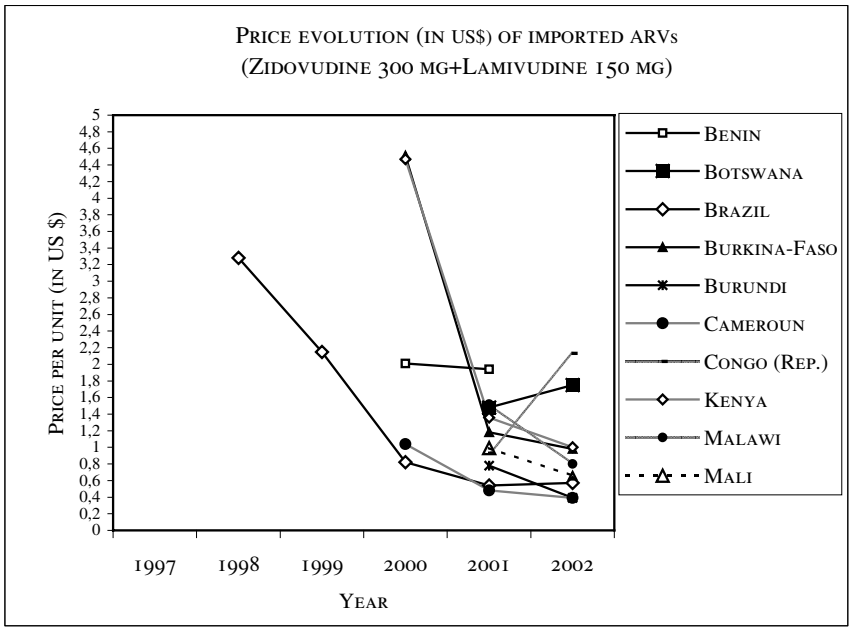


Figure 4: Evolution of average unit prices per year and per country of Stavudine 40 mg (n = 73)

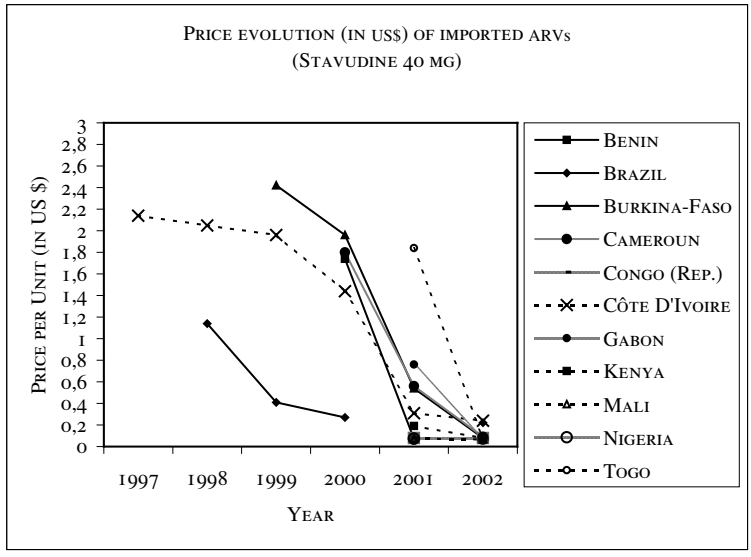


Figure 5: Evolution of average unit prices per year and per country of Efavirenz 200 mg (n = 58)

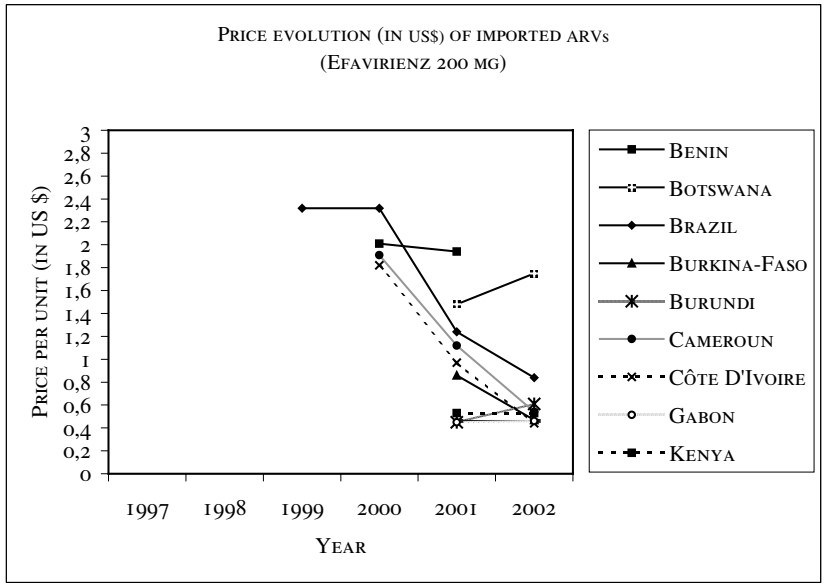


Figure 6: Evolution of average unit prices per year and per country of Nevirapine 200 mg (n = 36)

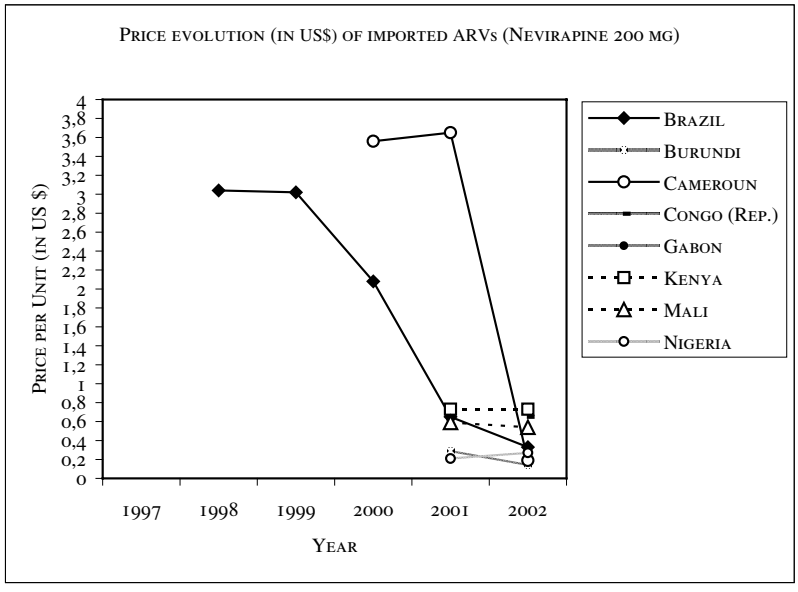


Figure 7: Evolution of average unit prices per year and per country of Indinavir 400 mg (n = 79)

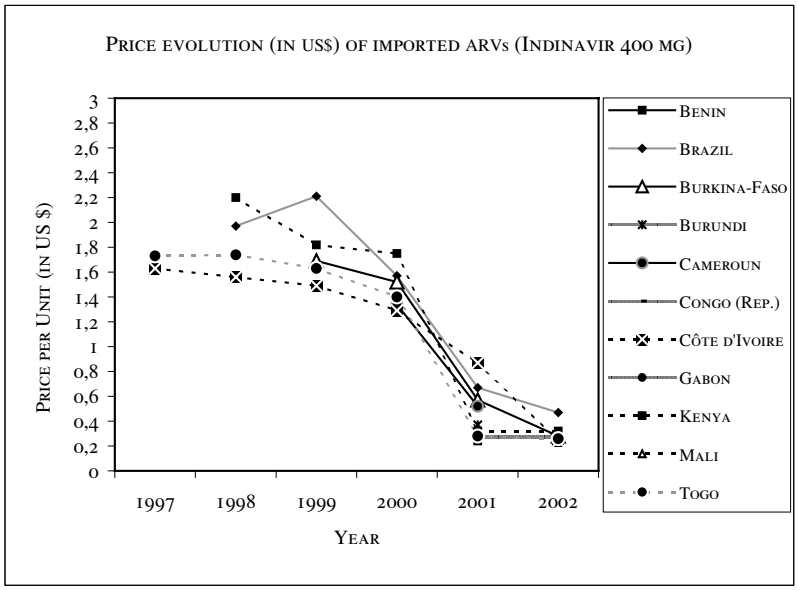
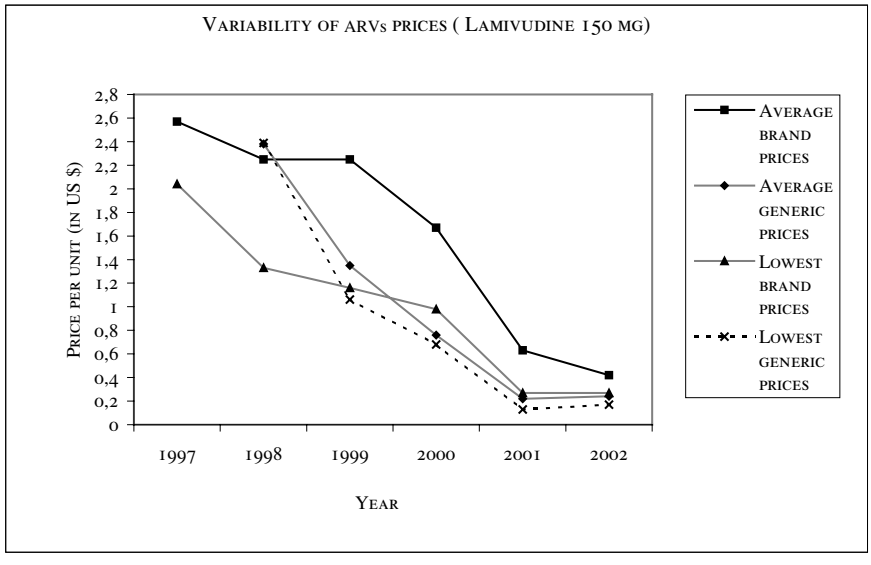


Figure 8: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes - Lamivudine 150 mg (n = 96)



For 5 out of these 7 drug dosages which have generic substitutes in observed transactions, Figures 8 to 12 compare the evolution of the average and lowest unit prices observed in each year for both the brand-named drug in the 14 countries and its generic substitutes. These figures show that generic prices have been systematically lower on average although the difference between average prices of brand drugs and their generic substitutes has decreased since 2001 (up to the point that it even disappears in the case of didanosine and lamivudine, two NRTI drugs for which generic substitutes have been available since 1998 on some markets). It must also be noted that the lowest prices offered by the patent-owner's companies in some countries tend to converge with the lowest deals proposed by generic manufacturers in the last two years (2001-2002). Overall, figures suggest that ARV prices have tended to stabilise in the last two years in parallel to the introduction of the AAI and to this convergence between brand and generic prices.

The determinants of ARV price decreases

Table 2 presents the Spearman's rho correlation coefficients between transaction prices and quantities respectively for the 13 African countries, and for Brazil in each year of observation, and suggests that a higher volume of drug purchase per transaction is effectively associated with lower unit price. Although these negative correlations are always significant at the 0.01 level, it must be noted that the value of the correlation coefficients have tended to decrease through time in African countries suggesting that the influence on unit prices of quantities purchased per transaction had a diminishing role in the latest years.

Table 2: Matrix of Spearman's rho correlation coefficients between ARV prices and quantities purchased per observed transaction (n=1030 transactions- 13 African countries and Brazil)

	1997	1998	1999	2000	2001	2002
Brazil		- 0.522	- 0.381	- 0.240^{NS}	- 0.302	- 0.405
African countries	- 0.795	- 0.788	- 0.695	- 0.601	- 0.542	- 0.432

All correlations are significant at the level of $p < 0.01$, unless specified (ns).

Figure 9: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Didanosine 100 mg (n = 90)

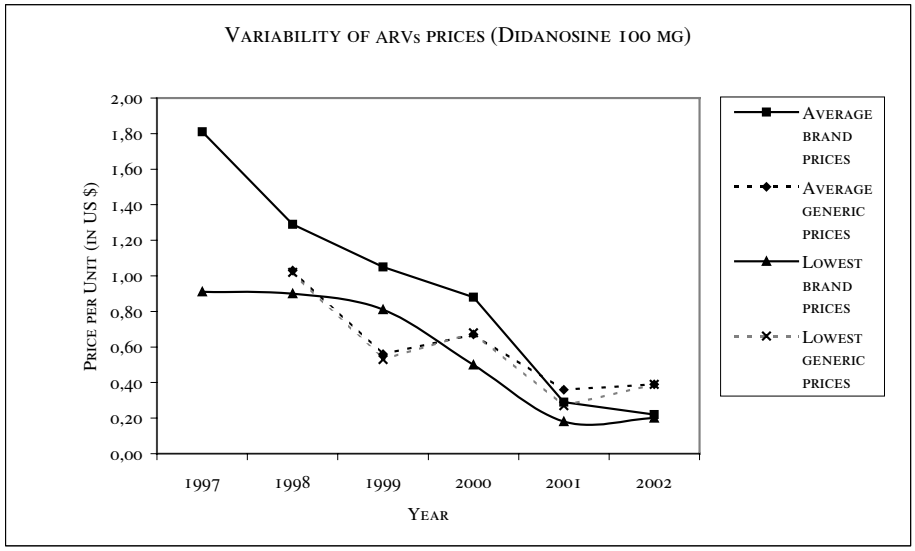


Figure 10: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Stavudine 40 mg (n=73)

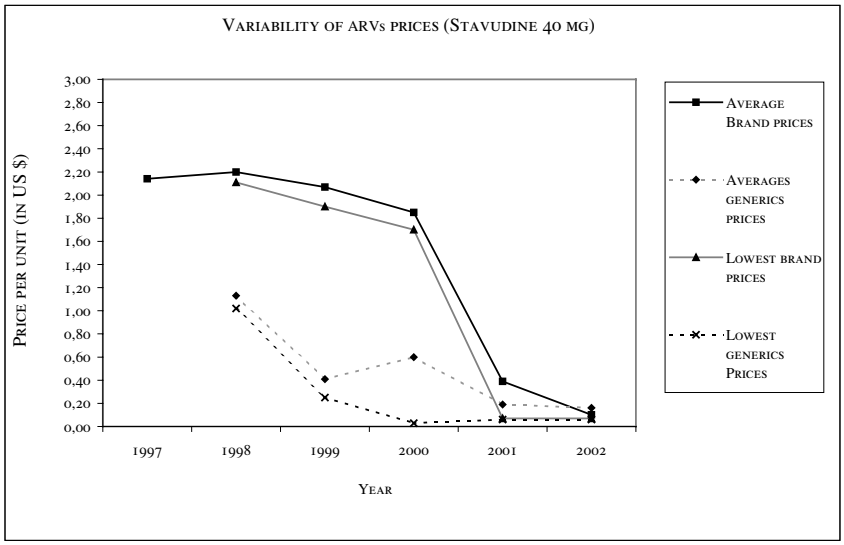


Figure 11: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Combination of Zidovudine 300 mg + Lamivudine 150 mg (n = 78)

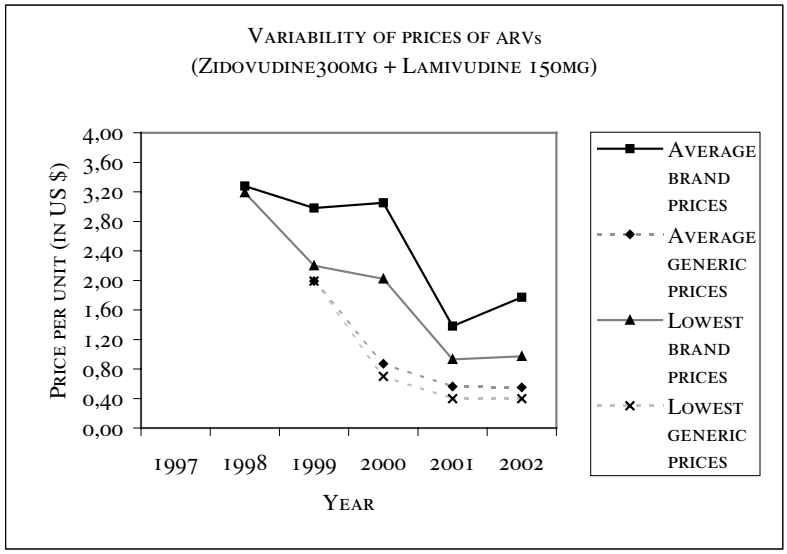


Figure 12: Comparison of the evolution of the average and lowest unit prices of the brand-named drug and its generic substitutes – Nevirapine 200 mg (n = 36)

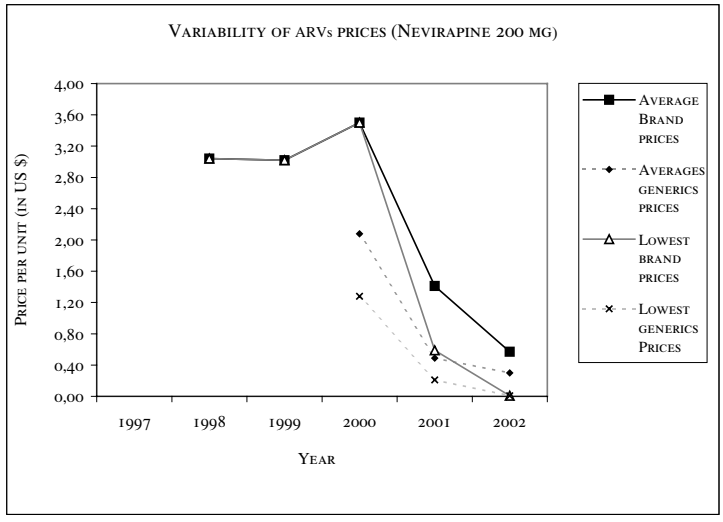


Table 3: Multiple linear regression of prices per daily dose of ARV drugs in 13 African countries and Brazil (n = 952 transactions)

Variable	*Parameter Estimate*	*Standard Error*	*t-Value*	*P-Value*
Intercept	*- 8.89017*	*31.67015*	*- 0.28*	*0.7790*
Dates of purchase:				
Year 2001	0.23108	0.06766	3.42	0.0007
Year 2000	0.83678	0.08823	9.48	<.0001
Year 1999	0.95220	0.09751	9.77	<.0001
Year 1998	1.11761	0.11298	9.89	<.0001
Year 1997	1.29211	0.18149	7.12	<.0001
Number of units sold per transaction/per drug	-1.91503E-06	6.603E-9	-2.90	0.0038
PI drugs	1.19256	0.10591	11.26	<.0001
NNRTI drugs	0.55571	0.10561	5.27	<.0001
Date of patent in country of origin	0.00462	0.1595	0.29	0.7720
Patent protection in purchasing country	0.30357	0.07112	4.27	<.0001
AAI-related transactions	- 0.84488	0.07857	-10.75	<.0001
Generic drugs	-1.00081	0.08638	-11.59	<.0001
GDP per capita	0.000232	0.000232	1.00	0.3178
HIV/Aids Prevalence	0.01411	0.00422	3.35	0.0009
PI in first-line HAART recommended by national guidelines	0.52665	0.11995	4.39	<.0001
National programme for ARV delivery	- 0.31506	0.06786	- 4.64	<.0001
Transaction through an intermediary wholesaler	0.28929	0.11414	2.53	0.0114

R-Square *0.59*
Adj R-Sq *0.58*
Error variance *104.29*

Due to some missing values for explanatory variables, regression analysis was carried out on 952 transactions for which complete data were available. All variables were initially introduced in the multivariate model and tested for statistical relevance with Student t-test. Table 3 presents the variables which remained significant in the final multiple regression model. The transaction of reference (represented by the intercept) is a transaction made in year 2002 for a brand NRTI drug. We describe in detail below each marginal effect on logarithm price per daily dose in current US dollars.

Table 3 confirms the already mentioned relationship between higher volumes per transaction and lower prices for the whole period. It also confirms the declining price trend for ARV drugs since 1997, the year Brazil introduced

its national programme for supply of generic ARVs. Indeed, the year in which the transaction was made (included as a dummy variable) is significant whatever the date considered. The parameter estimates present a decreasing trend which is nearly linear during the period 1997-2000, with an accelerated decrease for the year 2001, followed by a more limited decrease in 2002. In addition, results of econometric analysis presented in table 3 show that both generic competition and the introduction of the AAI since 2001 had significant impact on price decreases. In our model, the impact of these two parameters is of the same order of magnitude (when a Fisher test was applied to test the statistical difference between the two parameter estimates, it ended up not rejecting the null hypothesis of equivalence). However, as we will discuss below, interpretation of this result must take into account the temporal sequence of events that "determined" the price decrease of ARVs: it does not necessarily mean that the two mechanisms (international AAI agreements on the one hand, generic competition on the other hand) had independent effects of similar size on prices; it may alternatively be argued that this result rather suggests that the "philanthropic" attitude of the major brand ARV producers to lower their prices in the context of the AAI has indeed been a strategic "political" behaviour reacting to the competitive pressures of generic suppliers as well as international mobilisation of public opinion.

Not surprisingly, prices of PI and NNRTI drugs are statistically higher than those of NRTI drugs, with a larger impact on price for drugs belonging to the PI class than for NNRTI. Older drugs whose original patent was registered earlier in developed countries are associated with lower prices in univariate analysis. However, this relationship is not anymore statistically significant in multivariate analysis, when the existence (or absence) of patent protection for the drug in the country where the transaction occurred, is introduced in the model. Our results contradict the preceding allegations according to which intellectual property rights have no influence on access to antiretroviral treatment in developing countries [40]. Table 3 clearly shows that the existence of patent protection at country level is significantly related with an increase in the price of the drug.

While socio-economic characteristics which differentiate countries, such as GDP per capita, do not seem to influence the variability of prices in this sample, Table 3 reveals that a higher HIV/AIDS prevalence is associated with price increases. On the other hand, transactions which have occurred in countries

which have organised public strategies for ARV delivery are associated with lower prices. Clinical practices, at least as measured through the existence of national guidelines, also seem to influence prices: when guidelines include PI drugs for first-intention HAART therapies, which may suggest that cost-minimisation is not a priority concern for health care professionals, prices tend to be higher. As expected, transactions in which intermediary wholesalers have intervened between manufacturers and buyers to organise supply end up with higher prices.

IV
LESSONS LEARNT FOR PROCUREMENT OF HIV/AIDS DRUGS IN DEVELOPING COUNTRIES

To our knowledge, this study supported by the ANRS ETAPSUD programme is the first to be based on the observation of real transactions of HIV/AIDS drugs in a sample of developing countries severely hit by the epidemic. Of course, many limitations of these data must be acknowledged. First, our sample of African countries does not yet include all countries that have developed pilot projects for ARV delivery, like Senegal [45] or Uganda [46], as well as countries like South-Africa with significant dissemination of these drugs in the private sector [47]. Analysis should also be extended to other countries in Latin America and the Caribbean than Brazil, and in Asia, where both institutional and epidemiological contexts, as well as market structures may be quite different. Second, comparison between the dynamics of prices of ARV drugs and that of other drugs in the same countries, especially drugs that are used for treatment of HIV-related opportunistic infections, would certainly contribute to a better understanding of the degree of specificity of ARV procurement which has attracted the greatest attention at international level.

Third, some explanatory factors, that were introduced in this preliminary analysis, need further investigation. Current evidence about the impact of ARV patents at country level on the availability and prices of these drugs remains very heterogeneous across countries and over time [40, 48]. Our results clearly show that introduction of generic substitutes is influential for price decrease and that patent protection in a country is associated with price increase. However, the decision by a major pharmaceutical company to claim a patent for a drug in some developing countries rather than others may be a

proxy for various types of "strategic behaviour" from the management of the firm that should be better understood. Finally, our study was focused on source prices at entry inside the country in order to respect standardisation criteria which is often lacking in such international comparisons of drug prices [49]. Of course, we consequently do not capture other sources of variability in prices which may strongly affect HIV-infected patients'access to ART: high taxes, mark-ups, and dispensing fees, poor purchasing and distribution programmes all affect the difference between source and retail prices in many developing countries, including those in our sample, and may continue to undermine the availability of drugs at the consumer level[34].

According to conventional economic theory, price discrimination across different national markets must naturally emerge since firms will maximise their profits if they are able to segment their markets according to consumers'willingness-to-pay for their products. Firms will be in the best position to do so if they have some monopoly power on their markets. Evidence about drug price discrimination across developing countries remains unclear. A study about ARV drugs carried out on behalf of the WHO Commission on "Macroeconomics and Health" found that although brand drug companies seemed to follow such a price discrimination strategy in the first years, the relationship between prices and per capita income eroded over time, with virtually no evidence of lower prices with lower incomes in 1999[35]. Indeed, in our own sample of countries, although they vary considerably in terms of economic development, no clear relationship emerged between basic indicators like GDP per capita and prices of ARV drugs. It must however be noted that countries with the highest HIV prevalence tended to have higher prices, suggesting that firms tend to adapt to situations in which the urgency of the epidemic may induce a lower elasticity of demand for ARVs to price in the segments of population with some ability to pay for these drugs.

Making an explicit reference to the case of HIV/AIDS drugs, the 2001 report of the WHO Commission on "Macroeconomics and Health" strongly advocated that "the best solution will be for the global community to establish diffe-

34. WHO: *Essential drugs and medicines policy: the rationale for essential drugs*. Geneva: 2002. Available at: http://www.who.int/medicines/rationale.shtml.

35. Barton, J.H.: *Differentiated pricing of patented products. Working Paper for the Group 4 (Health and the International Economy) of the Commission on Macroeconomics and Health*. Geneva: WHO, 2001.

rential pricing in low-income markets as the operational norm, not the exception"[36]. Our results clearly confirm that since 2001, differential lower prices have been introduced for ARVs in African countries in comparison to the developed world. ARV prices have tended to come closer to marginal costs of production as suggested by the significant reduction in price differences between brand drugs and generic substitutes in these African countries and by the convergence of these prices with those of nationally produced ARV drugs in Brazil. Conclusions however remain ambiguous about the extent to which this observed North/South differential pricing for ARVs is rather the product of a temporary institutionalisation of "corporate philanthropy" from major pharmaceutical firms, in fact largely forced by international political pressures that have been handed over by UN organisations and that have been nourished by the political threat from some governments of developing countries, like Brazil, to use compulsory licensing to develop national capacities for production of generic drugs, or to the establishment of effective competitive mechanisms of procurement at country level which may even spread to other drugs than ARVs.

Remaining ambiguities are partly related to technical limitations of our analysis. There are important methodological considerations in the econometric literature that emphasise that price estimates require two stages and enough information to disentangle supply and demand aspects [49, 50]. In our preliminary OLS estimation, supply and demand factors are not clearly distinguished. In addition, some endogeneity bias, related to the implicit aggregation of error terms, may have occurred in the absence of differentiated structural equations for both supply and demand.

However, remaining ambiguities are also related to the actual situation of HIV/AIDS drugs procurement at international level. In particular, the actual status of the Accelerated Access Initiative (AAI) sponsored by the UN-organisations in partnership with six of the major brand companies involved in ARV supply remains unclear. The only explicit rationale for giving priority to this partnership, centrally negotiated by the UN at international level, dates back to its predecessor (the Drug Access Initiative), and refers to the idea that such international framework of negotiations for procurement would be consistent

36. Sachs, J. (Ed.): *Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health to the Director General of the World Health Organization*. Geneva: December 2001.

with the establishment of national channels of ARV delivery that would allow strong public control and guarantee a rational diffusion of these drugs. Experience in countries like Brazil has indeed shown that procurement mechanisms open to generic competition do not necessarily translate into a lack of public control on the delivery channels of ARV drugs to health care centres and ultimately to HIV-infected patients. The risk of dissemination of HIV strains that have become resistant to existing ARV drugs may flow from the unregulated availability of ARVs that will inevitably occur in developing countries in the absence of organised efforts by public health authorities to improve access to treatment, but restrictions on competition for ARV procurement at national level have nothing to do with mitigating this risk.

It is far from granted that the international reference pricing mechanism which has been established since 2001 for procurement of ARV drugs for limited experimental programmes in Africa will become perennial (and will be adapted to developing countries in other continents) as soon as the on-going process of scaling up access to ART will concern greater numbers of HIV-infected patients. The trend we have identified in the last two years of a relative disconnection between prices and quantities purchased may be an indicator of an increased pre-eminence of political and institutional factors in ARV procurement. Excessive reliance on "philanthropy" and international bargaining between UN organisations and representatives of the major brand named manufacturers will remain sensitive to the fickleness of public opinion and of media attention and to anecdotal reports of fraudulent parallel importing of drugs from the South to the North. It has already been shown that "philanthropic" drug donations by private companies or international agencies, although they have short-term benefits for limited groups of patients, may jeopardise the process of establishing safe and rational channels of drug procurement in the public health sector of developing countries [51].

As suggested by the spectacular reduction in inter-country price variations in our sample of 13 African countries during the last two years, it is quite clear that the major pharmaceutical companies have accepted (or more realistically have been forced to accept) an implicit international mechanism of reference pricing for ARVs in Africa. Our data also suggest that the cheapest generic product tends to set the reference in these countries. Reference pricing, which consists in assigning a drug to a group of products which receive the same level of reimbursement, has already been used to control drug prices in

some OECD countries (especially in New Zealand and Canada) and has produced substantial savings in drug expenditure [52, 53]. However, in these countries, the overall effects of this policy on patients' health and associated health care and administrative costs remain unclear [54].

Although the AAI never went as far as trying to institute a unique international mechanism for purchasing ARV drugs in the developing world and has only attempted to create a common framework for national procurement negotiations, an alternative rationale for this UN strategy could be found in previous international attempts to promote low-cost supply of medical goods for countries with limited ability to pay, such as the UNICEF/WHO Expanded Program for Immunization [55-56]. These attempts were based on the conventional wisdom that large buyers have an advantage in extracting price concessions from suppliers: globalisation of purchases would give the buyer some "monopsony" power which would be able to compensate for the power of a restricted number of firms operating in oligopolistic markets, while encouraging further private R&D efforts by guaranteeing the solvency of markets in developing countries. They have experienced some limited success in the field of vaccines and drugs for "neglected tropical diseases" [57], but they may be quite inappropriate in the case of drugs that already correspond to highly profitable markets in developed countries.

In fact, the economics literature on the sources of buyer-size effects offers two competing classes of theories. For the first category of models, often qualified as "bargaining models", there are conditions under which buyer-size discounts can emerge at equilibrium with a monopoly supplier under symetric information [58] or even asymmetric information [59]. On the other hand, the second category of models, the so-called "countervailing power" models, concludes that the buyer-size effect cannot emerge with a monopoly supplier [60]: tacitly-colluding suppliers will compete more aggressively for the business of large buyers and are forced to charge lower prices to large buyers to sustain collusion only to the extent that buyers have the power to substitute between multiple suppliers. Empirical evidence about the source prices of drugs according to the channels of distribution in developed countries is generally in favour of this second hypothesis[37]. A similar lesson emerges

37. Ellison SF, Snyder CM.: *Countervailing power in wholesale pharmaceuticals. Massachusetts Institute of Technology*. Department of Economics, Working Paper 01/27, July 2001.

from our data, and more globally from the experience of procurement of ARV drugs in developing countries, including the most advanced one that of the Brazilian programme. International "political bargaining" with the pharmaceutical industry centrally carried out by UN representatives would not have succeeded in lowering prices in the absence of the "countervailing power" that has been generated by the economic mechanism of decentralised negotiations at country level that have extended market competition to all potential drug suppliers, including manufacturers of generic substitutes. The long term sustainability of a differential pricing mechanism for HIV/AIDS drugs in favour of developing countries clearly implies an iterative process of competitive purchasing from all qualified suppliers at each country level. Of course, promotion of national effective market competition does not preclude inter-country cooperation at regional level for bulk purchasing of drugs (especially for countries with limited market size). As mentioned above, a growing number of African countries are evolving toward a "hybrid" model of ARV procurement in which they introduce generic competition in parallel to negotiations with brand companies through the AAI. UN-sponsors of the AAI have also come to recognise that a major limitation of this initiative has been its focus on the six major pharmaceutical companies and "a lack of promotion of generic pharmaceutical partners"[38].

Regulatory flexibility in local production and imports of generic drugs, which was supposed to be guaranteed by the November 2001 Doha Declaration on TRIPS, is an additional component of the establishment of competitive market mechanisms. The recent decision of the Global Fund to Fight Aids, Tuberculosis and Malaria to respect a country's freedom of choice for purchasing ARV drugs from any quality-controlled manufacturers (including generic manufacturers) in programmes supported by the Global Fund, coupled with incentives to buy drugs at the lowest price, goes in a similar direction to the main policy recommendation of our study[39]. Regulation of emerging market mechanisms for procurement also implies, as a prerequisite, public international support for systematic exchange of information about prices and characteristics between buyers. An indirect positive effect of our research is

38. On February 26, 2003, WHO and UNICEF have issued a joint statement in which they call for an increased collaboration between UN agencies and generic pharmaceutical companies to expand access to essential medicines.

39. Global Fund to Fight Aids, Tuberculosis and Malaria (Third Board Meeting). "Procurement and supply management". Decision text. Geneva, 10-11 October 2002.

its modest practical contribution to the establishment of an operational observatory for prices of HIV/AIDS drugs in some regions. Ministries of Health of the Economic Community of West African States (ECOWAS) have recently committed themselves to establish such a regional observatory to track the prices of HIV-related medicines and diagnostics with technical support from UNAIDS and ANRS[40]. The Horizontal Technical Cooperation Group (GCTH), which associates 21 countries from Latin America, Central America and the Caribbean, has a previous experience of exchange of information about drug prices and is also considering further improvements of this collaborative effort.

The 13 African countries visited by the authors are:
Benin, Botswana, Burkina Faso, Burundi, Cameroon, Congo (Republic), Côte d'Ivoire, Gabon, Kenya, Malawi, Mali, Nigeria and Togo.

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40. ECOWAS/CEDEAO: *For a subregional observatory of HIV-related medicines and diagnostics.* Meeting of the Ministries of Health, Accra, July 26, 2002.

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World Market Strategies for Drugs to Fight Aids

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Key words: AIDS; drugs; price;
developing countries.

Abstract

Faced with a situation where the market is unstable and the political context is crucial, we propose a three-part analysis. In the first part, an overview of the chronology of the main events shows that the evolution of the price of ARVs is interlinked with numerous issues of pharmaceutical patent rights. In the second part, we analyse the positions of stakeholders: how they behave in the market and influence market regulations. In the third part, we propose three scenarios which are both simplified interpretations of stakeholders' strategies and options for the future. The first scenario is the status quo, where prices are high. The second scenario is driven by multinational companies who work to enlarge the markets by price differentiation and product diversification. The third scenario is driven by International Organisations which achieve a political consensus to enlarge access to ARV drugs through broader international financing and a systematic opening of the market to generics.

Résumé

Face à une situation de marché instable où le contexte politique est primordial, nous proposons une analyse en trois parties. Dans la première partie une esquisse de la chronologie des événements montre que l'évolution des prix des

ARV est liée dans le temps à de nombreux débats sur les brevets des médicaments. Dans la seconde partie, nous analysons les positions des parties intéressées : comment elles agissent sur le marché et sur la réglementation du marché. Dans la troisième partie, sont proposés trois scénarios qui sont à la fois des interprétations simplifiées du jeu des acteurs et des perspectives sur les évolutions possibles. Le premier scénario est celui du statu quo ante, les prix restent élevés. Le second scénario est conduit par les firmes multinationales qui jouent l'extension du marché par différentiation des prix et diversification des produits. Le troisième scénario est conduit par les organisations internationales qui réalisent un consensus politique pour élargir l'accès aux ARV : par un large financement et/ou par l'ouverture systématique aux génériques.

Introduction

Since May 2000, the price of ARVs (antiretroviral drugs) has slumped dramatically [1]. This phenomenon is just one of the latest developments in the international ARV market to have received wide media coverage.

An increasing number of actions are being taken in this area, even though many of them are either on a limited scale or still in preparative phases. Market conditions are a paradox, with the theoretical needs being considered as huge, the existing demand already being strong, promises remaining cautious and actual achievements being nevertheless limited. Even if international debate often refers to "the ARV market" as if there were only one, the determinants of supply and demand and the regulatory conditions vary considerably from one country to the next. Can economic analysis give us an understanding of the mechanisms, particularly by looking at how markets are run and at the pertinence of the actions being taken? Should we introduce worldwide regulations to control the distribution of anti-retroviral drugs, or should we allow free competition by merely protecting innovation? These questions are at the heart of economic analysis of political transaction costs [2-4] and the institutional economics [5].

The concept of political transaction costs is used to improve and to deepen previous explanations of inefficient outcomes in economic policy-making. It focuses on political transaction costs such as failures of instrumental rationality in politics, the lack of adequate technology of commitment. Incentives to renege on agreements occur in many economic settings, but in such settings, repeated interactions often provide incentives for individuals to honour agreements in order to maintain a flow of benefits over time. Such reputational mechanisms of contract enforcement are however usually ineffective in a political setting.

Institutions behind the market are not considered only as constraints on the behaviour of pre-formed and unchanging individuals as they are in standard economics, but are considered also as shaping the individuals themselves. In order to understand the workings of the ARV market, we need to understand a wide range of institutions that affect and are affected by it. These institutions are, first, simply formal institutions like state, law and international regulation. Secondly, they include private-sector self-regulatory institutions (*e.g.* professional associations, producer associations) and informal institutions such as social conventions, although many of these institutions are supported by formal institutions (*e.g.* decisions by professional associations or social conventions are, when it comes to the crunch, enforceable through the legal system). With this approach, the institutions define who can hold what kinds of properties, who participate in what kind of exchanges, what are the legitimate objects to be exchanged, what are the acceptable conducts in the exchange process, and on what terms different types of agents may participate in which markets, and so on. In such an analysis, the market is a political construct. This approach is very useful for analysing the ARV market: the products are new and their market is under construction.

Using such a framework of analysis enables the working of the ARV market to be described, but does not allow us to build a formal testable model. So this chapter is complementary to the market analysis presented by Luchini *et al*. in this book [6].

Behind the announcement and the actual prices of ARVs, what conditions and what forces have led to that situation? Understanding the various stakeholder games will provide a framework for building similar scenarios. Given the number of non-homogenous stakeholders (governments, pharmaceutical industries, generic manufacturers, international organisations, NGOs), the situation is a complex one. What is publicly said by these actors does not always reflect their "true" objectives and strategies, and both of the latter change in accordance with events. Is it a question of explicitly designed and/or implicitly intended strategies, or rather a chaotic jumble of reactions to market shocks?

In order to analyse the future positions of the various actors, we will put forward scenarios, coherent alternatives, in line with a certain number of hypotheses (the conditions of which will have to be determined) essentially based upon the possible objectives of drug marketing. A return to economic theory would enable us to identify three types of approach (monopoly, competition and public property theories), each according a different role to ARVs and each enabling the different stakeholders to define more clearly differentiated strategies.

These scenarios represent extreme positions, whereas future change is likely to take an intermediary position. Nevertheless, this method illustrates the importance of the matter at stake. The evolution of the ARV market often appears to be the first step to future changes in other markets. Factors regarding the antiretroviral (ARV) market relate to vital questions in other domains: politics (the question of national sovereignty), economics (defence of a major industry), law (regulation of international trade). To what extent will debate and initiatives remain restricted to the ARV market? Or will they encompass other products? The answers to such questions might enable us to understand stakeholder positions and the level of tension in their relationships with one another, thus allowing us to use the scenarios to discuss likely evolutions which can then be compared with the desired goal of increasing access to appropriate HIV/AIDS care in developing countries.

The scenarios are fed by an analysis of the stakeholders' positions and a short chronology of main events which shows the intertwining of strategies. This analysis and this chronology result from interviews carried out in private companies, international organisations and NGOs and from examining numerous papers, publications which cannot all be mentioned.

I
CHRONOLOGY OF THE MAIN EVENTS

The chronology comprises two series of interlinked events that mutually affect one another: the anti-retroviral market on the one hand, with its very sharp drop in prices, its donations and the creation of the Global Fund to Fight Aids, Tuberculosis and Malaria, and, on the other hand, international announcements and debates related to the World Trade Organisation's (WTO) Trade Related Intellectual Property Agreement (TRIPS agreement). When the World Trade Organisation was created in 1994, little attention was paid to the risks of this agreement in terms of developing countries' access to drugs. In 1996, the arrival of tritherapy treatments changed the nature of the problem, as all ARV drugs were patented in developed countries. The debate began in the late 90s – at the WHO [7] for example – and revolved around the situation in Brazil, which partially treats all HIV/AIDS sufferers with low-priced generic drugs, and in Thailand, which is trying to produce generic drugs. Developed countries, led by the USA, attempted to restrict the room for manoeuvre created under the TRIPS agreement (essentially with regard to compulsory licensing and parallel

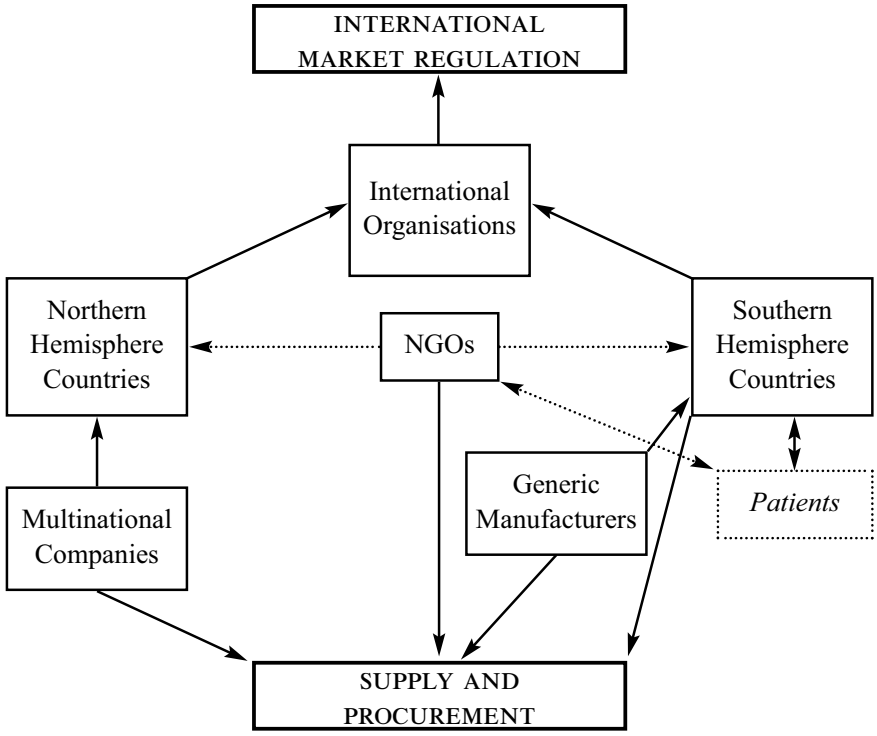
importations). At the same time, initiatives were taken to treat HIV/AIDS patients living in sub-Saharan Africa, with donations from companies and from the French government, and with special prices negotiated within the UNAIDS framework. The year 2000 saw the irruption of Indian generic manufacturers who offer prices which are far lower than those of multinational companies. The debate was growing, because lower prices allow far wider distribution of treatments; the WTO's regulation of patents thus became a major determinant in as much as it is able to forbid access to generic drugs. Most multinationals fell in line with these price drops whilst simultaneously increasing donations. In 2001, the question of AIDS and of access to ARV drugs became political: many countries took position, especially at the UN which suggested creating a Global Fund. In November 2001, members of the WTO approved the Doha declaration, which gave countries the right to compulsory licensing in cases of serious epidemics such as AIDS, malaria and tuberculosis (Doha Declaration on the TRIPS Agreement and Public Health art. 5 c) and to parallel imports (*idem*, art. 5 d). These members also promised to find a solution for compulsory licensing for parallel imports. The Global Fund to Fight AIDS, Tuberculosis and Malaria was created in 2002, when it granted its first funds. Through new funds, "the Global Fund will increase six-fold the number of people being treated with antiretrovirals (ARVs) in Africa with grants from its two initial proposal rounds, ensuring that 500,000 additional people receive these medicines in developing countries" [8]. The Fund agreed to finance the purchase of generic drugs. The WHO added ARV drugs to its list of essential pharmaceuticals and published two lists of pre-qualified suppliers. Yet in 2002 the members of the WTO were unable to agree upon import licences, with the USA attempting to restrict the diseases concerned to just a few epidemics, and developing countries trying to extend the scope to cover all public health problems.

II
THE POSITION OF THE STAKEHOLDERS

The market of ARV is not just an equilibrium between supply and demand. Market regulation is not yet stabilized, so suppliers (manufacturers) and demanders (southern hemisphere countries) exert an influence to curb these rules in favour of their own interests. Rules are laid down in International Organisations by agreement between countries. NGOs engaged in health care programmes act as buyers, but mostly as lobbyists representing patients. All stakeholders play

different roles which can be analysed. The position of different stakeholders can be represented simply by the following figure:

Figure 1: Position of the stakeholders



Pharmaceutical companies

Very few companies produce ARV drugs: 6 multinational firms in the northern hemisphere (including some of the biggest pharmaceutical laboratories) and a dozen or so generic manufacturers, mainly from the southern hemisphere[1].

1. If there is a problem about how to name the different types of pharmaceutical companies for the ARV market, in reality it is simple: on one hand, there are multinational companies based in the northern hemisphere who market ARVs as innovators, and on the other hand, there are southern hemisphere companies who market copies of ARVs (sometimes with improvements). So we have chosen to call them "multinational companies" and "generic manufacturers".

Multinational firms

Although they always describe themselves as R&D companies, they have not always been the creators of these products, some of which stem from public research (this point is developed in [9] in this book). How much they have really spent on R&D for ARV drugs is a well-guarded secret. These companies have a monopolistic strategy based upon intellectual property: patents and brand names. The main markets are in developed countries, which has led companies to set their prices to suit, *e.g.* approximately US$10,000 for annual treatment, a price which is totally beyond the means of patients in the southern hemisphere. To defend their monopolistic position, these companies have basically implemented two strategies in recent years: lobbying and pricing or donation policies.

Lobbying is mainly organised through the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and national associations which greatly influence debates and national authorities (*e.g.* PhRMA in the USA, LEEM – formerly SNIP – in France). It was pressure from the IFPMA that led developed countries to introduce measures to protect the patents included in the WTO's TRIPS agreement. The PhMRA works closely with the USTR (US Trade Representative) who is the American government's official on international trade policy and who has his own lists of countries under surveillance. The other northern hemisphere countries support most of the IFPMA's positions, as they have thriving pharmaceutical industries (especially in the United Kingdom, Germany and Switzerland).

The purpose of the donation policies is to protect the image of pharmaceutical companies, who thus come across as being concerned about public health [10]. Above all, they are designed to counter the low prices offered by producers of generic drugs. Most multinational companies have developed donation programmes, but in most cases it is not just a question of donating pharmaceuticals. Such programmes can also be a way of demonstrating that the price of drugs is not the only question. It is sometimes a means of beginning treatments with international funding in accordance with the old saying that "to know it is to love it".

Whilst pricing policies are sometimes put forward as having a humanitarian purpose, they in fact exist solely to protect commercial positions. The discounts offered by multinationals always lead to price cuts by generic manufacturers and never take place if no copies are on offer from generic manufacturers (*cf.* Efavirenz and Efinavir). These price-cutting policies are related to compulsory licensing in two ways: firstly in countering compulsory licensing policies, by

showing them to be of no future utility; secondly as a result of the threat of compulsory licensing made by Brazil [11]. The problem is that these differentiated prices lack transparency and are subject to conditions which are often unclear [12]. The objective is to make each buyer believe that he is getting a better deal than anyone else. How much multinational companies are in favour of lower prices is an indication of how much importance they attach to markets in the southern hemisphere.

Generic manufacturers

Producers of generic pharmaceuticals sell copies of original drugs. Their objectives will be different, depending on whether they are public companies or private companies.

There are currently two public generic manufacturers producing ARV drugs: Far-manguinhos in Brazil[2] and GPO in Thailand. A Chinese company is soon to begin production. Compared to multinationals, these are small companies whose prime objective is to supply their domestic markets at lower prices. Their entry into international markets is due less to the sales or transfers of technology (licences) that they announced, than to their participation in the debates on compulsory licensing and prices: they demonstrate that it is possible to negotiate [11, 14]. Generally speaking they do not offer prices as low as those of private generic manufacturers, as they are probably less efficient economically, searching to satisfy domestic needs in both quantity and quality rather than offering aggressive prices at international level.

The private manufacturers of ARV drugs are mainly Indian [5]: these companies sell many other generic drugs and have a large share of the world market in this domain (including in the USA). By offering very low prices to the international markets they triggered a price war. They also produce active substances for public Thai and Brazilian companies. Indian pharmaceutical companies benefit from their country's pharmaceutical policy, which for the last twenty years has been to favour local production. After conquering the domestic marketplace, they attacked the international market. Their low prices for ARV drugs (less than US$300 per annum for a tritherapy) gave them a potential huge customer base. We do not yet have detailed information, but their effective sales of ARV drugs in Africa remain limited. They have yet to make any major penetration

2. In Brazil, other private and public manufacturers operate on a much smaller scale than Far-manguinhos, and most are abandoning ARV production [11, 13].

into African markets for other products. They are not yet properly prepared for public offers to tender, or for meeting the requirements of public financing. They are nevertheless beginning to carry out promotional operations in several African countries, using the notoriety they acquired in the ARV drug campaign.

Countries

The "southern" hemisphere

We will distinguish between countries with and countries without a pharmaceutical industry, the former being both producers and consumers, the latter merely being consumers.

Countries with a pharmaceutical industry (that has been developed to at least some extent) follow strategies which aim to improve their production capacities. Such countries favour the development of compulsory licensing in a broad range of cases and not only for AIDS, because they offer a means of developing this sector in order to satisfy local demand (*cf.* Brazil and Thailand) or to export (*cf.* India and China). AIDS is a strong lever for this point of view. Negotiations on patent rights fit into the framework of pressure or action aimed at lowering the barriers (price or otherwise) put into place by developed countries in all sectors of production.

Countries with no significant industry, such as most of the countries in sub-Saharan Africa, adopt strategies which aim to acquire ARV drugs at the lowest possible cost. In the short term, severe budgetary restrictions can force such countries to accept offers which allow them to treat a certain number of patients. They will therefore accept offers which include donations and purchase clauses that will link them to the producers for the long term. In this way, the poorest countries – especially African countries – can add their voices to those of the intermediate countries in order to gain several sources of supply and lower prices (by acquiring generic drugs). Yet because they need a flow of aid (be this in the form of donations or reductions of debts), and given their weak negotiating position, they have to accept the choices of the developed countries and deal with pressure in international negotiations. As representatives of such countries, NGOs put on the pressure in order to avoid their needs being ignored. Due to their administrative and legal weaknesses, most of the developing countries in the southern hemisphere also have difficulty in developing any dynamic AIDS policy, in as much as there is no strong domestic social demand, and in defining a position with regard to international questions that take health problems into account.

The "northern" hemisphere

The purpose of northern hemisphere policies is that of maintaining and developing a position on the international stage. The reason behind public aid is therefore twofold: to help southern hemisphere companies, and to preserve influence, be it economic or political.

Some countries, such as the USA, believe that it is trade not aid which facilitates growth, and that it is therefore necessary to permit development by reducing trade barriers and by creating a path towards growth. Under this hypothesis, aid and cooperation are restricted to whatever cannot be supplied by the market (public property and a safety net). Hence the rules of competition introduced within the framework of both the WTO and the OECD forbid aid to sectors which are open to competition. All that remains for governments is to finance unprofitable sectors (be they infrastructures, authorities or social sectors). This position separates trade policy from cooperation policy, and trade strategy sometimes tends to predominate – hence a position on trade agreements which essentially enables them to defend interests proper to northern hemisphere countries. The balance between trade policies and policies of cooperation nevertheless varies considerably from one country to another.

More and more countries are delegating a share of their external actions to international or infranational institutions (local authorities) or even to private organisations (NGOs). Thus trade policy and policy regarding aid from European countries are now to a large extent delegated to the European Union. In order to improve the technical (not political) effectiveness of aid, many countries transfer their actions to private organisations (both profit and non-profit making) or to international organisations, themselves remaining mere sleeping partners. This has contributed towards the rise in strength of NGOs and International Organisations with regard to technical health questions, especially AIDS-related, and to "social" questions being removed from trade policy.

International Organisations

Regarding the price of ARV drugs, there are three distinct groups of international organisations: The International Monetary Fund (IMF) and the World Bank; the institutions governing intellectual property rights; the United Nations.

The Bretton Woods system

For the International Monetary Fund, the World Bank and its group members, trade is considered to be one of the essential factors for development, in parallel with proper monetary policy and loans for long-term investments, such as infrastructures. Indeed, free exchange is supposed to benefit everyone, as long as the rules of "fair competition" are obeyed. Exceptions to this market rule have to be restricted. Defence of intellectual property would appear to be one condition for the development of long-term exchange.

The World Bank began investing in vast social programmes back in the 60s, but its top priorities were growth and the fight against poverty. Its interest in public health appeared somewhat later, in the early 90s [15]. The World Bank thus became the first international backer in the field of healthcare, especially with regard to the social aspects of structural adjustment programmes. Its interest in the fight against AIDS gradually increased, first with the publication of the results of the first studies on the economic consequences of AIDS and then with its participation in UNAIDS in 1994. As everyone became aware of the economic costs of AIDS, the World Bank wanted to become involved in the work and discussions on access to ARV drugs and in the Global Fund. Its position on access to ARV drugs remained cautious. Its opinion was mainly based upon cost effectiveness studies, with anti-retroviral treatment being deemed "costly, with uncertain results" [16]. This report states the concern not to create any special status for dealing with AIDS, as opposed to other diseases. Now the World Bank has agreed to finance ARV expenditures for treating patients.

However, the leading priority remained that of prevention (principally of sexual transmission, but also mother-to-child transmission). On the basis of the results of the work in Uganda – to which it had allocated considerable funds, the Bank decided that governments should concentrate on preventing and reducing transmission, and that anti-retroviral drugs should not be financed by governments but by private insurance schemes and by companies. So the question of producing generic drugs does not arise. The Bank feels that drugs to fight against opportunistic infections should be procured by invitation to tender.

Aside from its support for the World Trade Organization (WTO), the IMF - guarantor of macro-economic stability - takes no specific action within the ARV market. On the other hand, it is involved in the initiative to reduce the debts of over-indebted countries. As part of this programme, some scenarios allow a share of the funds to be allocated to the fight against AIDS.

Organisations dealing specifically with patents

Two relatively new organisations (in their current form) – the World International Property Organisation (WIPO), created in 1967, and the WTO, created in 1994 - have as their vocations to defend intellectual property and to develop trade. Developing countries (the least developed in particular) are poorly represented within these institutions and often do not have permanent representatives; this means that they have very little influence upon decision-making processes, despite the support they receive from departments within these organisations [4]. After the Uruguay Round, the WTO's scope of action was enlarged. The result of the TRIPS agreement is that intellectual property rights are increasingly protected, and the stakes are higher than ever (new markets, new producers, greater investment in research) [17]. Although up until then the pharmaceutical sector in developing countries had evolved under less restrictive regulations, the pressure from developed countries – due to their influence within the Organisation – blocked the opportunity to build an innovative industry without any liberalising counterbalance in other sectors [18].

Whilst the regulations allow for exceptions, the specificity of healthcare product regulation is not explicitly mentioned. It was only during the Doha conference (2001) that the specific needs of public health began to be considered. Outside pressure from NGOs led to these exceptions being accepted, with international organisations playing more of a conciliatory role in order to preserve other decisions resulting from the negotiations. However, following the failure of the December 2002 negotiations on the application of the Doha decision, the scope of these exceptions remains limited.

The United Nations

Within the United Nations system, the consequences of HIV infection were initially examined by technical agencies, in particular those dealing with the health of populations and individuals. In 2001, the United Nations' extraordinary session on AIDS marked the Organisation's decision to take the global effects of the infection into account. The session led all agencies to examine the consequences of infection, and to the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria (UNAIDS, UNDP, WHO, UNICEF, FAO, Security Council, UNRISD).

With the present emphasis on sustainable human development, the United Nations Development Programme (UNDP), with fewer resources than the Bretton Woods institutions, stressed the importance of social sectors, and health within

development in particular (*cf.* the UNDP annual report on Human Development). Since 1999, the UNDP has been analysing AIDS as a factor of poverty. But given the search for consensus between member countries and between experts, the formulation of recommendations has sometimes remained hazy and has led to only a limited number of projects.

As from 1987 the WHO, along with the Global Programme on Aids, played a precursory role regarding AIDS, followed by a more cautious attitude, and then a partial move away with the creation of UNAIDS. Since 2001, the WHO has once again been playing an active role in two areas: the therapeutic treatment of AIDS, with the creation of a specialised division, and with its participation in debates on access to pharmaceuticals. With the former, it has returned to its role of technical expertise and has invested in the assessment of treatment experiments. It has thus become involved in the quality requirements of available products (pre-selection of manufacturers, monitoring resistance). Putting the accent on the prior conditions for the different experiments is sometimes criticised as being an excuse for non-decision, or as a factor which slows everything down. Progress has been faster in the area of drug policy. After an extremely cautious attitude which had a great deal to do with strong pressure from the pharmaceutical lobby, the WHO began to make decisions on trade exceptions which benefited generic manufacturers (qualification, decisions regarding differential prices). It wanted in this way to participate in rallying civil society, which, whilst often criticising the Organisation's overcautious attitude, was also asking it to play a greater role in international discussions. Yet the WHO still does not take part in certain international trade negotiations despite the fact that they involve the drugs market (November 2002 in Sydney for example).

UNICEF has evolved in parallel to the WHO and the UNDP. It now plays a major role in the field of mother-to-child prevention. After initially adopting a highly cautious attitude – largely due to its traditional campaigns in favour of breast-feeding – it began to insist upon prior conditions for experiments. Following the prescription of Nevirapine, UNICEF started to invest in programmes on a vast scale, and to negotiate with manufacturers. Like the World Bank, it remains very cautious with regard to tritherapy. It favours prevention (especially among the young) and social action to help AIDS orphans.

At first, UNAIDS adopted a very low-key position on tritherapy, and its branches, which mainly comprised people from civil society, essentially opted for actions of prevention and sensitisation. There was a lack of technical expertise on therapeutic treatment. In response to the pressure of demand, the "Access" programme was launched in 1998. Limited experiments were gradually started.

UNAIDS often follows the position of civil society (for example, regarding the free treatments in Ouagadougou in 2001), but then adopts a more cautious attitude due to a desire to achieve consensus. Since 2000, its actions have been reoriented towards preventive aspects, with curative actions once again falling under the umbrella of the WHO (with a new transfer of experts). This trivialisation of AIDS compared to other diseases does not help towards specific regulations for ARV drugs. Following this restructuring and the creation of the Global Fund to fight AIDS, tuberculosis and malaria, UNAIDS has had some trouble defining its role.

In some ways, the installation of the Global Fund in Geneva has strengthened the positions of the WHO and UNAIDS, due to the existing links between experts [19]. With the participation of NGOs, companies and governments, the Fund has become a new style of international organisation. It can be a platform for dialogue between the different stakeholders. But it is greatly influenced by financial backers, who are able to considerably reduce its actions. As a new institution, it can take an offensive stance in order to bestow particular status upon the ARV market. As a major financial backer, it can become a negotiating platform for the purchase of ARV drugs on a larger scale. For the time being, the Fund has authorised the purchase of ARV drugs (pre-qualified by the WHO [20]) for backed projects. US$ 1.8 billion have been allocated, although actual needs were assessed at five times that figure.

Non-Governmental Organisations (NGOs)

Unlike manufacturers, there are a huge number of NGOs. Whilst clusters of NGOs have joined together on many occasions to demand changes which would allow lower prices for ARV drugs, only a small group of forerunners have intervened on an active basis. Many NGOs from the southern hemisphere (with the notable exceptions of South Africa and Thailand) have chosen not to take concrete action, or are content simply to echo the opinions of the northern NGOs. They do not have sufficient resources, are mainly involved in prevention, and are highly dependent on backers (often International Organisations, government cooperation and sometimes even pharmaceutical companies) [21].

The Médecins sans Frontières (MSF) campaign is a good example of action being taken by NGOs from the northern hemisphere. This campaign for access to drugs did not immediately concentrate on AIDS treatment, access to ARV drugs only being mentioned as one example among many [22]. Similarly, the question of the TRIPS agreement was initially only a subsidiary one. The growing

importance of HIV/AIDS treatment within the campaign was powered by field projects, especially in Thailand and Africa. Legal aspects became very important due to a fairly remarkable convergence of events [22]. WTO deadlines and the international activity surrounding globalisation gave a considerable media boost to the campaign. It might be said that the latter successfully influenced many international organisations (the WHO in particular), governments (especially the French) and even (though gradually) the European Commission. Yet the lobby for African countries and trade organisations did not yield such good results [23], despite all the efforts that were made (ministerial meetings in Africa, participation in WIPO conferences).

The main objective of northern and southern hemisphere NGOs which are active in this field is to broaden access to ARV drugs in the name of human rights. Above and beyond the "humanitarian" aspect, their legitimacy resides in the proximity of sufferers, either as NGOs providing care (*e.g.* Médecins sans Frontières) or as associations for sufferers (like Act Up in France and the USA, Treatment Access Campaign in South Africa). These NGOs see themselves as representatives of sufferers' true interests, and as a counterweight, even if they do not possess the legitimacy of governments or the economic power of purchasers. One major aspect of their legitimacy stems from their technical competency, due to the fact that they remain very much au fait with all the medical and scientific details of AIDS. Legitimacy may also come from working on information on specific points – economic and legal for example (with Health Action International, Oxfam, Consumer Project Technology). The work covers both legal (patents) and price aspects. Networking enables them to rapidly share information and coordinate their actions, thus giving them considerable strategic power in an ever-changing situation.

Yet the power of NGOs must not be over-estimated. Their pioneering role and their work on the fringe are particularly useful when their ideas end up being adopted by other partners (international organisations for example) which then take over. They supply technical information to southern hemisphere countries, which whilst it makes them stronger, does not fundamentally change the influence of such countries in international negotiations. The effect of their actions depends upon the political context of the moment. Finally, they do not have sufficient financial resources to make them major purchasers. The NGO campaign is run by a limited and flexible structure which has a lobbying role but which is not directly involved in managing NGO projects. In practice, NGO field managers have a far more pragmatic attitude, which can also tend to slow down NGO lobbying action.

III
SCENARIOS FOR THE FUTURE

Theoretical framework

Standard microeconomic theory allows us to analyse drug market(s) by using the theoretical results obtained via hypotheses on the way a pharmaceutical company works, the product(s) manufactured, or the nature of the production. In order to study the way in which a drug market works, and the possible types of regulation, we need to differentiate between several configurations or approaches in answer to the following questions:

What objective is the company maximising: profit from the sale of one product, or profit from a portfolio of several different products?

Where there are one or several separate markets, is it possible to have different prices? In other words, can there be price discrimination, be it in a situation of questionable monopoly or not?

Is a drug a final product or a component in the production of public welfare?

Portfolio maximisation strategy

Any company producing an original drug wants to maximise profitability, and the latter must cover Research and Development (R&D) costs over a limited period. This limited period is the duration of the patent, which gives the company a monopoly. The length of time during which the drug is marketed under a monopoly is shorter than the duration of the protection under patent, and given that research is taking longer and longer, the marketing period is reduced.

But pharmaceutical companies do not produce one single product; they produce several products with markets that are to some extent identical in as much as several diseases can often occur within the same territory. In such a case, the company's strategy can be either to maximise profit for each individual drug, or to maximise profit for the entire drug portfolio as a whole. Another option is to maximise overall profit by taking into account any interactions between individual drugs. Like any business, pharmaceutical companies maximise their product portfolios (in this case, molecules). This hypothesis is even more realistic in as much as the costs of research are joint costs and laboratories try to finance new research with the profits made on molecules which have passed the break-even stage.

In such cases, the company can accept prices which are lower than the monopoly price as long as there is a positive correlation between the purchase of the drug in question and the purchase of other drugs which are already profitable. One supports the other. By offering several different pharmaceuticals, the company reduces some of these transaction costs, thus achieving economies of scale which can be shared between the manufacturer and the purchaser. Finally, this can create barriers to entry of newcomers to the local market, because the firm became a local leader and created prescription habits in favour of its own products.

This approach will lead companies to adopt strategies designed to preserve their monopolistic positions and to maintain the current status quo as firmly as possible (scenario 1). To achieve this, they will defend a single world market and absolute respect for patent rights.

One product, many different prices

To make the most of a new product during the limited time available, a company can either impose a single worldwide price, or decide to differentiate in accordance with demand, *e.g.* using third degree differentiation, because individual demand and reservation prices cannot be directly observed. Discrimination makes a product available to more people. In principle, collective well-being increases, due to the increase in satisfied demand. If prices are set in accordance with the opposite of elasticity (Ramsey's principle), as Danzon [24] has pointed out this will allow the most to be made of sunk research costs. Ramsey's price, linked to the opposite of elasticity, enables a company to cover the costs of monopoly under the constraint of a set profit. Some people therefore recommend pricing pharmaceuticals using Ramsey's system in order to satisfy world demand. Ramsey's price lies between the monopoly price and the marginal cost. In order for it to be applicable, and given both the high elasticity of developing countries and their low income, this would almost certainly involve financing via international aid. Price differentiation means that prices in developed countries will be both higher than those in developing countries and higher than the price they would have obtained if they were the sole purchasers.

Discrimination is only possible under certain conditions [25]. The first risk is that both markets – that of the developing countries and that of the developed countries – must be properly separated in order to prohibit parallel imports. This means that distribution must be controlled, and that the products must be differentiated (packaging, etc.). The second risk is that of "outside reference" where a purchaser uses the low price of a different market as its reference point for price regulation. Buyers in developed countries might therefore ask pharmaceutical companies to let them

benefit from the prices in developing countries. Finally, two further conditions restrict the opportunities for price differentiation. The first is that the application of differentiated prices leads to higher prices in countries with higher payment capacities. This can be taken to be an implicit transfer which can be refused. The second is that in developing countries the price cannot be lower than the marginal cost of production. However, a given country's capacity to pay for a drug may be lower than the marginal cost, in which case the solution has to include a subsidy, and is thus no longer a discriminatory monopoly regulated solely by the market.

A pharmaceutical company may therefore defend or enlarge its market through price differentiation as long as the products are differentiated and the markets separated; this will be examined in scenario 2.

Treatment of HIV infection and global public goods

A "public good" has two essential characteristics: there is no consumption rivalry, and the marginal cost is zero for any additional person, so each individual may enjoy the benefits of the said good (non-exclusion). These characteristics imply that it cannot be socially desirable to prevent a person from benefiting from the said good because the efficiency principle suggests that the price of the good is zero. Furthermore, non-rivalry implies that private manufacturers may not sell this good (though they may participate in its production), in as much as companies cannot make direct profits. The supply of public goods thus requires some form of public intervention. The concept of public goods was initially analysed within the framework of governments, and was used as a basis for numerous public policies, namely in the fields of information and health.

A global nature is applied to public goods under the following conditions [26]:

– the beneficiaries must reside in more than one "country group" (developing, developed, etc.);

– the benefits must reach a large part of the world's population, both rich and poor, whatever the zone;

– "beneficiaries" may include future generations.

On the basis of this definition, no pure global public good exists, but there are goods which, to a greater or lesser extent, include a public aspect. As stated by Tubiana and Sévérino [27], the assessment of a good having a public nature is a joint decision and leads to questions on its use and financing. Given that the utility of the good may vary from one zone to another, consensus is required on the utility of that good, a matter which is especially complex at an international level. Furthermore, there is the problem of identifying the beneficiaries and of the effective distribution of production to those who really need it the most.

As far as pharmaceuticals are concerned, we need to consider two public goods. The first is knowledge and information, the second is public health care. Scientific knowledge has long been considered to be a public good [28]. Drugs are thus produced by a public good (scientific knowledge) which is itself an input for healthcare production. Hence the question of public regulation is raised for patents, as patents lead to restrictions on the use of information and on access to drugs. The medical knowledge which enables production of anti-retroviral drugs is a global public good because it enables sufferers from several different zones to be treated. Yet this knowledge is partly financed by governments, through partnership between public research centres and private companies, or via subsidies. This implies that the patent rights belong in part to governments, which can choose between two strategies:

1) to let the patent rights to private companies for some royalties without restraint on pricing;

2) to act as full patent holder and to let the patent rights to the world community at lower prices.

Finally, both the prevention and treatment of HIV may be considered as not only national but also global public goods, due to the risks of infectious disease spreading, and due to the impact of the AIDS epidemic on individual economies [29]. Trade regulation is insufficient for such public goods, and price differentiation is ineffective; international intervention is required – what Tubiana and Sévérino call special governance. This can take two forms, depending on the type of product. The first aims to favour research into specific drugs, which involves financing research funds, as was the case for the vaccination initiative. This type of global governance is different from that of market governance alone, in as much as it encourages research and the creation of specific types of distribution. The second covers pharmaceuticals available in developed countries. If we want drugs to reach those who most need them, with no exclusion, then international negotiation must indicate both the most appropriate treatments and the means of funding. We must determine what we wish to treat, and thus exclude (at least temporarily) any totally commercial regulations and all standard rules (this is the role of the TRIPS agreement), and then agree on how to divide the cost between the various parties present[3]. We examine such a policy in scenario 3.

3. The application of the concept of global public goods to HIV/AIDS drugs needs to be discussed. Note that the concept is used here not for all pharmaceuticals, but for pharmaceuticals which address a typically severe pandemic.

Scenario methods

There are several reasons why it would appear difficult to analyse corporate strategies and validate them using data collected from the various stakeholders. The first reason is that the definition of corporate strategy and the calculation of R&D costs are industrial secrets. Our interviews with companies and their pressure groups revealed this culture of secrecy. The prices which can be obtained remain incomplete, and one rarely has much information on the conditions of the contracts (duration, etc.) or of the volumes involved. Finally, the creation of models containing several stakeholders of different sizes is still in its infancy. In order to demonstrate the effect of institutions such as the Global Fund to Fight AIDS, Tubeculosis and Malaria, one would need to be able to model stakeholders which are of different sizes and which are simultaneously involved in several different marketplaces.

This said, it is possible to highlight strategies which fall into the above-mentioned framework by developing scenarios that take into account the objectives and constraints of the different stakeholders within the anti-retroviral market(s). Scenario-based analysis has been developed through war-craft and corporate management techniques in order to determine strategies when faced with uncertain environments [30]. Several alternatives and a large number of possible combinations are grouped together within a limited number of coherent scenarios. A scenario is a way of bringing numerous events and complex interactions together as manageable information [31]. A scenario-based approach allows one to develop a dialogue within a heterogeneous group that speaks the same language [32].

The logic behind a scenario is to simulate situations which are extreme yet coherent, so that real choices can be revealed. This way of clarifying arguments does not necessarily lead to realistic forecasts. In reality, evolution will often occur in an intermediate manner which involves aspects from various scenarios. Scenarios serve to highlight probable configurations and configurations which are desirable for all. Comparison of these two configurations allows one to see what needs to be done in order to get from a probable configuration to one that is desired. Theoretical analysis enabled us to offer three possible scenarios based upon the three approaches to ARV drugs set out above. The three scenarios are summarized in Table 1.

Table 1: Outline of the scenarios

	Scenario 1 *Status Quo*	*Scenario 2* *Market Extension*	*Scenario 3* *ARV's drugs as a global public good*
Main Features	Multinational companies succeed in convincing northern hemisphere countries that both interests match for highest global Intellectual Property Rights guaranteed by International Organisations. Prices remain high.	The power of the different stakeholders is balanced, but the multinational companies take the lead in organising the market. Prices are differentiated and generic manufacturers increase their market share.	Driving force: an international commitment to broad access to ARV drugs in developing countries. International organisations take the lead, and manufacturers adapt their strategy to statutory regulations.
Stakeholders			
Multinational Companies	They will defend a single world market and absolute respect of patent rights. They are the leaders.	They develop their ARV sales through differentiation and diversification. They have an aggressive portfolio strategy.	Most of them withdraw from the market place.
Generic manufacturers	Only Brazil, India and China apply for Compulsory Licences and do not sell outside their countries.	Also have an aggressive strategy: ARVs are doorways to new markets.	Use new financing and new regulations to develop production dramatically.
Northern Hemisphere Governments	They defend their firms and distance themselves from the AIDS treatments issue.	Allow southern markets to open to generic drugs.	Support new financing and regulation by grants and donations.
Southern Hemisphere Governments	No initiative.	Use competition to reduce prices.	Abandon individual negotiations and accept joint solutions.
International Organisations	Reduced influence and a restrictive use of TRIPS room for manoeuvre.	Regulate the opening by allowing Compulsory Licensing and limited reference pricing in the Northern Hemisphere.	OI are the leaders. They achieve political consensus, and implement funds to buy drugs, to encourage research and to open southern hemisphere markets to generics industry.
NGOs	Have a delegation to treat AIDS/HIV patients only on a humanitarian basis.	Condemn multi-speed health care and have a reduced number of projects.	Help the funds and organize the treatment of patients.
Sustainability	Sustainable as long as the situation is under control and the epidemic growth only in Africa. All stakeholders are losers.	Very risky scenario, because it increases demand and inequalities which can spread to other pharmaceuticals.	Idealistic scenario which presumes political consensus, that could be achieved only if countries understand the dramatic consequences of AIDS.

Scenario 1: Maintaining the status quo

Multinational companies have succeeded in convincing northern hemisphere countries that both interest match for a highest global Intellectual Property Protection guaranteed by International Organisations.

The conditions for this scenario

In this scenario the monopolistic position of multinational companies is sustainable as long as patents bestow monopolistic power with poor possibilities for generic drugs. The room for manoeuvre created under the TRIPS agreement is hardly ever used. The fact that the patents come into play at the end of the product's lifetime does not really make any difference, because resistance to the virus is developing and only the major companies are able to offer a continuous supply of new products to replace the old ones. Their monopoly grows.

The roles of the different stakeholders

Developed countries support stronger rights for patent holders to the detriment of access to ARV drugs. They fully support the most restrictive interpretation of the TRIPS agreement, by refusing any broader interpretation of the room for manoeuvre, by prohibiting third-parties from using them to even a small extent, and even by strengthening intellectual property rights under the agreement (in accordance with what is referred to as TRIPS – PLUS). Developed countries remove themselves from the problem of AIDS treatment on an international scale by concentrating exclusively on prevention and by delegating the treatment of sufferers to NGOs.

The international political influence of developing countries is reduced. The majority of developing countries have no influence on market organisation; they have neither the means nor the capacity. They are afraid of developed countries taking them before the WTO. The matter of treating HIV/AIDS sufferers becomes almost entirely a national responsibility: with the exception of sub-Saharan Africa, rates of infection are relatively low, and countries manage to control the epidemic with preventive measures. Sub-Saharan Africa is left to its own devices.

For multinational companies, the significant ARV market is the northern hemisphere: they act mainly to protect profits in this market and do not try to develop sales in southern hemisphere markets. For other treatment categories they can implement other strategies. They protect themselves against ARV parallel imports via a single global price policy (thus rendering such imports of no interest), or by restricting the quantity of drugs sold at differentiated prices,

and by very carefully controlling the destination of all products sold in this manner. The contractual conditions currently covering such sales are already of this nature, and are hence strengthened. The companies sign specific contracts with countries, restricting access to their products and binding them over the long term. Donations are simply used to get a market going.

Extremely strict limitations are made to any possibility of producing generic drugs, through the most restrictive interpretation of the ADPIC agreement and using all of the available legal arsenal. This means that only countries capable of producing the active substances themselves (only India, China and Brazil at the present time) would be able to apply for compulsory licences. In this scenario, generic manufacturers cannot sell outside their country of origin, and, even in such a case, their market access can be very greatly restricted by legislation.

The sustainability of this scenario

For every stakeholder, this scenario is easy to follow as nothing changes: no political will is needed nor is organisational innovation.

The sale by major companies of ARV drugs outside developed countries is highly restricted, with such sales contributing very little towards company profits. The prices are rarely discriminatory as there is little competition from generic drugs. The profits are partly reinvested in research on drugs for other-diseases, the AIDS epidemic being contained at a low level in the northern hemisphere. Drug donations are of limited quantity and are distributed under restrictive conditions by NGOs which are subsidiaries of the pharmaceutical companies.

For various reasons, developing countries lack the political wherewithal to make themselves heard: they are divided by bilateral agreements made with northern hemisphere companies, and generic manufacturing countries are not interested in third-party countries, preferring to concentrate on their own markets – and their own needs. Furthermore, the deterioration of healthcare systems no longer allows proper administration of treatments, and is used by pharmaceutical companies as an excuse for limiting sales at reduced prices.

NGOs fall out over which strategy to adopt, and their popularity with the public is low: their cause is no longer taken up by the media, who are fascinated by the profits being made by the pharmaceutical industry and by the new drugs for typical health problems in the northern hemisphere: obesity, Alzheimer's, etc. Public opinion is only interested in southern hemisphere health when it is a question of neglected diseases such as trypanosomiasis. In developing countries, NGOs are no more than service providers – drug distribution for example.

International organisations (WHO, WTO, UNAIDS) are immobilised by pressure from developed countries and by divisions between developing countries, and thus concentrate on technical matters. The Global Fund is unable to increase the level of available funds. It can only finance a limited number of projects and concentrates on countries which are closest to controlling the epidemic: the most developed, those with the lowest rates of infection, those with the best health-care system… indeed, wherever the funds can be most effectively employed. Other countries receive only the crumbs. The scenario is sustainable as long as the situation does not spiral out of control.

Scenario 2: ARV drugs market extension

In this scenario, the power of the different stakeholders is balanced, but the multinational companies take the lead in organising the market.

The conditions for this scenario

ARV drugs are simply a part of a pharmaceutical company's portfolio, with the company developing strategies for its drug portfolio as a whole. ARV drugs are therefore only important when new products are introduced and a share of the demand is made solvent. The increasing inequality within and between developing countries means that private services – with customers who are aware of the latest treatment techniques – can be developed. The arrival of resistant strains, the serious side effects of ARV drugs, and an increasingly varied and sophisticated demand forces companies into aggressive strategies whereby they must constantly reorganise production in order to cope with competitors. The ARV market can become the motor for the development of other markets (not only opportunistic diseases, but also new types of viral infection). At the same time, the scope of the AIDS epidemic, especially in new countries (China, Asia, Middle East, etc.) creates new markets and makes debate on access increasingly unavoidable.

The roles of the different stakeholders

For multinational companies, ARV markets are developed through price differentiation and product diversification (different formulation or packaging, etc.) and differentiation (through incremental innovation from less effective-cheaper molecules or combinations to more effective/more expensive molecules, price being by far the most important factor). In this way, companies can build a larger product portfolio including a range of ARV drugs from the bottom to the top of the market. Price differentiation and product diversification allow

multinational companies to market drugs according to market segmentation between countries and in some countries between people: the cheapest drugs for the poorest and the more expensive for the affluent. This compartmentalisation is presented as a concession to the poorest countries, allowing companies to make the most of launching new products whilst at the same time maintaining their former positions. Such differentiation enables a market to expand to another clientele, which may be either the privileged members of a poor society or persons treated under new international aid programmes; it also helps remove the threat of any generic drugs which are unable to be significantly less expensive and which depreciate in comparison to branded products. Countries with intermediate revenues (Asia in particular) can become major new marketplaces. These companies try to maintain the specific nature of ARV drugs, in order to avoid the scope of more flexible international regulations being extended to cover the entire range of pharmaceuticals.

Generic manufacturers have an aggressive pricing strategy, because ARV drugs are doorways into new marketplaces. Whilst such companies may benefit, exceptionally, from waivers to patent rights, in the long term these exceptions are not a viable solution: generic manufacturers can sell older ARV drugs whose patents have moved into the public domain, or else make alliances with the northern hemisphere industry, as is the case in South Africa. As they develop, their strategy becomes increasingly similar to that of multinational companies, with certain generic manufacturers becoming powerful enough to also want to have their own branded products and protected patents.

Northern hemisphere countries back international organisations to allow southern hemisphere countries to open up their markets to generic drugs to a certain extent. They guarantee market segmentation by preventing re-importation and refraining from reference pricing based on southern hemisphere prices for their domestic market.

Southern hemisphere governments are trying to use this competition to obtain the lowest possible prices. To achieve this, they opt for individual negotiations with manufacturers, whilst at the same time using the threat of generic drugs or compulsory licensing. A few of the poorest countries can nevertheless have access to ARV drugs through donations or by participating in new drug trials. The product cycle thus starts fairly rapidly and at a lower cost in developing countries, albeit in small quantities, and then, once the research has been amortised, continues over a relatively short period, at a high cost, but in larger quantities in developed countries. Developing countries feel that the sacrifices they make in order to become part of world trade are negligible.

Both northern and southern NGOs condemn such multi-speed healthcare, but are obliged to adopt the same attitude, with a multitude of small projects and several sources of supply.

The sustainability of this scenario

This scenario is quick to reveal its contradictions: the profit-making private sector is ineffective in its treatment of costly diseases, the total cost of treatment is very high (even for the wealthy), increased demand and inequalities, risk of not being able to maintain market segmentation, etc. One factor is therefore knowing if specific regulations for ARV patents are going to be introduced, or whether there is to be no differentiation with other pharmaceuticals.

Scenario 3: ARV drugs as a global public good

The driving force in an international commitment for a large access to ARV drugs in developing countries. International organisations take the lead, and manufacturers adapt their strategy to international regulations.

The conditions for this scenario

ARV drugs are considered as a major component of a global public good-health. Their very characteristics, along with the political question of treating AIDS, gradually lead to special regulations. The international community takes the economic and social consequences of the epidemic on board (not only in Africa, but in all developing or emerging countries). Northern hemisphere countries thus directly or indirectly contribute towards the supply of anti-retroviral drugs, and also to the development of structures for treatment.

This process might be likened to that for vaccinations or products for treating tuberculosis. In 1994 UNICEF obtained an important agreement on vaccination supply which allowed a significant drop in prices. The Vaccination Independence Initiative has led to the release of public funds for financing and has enabled regional parity in West Africa.

The roles of the different stakeholders

International organisations have a major role in such a scenario. UN institutions in particular must work to achieve the political consensus which is required. As the concept of global public good can be implemented in different ways, different international organisations can take the lead. The first way (A) follows the line taken by the Global Fund: subsidizing ARV procurement by southern

hemisphere countries. With the second way (B), the Global Fund might become the main purchasing organisation to create pressure for lower drug prices and to encourage long-term research contracts in favour of pharmaceuticals to meet developing countries health needs. Its status would have to be defined to reconcile divergent interests and to ensure proper resource management. There would obviously be implications with regard to the way in which other international organisations were run. The third way (C) would be to open completely the southern hemisphere markets to ARV generic drugs. Developing countries would abandon Intellectual Property Rights. A new legal framework would be provided by WTO, restricting the scope of application to ARVs, in order to avoid it being extended to include other healthcare products.

In this scenario the majority of multinational companies withdraw from the marketplace. A small number nevertheless remain, adapting to make the most of not only having a single buyer and guaranteed long-term bulk purchases, but also of being able to split investment costs.

In the short term, AIDS drugs are produced by both multinational companies and generic manufacturers, and hence do not suit the strategy of the multinational companies which retain their specificities and their niches. The generic manufacturers use new financing and new regulations to develop production dramatically. This expansion, powered by public financing and free access to patents, must also lead to the production of new products, without which it will be difficult for the generic manufacturers to improve their reputation. Strong political support for generic drugs is therefore required.

In this scenario, southern hemisphere governments abandon individual negotiations and accept joint solutions. With solution A or B, they trade reduced autonomy for major financial advantages and for easier access to ARV drugs. On the other hand, in such a vital domain they might be wary of becoming too dependent upon the Global Fund, and may also be unhappy with international organisations and NGOs coming so much to the forefront. So, some could prefer open market solution (C) which also supposes that these developing countries undertake, in the long term, to finance a share of the treatments. Such financing might come from funds received under debt-reduction programmes.

It is highly likely that the NGOs will manage to increase their role within the Fund. They will use their projects to position themselves as one of the main potential beneficiaries for organising the treatment of patients. They will be able to use this experience to increase their role in healthcare systems within developing countries and to contribute towards the reform of healthcare funding. Such a situation raises important questions regarding the reliability, solidity

and legitimacy of NGOs. Yet the treatment of AIDS could become a shining example of healthcare management and even play a precursory role for a new type of international regulation.

The sustainability of this scenario

Many aspects of this scenario might seem idealistic. It supposes that political consensus can be achieved and that international organisations can play an important role in leadership. It also requires a certain structure for civil society which will nevertheless allow it to retain its dynamics. Management of an enlarged fund must not get bogged down in bureaucracy.

Finally, the exceptional situation of ARV drugs is likely to be increasingly difficult to justify. On the one hand there will be a strong temptation to extend this regulation to all healthcare products, with the subsequent risk of raising major economic questions. On the other hand, separation from the marketplace of rich countries cannot be watertight, especially with regard to the most wealthy people in the southern hemisphere countries who will demand the same healthcare as that available in the northern hemisphere. It will therefore be hard to avoid creating a "multi-level" system of treatment. There is the risk of an international black market being born, especially if the overly bureaucratic system is unable to meet demand.

If this system is not to discourage research, major public funding will be required in this area. The challenge is not just that of finding sufficient funds, but also of using them efficiently; to date, neither the world community nor companies have been able to do this.

Conclusion

Whilst we have attempted to demonstrate the positions of the different stakeholders, one might wonder whether they each have a real strategy with regard to the price of ARV drugs (*e.g.* objectives, and a decision to employ suitable resources). We have looked (essentially a posteriori) for the logic behind the sometimes erratic changes in reaction, and it is difficult to discern the medium and long-term strategies that lie behind what is said. It is not easy to develop such policies within an extremely uncertain context, where there are so many factors and where – despite what the media sometimes suggest – the ARV market is not always the real problem.

One might wonder whether, underneath the so-called victories or compromises voiced by the various stakeholders, lower prices do not in fact have negative

results for most stakeholders: it is estimated that in developing and East European countries only 5% of needs are covered (1% in sub-Saharan Africa) [33]. Certain increases (victoriously acclaimed) in the number of people treated are in fact based upon ridiculously small initial numbers and only affect small areas of the countries concerned [34]. Whilst major laboratories have had to agree to lower prices, as with generic manufacturers, such drops only relate to tiny quantities, and once again reveal the huge profits that the companies are making; this again calls the legitimacy of their pricing strategies into question. The UN's efforts to create the Global Fund has not yet significantly changed the amount of money available in developing countries for the purchase of ARV drugs. The problem of the exorbitant costs of the drugs and the difficulties of treatment has become a stalling tactic for the main stakeholders. It is true that the healthcare systems in many countries are incapable of providing treatment, due to technical weaknesses, lack of financial resources and poor doctor-patient relationships in most hospitals and clinics. But it is also true that even with additional funding, prices have not fallen enough to make these drugs truly accessible to the majority of sufferers in developing countries.

The market will probably not evolve in line with any of the above scenarios, but rather in accordance with a mixture of one dominant scenario and aspects of the others. It is also possible that given the extent of uncertainty, a different solution will be born from those offered. In some ways, the case of ARV prices is proof of the problems caused by the emergence of a new method of world governance. Europe, and France in particular, is starting to change its position (or at least its arguments) in favour of a method of regulation that is specific to healthcare. One should note the increasing role of NGOs as go-betweens not just between governments and international organisations, but also between companies in both hemispheres. This evolution nevertheless remains limited. Whilst we may have felt Doha to be an NGO victory, post-Doha negotiations have pretty much been a failure for such organisations. Poor countries have achieved only minor concessions, and their right to freely use the inventions of wealthy countries has been almost totally denied. This has obviously refused them any major access to such technologies, despite the fact that many researchers from (and trained in) southern hemisphere countries are participating in the advance of science and technology in northern hemisphere countries.

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SECOND PART

Impacts of AIDS and Expansion of Effective Therapeutic Strategies

Financing Efficient HIV Care and Antiretroviral Treatment to Mitigate the Impact of the AIDS Epidemic on Economic and Human Development

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In the first two decades of the HIV epidemic, the parallel efforts of activists, scientists and clinicians resulted in a largely successful paradigm and practice for confronting the epidemic in the rich regions of the world. This was structured around prevention of HIV infection and treatment of AIDS. In resource rich countries in the North, these two key modalities have reduced the rate of growth of the epidemic as well as mortality, morbidity and health care costs. By contrast, for the vast majority (95%) of the estimated 42 million HIV-infected persons who live in developing countries, surveillance, prevention and the development of future vaccines were thought to be the only feasible modalities to combat the epidemic. Although the success of Highly Active Antiretroviral Therapies (HAART) in reducing HIV-related mortality and morbidity became evident soon as 1996, at the 11th World Aids Conference in Vancouver, access to Anti-Retroviral Treatment (ART) was not considered a feasible technical and economic option for developing countries by most experts in the field [1-3].

Since then, the experience of the Brazilian National AIDS Program, presented in the first part of this book by Teixeira, Vitória & Barcarolo, has proved that the medium term goal of providing universal coverage for ART can be realistically achieved in middle income countries through appropriate public policies. Other middle income countries, such as Thailand [4] or Chile, whose experience is presented here by Morales, Cid & Souteyrand, are also implementing policies to reach this goal. Pilot projects sponsored by the governments of Côte d'Ivoire, Senegal and Uganda with the support of UN organisations have

proved the technical feasibility of Antiretroviral (ARV) delivery in sub-Saharan Africa. Although limited in size, these latter experiences have established that similar virological and immunological outcomes, probability of an adverse event, and estimated survival, levels of patients' adherence, while maintaining limited viral resistance, have been obtained with patients enrolled in these African Drug Access Initiatives (DAIs) than with ART treated patients in the USA and Europe [5-8]. An additional lesson, that emerges from the evaluations of the DAIs in these three African countries, is that strong public control is key for a successful diffusion of ART. In the African context of scarce resources and the huge unmet demands for HIV care, efficient programmes clearly necessitate that ARV drugs be properly delivered through organised channels which imply a strong involvement of governments to either promote access to ART in the public health sector or to regulate their delivery in the whole health care system (including the private not for profit and private sectors) or a mix of these policies. In the absence of organised efforts by public health authorities to improve access to ART, the alternative that will inevitably occur in developing countries is "antiretroviral anarchy" [9-11] that will restrict availability of ARV drugs to the most privileged, and maximise the risks of diversion to "black market" sales, of irrational prescriptions and consequently of dissemination of resistant viral strains. The efficiency of government systems – including national health-service systems – has gradually declined over the past decades in many developing countries, especially in Africa. It is obvious that scaling up access to ART will often take place in a context of failing government systems with limited absorption capacity [12, 13]. Legitimate concerns about the risk of bureaucratic inertia due to government intervention, however, fail to realize that even in the best cases, the market will simply not provide adequate delivery of ART especially to the poorest, and that it is market failures of this kind that prompt government action in the first place.

Although it is obvious that inequality between rich and poor nations regarding access to HIV care and treatment constitutes a "moral scandal" [14], many experts and policy-makers continue to argue that improved access to ART is not a good investment choice in developing countries [3, 15-17]. Most current arguments against devoting international and national efforts for scaling up access to ART in the South make an implicit or explicit reference to some forms of economic rationale. Because money targeted to improving public health in developing countries has to be spent, as elsewhere, where it can yield the highest returns, it is either argued that alternative use of resources (to prevention or treatment of opportunistic infections for fighting the HIV epidemic or to

other health improvements) would bring more social benefit for these societies; or that existing institutional, behavioural and cultural barriers, as well as tight constraints on government funds, would impede any efficient use and equitable diffusion of ART in the developing world. Papers in the second part of this book critically review these major "economic" arguments that have been raised against bridging the North/South gap in access to HIV treatment. They show that these arguments are indeed based on a very limited rationale based on a small range of costs defined by particular versions of "economic" discourse and excluding the larger costs associated with lost capacity for social and economic reproduction, non-traded goods and services in the economy and other goods such as "happiness" and "well-being" posited by welfare economics.

Although they may differ on specific issues, all papers in this book take a radically opposite view to that of economists and public health experts who oppose access to ART as one of the priorities for HIV/AIDS policies in developing countries. They rather bring evidence to support the idea that scaling up access to ART and other effective treatments for HIV can be a rational and well-thought economic choice for developing countries, and they discuss the conditions to be met and the policies to be implemented in order to maximise the benefits that these countries can achieve from such access. The message that the second part of this book tries to convey is that *denying expanded access to ART is not only bad ethics and bad public health, but also bad economic policy*.

The mistaken use of the "cost-effectiveness" argument

A frequent argument raised by some health economists [16, 17], and that is often uncritically accepted by decision-makers and health care professionals, is that even with more affordable drugs, ART would still not be "cost-effective" compared with alternative uses of resources for improving public health. In their paper reviewing the published cost-effectiveness literature in various areas of HIV care and prevention, Freedberg and Yazdanpanah show that this argument is based on scarce empirical evidence in developing countries with only limited comparability between studies and ignores the well-known pitfalls of utilizing cost-effectiveness studies for allocating resources to health-care programs that differ in scope. In addition, it ignores the fact that, in the absence of an effective AIDS vaccine, all prevention and care interventions will follow the law of diminishing returns, *i.e.*, that successive equal unit-additions of inputs will result, from some point on, in additions of output at a diminishing

rate [18]. For example, although the unit cost of condoms is low, increased efforts are needed to promote their use in groups where people, particularly women, are not in a position to adopt such risk avoiding strategies or where social and cultural barriers are difficult to overcome, to the extent that the cost-per-averted-infection increases exponentially. Indeed, the notion that ART will never be cost-effective in developing countries is based on the implied assumption that implementation of other strategies for HIV care and prevention, whatever their diminishing returns, will always dominate even the most cost-effective strategies using ARVs. In fact, it is more likely that, compared to alternative types of care, ART will prove to be more cost-effective, at least under certain conditions. As will be discussed below, in some extreme cases of countries like Swaziland with more than one out of three adults already infected, ART may even be the only feasible response if the nation is to survive.

In rich countries, the total cost of care for adults with HIV infection has declined since HAART was introduced [19]. The extent to which the cost of purchasing ARVs is totally, or partially, offset by savings through the reduced number of hospitalizations and episodes of HIV-related opportunistic infections remains unclear. However, once indirect costs (*i.e.*, productivity losses associated with morbidity in HIV-infected persons) are taken into account, HAART is clearly cost-saving in developed societies. This may also be the case among many population groups in developing countries and is suggested by the increasing number of private companies in Africa, including corporations with large workforces such as Anglo American, De Beers and Debswana, that have moved to provide ART for their employees at company expense, and, in some cases, their families [20]. The paper by Eholie *et al.* evaluates the health and economic impact of a comprehensive HIV care programme, including ART delivery, within one of the main private companies in Côte d'Ivoire, whereas the paper by Mc Greevey, Alkenbrack and Stover discusses various interventions for HIV/AIDS prevention, care, and treatment targeted at construction workers who account for a significant share of total employment in developing countries. Both papers illustrate how HIV/AIDS has a major impact on private business in terms of reduced labor supply, especially the loss of experienced workers in their most productive years, increased absenteeism, reduced profitability, loss of international competitiveness, and other financial impacts. They also confirm the fact that private companies currently embark on initiatives to provide ART because they estimate that their investment will, at a minimum, be cost-saving from the company's own perspective. Because non traded socially reproductive labor and other goods and services are of prime importance

in the economy of the developing world in ways which are not the case in "rich countries", ART may also be cost-saving in other productive groups of society outside the "formal" private sector.

Moreover, many health interventions that are considered cost-effective in the North do not save money *per se.* They involve net additional costs which are considered worth incurring to the extent that they "buy" additional health benefits. In high-income OECD countries (Organization for Economic Co-operation and Development), it is usually considered that medical innovations should be adopted if the marginal costs per additional life-year saved are below US$50,000 (circa twice the Gross Domestic Product [GDP] per capita), whereas those above US$150,000 (six times the GDP per capita) are judged too expensive for general use [21]. The implicit rationale for this pragmatic rule is that for values below the lower bound, one can be quite sure that the extra costs for the health care system will be more than compensated by the economic benefits deriving from increased life expectancy; whereas devoting resources to a specific intervention for saving one lifeyear "at the margin", at a cost above the upper threshold, will necessarily "kill a greater number of statistical life-years" through the global impact on the economy of such allocation. When applying this criterion to the data from the literature presented by Freedberg and Yazdanpanah, ART is clearly justified on cost-effectiveness grounds in OECD countries, and compares favorably with prophylaxis of opportunistic infections and a number of HIV-prevention interventions.

By applying a similar criterion developing countries with lower GDPs, the use of ARVs for the prevention of mother-to-child transmission (MTCT) of HIV is clearly cost-effective [22], and should be implemented on a large scale everywhere, including in the 49 Least-Developed countries of the world with a GDP per capita circa US$300. Continuing ART for the mother and child after delivery, if indicated, is also likely to meet this criterion, especially in situations where breastfeeding remains the norm [23], and is the focus of a new multi-country initiative, MTCT-Plus, which will provide continuing, life-long ART for HIV-positive mothers, their children and other family members at 40 sites in eight African and Asian countries. In the developing world an estimated 3.2 million children and adolescents under 15 years of age are living with HIV or AIDS, the vast majority of them in sub-Saharan Africa. Many of these children are orphans. Although it has also been proved in the North that HAART markedly reduces mortality among HIV-infected children and adolescents [24], access to treatment is virtually nil for these age groups in the South. The paper by Laguide *et al.* reports one of the preliminary studies on the feasibility of expanding ART to

children in Africa, that is carried out in Abidjan in the context of the Côte d'Ivoire DAI. It shows that the introduction of HAART logically increases the cost of pediatric treatment, but this has to be balanced with the two to three fold decrease in morbidity that is observed among HAART-treated children.

The paper by Boulle, Kenyon and Abdullah provides estimates of the additional net health care cost per life-year saved with HAART in the adult population of South Africa. These estimates (between US$700 –$1,400 per life-year saved) suggest that HAART can already be considered to be cost-effective in middle-income countries, such as Brazil and South Africa, which have GDPs per capita above US$3,000. Preliminary results from a World Bank study in India suggests even lower health care costs per additional life-year with ART (in the range of US$150-300) with further decreases to only US$30-50 per additional life-year in the "optimistic scenarios" in which access to ART has a positive impact on prevention by reducing the incidence on new infections [25]. As strongly pointed out by both papers of Boulle, Kenyon and Abdullah, and Freedberg and Yazdanpanah, the limited number of available studies on cost-effectiveness of ART in developing countries are based on simulation models and their results remain quite sensitive to the hypothetical assumptions they introduce in these models. These assumptions definitely need further empirical validation based on the evaluation of "true" large-scale programs for ARV delivery.

A key additional parameter for the "real" cost-effectiveness of ART will depend on what economists usually call "treatment externalities" in the case of infectious diseases, that is the future impact of access to effective treatment for those who are already HIV-infected on the rate of transmission of new infections. It has been recently argued that approaches to the prevention and control of the HIV epidemic in Africa have been too heavily based on early experiences and policies from developed countries where the disease has often affected specific risk groups, and that it is urgent to redefine HIV/AIDS in Africa and other developing regions as "a public health and infectious disease emergency" [26]. Reconsideration of policies and practices around HIV prevention and testing clearly need an increased focus on access to treatment [27]. While it is estimated that 9 out of 10 HIV-infected people in sub-Saharan Africa do not know their serostatus, it can be expected that motivations for adherence to voluntary HIV counseling and testing (VCT), which serve as a critical entry point for HIV prevention programs, would be significantly increased by prospects for access to treatment following a positive HIV test result. In addition, it is now established that HAART decreases the probability

of individual sexual transmission of HIV in the case of unprotected sexual intercourse [28]. However, at the level of the population as a whole, the preventive effect of HAART may be counteracted by the increase in life expectancy of treated patients which will predictably translate into an increased probability of sexual encounters between sero-different partners [29]. The overall impact on HIV incidence will further depend on the extent to which risk behaviors are affected by the availability of treatment. A pessimistic view will fear that access to treatment may produce a "dishinhibition effect" in both the seronegative and seropositive segments of the population and a consequent increase in HIV-related risky behaviours. In developed countries, there have been disturbing reports of an increased incidence of STDs and high-risk behaviors as HAART has become widely available [30, 31]. In Africa, there has been anecdotal reports that media announcements about the discovery of a "cure for AIDS" had translated in relapse to more risk behaviours in some groups particularly vulnerable for HIV transmission like sex workers. In contrast, an optimistic view will refer to the evidence from cohort studies in the North indicating that individuals receiving HAART tend to adopt protective behaviors more frequently than those who are not on treatment [32]. In order to facilitate their access to treatment, HIV-infected individuals may have more incentives to become aware of their serostatus and to share information about it with their "significant others". By giving a prospect of hope, longer survival and better quality of life, ART may also facilitate secondary prevention among infected individuals. In a survey conducted in Côte d'Ivoire in a sample of HIV-infected patients seeking care in the medical centers of Abidjan, those who had access to ART were more likely to maintain sexual activity, in association with the improvement of their health status, but declared significantly more frequent condom use than non ART-treated individuals [33]. Similar studies conducted in Rio de Janeiro and Chile found that adherence to condom use also increased in the ART-treated population [34, 35]. Rather than opposing these two views on the basis of a priori ideological arguments, the only way to reach clear-cut conclusions about the consequences of access to HAART on prevention will be to empirically monitor the evolution of risk behaviors, as treatment becomes available on a larger scale in developing countries. Availability of treatment will modify what Barnett calls the "risk environment" which influence, through collective processes, individual behaviors of those who are already infected and of the segments of the seronegative population who are the most exposed to the risk of HIV transmission. Adaptation of primary and secondary prevention strategies must be based on empirical evidence rather

than on a priori ideological arguments.

Another key parameter for the future "cost-effectiveness" of scaling up access to ART will depend whether delivery of treatment simply duplicates the practice and standards that have been developed in the North or are creatively adapted to the constraints of low-resource settings. In April 2002, WHO issued its first guidelines for ART in resource-limited settings that advocate the use of least expensive options for first- and second-line ART for adults and adolescents, as well as for special populations, including pregnant women, children, and persons co-infected with tuberculosis, as well as the use of simple and inexpensive laboratory tests to monitor the response to treatment [36]. In addition to policies for making drug prices more affordable, that have been discussed in the first part of this book, and for making available cheaper alternative techniques for biological monitoring of viral load and CD4 cell counts, such "adaptation" of guidelines should be driven by the goal of minimizing costs of ART delivery while maintaining its efficiency. For example, studies in rich countries have shown that because the probability of survival is the lowest in patients with AIDS, initiating HAART when the CD4 cell count is below 50/mm^3 produces a 50% increase in the cost per additional life-year saved as compared with initiating treatment at a CD4 count of 200/mm^3. In the DAI of Côte d'Ivoire and Uganda, the median CD4 counts of ARV-naïve patients at the initiation of therapy were 89 and 84 cells/mm^3, respectively. Implementing the current recommendations to initiate treatment at a level no lower than 200 CD4 cells/mm^3 should improve the cost-effectiveness ratio.

Health economists should stop making an "authoritarian" use of a mistaken version of the cost-effectiveness argument to legitimate delays and withdrawals from governments and donor organisations in launching large-scale programs for access to ART. They should rather focus on the existing data on the experience with ARVs in developing countries to help identifying the most cost-effective conditions for their use.

Finally, it must be reminded that cost-effectiveness techniques are a simplification of the basic analytic tools of welfare economics and always leave unresolved the fundamental issue of comparing extra costs to the value of additional benefits that are obtained by society from a collective investment [21]. In addition, using the metric of GDP per capita to determine the socially acceptable threshold for the marginal cost per life year saved raises an important and thorny ethical, but also methodological in a deeper epistemological sense, issue: the differential costing of human lives across societies that have reached

different levels of economic development. In this case, the issue has to deal with the value that a society affects to the increased life expectancy and enhanced quality of life of ART-treated patients, including reduced stigma, which go far beyond their direct impact for HIV-infected individuals but should include improved social and human development for their families, communities and country as a whole. Indeed, most economic calculations fail to take into account the "real" cost of the loss of a life from the perspective of the social reproduction of a particular society and locally relevant cultural and moral evaluations of individuals' social existence. Debating this issue is logically related to the way economics understands and measures the impact of HIV/AIDS on life expectancy and other demographic variables, as well as on macroeconomic and social development.

The underestimation of the economic impact of the epidemic

Micro-studies and sectorial approaches, such as the ones mentioned above about the impact on private business (Eholie *et al.*, Mc Greevey, Alkenbrack and Stover) and the literature on impact in affected households reviewed by Freire, generally show that HIV/AIDS is likely to increase and deepens the level of poverty in many developing countries and in the economies in transition of Eastern Europe. Making a comparison between Botswana and the emerging epidemic in the Russian Federation, Balkans and Baltic States, Barnett shows how the superimposition of two long wave events (the HIV epidemic on the one hand, endemic poverty on the other hand) poses unique problems for development. By contrast, most existing estimates of the macroeconomic costs of HIV/AIDS, as measured by the reduction in the growth rate of GDP, are quite modest. In their review of the literature of macroeconomic modeling approaches, Drouhin, Touzé and Ventelou remind us that for Africa, the continent where the epidemic has hit the hardest, they range between 0.3% and 1.5% annually. Barnett mentions similar estimates for the impact of AIDS on the rate of growth in the Russian Federation. Of course, even a loss of circa 1% growth does matter in developing countries, as well as in economies in transition of Eastern Europe, that desperately need very high rates of growth to catch up with international competition in the current context of globalization. However, policymakers need to have some clear idea of the way the epidemic undermines their economies and public budgets, and in the absence of education about the special features of HIV/AIDS impact, politicians and policy makers may mistakenly believe that a 1% loss is similar

to exogeneous shocks, such as the economic consequences of the terrorist attacks in the United States on September 11, 2002, that are more or less easily absorbed by most countries.

Departing from these previous approaches, the three papers by Freire, Drouhin, Touzé and Ventelou, and Barnett offer refreshing new conceptual approaches that altogether bring a message of major importance: *previous research has indeed strongly underestimated the long-run economic and social costs of HIV/AIDS and their detrimental impact on development*; consequently, they have led to an underestimation of the true social rate of return from programs to fight the epidemic, including resources for facilitating access to ART in the most vulnerable segments of the HIV-infected population. In the absence of active policies to mitigate the impact of the epidemic, a progressive collapse of human capital and productivity may occur in some of the countries with the highest HIV prevalence, leading them to fall in what Drouhin, Touzé and Ventelou call an "involution trap", corresponding to a catastrophic modification of the long-term growth regime of their economies. All three papers focus on a number of important potential economic ramifications of the HIV/AIDS epidemic in low-income countries that have as yet received little consideration.

In her paper, Freire shows that studies that have dealt with the impact of HIV/AIDS at the level of the households have tended to restrict themselves to the short-term consequences for those households with one or more members directly affected by the illness. She rightly argues that such approach is limited in scope and time horizon and does not take into account the impact which is very likely to be significant on other related households (extended families, communities) who are de facto involved in coping with the consequences of the illness and death of the HIV-infected as well as the related intergenerational effects. New empirical evidence about the impact of being orphaned in the context of AIDS supports Freire's arguments: the reduction in children's human capital following the loss of parents' presence seems less due to the direct associated loss in income from parental death(s) than a product of associated behavioral changes (in particular, the impact of orphanage on living arrangements and school enrollment seems to depend on the degree of relatedness of the orphans to the head of the household which takes care of them) [37, 38]. Making reference to the work of Nobel Prize of economics Amartya Sen, Barnett shows how the concept of human development, reflected, although imperfectly, by the Human Development Index that has been popularized by UNDP, puts light on the fact that a widespread HIV epidemic, by curtailing

adult life spans, seriously alter the calculus of investment in higher education and technical skills, thereby undermining the local process of investment in human capital. In addition, there is already the suggestion that high HIV rates affect international decisions about direct investment, technology transfer, and personnel allocation in places perceived to be of high health risk. Both factors suggest that HIV breakout could have lasting economic consequences that could be even more significant than the constraints the epidemic directly imposes on local labor supplies or savings.

In their paper, Drouhin, Touzé and Ventelou propose an explanation why existing macroeconomic exercises have concluded in rather modest net effects on the growth rate of per-capita GDP. They strongly suggest that these "optimistic" results are indeed an artefact of the models used and an underestimation of the real negative impact of the spread of HIV infection on the economies of developing countries. These previous estimates all stem from a particular view of how the economy functions, where the AIDS-induced increase in mortality reduces the pressure of population on existing land and capital, thereby raising the productivity of labour. Even if there is a decline in savings and investment, which will be partly due to reallocation of resources toward medical care for the HIV-infected, its negative impact on GDP growth will be limited by the countervailing effect of increased labor productivity. Drouhin, Touzé and Ventelou argue that a different view of how the economy functions over the long run should be adopted, the view of endogeneous growth models which consider a multiplicity of productivity variables and emphasise the importance of human capital and transmission mechanisms across generations. By killing mostly young adults, AIDS does more than destroy the human capital embodied in them. It weakens the whole mechanism through which human capital is accumulated and transmitted across generations. Classical macroeconomic models, which have focused either on the role of quasi-fixed factors or on the historical record to date, fail to capture this major impact that will become apparent only after a long lag. Quite interestingly, approaches in the line of that proposed here tend to attract increased interest in the international community of development economics [39].

Practical consequences for public policies directly derive from the convincing arguments of these papers that in terms of the economic damage that HIV/AIDS will cause, "the worst is still to come". As recommended by Barnett for Eastern Europe, where a "generalised" epidemic is starting to affect countries like Estonia, Russia and Ukraine, containment of the spread of infection should rank high, a lot higher than it does today, in priorities of

decision-makers. Where the epidemic is most advanced, as it is already the case in Sub-Saharan Africa, combating the disease in order to avoid catastrophic economic long-term consequences will require a massive investment effort.

From economic rationale to operational funding of antiretroviral treatment

When the French President Jacques Chirac made a plea, at the 10th Conference on AIDS and STDs in Africa held in Abidjan in December 1997, to promote access to ART for people living with HIV/AIDS in developing countries, and the French government subsequently initiated an International Fund for Therapeutic Solidarity (FSTI), this effort was viewed by many as a kind of naïve utopia that ignored the "harsh realities" of economic constraints. Six years later, the picture has dramatically changed. In June 2001, a watershed was reached when the United Nations General Assembly Special Session (UNGASS) on HIV/AIDS unanimously adopted a Declaration of Commitment recognising the need for implementing "national strategies, supported by regional and international strategies […], to address factors affecting the provision of HIV-related drugs, including antiretroviral drugs". As a direct follow-up of UNGASS, the Global Fund to Fight AIDS, Tuberculosis and Malaria has been put in place and has become operational in January 2002. Ambitious targets have been publicly set. In July 2002 at the XIVth International AIDS Conference in Barcelona, WHO and other UN organisations committed themselves to the goal of expanding access to ART to 3 million people in the developing world by 2005. A recent analysis of the national HIV/AIDS plans of 90 developing countries conducted by WHO indicates that about 60% of these countries have now either incorporated ART into their national strategies to fight the epidemic or have defined specific ART coverage targets.

However, practical accomplishments so far have remained modest. It is estimated that ART was initiated for only an additional 70,000 patients during 2002, leading to only 300,000 HIV-infected persons in developing countries currently receiving ARVs of any kind, nearly one half of them in Brazil alone. The first funding commitments by the Global Fund made in 2002 will allow a two-fold increase world-wide in the total number of individuals receiving ART in developing countries, and a six-fold increase in Africa. In spite of these advances, a large gap persists between the current level of funding for HIV care and treatment and the minimum required to guarantee access for the 4 million HIV-infected who are estimated to be in immediate need of ART in sub-Saharan Africa alone, and beyond that urgency to start having an effective

global impact against the pandemic. Recent estimates of the funding needs, which have taken into account the goal of increased access to ART, have been consistent in calling for an investment of between US$8 billion – $10 billion per year to be provided jointly by the international community and national resources [40-42].

This book is a modest contribution for convincing policy-makers and actors in the field that committing resources to HIV/AIDS care is strongly justified not only on ethical but also on economic grounds. *However, being convinced to invest in policies for scaling up access to HIV care does not necessarily mean that operational ways of funding these activities will be available.* Nearly all papers in this second part of the book give examples of how reallocation of existing resources and mobilisation of new resources can (or could) be obtained. For example, Boulle, Kenyon and Abdullah show that financial resources certainly exist for a treatment programme in South Africa in spite of the context of extreme polarisation and controversy on the role of ART that has characterised the debate about AIDS in this country. The South African case, as well as many others, also emphasize the multiple institutional, financial and political barriers that any process to scale up investment in HIV care has to face.

Two papers specifically deal with the issues raised by the establishment of practical mechanisms for funding ARV programs in the public health sector of developing countries. Vinard *et al.* discuss the plan recently adopted by the Senegalese health authorities and foreign donors to extend on a larger scale the successful experience of the country pilot Initiative for Access to Antiretroviral Drugs (ISAARV) that was introduced since 1998. Morales, Cid and Souteyrand analyze the funding mechanisms put in place to extend ART coverage for HIV-infected patients in the Chilean Public Health System. Although HIV prevalence is relatively low in both countries, the difficulties have been (and remain) numerous and are likely to be exacerbated in countries with higher treatment needs. Three issues are discussed in both papers that definitely need more research and investigation.

A first issue, which is a complicated matter whose practical solution may differ between countries, concerns *the ideal balance between public subsidies, private insurance and other sources of private funding, and patients' out-of-pocket participation to costs of care.* Both papers suggest that current calls for strengthening "public-private partnerships" must go beyond naive rhetoric and necessitate well-designed regulations and incentives to guarantee that they are not used by one sector or the other as an excuse for escaping its own financial responsibilities. Moreover, the classical debates about the fungibility of

development funds [43] will necessarily be revivified as soon as a significant increase in the level of international aid devoted to AIDS will reach a country, in particular following the approval of proposed plans to the Global Fund.

A second issue deals with *the logistic capacity of existing health infrastructure and human resources to guarantee an operational and efficient delivery of ART to those in need.* In their paper, Boulle, Kenyon and Abdullah clearly state that controversial debates in South Africa about affordability and universal access to ARV drugs have excessively overshadowed the practical, but critical, issues of service capacity and human skills that should be devoted to scaling up access to ART. Morales, Cid and Souteyrand describe how breakthroughs in ARV delivery have occurred several times in Chile, during the last few years, due to the quite complex organisation of the drug delivery system and how the Ministry of Health of this country has introduced organisational and managerial changes to overcome such events that may have disruptive consequences that go far beyond their immediate negative impact on ART-treated patients.

A third issue has to deal with *the equity of access to HIV care*. In general, equity in access to health care is far from being granted in lower-income countries [44]. Geographical access to health-care facilities is often limited especially in rural areas. Users of health-care services in urban areas of developing countries often have incomes far above the national average, while such services often do not reach the poorest among urban dwellers [45]. Therefore, the concern that the use of public funds to subsidise ART may be inequitable, or will shift health resources from the poor to those who are less poor, are legitimate [46]. Such concerns, however, fail to realise that even in the best cases, the market will simply not provide adequate services to the poorest, and that it is market failures of this kind that prompt government action in the first place. Obviously, constraints on government expenditures will prevent the public and private sector from establishing strict egalitarian access to ART in many developing countries. When resources are very scarce, trade-offs will be unavoidable, requiring the concentration of resources on some programs or groups at the expense of others. Analysing the difficult period of the Chilean program during which public resources were insufficient to cover all patients medically eligible for ART, Morales, Cid and Souteyrand show how such situation confront health care professionals to "tragic choices" with a risk that selection of those who benefit from treatment may be implicitly driven by social stereotypes. However, the experience of the Senegalese Drug Access Initiative, described by Vinard *et al.*, demonstrates that some national consensus could be reached, in each country, for defining the population groups that can benefit from public

support for expanded access to treatment. Local experiences also suggest that it is possible to directly involve communities in defining social priorities for access to treatment – a process that is under way between the government and TASO (The AIDS Support Organization) the national community – based organisation in Uganda, and in Khayelitsha, a township in the Western Cape province of South Africa, where the project supported by Médecins Sans Frontières has directly involved community representatives in the process of defining priorities for access to treatment. Debates on the issue of equity criteria for designing public subsidies for HIV care are likely to be controversial because collective preferences may legitimately differ between groups, but there is no doubt that the alternative, that would be leaving access to ART to pure market forces, will restrict its availability to the most privileged.

In his 1967 classic [47], economist Albert Hirschman critically opposed the popular ideas among experts of his time about the virtue of "social engineering" and argued that economic and social development was highly resistant to simplification and excessive quantification. The editors of this book hope that its readers will be convinced that economics, using either quantitative or qualitative tools or both, rather than giving legitimacy to denial and inaction, can play an active role in changing the paradigm of the fight against HIV/AIDS in developing countries.

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Cost-effectiveness of HIV Therapies in Resource-Poor Countries

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Key words: HIV/AIDS; cost;
cost-effectiveness; treatment.

Abstract

As more effective HIV therapies have become available, resource constraints and cost-effectiveness have increasingly been at the center of the debate on HIV care in resource-poor countries. In this paper, the authors briefly discuss the three different types of clinical economic analysis: cost analysis, cost-benefit analysis and cost-effectiveness (or cost-utility) analysis. They then describe the published cost-effectiveness literature in 4 areas of HIV therapeutics: chemotherapy for tuberculosis, preventive therapy for tuberculosis, antiretroviral therapy for HIV infection, and prevention of mother-to-child transmission of HIV. Tuberculosis therapy and prevention have been generally found to be reasonably cost-effective in a wide range of settings. Short-course regimens for prevention of mother-to-child transmission of HIV have also been shown to be cost-effective. While substantial discussion has taken place around the cost and cost-effectiveness of antiretroviral therapy as treatment in resource-poor countries, more research is needed to assess the impact and value of this therapy in the many countries in which it is now becoming available.

Résumé

Alors que des thérapies anti-VIH plus efficaces sont aujourd'hui disponibles, les ressources limitées et l'évaluation coût-efficacité prennent une place croissante

dans le débat sur la prise en charge du VIH dans les pays à faible niveau de développement. Dans cet article, les auteurs présentent brièvement trois types d'analyse clinico-économique : l'analyse des coûts, l'analyse coût-bénéfice et l'analyse coût-efficacité (ou coût-utilité). Ils font une revue de la littérature sur l'analyse coût-efficacité dans quatre domaines du traitement du VIH : la chimiothérapie pour la tuberculose, la thérapie préventive pour la tuberculose, la thérapie antirétrovirale pour l'infection par le VIH, la prévention de la transmission materno-fœtale. Dans la plupart des études, le traitement de la tuberculose et sa prévention sont raisonnablement coût-efficaces. Les régimes courts de prévention materno-fœtale sont également coût-efficaces. Pour alimenter le débat qui s'est ouvert sur le coût et le rapport coût-efficacité de la thérapie antirétrovirale comme traitement dans les pays à faible niveau de développement, il est nécessaire de développer la recherche afin d'évaluer l'impact et l'efficacité de cette thérapeutique dans les nombreux pays dans lesquels elle est en voie d'être disponible.

Introduction

With the advent of highly active antiretroviral therapy (HAART) in 1995, HIV infection in the developed world became a treatable chronic illness [1, 2]. Options for HIV care, which had been based on behavioral prevention activities, opportunistic infection prophylaxis, and nucleoside monotherapy and dual therapy, expanded to include combination antiretroviral therapy, which rapidly gained widespread use across Europe, the United States, and Australia [3-5]. However, the cost of HAART, averaging about US$13,100 per person per year in France and the United States, was prohibitive in less developed countries [6, 7]. With the dramatic decrease in the cost of HAART in less developed countries over the past several years, to approximately US$350 per person per year, as well as with increasing evidence of the feasibility and efficacy of HAART use in these settings, the demand for care has increased dramatically [8, 9]. Yet the estimated cost of HIV treatment in less developed countries, US$9.2 billion per year as estimated by UNAIDS, remains an unrealized goal of the Global Fund to Fight AIDS, Tuberculosis and Malaria [10, 11]. Given demands for care and constrained resources, cost-effectiveness analysis is an important methodological approach for understanding and prioritizing use of HAART and other HIV interventions [12]. While not the only input to clinical policy development, cost-effectiveness analysis can play an important role alongside issues including ethics, justice, and political will. In this paper

we present a review of cost-effectiveness analyses of HIV therapies in less developed countries.

I
OVERVIEW OF CLINICAL ECONOMICS

In understanding the role of economic analysis in general, and cost-effectiveness analysis in particular, it is critical to distinguish among the different types of economic analyses: cost analysis (or cost-minimization analysis), cost-benefit analysis, and cost-effectiveness analysis (or cost-utility analysis).

Cost analysis

Cost analysis is a methodology which estimates the resources used (or costs) for a particular type of care or for a specific illness. The outcome of interest is cost, and these studies are used primarily for budgeting and planning purposes. Early studies in the United States estimated lifetime costs of HIV care of US$141,800 [13] and US$146,100 [14]. A recent study from France in the HAART era estimated lifetime discounted HIV treatment costs of €217,400 (US$237,700) [7]. While the most important factor in defining the overall lifetime cost of HIV care in developed countries is the cost of antiretroviral therapy, total lifetime direct costs depend critically on the availability of therapy both for initial care and after failure of initial antiretroviral regimens [6]. At a hospital level, Hansen *et al* have shown hospital costs of HIV/AIDS patients in Zimbabwe of z$4,100 to z$9,700 (US$85 – US$150) per hospitalization, costs which were about double those for non-HIV patients [16]. Other studies report outpatient utilization and drug expenditures for HIV-infected adults [17] in Tanzania. However, while cost analysis is useful for planning purposes, it does not provide information as to the value of the interventions utilized in terms of lives saved, years of life saved (YLS), or disability-adjusted life years (DALYs) saved.

Cost-benefit analysis

Cost benefit analysis attempts to incorporate both resources used for clinical interventions, as well as a measure of the value of those resources defined in terms of clinical benefits. The outcome measure is currency, thus this methodology

requires valuing clinical benefits, such as lives saved or DALYs saved, in monetary terms [18]. Because estimating the value of a life in purely economic terms is challenging for ethical as well as methodological reasons, formal cost-benefit analysis is rarely done for medical interventions.

Cost-effectiveness analysis

Unlike cost-analysis and cost-benefit analysis, each of which has a single monetary outcome measure, cost-effectiveness analysis explicitly examines two outcome measures: cost in monetary terms, and effectiveness in YLS, DALYs, or quality-adjusted life years (QALYs). By convention, different clinical interventions and strategies are compared in terms of their cost-effectiveness ratio, defined as:

$$\frac{CA - CB}{EA - EB}$$

where CA – CB is the difference in the cost of interventions A and B, and EA – EB is the difference in effectiveness of these interventions. When quality of life, or utility, estimates are incorporated into the measure of effectiveness, the ratio is expressed in dollars per QALY (or DALY, if disability is used in place of utility), and the analysis is known as cost-utility analysis. These ratios, the difference in cost divided by the difference in effectiveness, are termed "cost-effectiveness ratios" and are a measure of value for money; the higher the ratio, the less cost-effective the intervention. By using agreed-upon conventions for cost-effectiveness analysis [18, 19] one can compare the cost-effectiveness of different health interventions within a given clinical setting or country.

II
COST-EFFECTIVENESS IN DEVELOPED COUNTRIES

Cost-effectiveness (or cost-utility, hereafter also referred to as cost-effectiveness) studies have been widely reported, primarily in the US, since early in the HIV epidemic. Before the advent of HAART, studies reported on the cost-effectiveness of prophylaxis for *Pneumocystis carinii* pneumonia (PCP) [20- 22], *Mycobacterium avium* complex (MAC) [23], CMV [24, 25], *tuberculosis* [26] and the use of pneumococcal and influenza vaccines [27]. Results of these

studies generally found prophylaxis for tuberculosis, PCP and MAC to be the most cost-effective (ratios US$2,200/QALY to US$32,400/QALY gained), with CMV prophylaxis the least cost-effective use of resources (US$164,000/QALY gained). These analyses have been used in developing guidelines for opportunistic infection prophylaxis in the United States, guidelines that have been widely adopted in Europe [28, 29]. Yazdanpanah *et al*. have recently reported on the cost-effectiveness of various prophylaxis strategies for opportunistic infections in France, in the era of HAART, with ratios ranging from €19,000/QALY gained for PCP and toxoplasmosis prophylaxis to over €100,000/QALY gained for CMV prophylaxis [15].

Several studies in the US and Europe have assessed the cost-effectiveness of HAART therapy. In 1995, Moore estimated a cost-effectiveness ratio of US$13,400/YLS for HAART [30]. This has been followed by estimates from Switzerland of US$25,900/YLS [31], the United Kingdom (£15,200/YLS) [32], and the United States (US$13,600 to US$24,000/QALY gained) [33]. While using different methods and country-specific input data, the results across these studies are remarkably consistent, with an estimated cost-effectiveness ratio of about US$20,000/QALY for HAART compared with no HAART, based on drug costs and treatment patterns in both the US and Europe. The cost-effectiveness of HAART compares favorably with the treatment of breast cancer (US$31,800/QALY gained), hypercholesterolemia (US$49,800/QALY gained), and dialysis in patients expected to live less than 6 months (US$159,000/QALY gained) [34-36].

III
COST-EFFECTIVENESS IN RESOURCE-POOR COUNTRIES

Review of published studies

In this section we report studies that have evaluated the cost-effectiveness of HIV therapies in resource-poor countries in 4 areas: (i) chemotherapy for tuberculosis, (ii) tuberculosis preventive therapy, (iii) antiretroviral therapy for HIV infection; and (iv) prevention of mother-to-child transmission of HIV. In addition, we review studies that have reported cost and effectiveness of laboratory tests available for evaluation of HIV stage and level of immunosuppression.

We examined studies from January 1990 through February 2003, in Medline and AIDSLINE databases. Citation and reference lists were then reviewed to identify any additional relevant studies. Abstracts from major international

AIDS conferences were screened but were not included in this review because they provided insufficient detail to draw firm conclusions. Table 1 provides a summary of the results and some of the methodological features of the cost-effectiveness analyses from resource-poor countries that have been published.

Chemotherapy for tuberculosis

Studies on the cost-effectiveness of opportunistic infection prophylaxis or treatment in HIV-infected patients are limited to tuberculosis, the leading cause of morbidity and mortality for HIV-infected individuals in resource-poor countries.

In 1991, Murray *et al.* examined the cost-effectiveness of chemotherapy programs for the control of pulmonary sputum-smear-positive tuberculosis in Malawi, Mozambique, and Tanzania [37]. The cost-effectiveness of two regimens was assessed: (I) a short-course regimen that consisted of a 2-month intensive phase of streptomycin, rifampicin, isoniazid, and pyrazinamide followed by a 6-month continuation of isoniazid and thiacetazone; and (II) a standard drug regimen that consisted of 2 months of streptomycin, isoniazid, and thiacetazone followed by 10 months of isoniazid and thiacetazone. The cost of the program was divided into three components: fixed costs associated with use of facilities outside the tuberculosis program, such as hospital, clinic and routine laboratory services; fixed costs associated with the tuberculosis program itself; and variable costs, which were a function of the number of patients treated, including drugs, and reagents for sputum examination and culture. The benefits of chemotherapy were divided into the direct benefits to the patient and the indirect benefits to others through reduced transmission of tuberculosis. Compared to no treatment, the average incremental cost per YLS was lower for short course chemotherapy than for standard chemotherapy.

In 1997, Floyd *et al*. conducted an analysis to compare the cost-effectiveness of directly observed therapy (DOT) and conventionally delivered treatment for tuberculosis in rural South Africa [38]. Health system costs for each strategy included inpatient and outpatient costs, health clinic costs, community health worker costs, and drug costs. Patient cost components included time and travel costs associated with visits to hospitals and health clinics. Community costs were those incurred when patients were accompanied on hospital visits. Cure was chosen as the measure of effectiveness and was estimated through cohort studies. DOT cost US$1,300 per patient cured, compared with US$3,000 or US$5,200 for conventional treatment, depending on the likely effectiveness of

this strategy. The authors did not report the incremental cost-effectiveness of DOT compared to conventionally delivered treatment.

These studies confirm the cost-effectiveness of tuberculosis chemotherapy interventions. However, they did not disaggregate HIV-infected from HIV-uninfected patients. There is a concern that treating tuberculosis in patients who are HIV-infected may be less cost-effective, because of the decreased direct benefit of chemotherapy on patient survival because of competing risks, although there may also be indirect benefits due to reduced disease transmission.

Tuberculosis preventive therapy

Several studies on the cost-effectiveness of tuberculosis preventive therapy have been published, based primarily on mathematical computer modeling. In 1995, Masobe *et al.* performed a cost-minimization study and estimated the costs and benefits of 6 months of isoniazid chemoprophylaxis for tuberculosis in a hypothetical cohort of 100,000 patients with HIV disease in South Africa [39]. They used a computer spreadsheet model, and in the baseline analysis they assumed that the prevalence of tuberculosis infection among those with a high background risk approaches 50%, and varied this rate between 5% and 10% for those at lower background risk. If the benefits of chemoprophylaxis were defined in terms of averted health care costs, such a policy would have resulted in net savings of 62.1 million Rands (US$10.2 million). This study did not estimate losses in production associated with tuberculosis, and the cost of identifying HIV-infected individuals was not considered in this analysis.

In 1997, Foster *et al.* assessed the economic benefits and costs of providing isoniazid preventive therapy for tuberculosis in HIV-infected persons in Zambia [40]. This was a cost-minimization study to identify the least costly alternative for preventive therapy. The strategy tested involved three main steps: (I) initial HIV counseling, testing, and referral of eligible persons; (II) physical examination, confirmatory HIV testing, and exclusion of active tuberculosis; (III) tuberculosis preventive therapy, regardless of tuberculin skin tests. The authors used a spreadsheet model incorporating data drawn from both published studies and unpublished data. When medical care costs were included (*i.e.* HIV pre and post-test counseling and tuberculosis treatment costs), costs exceeded benefits, with a benefit/cost ratio of 0.86. When the analysis included the value of patients' lost income (*i.e.* lost wages of tuberculosis patients who are hospitalized or unable to work to capacity for two months), the benefits exceeded costs by a factor of 1.86. In the sensitivity analysis, the

authors found that if secondary cases prevented increased from two (the baseline assumption) to five per person, isoniazid preventive therapy would be cost-saving, even when only direct medical costs were included.

In 1999, Bell *et al.* studied the cost-effectiveness of different strategies of tuberculosis preventive therapy for HIV-infected people with positive tuberculin skin tests in sub-Saharan Africa [41]. They compared three preventive therapy regimens: (I) daily isoniazid for 6 months; (II) daily isoniazid and rifampin for 3 months; and (III) directly observed preventive therapy with rifampin and pyrazinamide twice weekly for 2 months. The authors used a Markov model to calculate outcomes for hypothetical patients. The effectiveness of preventive therapy, survival of HIV-infected patients with tuberculosis, and cost data were derived primarily from clinical trials and cohort studies in Uganda. When medical care costs were considered, the cost-effectiveness of preventive therapy compared to no preventive therapy varied from US$140 to US$340 per QALY gained. The inclusion of "social costs" (*i.e.* transport, lodging and food for the patient and an accompanying relative) and costs associated with treating secondary infections made all strategies cost-saving compared to no preventive therapy. This study, however, did not consider the cost of treating other HIV-related illnesses. Observational studies have shown that HIV-infected people have a higher incidence of opportunistic infections after an episode of active tuberculosis [42]. If the cost of treating HIV-related infections were included, it is likely that preventive therapy would be even more cost-effective.

Overall, these tuberculosis treatment and preventive therapy analyses show that investing resources in chemoprophylaxis is good value for money and makes both economic and clinical sense. As with any disease prevention strategy, in some cases these required initial investments, but the investments were generally recovered, especially when social and secondary case costs were considered. Future analyses should, however, take into account issues such as adherence to therapy and drug resistance, as well as the impact of HAART therapy on the need for tuberculosis preventive therapy [43].

Antiretroviral therapy for HIV infection

Given the important worldwide debate and concern about the cost of antiretroviral therapy in resource-poor countries, it is surprising how little published literature addresses the issue of cost-effectiveness of antiretroviral therapy. Wood *et al*. used a population projection model to examine the cost and cost-effectiveness of both short-course antiretroviral prophylaxis of

mother-to-child transmission, as well as triple-combination treatment of HIV-infected adults in South Africa [44]. Projecting outcomes from 2000 to 2005, they estimated that prevention of mother-to-child transmission would cost from US$1.9 million to US$5.9 million, with a cost-effectiveness ratio of US$20/year of life gained. Assuming an annual HAART cost of US$3,100/person, treatment of 25% of the HIV-infected adults in South Africa was associated with a drug cost of US$20.5 billion, and a cost-effectiveness ratio of US$16,100/ YLS. The authors did not include a sensitivity analysis adjusting for current HAART costs of about US$350/person in many countries.

The experience of the National AIDS Control Program of Brazil in combating the AIDS epidemic there has been well documented [45]. With regard to antiretroviral therapy, in 1996 a federal law mandated free provision of drugs through the public health system. In 2001, 105,000 people, or 99% of those receiving HIV care in Brazil, were provided therapy through the public health system, with a total drug cost of US$258 million. For the years 1997-2001, a total of US$954 million was spent on antiretroviral drugs, with an estimated saving of over US$1.0 billion in hospitalization costs. While no long-term cost-effectiveness data for Brazil are available, treatment of the sickest patients in the first several years of HAART availability was associated with these important cost trade-offs due to prevention of opportunistic infections and hospitalizations, as well as dramatic survival benefits.

In a paper from 2002, Marseille *et al*. [46] argue that based on current estimates, HIV prevention activities are likely to be at least 28 times more cost-effective than provision of antiretroviral therapy. They assumed an annual HAART cost of US$350 per person, with cost-effectiveness of prevention activities averaging US$12.50/DALY and a cost-effectiveness ratio for HAART estimated at US$350/DALY. There is no formal analysis in this study of the effectiveness of HAART. The authors do not include the productivity costs in their analysis, nor do they discount the costs or life years for either prevention or HAART. Since the benefits of HAART are immediate, as seen in the Brazil experience, and the benefits of prevention occur years later, discounting would make HAART more cost-effective compared with prevention and these results would be very sensitive to the discount rate chosen [19]. In addition, the authors assume that at any given point in time the resources available for HIV care are fixed, and that resources which will be made available in the future do not depend on whether successful treatment is undertaken now. It seems likely that effective treatment programs will provide important leverage to increase funds available in the future [8, 10].

Prevention of mother-to-child transmission of HIV

Economic evaluation in general and cost-effectiveness analysis in particular have been more widely used to develop policies regarding prevention of mother-to-child transmission of HIV in resource-poor countries. The cost-effectiveness of antiretroviral therapy interventions with different drugs, different combinations, and different infant-feeding regimens has been extensively studied.

In the developed world, shortly after the results of the ACTG076/ANRS024 clinical trial showed a significant reduction of mother-to-child transmission of HIV with zidovudine treatment, guidelines were published for using zidovudine in pregnant women [47]. However, because of the cost and complexity of the zidovudine regimen used in ACTG076/ANRS024, the World Health Organization recommended trials to evaluate simpler and less costly regimens [48-50]. Cost-effectiveness studies were subsequently performed to evaluate whether resource-poor countries would be able to implement these prevention strategies and whether this would be an appropriate use of limited resources.

In 1998, Mansergh *et al.* evaluated the cost-effectiveness of short-course zidovudine to prevent perinatal HIV infection in a sub-Saharan African setting [51]. They conducted their study from the perspective of the health care system and of society. A decision model was used to examine the cost-effectiveness of 2 doses of zidovudine per day given orally for the last 2 to 6 weeks prior to delivery, and labor dosing of oral zidovudine at 3-hour intervals. Costs were included for counseling and testing, zidovudine treatment, lifetime medical care for HIV-infected infants, and lost productivity due to premature mortality of HIV-infected infants. The model estimated that the cost to the health care system of a national zidovudine program in a setting with a 12.5% HIV seroprevalence would be US$6,300 per infant HIV-infection prevented. When productivity losses were included in the model, the cost decreased to US$1,900 per infant HIV-infection prevented. Sensitivity analysis showed that the program would be cost-saving from the societal perspective when maternal HIV prevalence exceeded 18%, or the perinatal transmission rate was lower than 13.7 infected infants per 100 infected mothers with zidovudine.

Marseille *et al.* considered three short regimens of combination antiretroviral therapy (zidovudine and lamividine): (I) prepartum therapy started at 36 weeks of pregnancy, intrapartum treatment, and 1 week of maternal and infant post-partum treatment; (II) omitting prepartum therapy; (III) omitting both pre- and postpartum therapy [52]. The cost-effectiveness of these regimens was compared

to no intervention. The model employed a baseline HIV seroprevalence of 15% among pregnant women. Without treatment, 25.5% of HIV-positive mothers were estimated to transmit HIV to their infants during pregnancy. The percentage reductions in transmission were estimated at 12.4%, 8.6%, and 4.3%, for the three interventions above. Both intervention costs and the lifetime costs of treating the HIV-infected children were considered in this study. The shortest and most cost-effective option was regimen (III) with a ratio of US$73/DALY gained. Sensitivity analysis showed that results were sensitive to maternal prevalence, intervention efficacy, drug costs, and voluntary counseling and testing costs. For example, in a setting with a 30% HIV prevalence and drug costs at 28% of baseline, the cost-effectiveness of intervention (III) decreased to US$27/DALY gained.

Wilkinson *et al*. evaluated three strategies in the context of a rural population in South Africa: (I) a long zidovudine regimen (used in the ACTG 076/ANRS 024 trial), through existing health service infrastructure; (II) a long zidovudine regimen, with substantial effort to improve drug provision and delivery; (III) a short zidovudine and lamivudine combination regimen with the same enhancement in strategy as in (II) [53]. The cost analysis was undertaken from the perspective of the health care system. With the short-course regimen, the cost per infection averted was US$3,000, with a discounted cost-effectiveness ratio of US$110/YLS.

Söderlund *et al*. evaluated the impact of combined interventions including substitution of formula feeding for breast feeding and antiretroviral therapy on vertical transmission of HIV [54]. Different antiretroviral regimens considered were: (I) zidovudine before and during birth (the ACTG 076/ANRS 024 regimen); (II) zidovudine plus lamivudine during and after birth (the PETRA arm B regimen); and (III) zidovudine during and after birth (the CDC-Thai regimen). A Markov chain simulation model was used and was applied to the Soweto community in South Africa (*i.e.* HIV infection rates, 15%; proportion of infants born to HIV-infected mothers infected at birth, with no intervention, 26%). Intervention costs, health care costs because of additional morbidity in formula-fed children not infected with HIV, costs of HIV-related care avoided by preventing infections were all considered. Based on the 1993 World Development Report suggesting that interventions costing less than US$100/YLS are cost-effective for middle income countries, the authors concluded that compared to the no intervention group, regimen (II), the PETRA arm B regimen, represents good value for money, while regimen (III), the CDC-Thai regimen alone or combined with formula feeding, is cost-saving. In sensitivity analysis the authors demonstrated that breast feeding should not be eliminated in settings with high infant mortality.

In July 1999, results of the HIVNET 012 study of a short course regimen using nevirapine were announced in Kampala, Uganda [56]. This regimen consisted of a single dose of nevirapine given to women at onset of labor and another dose given to neonates within 72 hours of birth. It was compared with a zidovudine oral regimen that consisted of a dose to women at onset of labor and another dose every 3 hours until delivery, in addition to zidovudine orally twice daily for 7 days after birth to the neonates. Nevirapine decreased the transmission of HIV by 47%. In addition, because the nevirapine regimen was less expensive than the zidovudine regimen, it was potentially the most cost-effective.

Marseille *et al.* then formally compared the cost-effectiveness of this nevirapine regimen with other short-course regimens [56]. They compared two implementation strategies, counseling and HIV testing before treatment (targeted treatment), or nevirapine for all pregnant women without HIV testing (universal treatment). The analysis was performed from the point of view of a public-sector health care payer using a mathematic model. HIV seroprevalence rates of 15% to 30% were considered, as well as the cost of counseling, testing and treatment. At a 30% HIV prevalence rate, compared to no intervention, the cost-effectiveness of the universal nevirapine regimen was estimated at US$6/DALY, and the targeted nevirapine regimen at US$13/DALY. The incremental cost-effectiveness analysis showed that the universal nevirapine regimen was more effective and less costly than the other regimens. However, differences in resistance and subsequent therapy for either the mothers or infants was not included.

In a second analysis, Stringer *et al.* supported the conclusions of Marseille *et al.* that a universal nevirapine regimen would be a cost-effective approach to the prevention of vertical HIV transmission in sub-Saharan Africa [57]. Their analysis suggested that nevirapine is likely to be cost-effective not only when provided to women prenatally *(i.e.* HIVNET 012 study), but also when administered upon presentation for delivery. Both prenatal nevirapine on presentation, followed by postpartum nevirapine for the infant and therapy for only the infant appear to offer cost-effective alternatives to no prevention intervention. However, the efficacy of these regimens has not been evaluated in clinical trials.

The studies conducted to evaluate these interventions do not take into account the fact that many pregnant women decline both HIV testing and if infected, nevirapine therapy. The rates of these refusals may have a major impact on the cost-effectiveness results. In a recent study that used a stochastic model and included refusal of HIV testing, refusal of nevirapine, and failure to take nevirapine, Sweat *et al.* found the cost-effectiveness of a targeted regimen to be at US$180/DALY saved compared to no prevention [58].

Although better clinical assessment of adherence to these treatments is needed, several analyses on the prevention of mother-to-child HIV transmission suggest that strategies such as targeted regimens or universal nevirapine provide the best value for money. In addition, these interventions are reasonably cost-effective compared to a wide range of accepted public-health interventions in sub-Saharan Africa.

Laboratory tests for evaluation of HIV stage and treatment monitoring

Evaluation of HIV stage and monitoring of treatment efficacy in developed countries is based on measurements of both CD4 cell count and HIV RNA. In resource-poor countries these tests are not generally available, because of cost and the lack of necessary equipment. Other potentially inexpensive and more readily available markers are therefore under investigation. In a recent study from India, Kumarasamy *et al*. demonstrated the usefulness of total lymphocyte count for evaluation of the level of immune suppression [59]. They noted a high degree of correlation between CD4 cell count and total lymphocyte count, and found that in their setting, four CD4 cell counts per year cost US$137 compared with US$3 for total lymphocyte counts. No formal cost-effectiveness studies have been performed to date on the use of CD4 counts or other laboratory tests for monitoring therapy.

Table 1: Cost-effectiveness of HIV treatment strategies in ressource-poor countries

Reference	*Setting*	*Compared Interventions*	*Methods*	*Cost Measure*	*Effectiveness Measure*
(1) Chemotherapy for sputum-smear-positive tuberculosis					
Murray *et al.* 1991	Malawi Mozambique Tanzania	No treatment Short-course ambulatory* Standard ambulatory Short-course hospital Standard hospital	Costs and cure rate: observational data Transmission: model Survival: lifetables	Intervention costs	Survival
Floyd *et al.*	South Africa (rural)	No treatment DOT Conventionally delivered treatment	Observational data	Medical care, time, and travel costs	Cure
(11) Tuberculosis preventive therapy					
Masobe *et al.*¤	South Africa	No preventive therapy INH for 6 months	Spreadsheet model†	Medical care costs	Saving in health care costs¤
Foster *et al.*¤	Zambia	No preventive therapy HIV testing and INH for 6m for all HIV patients w/out active tuberculosis	Spreadsheet model†	Medical care costs	Saving in health care costs¤
Bell *et al.*	Uganda	No preventive therapy INH for 6 months INH and RIF for 3 months RIF and PZA for 2 months (DOT)	Markov model	Medical care costs	Survival
(111) Antiretroviral therapy fo HIV infection					
Wood *et al.*	South Africa	No ART Preventive therapy to 25% of HIV+ mothers Preventive therapy to 75% of HIV+ mothers Preventive therapy to 100% of all pregnant women ART to 25% of all HIV+ adults	Population projection model	Drug cost Per-person health-care expenditure	Life-years gained
Levi *et al.*	Brazil	ART for adults	Budget impact analysis	Medical care costs	Prevalence/ incidence of AIDS

Abbreviations: YLS: Years of life saved; DOT: directly observed treatment; INH: isoniazid; Rif: rifampin; PZA: pyrazinamide; QALY: quality adjusted life year; AZT: zidovudine; 3TC: lamivudine; DALY: disability-adjusted life year; CS: cost saving; ART: Antiretroviral therapy; *Ambulatory: no hospital admission; hospital: hospital admission during the first 2 months of therapy; ¤A cost minimisation analysis; †No additional information on the model was available;

Time Horizon	*Discount Rate*	*Perspective*	*Results*	*Sensitivity Analysis*	*Comments*
18.5 yrs	3%	Government and non-goverment organizations	Reference group $20/YLS $20/YLS $39/YLS $59/YLS	Not available	Results expressed vs. no intervention Cost for lost income not included
1 yr	Not done	Societal	Reference group $1300/case cured $3000/case cured	 $5200/case cured	Results expressed vs. no intervention
8 yrs	4%	Payer of medical costs	Reference group Cost-saving	 Benefits - costs = $6.5	Productivity losses not included Results dependant on the risk of developing tuberculosis, patient adherence, INH efficacy
<1 yr	Not done	Not specified	Reference group Benefits/costs =0.86	 Cost-saving	Cost-saving w/inclusion of lost income or increase in secondary cases prevented
Lifetime	3%	Societal	Reference group $140/QALY $340/QALY $320/QALY	 Cost-saving Cost-saving Cost-saving	Results expressed vs. no intervention Inclusion of social costs and costs of treating secondary infections made all strategies cost-saving
Lifetime	Not done	Public sector health-care payer	Reference group $20/YLS $20/YLS $140/YLS $16,000/YLS	Not done	ART costs estimated at $2,900 per person per year Productivity losses not included
1997-2000	Not done	Public sector health-care payer	69% decrease in medication costs 48% decrease in per patient ART costs** 84% decrease in hospitalization rate	Not done	

**Based on drug cost reductions through manufacturing; ¤¤Long AZT: zidovudine regimen, used in ACTG076/ANRS024 trial; Enhancement: substantial effort to improve drug provision and delivery; ††Targeted nevirapine: counseling and HIV testing before treatment; Universal nevirapine: treatment for all pregnant women; § Dominated: more costly and less effective than an alternative strategy.

Table 1 (suite)

Reference	*Setting*	*Compared Interventions*	*Methods*	*Cost Measure*
(iv) Prevention of mother-to-child transmission of HIV				
Mansergh *et al.*	Sub-Saharan Africa	No preventive therapy AZT 6w prior to delivery + labor dosing (every 3h)	Decision model	Medical care costs and productivity losses
Marseille *et al.* 1998	Sub-Saharan Africa	No preventive therapy AZT+3TC pre-, intra-, postpartum Intra + postpartum Intrapartum	Decision model	Medical care costs
Wilkinson *et al.*	South Africa (rural)	No preventive therapy Long AZT regimen Long AZT w/enhancement¤¤ Short AZT+3TC w/ enhancement	Decision model	Intervention costs
Söderlund *et al.*	South Africa (urban)	No preventive therapy AZT prepartum, and intrapartum AZT+3TC intra +postpartum AZT intra + postpartum	Markov model	Medical care costs
Marseille *et al.* 1999	Sub-Saharan Africa	No preventive therapy Targeted nevirapine†† Universal nevirapine Universal nevirapine AZT+3TC intra +postpartum AZT intra- + postpartum	Decision model	Intervention costs
Stringer *et al.*	Sub-Saharan Africa	No preventive therapy Targeted nevirapine Universal nevirapine No preventive therapy Infant only therapy Nevirapine on admission to labor and delivery unit	Decision model	Medical care costs

Abbreviations: YLS: Years of life saved; DOT: directly observed treatment; INH: isoniazid; Rif: rifampin; PZA: pyrazinamide; QALY: quality adjusted life year; AZT: zidovudine; 3TC: lamivudine; DALY: disability-adjusted life year; CS: cost saving; ART: Antiretroviral therapy; *Ambulatory: no hospital admission; hospital: hospital admission during the first 2 months of therapy; ¤A cost minimisation analysis; †No additional information on the model was available;

Time Horizon	*Discount Rate*	*Perspective*	*Results*	*Sensitivity Analysis*	*Comments*
Lifetime	5%	Societal	Reference group $1900/infection averted	Cost-saving	If >18% mothers HIV+ or perinatal transmission rate < 13.7% with AZT, the intervention cost saving
Lifetime	5%	Public sector medical system	Reference group $335/DALY $175/DALY $73/DALY	 $53 to $1,700/DALY $31 to $790/DALY $27 to $340/DALY	Results expressed vs. no intervention Productivity losses not included Results sensitive to HIV prevalence, intervention efficacy, drugs and voluntary counseling + testing costs
Lifetime	3%	Health system	Reference group $250/YLS $240/YLS $110/YLS	 $31 to $435/YLS $50 to $419/YLS $34 to $187/YLS	Results expressed vs. no intervention Productivity losses not included Results sensitive to discount rate and drug costs
Lifetime	5%	Not specified	Reference group $150/YLS $16/YLS Cost-saving (CS)	 $34 to $5,100/YLS CS to $8,000/YLS CS to $6,200/YLS	Results expressed vs. no intervention Productivity losses not included Results sensitive to HIV prevalence
Lifetime	3%	Public-sector health-care payer	Reference Group $13/DALY $6/DALY Dominated§ Dominated	 CS to $124/DALY CS to $28/DALY 	Results expressed vs. no intervention Child medical costs not in baseline analysis Results sensitive to child medical costs (CS) Incremental cost-effectiveness Incremental cost-effectiveness Incremental cost-effectiveness
Lifetime	3%	Public-sector health-care payer	Reference group $93/infection averted $794/infection averted Reference group Cost-saving 596	 Targeted therapy preferred strategy if HIV prevalence <7% or nevirapine cost >$5.4 Results sensitive to the efficacy of regimens	Incremental cost-effectveness Productivity losses not included Strategies applied to women not eligible for nevirapine prenatal care Incremental cost-effectiveness

**Based on drug cost reductions through manufacturing; ¤¤Long AZT: zidovudine regimen, used in ACTG076/ANRS024 trial; Enhancement: substantial effort to improve drug provision and delivery; ††Targeted nevirapine: counseling and HIV testing before treatment; Universal nevirapine: treatment for all pregnant women; § Dominated: more costly and less effective than an alternative strategy.

V
LIMITATIONS

There are several limitations in the studies reviewed above. First, not all of the studies evaluated the impact of interventions for the duration of patients' lives. The time horizon of a cost-effectiveness analysis should extend far enough into the future to capture major health and economic outcomes, generally the duration of life for patients with HIV disease. For interventions such as prevention of mother-to-child HIV infection, the effect of the program should ideally include the impact on both mother and child. Because of the impact of some interventions in the distant future, discounting of both future cost and benefits should be considered and made explicit [18].

Second, there is wide variation in the outcomes used as the measure of effect in these cost-effectiveness studies (*i.e.* infections averted, YLS, QALYs or DALYs saved), and there is a need to standardize the reporting of these outcomes. QALYs or DALYs saved that combine the duration of life with some measure of health-related quality of life and disability are a truer gauge of the impact of an intervention. While there are weaknesses to these methods, one can test whether results are sensitive to variations in the health-related quality weights used. This has generally not been done in the studies reviewed.

Third, in most of these studies, and particularly in those that have evaluated interventions preventing mother-to-child HIV transmission, data on the effectiveness of the strategies were from randomized controlled trials and not observational studies. Randomized trials are less prone to bias than observational cohort studies because they minimize observer bias and confounding due to both known and unknown variables. However, they are less likely to yield "real world" effectiveness data. Moreover, in most of these studies, the effectiveness of the interventions beyond the clinical trial endpoints was based on simulation models which include multiple assumptions. Using alternative methods of modeling may produce different results. Sensitivity analysis should test whether the results are sensitive to different methods of modeling and this has also not been done in the reported studies.

Fourth, the components of cost included in these studies varied widely. The use of any health intervention has different economic implications. The intervention itself requires health care resources. However, changes in health status can affect the amount or type of work done (*i.e.* productivity). In addition,

changes in health status often result in a change in the future use of resources (*i.e.* health care resources and other resources). Although the mean cost of resources consumed in the provision of each intervention was generally considered in these studies, future costs and productivity costs were often not considered. For example, the future cost of treating secondary tuberculosis infections, and the medical costs of HIV-infected children were not always considered in the strategies that evaluated tuberculosis preventive therapy and prevention of mother-to-child HIV infection transmission. This heterogeneity in the cost components included makes the comparison of results difficult.

Finally, results of studies performed in one resource-limited setting may not be generalizable to other areas where practice settings, patient populations, patterns of opportunistic infections and costs of care may differ substantially.

VI
THE COST-EFFECTIVENESS RESEARCH AGENDA

It is imperative that treatment efforts for HIV disease in less developed countries be enhanced [11]. Because of multiple competing demands for resources, regardless of the level at which they are available in a particular region or country, some method for prioritizing care must be utilized. Cost-effectiveness analysis is a methodology that allows just such prioritizing to take place. While many interventions may be effective, the interplay between efficacy and cost, as defined by the cost-effectiveness ratio, is a measure of value for money. These results can be directly used by clinical policymakers to inform standards of care and help establish guidelines for treatment [28, 29]. In order for cost-effectiveness analysis to be informative and to provide input into clinical and policy decisions, these analyses need to be credible, up-to-date, relevant to the local situation, and available to decision-makers. To accomplish these aims, data in four major domains are needed: natural history, efficacy, cost, and quality of life or disability.

1) Natural history: In order to understand the value of opportunistic infection prophylaxis interventions, an assessment of disease progression and complications in the absence of therapy needs to be understood. Many of these data are available in cohorts which have been followed [60, 61] or from clinical trials which have been reported.

2) Efficacy: For HAART, the efficacy of initial, 2nd line, and subsequent regimens in terms of virological suppression, immunologic improvement, and

clinical outcomes can be used to assess both short-term clinical impact and cost-effectiveness, for example, during the course of a clinical study or demonstration project [8, 9]. These data can also be used in formal modeling efforts to project long term cost-effectiveness of HIV care [33, 44].

3) Costs: Much of the literature on HIV in resource-poor countries has focused on the overall cost of care. Components of cost that will be critical for including in future cost-effectiveness analyses include direct medical costs, indirect medical costs, time costs, and productivity costs. Because productivity costs represent a higher proportion of total costs in resource-poor compared to resource-rich countries, better data on these costs are needed, as they will have a greater impact on the overall cost-effectiveness of HIV care.

4) Quality of life/disability: Experience with HAART in developed countries has shown both tremendous survival benefits from these drugs, as well as increasingly well-understood toxicity in both the short-term and long-term [62]. As treatment programs expand in resource-poor countries, better data on quality of life and disability, for those with untreated HIV as well as treated, will be needed to refine these analyses.

In addition to data needs, increased training of clinical and health policy officials in both conducting cost-effectiveness analyses and in utilizing them needs to be accomplished [19, 12]. Cost-effectiveness analysis is a methodology with clearly defined standards which can be used as one important component in developing, prioritizing, and improving HIV care. As resource-poor countries across the globe struggle to cope with both the growing HIV epidemic and severely constrained resources, developing the skills to quantify the impact and cost-effectiveness of the many available HIV interventions is imperative.

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A Review of Antiretroviral Costing Models in South Africa

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Key words: highly active antiretroviral therapy; haart; costs and cost analysis; health care; rationing; South Africa; developing countries.

Abstract

In the South African context of extreme polarisation and contestation on the role of antiretroviral therapy, a number of costing studies have been done over the last three years with a view to informing policy. The approaches to these studies are reviewed and key findings presented. The anticipated coverage of those in need of antiretroviral treatment is identified as a key uncertainty and major determinant of overall programme cost, perhaps outweighing differences in costing study design. Financial resources certainly exist for a treatment programme in South Africa, and issues of service capacity and readiness are identified as critical areas that have been overshadowed due to the elevation of the questions of affordability and universal access to the forefront of a highly contested and politicised policy process.

Résumé

En Afrique du Sud, où le débat s'est polarisé sur l'accès aux antirétroviraux et sur la contestation de leur rôle, plusieurs études sur les coûts de ces traitements ont été réalisées au cours des trois dernières années afin d'alimenter ce débat. Cet article décrit les approches développées dans ces études et leurs principaux résultats. Le niveau prévu de couverture des personnes qui ont besoin

d'antirétroviraux constitue la principale incertitude et le déterminant majeur du coût global des programmes, au-delà même des différences dans les modes d'évaluation des coûts. À l'évidence, des ressources existent pour un programme de traitement en Afrique du Sud mais les questions relatives à la capacité des services de santé et à leur degré de préparation sont des enjeux clés qui ont été mis au second plan. L'essentiel des débats et des controverses politiques porte sur les questions de l'accès universel et du prix des traitements.

Introduction

At the time of writing it is hoped that a National Treatment Plan that includes the provision of antiretrovirals in South Africa is imminent. If a plan does emerge, it will mark a turning point in a struggle characterised by extreme polarisation. In South Africa, marginal issues, such as the role of nutrition, and doubts about the effectiveness of treatment have dominated a debate that should rather be focused on the logistics of service delivery.

Following the announcement of the recipients of the second round of funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria, plans were on the table with secured funding for significant treatment programmes in Lesotho, Swaziland, Botswana, Namibia and Mozambique [1, 2]. At the same time, South Africa, with the largest burden and the most resources in the region, had not yet announced an antiretroviral treatment programme.

Although it is not within the scope of this paper to explore the possible reasons for this polarisation, the context is important in any discussion of costs and cost-effectiveness, as issues of cost and affordability have been utilised by both proponents and opponents to argue for and against Anti-Retroviral Therapy (ART). This paper seeks to review costing exercises undertaken in South Africa to date, and to explore common themes, approaches and deficiencies.

I
QUESTIONS BEING ASKED OF THE COSTS

Costing studies have been invoked to answer a number of different questions with respect to ART in South Africa.

Justifying the intervention

As alluded to above, one assertion has been that the intervention may not be affordable in South Africa, and that studies could assist in determining whether or not ART would be a good buy for South Africa compared to competing alternatives. The first study that sought to comprehensively cost a national intervention took this approach and concluded in 2000 that the intervention was not affordable [3]. A single intervention was modelled for a fixed estimate of the proportion of those with the potential to benefit from treatment accessing treatment, with scenarios representing different assumptions on future drug prices.

Maximising the roll-out or minimizing the cost

A further approach presupposes financial and other resource constraints and is one of economic efficiency, determining the intervention design that would yield the maximum benefit for the financial resources. One study adopting this approach has been published, where different scenarios represented different intervention options for the same numbers of people receiving treatment [4].

Calculating the resource implications

Justifiably, the major focus of current attempts to calculate the costs of treatment have tried to ascertain the financial implications for the government on the assumption of the inevitability of public sector provision of ART. The most recent studies have taken this approach, with scenarios representing different levels of coverage of those in need with one or two uniform intervention designs [5, 6].

Available resources

The above approaches are to varying degrees premised on the assumption of fixed and limited financial resources for the intervention. The assumption of costs being the limiting factor to the provision of ART requires revisiting for two reasons. The first is that in the South African context it could be argued that, at the levels of feasible provision in the next five years, sufficient resources exist. The second is that even if there were significant financial constraints, the nature of the public health catastrophe being faced would justify extraordinary

measures to find the financial resources for the intervention. Both arguments have been invoked in support of public sector ART provision, and the same cost-estimates can be utilised to argue both sides of the controversy, namely the affordability and unaffordability of ART.

The highest estimates of the potential financial burden the government could face if implementing a national treatment plan estimate this peaking at around R 20 billion (US$2.35 billion[1]) in 2015 [6], with lower expenditures before this. In the last two financial years the government has introduced adjustments to taxation that have cumulatively foregone R 30 billion (US$3.5 billion) in annual revenue [7, 8]. Geffen and Nattrass have argued that the worst case scenario would see the treatment plan constituting 2% of Gross National Product (GNP) in 2015 [6]. South Africa is currently in the process of an ambitious and costly arms procurement process of an order of magnitude that could potentially have covered the entire cost of an ART intervention. The potential affordability of the highest estimates is presented, not to justify the costs of the intervention or to argue that this is the best employment of those resources, but rather to support the view that in the likely scenario of a much more modest treatment plan than many of those being modelled, resources could be found if the political will existed. It is interesting that comparative cost effectiveness measures of alternative strategies for fighting the epidemic have not been a feature of arguments for or against ART, but rather the total financial burden of a national programme.

Costing studies

At least four separate attempts have sought to estimate the anticipated costs of a national antiretroviral treatment programme. Before considering the findings of each of these studies, it is of interest to look at the modelling approaches they had adopted.

Model topology

All of the studies to date have utilised similar deterministic approaches for estimating costs. Components include:

– demographic models to estimate the number of patients on treatment each year under different scenarios, as well as the numbers of people in each clinical stage;

1. All dollar prices reflect US$, and are calculated at an exchange rate of R 8.50 to US$1.00.

– estimates of antiretroviral medicine costs on a per-patient-per-year basis;
– estimates of the number of consultations per patient per year, and the costs of consultations;
– estimates of laboratory testing costs on a per-patient-per-year basis.

Different approaches have been used to determine numbers of individuals requiring treatment. In the case of Abt Associates Inc. [3], demographic inputs are obtained from the Doyle model, a proprietary model developed by Metropolitan Life [9]. The studies of Geffen *et al.* [6] and Abdullah [5] are based on levels of AIDS morbidity estimated by the *interventions* version of the ASSA2000 model [10]. While Boulle *et al.* [4] do not explicitly link their numbers on treatment to an external demographic model, they estimate that in 2007 the number of people starting ART in their model will be roughly 10% of the new AIDS cases estimated by the original version of the ASSA2000 model [10].

Both the Doyle model and the ASSA2000 model are combined demographic and epidemiological models, developed for the South African population. Both model the spread of the epidemic by dividing the sexually active population into four distinct risk groups, which represent different levels of sexual activity. In both cases, the sizes of the risk groups and the patterns of interaction between them are set at levels that maintain consistency with HIV prevalence data from antenatal clinics and (in the case of the ASSA2000 model) reported death data. The *interventions* version of the ASSA2000 model builds on the original ASSA2000 model by including scenarios in which antiretroviral treatment and other interventions can be modelled. Although structurally similar, the ASSA2000 and Doyle models produce significantly different results. The Doyle model produces lower estimates of HIV prevalence and AIDS morbidity at the current time, but predicts a later peak in prevalence than that estimated by ASSA2000.

Estimates of treatment effectiveness have been built into the demographic models. Three of the studies relied on the same demographic model-base (ASSA2000), where survival probability is explicitly adjusted on an individual basis for the presence or absence of ART. The survival benefit for these three studies has been assumed to be a median of 4.5 to 5 years [11].

Those studies that have attempted to provide cost-effectiveness estimates or account for cost savings have additionally costed the following under ART and no-ART scenarios:

– hospital and primary care costs for non-ART HIV management;
– costs of tuberculosis care.

Although some studies have assumed future price reductions for medicines and laboratory testing, no discounting was applied.

Four models are contrasted below (summarised in Table 1, pages 306).

Model commissioned by the National Department of Health, 2000

In 2000, the National Department of Health commissioned a study to look at the projected financial costs to the health sector as a result of HIV [3]. The demographic projections were based on a proprietary demographic model. All projected patients in WHO clinical stages 3 and 4 were considered eligible for treatment, with 80% assumed to access treatment. No explicit phase-in assumptions were apparent, and the benefit was assumed to be equivalent to a 75% reduction in mortality for those patients in clinical stages 3 and 4.

The study projected a total additional cost in 2010 of R 70 billion (US$8.23 billion)[2], and interpreted the intervention as unaffordable at then existing prices, as well as if significant reductions in medicine prices subsequently occurred[3]. The annual treatment costs were anticipated on a uniform per-patient-per-year basis at R 51,000 (US$6000).

A rationed approach to treatment

In late 2002, a separate study sought to explore the costs of a rationed programme, arguing at the same time the inevitability of rationing [4]. The study also sought to explore various trade-offs in programme design. Cost-effectiveness estimates were provided for the direct costs only, based on demographic estimates of life years saved (LYS). Potential savings were considered separately. All calculations were cumulative over five years of a phased intervention which was estimated to provide treatment to 10% of those becoming AIDS-symptomatic by 2007 based on mortality estimates from the ASSA2000 model.

2. Public sector only, net of cost-savings from reduced hospitalisation, outpatient visits, and tuberculosis.

3. The estimate in the event of medicine prices being 10% of the then current prices across all years was that in 2010 the additional expenditure as a result of HAART would be R 13 billion (US$1.53 billion).

Medicine prices had fallen significantly by this time, and the estimates of annual per-patient costs were substantially lower than the previous study. Additional reductions in medicine prices (34% over 5 years) were assumed. Explicit provision was made for intolerance-driven individual medicine switches impacting over time on regimen costs. Key findings included:

– the annual direct intervention cost per life-year saved, averaged over the five years, ranged from R 5,923 (US$697) to R 11,829 (US$1,392) depending on whether or not generic medicines were accessed, the inclusion of viral load testing, and the number of regimens offered;

– the annual medicine costs on first line regimens in the least expensive scenario (generic medicines) ranged from R 3,298 (US$388) to R 4,612 (US$543) in the initial projection year, depending on the duration of treatment;

– the total cost in 2007 with 107,000 patients on treatment was estimated to be R 409 million (US$48 million) in the most cost-effective scenario;

– the marginal cost per life-year saved for second line treatment at the point of virological failure was estimated to be approximately R 8,100 (US$950) for the most cost-effective scenario (36% – 39% more expensive)[4];

– the use of patented medicines instead of generic drugs increased cost per life-year saved by 53% and optimal laboratory monitoring by 45%;

– assuming no further reduction in medicine prices increased the cost per life-year saved by 23% on average over five years for the most cost-effective scenario;

– If the same health care utilisation assumptions that were utilised in the earlier study by clinical stage of illness were again applied [12, 13], the averted costs would have covered the intervention costs. The authors were however cautious about the applicability of these assumptions, and chose not to emphasise this aspect.

Treatment Action Campaign study

A group of researchers from the University of Cape Town and the Treatment Action Campaign published in late 2002 a costing study of a number of treatment interventions [6]. Details of one of the interventions, the costs of ART, are presented here.

4. Calculated by dividing the additional expenditure by the additional life years saved, on the assumption of a 60: 40 split in the survival benefit between first and second line treatment.

The ASSA2000 *interventions* model was used to provide estimates of the numbers requiring treatment as well as of effectiveness. The study included a single scenario that sought to cost the provision of ART for 90% of those projected to be clinically eligible by the year 2007, phased in over 5 years.

Medicine prices were assumed to be static over time, although a number of procurement and regimen options were considered, with provision for regimen variation provided for by a 20% factor on consultation costs to cover additional care.

Scenarios including and excluding viral load testing were developed. Limited provision was made for infrastructure expenditure and educational interventions. All costs associated with Voluntary Counselling and Testing (VLT) were included. The clinical consultation costs were calculated on the basis of assumed consultation durations, available working hours and salaries.

Key findings included:

– direct intervention costs of R 11 billion (US$1.29 billion) in 2007, peaking around R 20 billion (US$2.35 billion) in 2015. This assumes 1,257,000 and 2,483,000 people on treatment in each year respectively ;

– average annual first line medicine cost of R 4,260 (US$500), and second line cost of R 7,332 (US$863) for adults, and R 7,350 (US$865) for all regimens for children ;

– an additional 14 – 21% would need to be spent in order to include viral load testing in 2015, depending on the projected price of the test[5];

– an additional 35% would need to be spent in 2015 if patented medicines were utilised, whilst 19% of costs could be averted if first line and second line regimen costs could be reduced to R 3,600 (US$424) and R 5,400 (US$635) respectively;

– between R 6 billion and R 7 billion (US$0.70 – US$0.82 billion) could be saved through averted hospital costs by 2007;

– an additional R 1 billion (US$0.12 billion) could be saved in 2015 through averted social grants for orphans;

– the projected expenditure on hospitalisation in the absence of ART outstrips the anticipated health budget in projections, suggesting underprovision of services for HIV in general.

5. R 500 (US$59) for both viral load and CD4 cell count versus R 707.40 (US$83) for both these tests.

Western Cape Provincial Department of Health estimates

A separate study is currently being conducted under the auspices of one of the South-African provinces [5]. Results from the application of this model to a national dataset were not available at the time of writing.

The ASSA2000 interventions model was once again utilised for the demographic estimates in this study. Assuming treatment is initiated on average at the time of becoming AIDS-sick, a number of scenarios were built anticipating 20%, 50% and 90% of those in need accessing the intervention by the fifth year. Costs were varied by duration of treatment (crudely between the first six months on a regimen and treatment thereafter) to account for different monitoring and consultation frequencies, as well as regimen composition. Consensus amongst clinicians informed the choice of regimens, with first and second line regimens being available to each patient. The study did not attempt to determine cost-effectiveness ratios.

This study extends the earlier methodology [4] by including a range of starting regimens, costing a fixed intervention design that includes viral load testing and provision for first and second line treatment, and adding provision for a number of additional items such as resistance surveillance, and support for NGO's to assist in promoting adherence over and above existing counselling capacity. For each coverage scenario both generic and patented medicine prices are included with allowance for procurement, distribution and shrinkage. Further reductions in the prices of antiretrovirals are assumed, cumulatively totalling 47% reduction in 2007-2008. Key findings from the provincial dataset include:

– the major cost components of medicines, laboratory testing and consultations account for 43%, 22% and 17% of total costs in 2007-2008 respectively;

– patented medicines would increase direct intervention costs by 27% in 2007-2008 compared to WHO pre-qualified generic medicine prices.

A national task team has been established between the Ministries of Health and Finance to report amongst other things on the anticipated costs of a national treatment plan. Although the team has yet to report their findings, it is likely that similar approaches to those discussed above have been utilised. In addition, a cost-effectiveness study of a pilot public sector antiretroviral treatment programme in a peri-urban township near Cape Town should be available towards the end of 2003 [14].

II
KEY DETERMINANTS OF ANTICIPATED COSTS

The meaning of universal and progressive

What becomes immediately apparent when looking at these four studies is that the central determinant of overall resource implications is the estimated coverage and uptake. Three of the four studies included scenarios that anticipate 80% or more of those patients projected to be clinically eligible accessing ART. These scenarios are unrealistic for a number of reasons.

The need for close to perfect adherence for the individual benefit of ART, and the population risk of increased viral resistance, often lead health care professionals to suggest that eligibility has to take into account the presumed likelihood of adherence in spite of the difficulties in a priori identifying those patients who are most likely to be adherent [15]. In this context, the notion of "progressive realisation" enshrined in the South African constitution should be employed to ensure that the most marginalised in society are not systematically discriminated against in the process of responsibly scaling up services, rather than to force a dichotomous choice between rapid universal access and no access.

Geffen and Nattrass have poignantly contrasted the projected financial demand on the public health sector on account of HIV/AIDS and the total public sector health budget [6]. If estimates of optimal health service utilisation in the absence of ART are anywhere close to being accurate, it is clear from this comparison that the public health sector is significantly underproviding hospital services for those with HIV/AIDS. Many forms of implicit rationing pervade service provision in South Africa. For example, the uptake of a significant social grant for those caring for orphans is estimated to be less that 40% [6].

Perhaps most importantly, the responsible implementation of ART requires that services are progressively strengthened until they are in a position to provide the intervention. This suggests that many simpler interventions should be in place if ART is to be the final component of a comprehensive and synergistic health service response at a health district level. Some of the building blocks include adequate tuberculosis cure rates, existing HIV/AIDS treatment services that can provide a platform for identifying patients and developing treatment literacy, existing implementation of cotrimoxazole and isoniazid prophylaxis, and a well-functioning programme to prevent mother-to-child transmission of HIV. There are currently extensive human resource backlogs in public sector health provision in South Africa [16]. Even with financial resources available,

the crucial input of additional doctors and nurses may prove disconcertingly inflexible. Whatever steps are taken to set the public health system on a new footing to meet these challenges, it is unlikely that the universal coverage estimates utilised to date will be achieved.

Viral loads

Viral load testing remains disproportionately expensive, adding between 19% and 45% to the direct cost or cost-effectiveness estimates in two of the studies [4, 6].

Regimens

The above studies have varying degrees of detail in how the medicine costs are calculated. Perhaps even more important than the current cost estimate for medicines is the anticipated change in prices over time. There is no consensus on the reasonableness of assuming future price reductions beyond the best currently available generic prices. Even the most optimistic of the above models assumes that the annual cost for first line treatment will not fall below the oft-quoted target of $200 per year [17].

Consultation costs

The relative efficiency of clinical consultations for ART compared to other services at either primary care facilities or hospitals remains unknown. Three of the four reviewed studies have made assumptions for consultation costs in the absence of data. This is one area where the results of costing exercises currently being conducted in parallel with public sector ART pilot projects will improve the precision of estimates, in spite of the pilot nature of the projects.

III
KEY DETERMINANTS OF ANTICIPATED BENEFITS

Knock-on

One of the reasons for the inclusion of near-universal coverage estimates in treatment plans, is that if the population benefit is quantified only as an aggregate of the benefits to individuals on ART, it is only these scenarios that demonstrate

significant shifts in morbidity and mortality at a population level. There is no shortage of persuasive arguments on the importance of treatment in increasing the uptake and effectiveness of other HIV/AIDS interventions. The extent to which these still apply at much lower levels of coverage is uncertain. The arguments that a significantly rationed ART programme will retain these effects disproportionate to the rationing are central to supporting a rationed approach. Examples of these effects include the presumed increase in uptake of VCT, the reduction of stigma and denial, and the provision of hope in an increasingly desperate health care setting. It is unlikely that these effects will ever be able to be attributed to treatment programmes from a research perspective, as the introduction of programmes parallels the changing nature of the epidemic which in itself is likely to have enormous effects on the same parameters.

Component effects

The demographic modelling underpinning three of the studies has also attempted to quantify the population level impact of VCT associated with ART [11]. The additional testing required to enrol patients into ART programmes has been assumed to deliver independent benefits in line with those that have been seen with VCT alone. It is uncertain if these effects would be constant as the uptake increased. These effects result in infections averted and mortality and morbidity reductions many years later. To include the reductions in morbidity and mortality on account of these requires long-term projections with increasing uncertainty. These "component effects" have not to date been included in the benefit side of a cost-effectiveness comparison.

Non-ARV treatment costs

The difficulty in applying utilisation assumptions from cohort studies to whole population modelling exercises has already been demonstrated on the basis of the implausibility of the cost estimates this generates. It is also likely that the increasing pressure on services is constantly changing the service levels offered to those seeking care for HIV, with reducing lengths of stay in hospitals, higher admission thresholds, increased reliance on home-based care and reduced access to care.

Conclusions

This paper has demonstrated the range of work done to date on anticipating the costs of a national antiretroviral treatment programme in South Africa. A number of common determinants of cost across all of the studies have been identified. The key assumption on the projected extent or size of the programme has been highlighted and discussed.

Although projected costs have been utilised to argue both for affordability and unaffordability, it is argued here that other constraints are more likely to limit a future programme in the coming years. The politically contested role of ART may have led to an overemphasis on the use of cost estimates as justification for policy choices in a context where some of the key determinants of these estimates are subject to immense uncertainty. On the premise that a programme is desirable and inevitable, and that the projected costs are relevant mostly in facilitating financial planning, it is important for the debate on costs to shift to one of economic efficiency. South Africa would gain more by focusing on different dimensions of provision, with a keen sense of capacity at all levels, than on the affordability of universal access.

An argument frequently offered in response to the lack of capacity to deliver ART at the projected levels of need, is that the introduction of ART can be used to build health systems, rather than being limited by them. If true, this requires more attention being focused on health system issues and roll-out strategies. This is certainly the major challenge for South Africa.

This conclusion must however be tempered with the acknowledgement that simply because South Africa can find the financial resources to begin a programme now does not excuse the system of global Apartheid that makes treatments for HIV and other diseases an extreme financial burden for those countries most affected by them [18].

Table 1: Comparison of four costing studies. All prices in South African Rands.

	National Department of Health (2000)	Rationed approach (2002)	Treatment Action Campaign (2003)	Western Cape Department of Health (2003)
Demographic model	Doyle	Aligned with ASSA2000	ASSA2000	ASSA2000
Definition of clinical eligibility	Everyone in stages 3 and 4	At the onset of AIDS	At the onset of AIDS	At the onset of AIDS
Coverage of those projected to be clinically eligible for ART	80% of all in clinical stages 3 and 4	10% by 2007	90% by 2007	20, 50 and 90% by 2008
Phasing in	No	Yes, over 5 years	Yes, over 5 years	Yes, over 5 years
Modelling period	2000 - 2010	2002-2007	2002- 2015	2003-2015
Adults/Children	Both	Adults	Both	Both
Scenarios and sensitivity analyses	Uniformly reduced medicine prices	First line only; two regimens; no medicine price reductions; with and without viral loads; increased survival benefit; generic/patent	With and without viral loads; uniformly different medicine price structures	Generic/patent; different levels of coverage of need
First line annual medicine costs (adults)	R 44,000	R 4,612 - R 15,288	R 4,260	R 3,744
		R 8,933 - R 15,288	R 7,332	R 8,913
Initial first line regimen (adults)	Not stated	d4T / 3TC / NVP	AZT / 3TC / NVP (generic)	d4T / 3TC / NVP (55%) or EFV (45%)
Assumed medicine price reductions over time	Scenarios of uniform reductions across all years of between 10% and 90%	34% reduction by 2007	No change, but a scenario presented with lower prices across the whole study	47% by 2008
Impact of patented medicine prices over generic medicines	Not explicitly calculated	53% increase in cost per LYS in most cost-effective scenario	35% increase in direct costs in 2015	27% increase in direct costs in 2007-2008
Regimen variation	Uniform regimen	Uniform starting regimen with explicit assumptions on individual medicine changes	Uniform costs, but 20% factor on consultation costs to cover changes	Variable starting regimen, with explicit provision for within-regimen changes

Viral loads included	Not explicit - R 3,500* per year for monitoring	Increased baseline cost-effectiveness ratio by 45% in a scenario which included more frequent CD4 cell counts as well as viral loads	Increased direct costs by 14 - 21% in 2015	Included in all scenarios
Basis of clinical consultation costs	Not explicit	Cost per visit based on current primary care per consultation costs with a cost factor of 1.5	Explicit calculation of clinical costs based on consultation durations and salaries	Cost per visit based on current primary care costs with a cost factor of 1.5. Counselling considered already-funded
Other components included	None	Pre-ART treatment costs to ensure feeder services at a ratio of three people in treatment for each person started on ART	VCT component fully costed, with limited costing of infrastructure and educational campaigns	Pre-ART treatment costs to ensure feeder services at a ratio of three people in treatment for each person started on ART, resistance monitoring, and adherence support services

Direct costs in 2007/2008	R13 billion* to R 70 billion* additional cost (number on treatment unclear, but at least 80% of those projected to be in stages 3 and 4)	R 409 million in 2007 (107,000 on treatment)	R 11 billion* in 2007 (1,257,000 on treatment)	Estimates from model applied to national demographic data not yet available
Maximum direct costs (note the different projection periods)	R 70 billion in 2010	R 409 million* in 2007 (107,000 on treatment)	R20.3 billion* in 2015 (2,483,000 on treatment)	

Cost-effectiveness calculations for direct costs only	NOT DONE	Cumulative over 5 years, R 5,923 to R 11,829 per life-year saved depending on scenarios	Not done	Not done
Savings in the health sector as a consequence of treatment	The direct costs quoted above are additional to other HIV-related health sector expenditures and already account for averted costs	Averted hospital, primary care and tuberculosis treatment fully cover the most cost-effective scenario if those accessing ART are assumed to have optimally utilised services in the absence of ART	Up to R 10 billion per year could be saved from the time of full phase-in through averted hospitalisations and social grants for orphans	

**Rate of R 8.50 to US$1.00.*

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Direct Costs of Medical Care for HIV-Infected Children Before and During HAART in Abidjan, Côte d'Ivoire, 2000–2002

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Key words: cost; medical care; HAART;
paediatric HIV infection; Africa.

Abstract

The objectives of this study were to obtain an estimation of the cost of care for HIV-infected children in Africa. In Abidjan, Côte d'Ivoire, with the Drug Access Initiative, HIV-infected children obtain antiretroviral (ARV) drugs free of charge. Since October 2000, HIV-infected children have been monitored in an observational cohort in Abidjan. Criteria for eligibility for Highly Active Antiretroviral Treatments (HAART) are to be HIV-symptomatic or have a CD4 percentage below 15%. From the time they became eligible for HAART until they started the treatment we analysed all health events occurring in HIV-infected children and all costs related to medical care. We compared these to events and expenses occurring from the time they started HAART until September 2002. All direct medical costs were taken into account (outpatient visits, day hospital, hospitalizations, drug expenses, laboratory tests, X-rays, travel costs) for each child and for the two time periods.

Fifty four HIV-infected children, eligible for treatment, were monitored before and during HAART prescription. Follow-up periods before and during HAART were respectively 310 and 638 children/months. In Abidjan, mean costs for care management per year for a symptomatic HIV-infected child were €666.13 without HAART, and €3,037.81 with HAART for the same child. Morbidity decreased two to three-fold with this treatment. Antiretroviral

drugs and biological tests represented respectively 84% and 8% of the costs during HAART. This represents 3 to 4 times the minimum salary in Côte d'Ivoire and there is no realistic possibility of covering these care costs without the support of the government and the international community.

Résumé

Les objectifs de cette étude étaient d'obtenir une estimation du coût de la prise en charge médicale des enfants infectés par le VIH en Afrique. À Abidjan, dans le cadre de l'initiative d'accès aux médicaments antirétroviraux (ARV), l'État prend totalement en charge le coût de ces médicaments pour les enfants. Depuis octobre 2000, des enfants infectés par le VIH sont suivis dans une cohorte observationnelle à Abidjan. Les enfants éligibles pour ces traitements sont cliniquement symptomatiques ou ont un pourcentage de CD_4 inférieur à 15%.

Depuis le moment de leur éligibilité jusqu'au début du traitement, nous avons observé et analysé les évènements morbides et les coûts de traitement. Ces dépenses ont été comparées à celles survenues chez les mêmes enfants du début de leur traitement par ARV jusqu'en septembre 2002. Tous les coûts médicaux directs ont été pris en compte (consultations, hospitalisations, médicaments, examens de laboratoire, transport) pour chaque enfant et pour les deux périodes.

Cinquante-quatre enfants infectés ont été suivis avant traitement, puis sous traitement. Le suivi a été de 310 et 638 enfants/mois avant et pendant les ARV. À Abidjan, le coût moyen annuel de la prise en charge médicale d'un enfant infecté par le VIH symptomatique, sans ARV est de 666.13 € et, pour le même enfant de 3037,81 € avec les ARV. La morbidité est diminuée d'un facteur de 2 à 3 sous ARV. Les ARV et les tests de laboratoire représentent respectivement 84% et 8% des dépenses sous ARV. Ils représentent trois à quatre fois le salaire minimum en Côte d'Ivoire. Une approche réaliste du problème du coût des soins médicaux ne peut se faire sans un soutien financier effectif des états et de la communauté internationale.

Introduction

AIDS epidemic in Côte d'Ivoire in children

At the end of 2002, UNAIDS estimated the total number of persons living with HIV/AIDS (PLWA) at 42 million, with 3.2 million children worldwide.

The AIDS epidemic started early in Côte d'Ivoire the first case of AIDS being identified in 1985. Côte d'Ivoire is the most HIV-infected country in West Africa with 9.7% of 15-49 year-olds being HIV-infected. In this country, around 690,000 adults and 80,000 children under 15 are HIV-infected [1], the vast majority remaining undiagnosed or, if diagnosed, without any access to HAART.

Access to antiretroviral therapies

In Côte d'Ivoire, less than 5,000 HIV-infected patients, adults and children currently have access to HAART. Even if estimations are difficult to make, we can consider that less than 10% of HIV-infected adults know they are infected. Among children, the proportion is probably even lower. It is not usual to test children for HIV, especially those over 4 or 5 years old. Generally, health workers consider that HIV-infected children do not survive beyond five, thus they rarely think about testing older children. However, as the epidemic has existed for more than fifteen years, particularly among adults of reproductive age, there are many children 5 years old or more who are infected and live in the community. In the different centers where health professionals and Non Governmental Organizations (NGOs) care for HIV-infected children in Abidjan, it can be estimated that not more than one thousand HIV-infected children receive care, and there are probably only another thousand throughout the country receiving care.

The mortality of HIV-infected children living in Africa is very high, in the absence of antiretroviral treatment and cotrimoxazole prophylaxis: prospective studies of HIV-infected infants report over 50% mortality before the age of 15 months [2-4]. Available data for children over 5 years old is scarce and mostly from hospital-based or cross sectional studies [5, 6].

Several studies in Europe and the United States have however demonstrated the efficacy of antiretroviral treatments, and shown that they substantially reduce child mortality [7-10]. Despite studies describing the feasibility and efficacy of antiretroviral multitherapy in adults [11], including Africa [12-14], there are still very few data available on Highly Active Antiretroviral Treatments (HAART) in children in Africa [15]. There are also very few data on costs of paediatric HIV infection in Africa [16], and no study of this kind has included the costs of HAART.

In Côte d'Ivoire, the UNAIDS/Ministry of Health Drug Access Initiative, with the support of the International Therapeutic Solidarity Fund (ITSF), provides free access to antiretroviral therapies for HIV-infected children, after registration and confirmation of eligibility in the only accredited Paediatric Department (Centre Hospitalier de Yopougon, Abidjan) in Côte d'Ivoire. In fact there are less than 300 HIV-infected children on HAART, mainly in this paediatric department of Yopougon and a private health structure, the CIRBA, although a small number of HIV-infected children receive HAART in other accredited departments for HIV care. Although HAART treatment is subsidized and free of charge for families of HIV-infected children, there are several other limits to accessing these treatments. First, as mentioned above, many families do not know that the children they look after are HIV-infected. Second, even when they know the children are HIV-infected because their parents are ill or deceased, the extended family is not always well-informed about the health structures which can care for these children. Finally, as in adults [17], it is not only the costs of the drugs that families have to consider in getting access to HIV treatment for these children. In addition, there are travel costs, consultations, hospitalisations and biological tests (although biological follow-up of HAART is free of charge in the DAI). Other drugs, for bacterial infections, tuberculosis and opportunistic infections can be very expensive too, especially when symptoms are chronic, and often have poor results.

As part of a research project in Abidjan, we have been able to offer HAART to a group of children in an observational cohort, with all other medical costs covered by the program. HAART was offered in accordance with recent recommendations for antiretroviral treatment in Africa [18].

It is very important to estimate the cost of care for HIV-infected children in Africa, especially when we can expect an improvement in the health of these children with HAART, in order to clarify its impact on direct medical costs: to what extent will extra costs due to the price of HAART combinations be offset by savings in other direct costs of care, especially those for clinical episodes of opportunistic infections and other HIV-related morbidity?

In Abidjan, Côte d'Ivoire, among the 2 to 15-year-old HIV-infected children recruited and monitored in our cohort, some clearly needed initiation of antiretroviral therapies. Through the Drug Access Initiative, these medically eligible children could obtain antiretroviral drugs free of charge from the Ministry of Health. However, between 1998 and the end of 2001, there were often long

delays in obtaining HAART, and children sometimes spent months waiting for treatment, with an associated decline in their immune system.

Our objective was to estimate, in the short- and mid-term, the direct cost of all medical care of HIV-infected children who needed antiretroviral therapies, before and after initiation of this treatment. Even though our program is only a pilot, mainly funded by research organizations and the government, the collection of such information is important for future public health policy regarding the care of HIV-infected children and for raising funds for their care management.

I
METHODS

All the children are monitored in a dedicated Abidjan health center through standardized procedures. After inclusion in the cohort, once families have given their consent, there are quarterly routine visits, and a day-clinic is open all week for sick children. When necessary, children are seen for any intercurrent disease free of charge. Paediatricians have developed a clinical form to record any pathological event occurring during the follow-up of these children.

Criteria for children's eligibility for HAART are the following: to be HIV-symptomatic (CDC stages B or C) or to present a CD4 percentage below 15%. Under 25% of CD4 lymphocytes, all children were systematically put on daily cotrimoxazole prophylaxis.

For this study we selected all the children in our cohort who satisfied these eligibility criteria for HAART at some point during follow-up and who had experienced a delay of more than ten days. Children in the cohort who did not fulfil the eligibility criteria for HAART during follow-up, those who were already HAART-treated at inclusion and those who had access to HAART less than ten days after reaching the eligibility criteria were not included in the present analysis.

The choice of this sub-sample allowed us to analyze all health events and related medical costs that occurred during the period in which eligible children were waiting for access to HAART, and to compare them to those occurring after HAART initiation up to September 2002.

For each child, the length of follow-up time without HAART was calculated in months and we summed all follow-up periods in months. We followed

the same procedure for the time on HAART. In this way, we obtained a common unit of person/follow-up time in months. In this article we have chosen a child/year of follow-up as the common unit of calculation in order to calculate the mean direct costs of medical care per year per child and to compare periods with and without HAART.

We systematically and retrospectively reviewed the medical records of the children from inclusion to mid-September 2002, compiling drug prescriptions, clinical and biological investigations, specialized medical consultations, hospitalizations. All costs were expressed in Euro (€1 = US$1). All direct costs (outpatient visits, hospitalization in day-care units, hospitalizations in paediatric departments, drug expenditures, laboratory tests, other investigations) were taken into account for each child and for the two time periods. We compared these costs by type of expenses and also in total, including the cost of antiretroviral drugs.

For follow-up visits, we took the cost of a paediatric outpatient consultation in the public hospital (€3.05). The routine biological tests were a CD4 lymphocyte count (€11.89) and viral load (€102.06) at onset and then every six months. The costs of these biological tests remained unchanged between 2000 and 2002. For a day clinic stay, the cost of a one-day stay was estimated at €7.62. Lastly, the cost of biological screening (urea, creatinine, SGOT, SGPT, alkaline phosphatase, amylase, glycemia) for patients included in the Initiative was estimated at €15 [14]. In our case, we took into account two such screenings for each child starting HAART, one just before and one every six months. For travel costs, we estimated an average cost of €1.52 for each contact with our care network. For drug costs (other than HAART), we used our actual costs: drugs were bought through the Public Pharmacy or drug wholesalers. We only took the private pharmacy price for drugs which were not available through these systems. We used the 2002 prices in our calculations, as we were not able to obtain the original prices for 2000 and 2001 for each child. Comparison of drug prices for each year showed a price rise of less than 2% in frequently used drugs. We therefore used only 2002 prices, in order to simplify calculations.

As this program involves several partners, expenses are currently covered as follows: the Ivorian Government, with the help of International Therapeutic Solidarity Fund (ITSF) up to the end of 2002, pays for antiretroviral drugs; all biological follow-up necessary for antiretroviral prescription and monitoring is paid by the Projet Retro-CI (a research program of Centers for Disease Control

in Côte d'Ivoire); all other medical care expenses are covered by the research program which is funded by the French National Agency for AIDS Research (ANRS). Families generally pay travel expenses.

We did not include costs of the psychological follow-up (visits, group meetings) and community care (food and school support), choosing to focus on medical care. Psychological visits are routine for all children in our research program. But this type of consultation is rather unusual in Abidjan and cannot be considered as included in the "standard of care", although it should be. However, compared to medical expenditures, the community care costs remain quite small with no difference before and after treatment, as they correspond to the economic situation of the family and not to the health status of the child.

Antiretroviral drugs were obtained through the Public Health Pharmacy, the only official route available for their acquisition in Côte d'Ivoire since 1998 [19]. The drugs available were trademark drugs. Multitherapy consisted of two nucleoside analogues and either a protease inhibitor (Nelfinavir) or a non-nucleoside reverse transcriptase inhibitor (Efavirenz). Drug doses were calculated according to child weight as recommended by each manufacturer. Costs were calculated from the purchase price paid by the Public Health Pharmacy. These prices are fixed yearly following tenders to the MOH, and are applied from 1st June every year. Costs were therefore calculated in relation to the year of treatment. For each child, we calculated the time period (in days) he or she received HAART, and applied 2000 prices for the period up to 31st May 2001, 2001 prices for the period up to 31st May 2002, and 2002 prices for the period from 1st June 2002 to 15th September 2002.

Epi-Info 6.04 cfr (CDC, Atlanta, USA and WHO, Geneva, Switzerland) was used for comparison of incidence densities of medical events.

II
RESULTS

From October 2000 to mid-September 2002, 161 HIV-infected children were recruited in our cohort. Altogether, 81 children received antiretroviral therapies at some point during follow-up: 22 were already HAART-treated before inclusion in the cohort and 59 were not on antiretroviral treatment at inclusion. Most of

these 59 children (n = 54) had had a follow-up period in the cohort during which they were already medically eligible for HAART but had not yet had the opportunity to start this treatment. Altogether, these "delays" in accessing HAART amounted to a total of 310 child. month (mean 5.5 months). For these same 54 children, the total length of follow-up after HAART initiation was 638 child/month (mean 11.4 months). General characteristics of these 54 children at recruitment are described in Table 1.

Table 1:
Characteristics at baseline of HIV-infected children (N=54) before HAART treatment,
Programme Enfant Yopougon, Abidjan, 2000-2002

Characteristics	N=54
Age, median years (range)	6.6 (1.5 –13.4 YEARS)
Number of males (%)	33 (61)
Route of HIV-transmission	
Mother to Child	54 (100)
Both parents living	30 (55%)
Only one parent living	20 (37%)
Orphan	4 (7%)
Clinical stage	
N	1 (2)
A	13 (24)
B	33 (61)
C	7 (13)
Median plasma HIV-RNA viral load in Log/ml (range)	5.28 (3.31 –6.99)
CD4 lymphocyte % (median)	
< 2 years old (n=4)	9.6%
2 –5 years old (n=19)	8.8%
> 5 years old (n=31)	4.2%
CD4 lymphocyte count (median)	
< 2 years old (n=4)	704
2 –5 years old (n=19)	229
> 5 years old (n=31)	108

Medical events, care and costs before HAART

Before HAART, there were 328 recorded medical events for these 54 children (Table 2). The five most frequent diagnoses were: skin complaints, upper respiratory tract infections, bronchitis, diarrhoea and fever of unidentified origin.

These medical events involved 327 general outpatient consultations, 9 specialized consultations, 16 day-clinic hospitalisations and 4 hospitalisations in the paediatric department, corresponding to a total period of 15 days. There were 125 routine follow-up visits for the research program, of which 68 involved drug prescription.

The costs are listed in Table 3. For one HIV-infected child, routine follow-up visits for research amounted to €14.77 per year, and HIV immunological and virological screening came to €348.78, mostly in relation to viral load (89.6% of the cost). Medical visits, hospitalizations and diagnostic tests were estimated at a mean cost of €98.2, travel costs at €27.44, and total care at €191.7 per year of follow-up per child. Thus the global cost including follow-up expenditures was €680.90 per year. The specific follow-up for research represented only 2.2% of the total costs and, excluding these costs, care per year per HIV-infected child at a symptomatic stage came to a total of €666.13.

Table 2:
Medical events among HIV-infected children (N=54), before and during HAART treatment, Programme Enfant Yopougon, Abidjan, 2000-2002

	Before HAART		*During HAART*			
	N	Incidence per 100 months-child	N	Incidence per 100 months-child	Relative risk	p value
Length of follow-up (in months)	310		637			
Skin disorders	61	19.68	65	10.20	1.93 (1.36-2.73)	<0.0002
Upper respiratory tract infections	55	17.74	67	10.52	1.69 (1.18-4.35)	<0.003
Bronchitis	53	17.1	38	5.96	2.87 (1.89-4.35)	<0.0001
Diarrhoea	45	14.52	31	4.87	2.98 (1.89-4.71)	< 0.0001
Fever of unidentified origin	23	7.42	28	4.4	1.69 (0.97-2.93)	0.06
Pneumonia	20	6.45	15	2.35	2.74 (1.4-5.35)	0.0025
Oral candidiasis	16	5.16	5	0.78	6.58 (2.41-17.95)	<0.0001
Other infections	16	5.16	16	2.51	1.82 (1.18-2.85)	0.005
Conjunctivitis	10	3.23	16	2.51	1.28 (0.58-2.83)	0.33
Biological disorders	8	2.58	6	0.94	2.74 (0.95-7.90)	0.052
Mycobacteria	6	1.93	1	0.16	12.33 (1.48-102.4)	0.006
Malaria	1	0.32	15	2.35	0.14 (0.01-1.04)	0.015
Other	14	4.52	10	1.6	2.88 (1.28-6.48)	0.0087
Total	328	105.8	313	49.14	2.15 (1.84-2.51)	<0.0001

Table 3: Cost of medical care for HIV-infected children, before and during HAART treatment, Programme Enfant Yopougon, Abidjan, 2000-2002

	Before HAART			*During HAART*		
	N	Total cost (range)	Cost for a year of follow-up	N	Total cost (range)	Cost for a year of follow-up
Length of follow-up in months (years)	310 (25.81)			638 (53.21)		
Routine visits	**125**	**381.25** (3.05-15.25)	**14.77**	**214**	**652.7** (0-21.35)	**12.27**
HIV immunological and virological tests	79	9002.05 (113.9-341.8)	348.78	103	11736.85 (0-341.85)	220.58
HAART biological screening				135	2025.00 (15-60)	38.06
General consultations	327	997.01 (0-97.6)		348	1061.04 (0-76.25)	
Specialized consultations	9	59.45 (0-15.2)		15	109.76 (0-22.9)	
Day clinic	16	121.96 (0-30.5)		23	175.32 (0-38.1)	
Hospitalizations	4	243.92 (0-106.7)		8	1875.11 (0-899.4)	
Other biological tests		736.33 (0-101.4)			717.57 (0-78.6)	
Other tests		375.78 (0-53.4)			573.21 (0-183)	
a Sub total visits, tests and hospitalizations@		**11536.5**	**446.98**		**18273.86**	**343.43**
b *Travel Costs* *	**466**	**708.32 (4.6-59.3)**	**27.44**	**552**	**839.04 (3.0-54.7)**	**15.77**
Antibiotics		1325.31 (0-176.3)			1399.83 (0-225.0)	
Cotrimoxazole prophylaxis**		1299.89 (0-121.6)			2770.68 (0-137.24)	
Other drugs		2172.50 (0-130.6)			2508.21 (0-130.5)	
Other care £		150.16 (0-64)			89.94 (0-45.7)	
c Sub total care without HAART		**4947.86**	**191.70**		**6768.66**	**127.21**
Sub Total without HAART		**17573.93**	**680.90**		**26534.26**	**498.67**
d *HAART*		NA			135760.65 (20.4-6225.4)	2551.41
Total		**17573.93**	**680.90**		**162294.91**	**3050.08**

@ Excluding routine visits; £ including immunizations, transfusions, anti-tuberculous treatments, and physiotherapy; * travel costs were paid by the program for routine visits, and by families for medical events; ** in children, more than 70% of cotrimoxazole prophylaxis is taken in syrup form, which is more expensive than pills.

Medical events, care and costs during HAART

Among the same 54 children during HAART, there were 313 recorded medical events (Table 2). The five most frequent diagnoses were also skin disorders, upper respiratory tract infections, bronchitis, diarrhea and fever of unidentified origin, but with a much lower incidence, characterized by a two – to three – fold decrease with HAART (Table 2).

These events involved 348 general outpatient consultations, 15 specialized consultations, 23 day clinic hospitalizations and 8 hospitalizations in the paediatric department, amounting to a total of 120 days. There were 214 routine follow-up visits for the research program, of which 94 included drug prescription.

The costs are listed in Table 3. One year of follow-up of one treated HIV-infected child in the cohort cost €12.27, with €220.58 for HIV immunological and virological screening, essentially for viral load (89.6% of these costs). Biochemical screening cost €38.06. Medical visits, hospitalisations and diagnostic tests were estimated at a mean cost of €84.79, travel costs at €15.77, and drugs and care without HAART at €127.21. Thus care management per year per HIV-infected child at a symptomatic stage, excluding the cost of HAART, cost €498.67, *i.e.* €486.4 excluding costs of routine visits (73% of costs before HAART).

The price of antiretroviral drugs decreased dramatically during these years (Table 4). However, it represented an expense of €2,551.41 per child per year, the cost of nelfinavir accounting for 72.5% of this expenditure. The global cost, including HAART and follow-up, was therefore €3,050.08 per year. The cost of HAART represented 83.6% of the total.

If we compare the proportion of each type of cost before and during treatment, excluding HAART, we can see that the proportion of each type of expense is fairly similar: biological tests represent 51% and 52% of expenses before and after treatment respectively, medical visits and hospitalizations 14.4% and 17%, drugs 28% and 25.5%.

Table 4:
Evolution of antiretroviral drugs prices used in children in Abidjan 2000-2002 (in F CFA and Euros)

	2000		2001		2002	
	F CFA	€	F CFA	€	F CFA	€
EPIVIR ™ 150 mg, 60 tabs	48180	73.45	14160	21.59	13500	20.58
EPIVIR ™ syrup	14000	21.34	8100	12.35	7705	11.75
RETROVIR ™ 100 mg, 100 tabs	27800	42.38	19600	29.88	18701	28.51
RETROVIR ™ syrup	16200	24.7	13200	20.12	12601	19.21
STOCRIN ™ 200 mg, 90 tabs	132750	202.38	29340	44.73	31590	48.16
VIDEX ™ 150 mg 60 tabs	NA		14200	21.65	14200	21.65
VIDEX ™ 100 mg 60 tabs	33840	51.59	9420	14.36	9420	14.36
VIDEX ™ 50 mg 60 tabs	17940	27.35	7020	10.70	7020	10.70
VIRACEPT ™ 250 mg, 270 tabs	213840	326	213840	326	190350	290.19
VIRACEPT ™ syrup	NA		22684	34.58	21873	33.35
ZERIT ™ 20 mg 56 tabs	NA		3864	5.89	3864	5.89
ZERIT ™ syrup	18700	28.51	7002	10.67	7025	10.71

Discussion

Medical care costs for HIV-infected children are not well-documented in Africa. In this study, mean costs for care management of a symptomatic HIV-infected child without HAART per year are €666.13 and €3,037.81 for the same child with HAART. The incidence of disease events decreases two – or three – fold with such treatment. Even when we compare these incidences before and after initiation of treatment using a statistical test for matched pairs, which is possible with this group of children, these differences remain. Our study does not indicate the impact of HAART on mortality, as these children

survived long enough to be on HAART, but we know the positive impact on mortality from other studies [9, 12]. The main expense with HAART is, of course, the treatment itself which is very expensive, representing around 84% of the global cost. Biological screening is also a major expense, representing 8.5% of the cost. More interestingly, the only protease inhibitor used with children in Abidjan is nelfinavir, which represents 72.5% of the expenses for HAART, and is produced by the firm Roche TM which refused to participate in price negotiations on HAART for developing countries until very recently.

We have no way at the moment of estimating the representativeness of this cohort of HIV-infected children among the same population in Abidjan, as it is a specifically-recruited observational cohort. Moreover, only short and mid-term calculations were possible in our study, as the cohort was only set up two years ago. However, the care received by children in this cohort represents the standard of care HIV-infected children should receive in Côte d'Ivoire, as we only used drugs and technical means available in Côte d'Ivoire. Therefore, the costs we calculated for HIV infection with HAART are probably close to the mean cost of such a disease. But for HIV infection without treatment they are undoubtedly an underestimate as we selected only children who survived long enough to obtain antiretroviral drugs. If we had taken into account children in the final stage of the disease, the costs would probably have been higher.

It is also probable that we underestimated costs such as drugs (other than HAART) because of possible (and usually frequent) self-prescription of drugs for example, or visits to traditional healers, which are not reported in our system and could be significant, especially among untreated and symptomatic HIV-infected children. Moreover, as we took the prices we paid through the national Public Pharmacy and wholesalers, the expenses for drugs were lower than if families had had to pay for all drugs through private pharmacies.

The costs of care for a symptomatic HIV-infected child with HAART are 4.5 times higher than without HAART, and are well beyond the means of the families who take care of such sick children. Moreover, these treatments continue for many years, as HIV is a chronic infection without cure. But we need to emphasize that without such treatment, HIV-infected children die, often after a long and painful illness which usually mobilizes a large part of the family's resources. In any event, even the care of HIV-infected children without HAART is beyond the means of families, as it represents more than the minimum salary in Abidjan.

In addition to the cost of antiretroviral therapies which have decreased in the last few years and continue to decrease, other costs could also be reduced. For immunological monitoring, there are alternative methods which have been validated and could be 4 to 5 times less expensive [20]. Viral load measurement is not always necessary and could be omitted for most children. If absolutely necessary, viral load measures could be replaced by much cheaper methods, such as Taqman technology, in the near future [21].

In 1997, the cost of care of HIV-infected children in Abidjan in the first year of life was estimated at €255, excluding HAART which was not available at that time [16]. That cost was an average of all asymptomatic and symptomatic children under one year of age taken together. In this study, costs are higher, but for much older children and all HIV-symptomatic. The cost for asymptomatic children is probably considerably lower.

The cost of care for symptomatic HIV-infected children represents about 3 or 4 times the minimum salary in Côte d'Ivoire. It should include HAART, in developing as well as rich countries, as it gives the same dramatic decrease in morbidity and mortality. These figures give the real size of the problem. The Ministry of Health in Côte d'Ivoire, supported for a time by the International Therapeutic Solidarity Fund, provided one of the keys to caring for these children by subsidizing antiretroviral therapies for children. From our point of view as an external funding agency involved in research, other sources of funding are possible, such as private foundations, NGOs, companies, private donors, etc. In countries such as Côte d'Ivoire there are also public and private health insurance policies which cover part of the health expenditures of some people (*e.g.* workers and office staff in large companies) and could be involved in funding such treatment, as some firms already do [22]. In any event, even if we can obtain a dramatic reduction in the costs of drugs and biological screening, if international organisations and countries really wish HIV-infected children to be treated, the only way is to give families extensive support.

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Antiretroviral Treatment can be Cost-saving for Industry and Life-saving for Workers: a Case Study from Côte d'Ivoire's Private Sector

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Key-words: HIV/AIDS infections; cost effectiveness; HAART; private company; Côte d'Ivoire.

Abstract

Objectives: To describe the health and economic impact of comprehensive HIV care with Anti-Retroviral Treatments (ART) within a private enterprise in Côte d'Ivoire.

Methods: We describe how an "HIV solidarity fund" is used to finance ART to HIV-infected workers in Côte d'Ivoire. The treating physicians abstracted data from medical and company records including the year before and the two years after the introduction of comprehensive HIV care with ART. The human resources department estimated direct costs associated with morbidity and absenteeism.

Results: From 1995 to 1999 HIV was the leading cause of death for employees. Comparing the 12-months period before and 24-months period after the introduction of comprehensive HIV care with ART, there was a five-fold increase in company-based voluntary testing among HIV-infected persons, a 94% decrease in HIV-related absenteeism, an 81% decrease in HIV-related hospitalizations, a 78% decrease in new AIDS cases, a 58% decrease in HIV-related mortality. This resulted in dramatic health and survival benefits to HIV-infected workers and an estimated 2-year net direct profit of US$558,000 over the 2-year period. The HIV solidarity fund contributed US$217,000 and the program made a saving of US$287,000 due to reduced absenteeism, US$294,000 related to health care costs and US$194,000 in funeral costs.

Conclusions: Comprehensive HIV care with ART is cost-effective for HIV-infected workers in a private company with increased uptake for voluntary HIV testing and other prevention services.

Résumé

À partir d'une étude rétrospective, nous avons comparé l'impact socio-économique de l'infection à VIH au sein d'une entreprise privée en Côte d'Ivoire avant et après l'introduction des antirétroviraux. Le financement des traitements se fait par le système du Fonds de Solidarité Sida dans lequel tous les employés contribuent.

De 1995 à 1999 la principale cause de décès des employés de l'entreprise est l'infection à VIH. Suite à l'introduction des antirétroviraux, on constate une augmentation des dépistages volontaires, une réduction de 58 % de la mortalité, de 78 % des nouveaux cas de sida, de 81 % des hospitalisations en rapport avec le VIH, et de 94 % de l'absentéisme. Sur les deux années une économie substantielle de US$558,000 a été réalisée. Le fonds de solidarité a contribué à hauteur de $217,000. Les coûts de l'absentéisme ont été réduits de US$287,000, ceux des soins de santé de US$294,000 et les coûts funéraires de US$194,000.

Cette étude montre l'intérêt au plan économique d'une prise en charge globale des employés infectés par le VIH/sida incluant les antirétroviraux au sein d'une entreprise privée.

Introduction

Sub-Saharan Africa is the region which is the hardest hit by HIV/AIDS infection, with 70% of the 42 million world cases registered at the end of year 2002 by UNAIDS [1]. The hardest hit age groups in such countries are the working-age populations which constitute vital national human resources. In rural (agricultural environment), industrial (minerals or energy) and teaching areas (teachers), many surveys have shown the threat of the expansion of HIV/AIDS [2,3]. For example, people who are unable to carry on their professional business are experiencing a notable reduction in their family income. This is all the more significant in the African context as the disease is still badly perceived due to the stigma which sometimes causes absenteeism related either to the disease itself or to solidarity in the event of death [3,4]. At the present time, thanks to available data in the literature and to the expertise acquired locally for 3 years in Côte d'Ivoire with the antiretroviral treatment access

initiative [5,6], Ivorian researchers recognize the importance of antiretroviral tri-therapies in terms of mortality and morbidity reduction, improvement of quality of life and business revival [7,8]. Based upon this, we deemed expedient to initiate a survey of the socio-economic impact of HIV infection within private companies and assess the utilization of these antiretroviral therapies in this sector. Private companies are one of the targets of the National Initiative following the UNAIDS program.

In 1998, UNAIDS implemented an HIV Drug Access Initiative (DAI) in Côte d'Ivoire, Uganda, Chile and Vietnam in partnership with the Ministry of Health of each country. The DAI was a 2 to 3-year pilot project designed to develop model programs for providing antiretroviral drugs in resource-poor countries. Côte d'Ivoire was required to develop the infrastructures and systems necessary for providing antiretroviral drugs and monitoring the follow-up of patients. The DAI started in the country in October 1998, and the first line regimen was the double therapy associating 2 NRTI (Nucleoside Reverse Transcriptase Inhibitors). Monitoring was undertaken by the Projet Retro-CI (CDC of Atlanta). The government gave a subsidy (50-75%) and was helped by the ISTF [6]. Currently, the costs of the drugs are decreasing in the country but the amount of HAART (US$70-100 per month) is still non-affordable for people living with AIDS (PLWA) [7]. Less than 3% of the 1 million PLWA living in Côte d'Ivoire benefit from the treatment. The government aims to expand the DAI and to increase the numbers of PLWA on treatment.

I
OBJECTIVES

To describe how an existing mechanism to finance health-related costs was expanded to include comprehensive HIV care with antiretroviral therapy within a private enterprise in Abidjan, Côte d'Ivoire.

To describe the socioeconomic impact of HIV/AIDS before and after the introduction of antiretroviral treatment (ART) from the perspective of the HIV-infected worker and the perspective of the employer.

II
MATERIAL AND METHODS

Place of study

The Electricity Company of Côte d'Ivoire (C I E) has 3,500 employees and reported an annual turnover of US$268,000,000 and a profit of US$5,637,584. It has a central office in Abidjan and 12 regional offices in Côte d'Ivoire. Most of the approximately 3,500 employees are professionals and skilled workers with between one and five years of training.

In this private company, (as is a common arrangement in the absence of established health insurance systems in Africa) the employer and worker have shared health-related costs. The employer contributes a set annual amount per worker to a fund that is then managed by a broker. This fund is then drawn upon to cover a standard set of medical fees including all hospitalization and outpatient fees and medication costs, but does not include antiretroviral therapy and other expensive HIV medications. This fund first pays 100% of the health care costs and then seeks to obtain a 20% co-payment from the worker. In effect, the employer fund pays between 80 and 100% of the health care costs as the worker may not be able to repay the 20% co-payment. Workers also contribute to health care and funeral costs through their collective "death or hardship" solidarity fund; this involves a regular contribution from each worker which differs according to worker category and is used in the event of illness or death of a colleague (Table 1). In the case of prolonged illness, the company pays the full salary for a period of 6 months (employees are protected by national law through the "Collective Convention") and permits workers to resume full or light duties. After more than 6 months of continuous absenteeism the company may halve the salary or dismiss the employee [9]. The company also makes a financial contribution in the event of early retirement or death.

This private company has demonstrated a prolonged commitment to workers' health and HIV over the last decade. In 1992 a company AIDS committee was established in recognition of the growing impact of HIV/AIDS on workers and productivity. The committee members include the Chief Executive officer (Honorary Chairman), the medico-social team (doctors, nurses, social workers) and union representatives, and is chaired by the Central Human Resources Manager.

In 1999 the health care package was expanded to include comprehensive HIV care including combination antiretroviral therapy (ART) and other medication costs. Access to medication was largely paid for by a new "HIV and health" solidarity fund that required a greater monthly contribution by the workers (Table 1). The workers'HIV solidarity fund made a start-up contribution of US$80,537 in December 1999. The employer also undertook to provide additional financial support up to US$135,000 if required to meet expanded health costs.

Table 1: Workers category, monthly salary and HIV solidarity fund "sharing and support"

Worker category	Monthly salary	Monthly contribution to the HIV solidarity fund	Total monthly contribution to the HIV solidarity fund	Total annual contribution to the HIV solidarity fund
Directors1 (n = 28)	$1,181	$6.7	$187.6	$2,251.2
Executives (n = 294)	$1,181	$4.2	$1,234.8	$14,817.6
Supervisors (n = 2139)	$540	$2.7	$5,775.3	$69,303.6
Technicians (n = 1021)	$298	$1.3	$1,327.3	$15,927.6
Total. (n=3459)1 1			**$8,525**	**$102,300**

1 Directors receive a benefit in addition to their monthly salary.

11 Staff numbers increased from 3,459 in 1999 to 3,482 in 2000 and 3,728 in 2001

Methods

The study was conducted between 1995 and 2001. Prior to the introduction of the comprehensive HIV care program, the company's HIV/AIDS board (including company, health provider and union representatives) gave approval for the treating physicians to review medical and company records to obtain base-line data and forecast the impact of the company's HIV program. The program evaluation was also approved by the management of public and private health facilities to allow the treating physicians to review medical records related to workers'hospitalizations at those facilities. Strict protection of confidentiality

and promotion of access to care were guaranteed by the treating physicians and strict separation of medical and human resource files was maintained. Only the treating physicians had access to the names of HIV-infected persons.

Data abstracted from the company's human resources records included: number of workers'numbers of deaths (retrospective from 1995), duration of sick-leave, absenteeism including that related to funeral attendance. Data abstracted from company and external medical records included: number of voluntary HIV-tests provided with pre- and post-test counseling (VCT), workers with documented HIV-positive status and their HIV-disease stage, total deaths including cause (HIV/AIDS, accidents and other), and number and duration of hospitalizations including cause (malaria, HIV-related and other). We chose to be conservative with our definitions. All hospitalizations and deaths were coded as "HIV-related" when there was documentation in the medical record of the workers' HIV-positive status with serological confirmation. We classified all workers who died without documentation of their HIV status under "other cause". We only included the number of voluntary HIV tests performed by company physicians as we could not confirm that external HIV-tests were done with patient consent and pre- and post-test counseling.

With the assistance of the company's human resource department, we described the major costs associated with HIV morbidity and mortality from a societal perspective.

We report costs in US dollars using a conversion rate of US$1 = 745 FCFA and have not discounted to current values as we report costs over a short 3-year period.

We defined the major costs as those related to: provision of health care costs (hospitalization and health care costs including HIV-medication paid by the solidarity fund), absenteeism costs, direct funeral and invalid retirement costs.

We classified all sick-leave, funeral-related absenteeism, hospitalizations and death-benefits by worker category to calculate costs as these vary according to worker category (Table 1).

Direct funeral and invalid retirement costs are worker entitlements in the case of death or early retirement due to illness, which vary according to worker category and length of service. Absenteeism was divided into sick-leave and funeral attendance costs. When a worker is sick, a replacement must perform his tasks and the employer incurs the cost of the replacement salary in addition to full salary benefits for the sick employee. In terms of funeral-related absenteeism, when a worker dies it is standard company practice to send an official delegation of 50 company employees of various ranks. A typical delegation

consists of one executive, four managers, 20 skilled technicians and 25 unskilled workers. As funerals may be held away from the work location, funeral-related absenteeism varies but averages 48 hours. Salary costs for this typical 50-member delegation for two days is US$2,229.

We compared the voluntary uptake of HIV testing, antiretroviral treatment, morbidity, absenteeism, mortality and the major program costs for a 1-year baseline period before and the average for the 2-year period after the program began in December 1999. We estimated savings attributable to the program by calculating the observed expenditures and subtracting those expected, if baseline values had continued. We chose to be conservative in our assumptions and did not correct for the 7.8% increase in the worker population during the 3-year period (Table 1).

This program also received subsidies from external funding sources. As part of the UNAIDS/Ministry of Public Health drug access initiative, laboratory monitoring for toxicity and immunologic and virological response were fully supported by the US Centers for Disease Control and Prevention through Projet RETRO-CI and clinical care was supported and supervised by infectious disease experts from the Tropical and Infectious Disease Division of the tertiary referral hospital in Treichville. Medication was supplied by the national pharmaceutical store at prices negotiated with the major pharmaceutical companies.

The prescription criteria and laboratory monitoring were in accordance with prevailing international standards [10].

III
RESULTS

Impact of HIV on worker mortality

A review of the company medical records revealed that a total of 200 employees were documented with HIV infection from 1995 to 2001. From 1999 to the present, company medical records indicated that a stable 2.7-2.8% of current employees were known to be HIV-positive. Prior to the introduction of antiretroviral treatment, HIV/AIDS was the leading cause of death among workers; and consistently represented more than half of total mortalities (Figure 1). Following the introduction of comprehensive HIV care with antiretroviral therapy, both overall and HIV-related mortality decreased substantially; annual HIV-related mortality decreased by 58% from the 1999 baseline and during the first two years of program implementation (Table 2).

This represents a 75% decline from the 1998 peak of 0.52 workers to 0.13 workers in 2001. After antiretroviral treatment became accessible, HIV/AIDS was no longer the leading cause of mortality within the company (Figure 1). Mortality attributable to accidents and to "other" (without documentation of HIV infection) remained stable.

Figure 1: Employee annual death rate due to documented HIV/AIDS, accident or other cause, 1995-2001

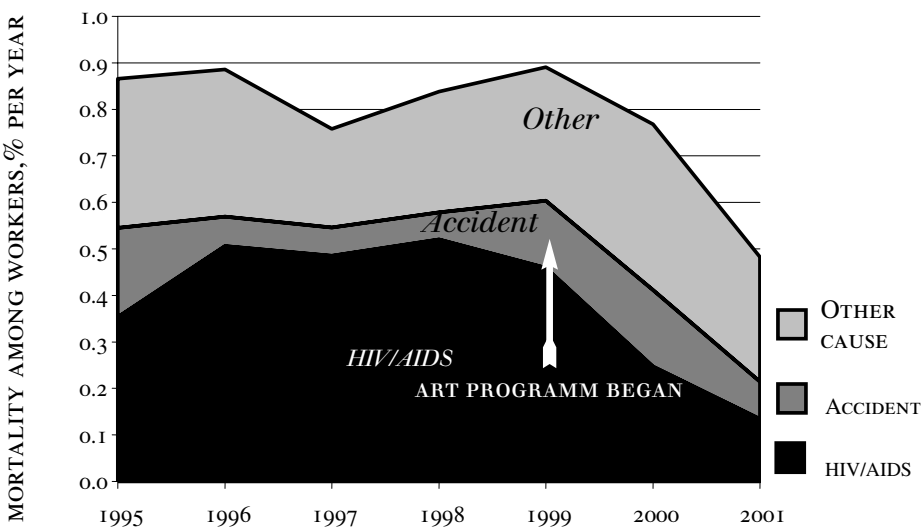

Table 2: Comparison of HIV status, AIDS absenteeism, morbidity and deaths before and after the use of ART

	1999 n= 3459	**2000** n=3482	**2001** n=3728
HIV status (number of employees)			
Known HIV+ employees	96	94	101
Receiving ART	0	62	74
Newly HIV diagnosed	25	22	16
On site voluntary counseling and testing	3	20	14
New AIDS cases	20	5	4
Performing full duties (%)	12 (12.5%)	79 (84%)	92 (91%)
Retirement (HIV+ workers)	8	3	0
Morbidity			
Total hospitalization	898	920	892
HIV+ hospitalization	123	32	16
Absenteeism (months)			
HIV related	335	22.7	15.5
Total	694.3	609.4	506.9
Deaths			
HIV/AIDS	16	9	5
Accident	5	6	3
Others	11	13	10
Total	32	28	18

Risk reduction counseling and HIV testing

The health benefits of comprehensive HIV care also included increased uptake of HIV risk-reduction counseling and voluntary confidential HIV testing (VCT). As seen elsewhere in sub-Saharan Africa, we found that HIV testing is still often performed without the knowledge and informed consent of patients in many health facilities in Côte d'Ivoire. In the year before comprehensive HIV care was implemented we found medical record documentation that 25 workers had been diagnosed with HIV but found only three (12%) of these persons had received VCT through company services. In contrast, in the two years after program implementation, 34 (89%) of 38 persons diagnosed with HIV received VCT through company facilities. Following this review, the company physicians were able to provide HIV counseling, voluntary testing and subsequent care to the HIV-infected persons who had been tested without their knowledge. There was also an increase in the number of HIV-negative employees who received risk-reduction counseling as voluntary confidential HIV testing in the workplace increased; in 2001, after the introduction of the comprehensive HIV care program, 30 workers (0.8% of the total workforce) chose to use company-based VCT services and learn their HIV status.

Morbidity, absenteeism and work-place disruption before the introduction of comprehensive HIV-care

In the year prior to program implementation, medical records documented 96 HIV-infected workers; most had advanced disease with 77% classified as CDC Stage C, 19% Stage B and only 4% were asymptomatic. None had received comprehensive HIV care with antiretroviral therapy prior to the beginning of the program. Twelve workers (12.5%) were able to perform full work duties; 34 (35.5%) required modified work duties, 28 (29.1%) took sick-leave of less than 3 months duration, 14 (14.6%) were on sick-leave for between 3 and 6 months and 8 (8.3%) were on sick-leave for more than 6 months. Eight HIV-infected employees reached the age of retirement at the end of 1999, and 3 at the end of 2000. These 96 known HIV-infected workers required a substantial amount of sick leave; they had an average sick leave of 3.5 months/year and an average 1.3 hospitalization/year with an average duration of 18.5 days/hospitalization. Sixteen deaths occurred including 6 among the patients on sick leave for between 3 and 6 months and 10 among those with sick leave longer than 6 months.

The deceased employees had worked for an average of 15 years with the company and represent a profound loss of skills and experience for the company. Because of the HIV-associated morbidity, workplace schedules were disrupted considerably; 10 temporary replacements involved the substitution of a less-skilled or less-experienced worker to perform duties of the absent employee; 7 workers could only work part-time, 18 workers were redeployed to accommodate ill-health which created difficulties to find suitable positions (*e.g.*a highly-skilled senior technician performing switchboard operator duties). The absenteeism among the 96 HIV-infected workers represented a substantial proportion (48.2%) of the total company absenteeism for all 3,459 workers (Table 2).

Morbidity and absenteeism after the introduction of comprehensive HIV-care

Following the implementation of the comprehensive HIV care program, morbidity and mortality declined dramatically while the proportion of workers known to be infected remained stable. During the first year of the program there were 94 (2.7%) current employees known to be HIV infected and 101 (2.7%) in the second year, including 72 workers who were known to be HIV-infected prior to the program and 22 new HIV diagnoses in 2000 and 16 in 2001. After clinical assessment and laboratory evaluations, company physicians recommended combination antiretroviral therapy for those with advanced disease based on international and national recommendations [6,10]. In 2000, 62 (66%) HIV-infected workers elected to commence combination antiretroviral therapy (ART) and four refused the physician's recommendations to begin ART. In 2001, 74 (73%) of HIV-positive workers elected to start ART and none refused the physician's recommendations to begin ART.

Comparing the one-year baseline with the average of the two years after ART became accessible, absenteeism declined by 94% among HIV-infected workers; annual sick leave decreased dramatically from a pre-intervention baseline of 3.5 months/HIV-infected worker to 0.24 month/HIV-infected worker in 2000 (Table 2). In 2001, it decreased further to 0.16 month/HIV-infected worker, an absenteeism rate similar to the average sick leave of 0.14 months among all workers. The average number of annual hospitalizations among HIV-infected persons decreased by 81%; from a pre-intervention baseline of 1.3 to 0.34 in the first year and a further decline to 0.16 hospitalization/HIV-infected worker in the second year. Workplace schedules were minimally disrupted by absenteeism; in 2000, 27 (29%) HIV-infected workers required some sick-leave, and 11 (22%)

in 2001. With access to HIV care, most HIV-infected workers were able to perform full work duties: 79 (84%) in 2000 and 92 (91%) in 2001.

In the first year, 9 deaths occurred among HIV-infected workers on prolonged sick-leave: 7 for longer than 6 months. Of these, 4 refused antiretroviral treatment preferring traditional treatments and 5 received antiretroviral therapy for less than 2 months before dying. Six other workers on prolonged sick-leave recovered to resume full duties. In the second year there were 5 deaths, of which 74 had received ART, and 4 in 2000.

Among all workers, annual new AIDS diagnoses decreased by 78%; from a baseline of 0.58/100 workers to 0.14/100 workers in 2000 and 0.11/100 workers in 2001. Known HIV-related mortality declined by 58%; from a baseline of 0.46/100 workers in 1999 to 0.26/100 workers in 2000 and to 0.13/100 workers in 2001. Overall mortality declined by 28%; from a baseline of 0.9/100 workers in 1999 to 0.8/100 workers in the first year and 0.5/100 workers in the second year.

In addition to sick leave, HIV causes substantial absenteeism related to funeral attendance by the official delegation of 50 company employees. Thus the 58% decrease in annual HIV-related mortality from 16 workers in 1998/99 to 9 deaths in 2000 and 5 deaths in 2001 (or -0.26/100 workers) translates into an estimated decrease in funeral-related absenteeism of 1,800 worker-days (18 deaths x 2 days x 50 workers) over the 2-year period.

Economic costs and estimated saving attributable to the program

In Table 3 we describe the direct health and work-related economic costs before and after the introduction of the comprehensive care program. Overall the program resulted in an estimated saving of US$558,205, as observed expenditures were substantially less than those expected from baseline data. The direct cost of sick-leave fell by 96% from a baseline of US$136,000 in 1999 to US$5,700 in 2001, resulting in a saving of US$256,000 above that expected during the 2-year period. The declining mortality also resulted in a net estimated saving of US$30,800 for absenteeism related to funeral attendance by co-workers with a more than 3-fold decline from a baseline of US$22,700 in 1999 to US$4,300 in 2001. Fewer deaths also resulted in a net saving of approximately US$9,000 in death benefits to the families of the deceased.

Hospitalization expenditures fell by 81% from a pre-intervention baseline of US$180,937 in 1999 to US$17,315 in 2001, an estimated saving of US$293,700 over the 2-year period. Expenditures from the employee "death and hardship fund" decreased by 82% from US$24,000 at baseline to US$4,000 in

2001. Net expenditures out of the newly-created "HIV solidarity fund" for antiretroviral and other HIV-related medications were US$217,000 (Table 3).

Table 3: Variation of medico-social costs before and after introduction of ART

	1999	2000	2001
Medical costs			
Hospitalization	$180,937	$50,872	$17,315
ART "Solidarity Fund"	$0	$117,450	$99,530**
Costs related to deaths			
Legal rights	$93,825	$18,523	$11,275
Death and hardship fund expenditures	$24,027	$7,248	$4,027
Costs related to absenteeism			
Funeral attendance by co-workers	$22,684	$10,290	$4,295
Sick-leave	$135,973	$10,225	$5,637
Total	$457,446	$214,608	$142,079

** *Prices negotiated with the major pharmaceutical companies. The decreases are substantial (85-90%), excluding for Nelfinavir .*

IV
DISCUSSION

First it is necessary to note the limits of this study. As many employees have not sought HIV-testing, the 2.8% of workers who were documented to be HIV-positive do not reflect HIV prevalence among workers and is substantially lower than the national antenatal HIV-prevalence of approximately 10%

during the same period [1]. In other settings (South African miners etc.) workers have been shown to have an even higher prevalence than pregnant women [3]. It is also difficult to capture the psychological and social impact of living in an environment of high HIV-prevalence with poor access to information and treatment. We have not been able to quantify accurately other HIV-related costs such as those associated with replacing and redeploying workers, the additional training required to replace skilled workers and the substantial costs associated with drugs paid out to hospitals.

However, this case study shows the critical role of leadership in the fight against HIV/AIDS and the savings which can be achieved through ART. Over a ten-year period, one visionary private company in Côte d'Ivoire has been able to work with its employees to finance a comprehensive HIV prevention and care program.

In the African context, this is a major step towards de-stigmatization. In our view this is a marked departure from previous private-public partnerships. What we consider as an innovation and example in our company is this very social mutual aid system, that consists of a monthly contribution paid by all socio-professional classes of the company. The revenue from these monthly contributions is earmarked for the purchase of medicines for HIV + staff. In ourprocedure, the psychological approach therefore consists in getting the various people concerned to understand that "it is better to contribute for life than for death".

In our opinion, this strategy of "awareness through monthly deduction" is an excellent means of encouraging prevention. The current data clearly indicate that access to treatment is a reinforcement and an essential condition for successful prevention programs by increasing screening tests, as is shown by our findings [11]. But for all employees to be involved, it is imperative to take stock of the situation on mortality and the rate of HIV/AIDS within companies.

In fact, antiretroviral medicines are known to be those which are the most expensive in countries with limited resources where AIDS is the major cause of mortality, and where over 90% of patients are not treated, essentially for financial reasons [1,6].With an average of US$30 per year, ART is no longer the most expensive effective HIV/AIDS intervention (US$700-1000 per year) [12].

This insurance system is clearly not free for patients, since they pay a monthly sum into the solidarity fund which entitles them to medicine. Therefore, the company does not have to bear the cost of free treatments or cost overruns. In our experience, this approach appears to be the best guarantee for good observance of the treatment in countries with low resources, as is

shown by Ivorian and Senegalese data [6,13]. In fact, one of the obstacles to the optimal observance of treatment in Africa is patients' insufficient means, which compels most of them to stop the therapy and use traditional treatments. However, it is clear that not enough is being done, and we need a multidisciplinary approach involving not only nursing staff but also social workers and counselors to ensure psychosocial support. In private companies, confidentiality principles should be observed as part of the "shared secret" [14].

As has been shown in other observational studies [2,3], we have been able to document a substantial and increasing economic and health burden due to HIV in a large company in Abidjan. We used very conservative definitions to provide minimum estimates of HIV-prevalence and the HIV-related impact on absenteeism, morbidity and mortality and have been able to demonstrate that most deaths and absenteeism were related to HIV/AIDS.

Our survey analyzes the medico-economic benefits associated with the utilization of antiretroviral tri-therapies in the treatment of HIV positive employees. Economically, this work highlights the fact that despite a minor acquisition cost of molecules both for every treated patient and for the company, the antiretroviral treatment offers excellent cost-effectiveness or cost-profit ratio, as shown in other studies [15,16]. Application of highly active antiretroviral treatments (HAARTs) significantly reduces morbidity and HIV-related death risk and prolongs patients' survival as a result of the reduction in the frequency of opportunistic diseases [5,7,15,16]. This saves patients from absenteeism, prolonged and repeated hospitalizations, even death and funerals, thereby releasing significant financial resources for the company [8,17]. Employees' savings may be enough to help treat them, and possibly also their husbands/wives and children, with antiretroviral medicines. This scheme, with its beneficial results for the company in terms of the cost of finding and keeping skilled and experienced staff, has been emulated to such an extent that to date 12 private companies in Côte d'Ivoire have selected this model and are providing cover for their employees.

This initiative should be extended to the public sector where many surveys show the threat of the expansion of HIV/AIDS. In addition, medico-social staff must be trained in good medical practice and information, and training must be provided for patients as well [18]. All these safeguards should guarantee a successful fight against HIV/AIDS in Africa.

Conclusion

This innovative case study shows that comprehensive HIV care including antiretroviral therapy can result in substantial cost-savings for industry, in social, economic and health benefits for HIV-infected workers, and in increased uptake for VCT and other prevention services. It has provided a best practice model that many Ivorian businesses are now emulating, which draws on existing worker-worker and worker-employer co-operative relationships. It also shows that it would be a sound business decision for many enterprises to invest substantial financial support in expanding workers'health care to include HIV prevention with VCT and comprehensive HIV care with HAART. This shows a feasible, sustainable and potentially replicable model for financing comprehensive HIV prevention and care within industry in sub-Saharan Africa.

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Construction Workplace Interventions for Prevention, Care, Support and Treatment of HIV/AIDS

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Key words: AIDS; construction; economics; financing; workplace.

Abstract

This paper identifies eight interventions for HIV/AIDS prevention, care, and treatment of construction workers. Where prevalence is low, cost of the eight interventions is 0.14% of the cost of a major construction project. With high prevalence levels of 10% of the workforce, costs of the package of interventions would still fall below 1% of total project costs. These percentages are low enough to permit contractors to include the costs of such services among the indirect costs for worker injury protection, insurance and emergency care without substantially increasing total project costs.

Sustained contracting agency financing of the package could provide a model for local sustainability of HIV/AIDS services. Contract agreements, labor legislation, and regulation of this industry could lead the way toward reducing stigma, financing essential interventions on a sustainable basis independent of general taxation, and generating new attitudes toward HIV/AIDS as a multisectoral issue.

Résumé

Ce papier identifie huit interventions en matière de prévention, de prise en charge et de traitement du VIH/sida dans le secteur économique de la

construction. Lorsque la prévalence est faible, le coût de ces huit interventions représente 0,14% du coût d'un programme de construction. Avec des niveaux de prévalence de l'ordre de 10% au sein du personnel, le coût de ces interventions resterait largement inférieur à 1% du coût total des programmes de construction. Ces pourcentages sont suffisamment faibles pour que les contractants puissent intégrer le coût de ces interventions dans les coûts indirects de protection contre les accidents du travail, d'assurances, et de soins d'urgence sans accroître substantiellement le coût total des programmes.

Ainsi, à travers les accords contractuels, la législation du travail et les mécanismes de régulation, la voie serait ouverte, dans ce secteur industriel, à la réduction du stigma, au financement d'interventions éventuelles sur une base continue, indépendante de l'impôt, et à la création de nouvelles attitudes vis-à-vis du VIH/sida au niveau local.

Introduction

There is now broad recognition that HIV/AIDS poses a generalized global health threat of unparalleled proportions. Over forty million persons are HIV positive; the percentage of adults aged 15-49 infected exceeds 10% in much of southern and eastern Africa. Infection rates are lower in other parts of the developing world, but the risks of further spread of the disease continue to grow.

The fight against HIV/AIDS will most likely be won or lost among the young. Persons between ages thirteen and thirty are those most vulnerable to contract HIV/AIDS. Thanks to improvements in blood supply management and control, risks of infection through contaminated transfusions in medical settings are greatly diminished compared to a decade ago. In contrast, risky sexual behavior, the use of intravenous drugs and related habits that may begin in youth continue to risk transmission of this disease. For that reason, many preventive interventions focus on behavior change among youth. This approach merits high priority in any multi-sectoral strategy to confront HIV/AIDS.

Among key groups at high risk of contracting HIV/AIDS are mobile populations. These are persons who travel away from their residences to seek work in unfamiliar environments. International workers in Bangladesh and Philippines, for example, exhibit far higher rates of HIV/AIDS infection than do similar groups from which they have departed in their home countries.

There are significant mobile populations within countries as well, usually from rural to urban areas. Young men seeking work away from limited farming

opportunities go to mining and construction – both occupations with limited skill requirements at the entry level.

Across time and space, construction trades employ more young workers at lower skill levels than all sectors except agriculture. These young workers, perhaps leaving families at home, may be among the mobile populations most at risk for contracting HIV/AIDS. They may be drawn to sex workers, or they may engage in other risky behavior heightening the chance they will join the ranks of the HIV positives.

7% of a country's labor force typically work in construction of housing, commercial buildings, and physical infrastructure, such as ports, roads, and bridges, that make life and commerce feasible[1]. An estimated thirty million persons work in construction in India. Most construction workers in low- and middle-income countries lack permanent employment contracts. They may have few, if any, non-wage benefits, such as protection in case of job-related injury, much less health insurance coverage for themselves or their families. They are key parts of the informal sector of the labor force and of the economy. Neither labor legislation nor employer-employee bargaining rights do much to protect them.

Still other construction workers, both more fortunate and probably more productive, have specified contract rights, non-wage benefits, protection in the case of illness and injury, rights to housing, childcare, and retirement benefits. They are properly designated as formal-sector workers, and they enjoy protection provided by labor legislation and bargaining rights.

There is no hard and fast dividing line between these two groups, formal and informal. Their relative shares vary substantially between countries depending on the success of labor movements to advocate for and win worker rights. Generally speaking, the richer and more homogeneous the country's population, the greater is the share of labor in the formal sector. Poor countries, marked by substantial immigrant groups, or even of interregional migrants coming from poor rural areas, have a larger share of their labor force in the informal sector. Low skilled construction workers are those most likely to be locked into informal, low-paying work that yields limited non-wage benefits.

1. The share of workers in construction varies with the business cycle, rising during periods of high net investment, falling during periods of slower economic growth. Among low-income countries, only a small share of construction workers, perhaps as little as 10%, has access to any non-wage benefits, such as retirement or disability security, or job-related safety protection beyond minimal training and supervision.

Formal-sector construction workers, those protected by national legislation and highly specific rights, are particularly likely to be found on major infrastructure projects financed by governments in low-income countries with the benefit of donor financial assistance. Major ports, highways, airports, and metropolitan railways are particularly likely to assure that labor legislation protects workers on such projects.

In countries with vigorous social security systems, construction workers may qualify for access to excellent health care services. In the Latin America and Caribbean (LAC) region, for example, a large share of HIV/AIDS programs are financed through social security: Argentina, 18%, Brazil, 21%, Chile, 26%, and Mexico, 72% [1]. Countries outside the LAC region generally do not have extensive social security system financing for HIV/AIDS. India, for example, has the Employee State Insurance Company (ESIC), but it has no HIV/AIDS assistance program in place. It could be engaged in assuring provision of services, including prevention, as part of its remit for protection of labor force members. Similarly, other countries of Asia and Africa can be expected gradually to strengthen social health insurance to include HIV/AIDS interventions.

Three options for construction workplace interventions to combat HIV/AIDS

The growing threat of HIV/AIDS in the construction workplace can induce any of three possible responses: (I) Contractors can be paid to do the right thing, usually sub-contracting to effective NGOs to provide an essential package of eight services. (II) Governments and donors can intervene and provide services directly. Performance to date has been mixed and uneven at best. (III) All parties may act irresponsibly and do nothing. In the poorest countries, neither prevention nor care and treatment programs are well developed. But in most of sub-Saharan Africa, South and Southeast Asia, Latin American and the Caribbean, there are NGOs and national AIDS control programs ready to implement effective interventions if means can be found to finance them. The following paragraphs seek to demonstrate that option 1 is best; option 3 runs the risk of ever-higher infection rates and costly future consequences. Option 2, preferable to Option 3, may impose a financial burden the state cannot bear.

Option 1
Require contractor(s) to sub-contract to an NGO group to provide eight basic workplace prevention, care, and support interventions to all on-site workers at construction sites

When a government agency undertakes a major infrastructure project, it initially invites potential bidders to respond to a general statement of the project with an expression of interest. The general statement does not now, but could include notice that HIV/AIDS prevention, care, and treatment for all project workers will be a required service to be provided as part of the task. The statement could even include a list of NGOs or government agencies for potential bidders to contact as potential sub-contractors for the provision of those services. A condition of qualifying as a bidder could be an adequate statement of how the HIV/AIDS interventions would be provided [2, 3].

The Request for Proposals (RFP) sent to potential bidders could build on UNAIDS and WHO guidance and hence include four prevention interventions (Table 1):

– condom distribution to all workers;
– treatment of sexually transmitted infections;
– peer counseling for safe behavior;
– voluntary counseling and testing (VCT) for those who seek tests to learn if they are HIV + and, if so, to be counseled on best health maintenance strategies.

The package would also include four care and treatment interventions:

– palliative care for HIV + persons showing symptoms of AIDS;
– treatment of Opportunistic Infections associated with HIV/AIDS;
– Opportunistic Illness prophylaxis (especially TB);
– Highly Active Anti-Retroviral Therapy (HAART) and related lab services to reduce risk of death from AIDS.

The cost of the eight-intervention package, when prevalence = 1%, is US$6,970 per annum per thousand workers. Cost data on prevention services, as well as treatment and prophylaxis for opportunistic infections, derive from a comprehensive review of case studies and pilot studies [4, 5]. Much of the task of assessment and compilation of the studies was done at the London School of Hygiene and Tropical Medicine by L. Kumaranayake and C. Watts. These same analysts prepared a background paper on scaling up interventions for the WHO Commission on Macroeconomics and Health.

Table 1. Selected construction workplace interventions for prevention, care, and treatment; coverage, unit costs, and annual cost per 1,000 workers in two HIV/AIDS environments, low prevalence (1%) and high prevalence (10%).

Intervention	*Coverage*	*Unit Cost*	*Annual Cost $ per 1,000 Workers, 1% prevalence*	*Annual Cost $ per 1,000 Workers, 10% prevalence*
Condom promotion and distribution	Distribute 10 condoms per month per worker	$0.05 per male condom distributed	600	600
Treatment of sexually transmitted infections	All employees with symptomatic STIs treated (estimated 20% of all employees annually)	$10 per STI case treated	2,000	2,000
Peer Counseling on Safe Behavior	All employees counseled by peers (unskilled workers); providing 1 peer counselor for every 500 employees at 1% prevalence, 1 counselor for every 100 employees at 10% prevalence	Wage cost of each peer counselor is US$2/day, US$500/annum	1,000	5,000
Voluntary counseling and testing (VCT) for those who seek it	VCT annually for 3% of all workers where 1% prevalence prevails; 30% of all workers when 10% prevalence prevails, but always on entirely voluntary basis	$10 per person counseled and tested	300	3,000
Sub-Total, four basic construction workplace prevention interventions			3,900	10,600
Palliative Care	Symptomatic care and support provided to estimated 1% of workers nearing death at prevalence = 1%; 10% of workers nearing death at prevalence = 10%	$40 per person per annum but care continuing over a two-year period	400	3,750
Treatment of Opportunistic Infections	Medications and care for 1% of all employees with prevalence = 1%; 10% of all employees with prevalence = 10%; costs usually spread over two years	$400 per treated worker for last two years of life, $200/yr	2,000	20,000
Opportunistic Illness prophylaxis (especially TB)	Isoniazid and cotrimoxazole prophylaxis treatments for 1% of all employees where prevalence = 1%, 10% of all employees where prevalence = 10%	$32 per treated worker per annum	320	3,200
HAART and related lab services	Provide HAART for 0.1% of all employees where prevalence = 1%, 1.0% of all employees where prevalence = 10%	$350 per treated worker per annum	350	3,500
Sub-Total, four additional care and treatment interventions			3,070	30,450
Total package of prevention, care, and treatment, cost per 1,000 workers			6,970	41,050

Source: Cost estimates referenced in [4], adjusted. For details see the website, www.futuresgroup.com.

The most controversial estimates concern likely costs of HAART. Cipla, an Indian producer of generics, states that its HAART combination can be sold for about US$350. A Thai report points to a daily dosage combination of three drugs that can be made available for about US$0,50 per day. The downward trend in costs may depend on successful negotiation of intellectual property rights (TRIPS) under the current Doha round of trade negotiations. A new drug introduced recently in Switzerland may, in contrast to this downward trend, cost more than US$20,000 per person per year.

The pertinence of unit cost estimates drawn from pilot and case studies is of course a matter of contention when considering scaling up to coverage of larger groups. However, until additional empirical results can be assembled, these estimates are the best available.

With HIV prevalence at 10% of the adult population, the estimated cost of providing the eight interventions is far higher than it is when prevalence is only 1% of adults (Table 1, last column). In the high-prevalence case, the cost of prevention alone is US$10,600 per thousand workers. This higher cost is attributable to more intensive peer counseling, with one counselor for each 100 employees in a high prevalence setting, compared to one counselor for each 500 employees in the low prevalence setting. Similarly, a far higher use of VCT would be appropriate in the high than in the low prevalence setting. The high prevalence setting requires about two and a half times more prevention spending than the low-prevalence setting.

The four care, support, and treatment interventions cost US$30,450 per thousand workers in the high-prevalence setting. This amount is ten times the resource requirement level of the low-prevalence setting. Treatment of opportunistic infections and provision of HAART both cost much more in the high-prevalence setting. The total cost of all eight interventions in the high prevalence setting is US$41,050 per thousand workers. Where there is substantial worker turnover, costs would be higher. These intervention costs also abstract from additional costs imposed on employers by losing workers to AIDS deaths and hence having to bear costs of retraining. Analysis of these contingencies would require study of specific case studies, a task for future analysts.

It is an important and useful step to learn the cost of an essential package of interventions. Strategic planning for HIV/AIDS programs requires such knowledge. A next step is to answer these subsidiary, important questions: How do these costs compare to the aggregate wage bill? How do they compare to total project costs? With answers to these questions, planners can assess the feasibility of including these services in the overall cost of implementing projects.

HIV/AIDS intervention package cost as a share of wages

Regardless of the infection rate, the annual wage bill for a thousand construction workers, at US$2 per worker per day for 250 workdays per annum, is US$500,000. The package of interventions thus adds 1.4% to the wage bill in the low prevalence setting, and 8.2% to the wage bill in the high prevalence setting. Considered as part of the wage bill, these amounts are of course considerable. And for any business in which wages are a large share of total costs, these amounts could be a major cost factor and a reason justifying resistance by employers to financing the package of interventions.

HIV/AIDS intervention package cost as a share of total project cost

Construction differs from many other industries in an important way. As a rule of thumb, major infrastructure projects use only 10% of total project costs in paying for direct construction labor. The reason is that much embodied capital in the form of wooden beams, nails, sand, gravel, steel, concrete, and related building materials constitute a major cost of the infrastructure project as a whole. Unlike many service trades in which direct labor may constitute half and even more of the total cost of the delivery of a product to its final consumer, construction activities use little direct labor to achieve project objectives.

Because labor is so small a share of total project costs, the burden of HIV/AIDS interventions, as a percentage of total project cost, is proportionately small for major construction infrastructure projects. The cost of the essential package of services adds only 0.14% to aggregate project costs in the low prevalence environment, and it adds 0.82% to total project costs in the high prevalence case. Three conclusions emerge:

– high profile infrastructure projects could incorporate the essential package of HIV/AIDS services at relatively modest cost when compared to the total project effort; this is true because of the low ratio of labor input costs to total project costs, a feature not common to other production sectors;

– stopping the spread of the disease before it reaches a large share of workers can yield very substantial long-term savings in the costs of prevention, care, and treatment;

– even at high prevalence rates, the costs of adding this package of interventions into a construction workplace setting is not so expensive as to pose an insurmountable cost problem.

The provision of these services does not affect the profit of the firm. Bidders and eventual winning contractors will all have been instructed to include the cost of these services in their total bid. The anticipated addition of a profit rate would not be affected by inclusion of this cost. The cost of providing these services thus falls not upon the construction company but rather on the public agency that issues a contract for the whole body of services, including such non-wage benefits as worker health care, which now would specifically include these eight HIV/AIDS interventions.

Would inclusion of required HIV/AIDS interventions unfairly favor multi-national construction companies over smaller, local firms? There is a risk that multi-nationals learn how to comply with such regulations in one country and then transfer skills easily to another, winning contracts that might have gone to local firms. A solution may be for the government agency to short-list qualified local NGOs that can deliver the services. These NGOs would have an incentive to work closely with local firms in designing specific approaches to the required interventions. Informal conversations with construction firms in India, both local and international, revealed no sense of disadvantage among the locals. They believe they may better understand how to work effectively with sub-contractors and unskilled workers in this sensitive area. The risk that multi-nationals might gain unfair advantage can be corrected with carefully designed requests for proposals.

NGOs and government clinics as sub-contractors

In most major infrastructure projects, a prime contractor engages many sub-contractors. Some sub-contractors in turn employ workers who specialize in moving materials, others in erecting structures, still others for security. Public and private health clinics are engaged to receive and treat injured workers, either on a contingency or flat rate basis depending on local custom. At isolated constructions sites, as for construction of dams, long distance highways or electrical lines, sub-contractors may be engaged to provide housing, canteen services, even mobile creches and schooling arrangements for the children of workers and their families. Adding the package of HIV/AIDS services to a varied menu of non-wage benefits would imply few or no additional complications for such projects.

Interviews with infrastructure project managers indicate that it is normal practice to estimate the cost of the required non-wage services to be provided as part of the project. That cost is then compared to direct project costs for

labor, materials, and capital and interest charges. That percentage, which may be in the order of 20 to 25% of direct costs, is then added to the bid price that is offered to the contracting government agency. Since the HIV/AIDS package could be added to this overhead charge, it could be included in total project costs without being identified, except as a required contractor obligation. This arrangement can work if the cost of the HIV/AIDS package is sufficiently small to be accommodated along with the other overheads identified above. The costs identified in Table 1 show that this condition is almost certainly met when prevalence is low. The HIV/AIDS package might add no more than one percentage point to the 20-percentage point overhead rate.

At higher levels of prevalence, the HIV/AIDS package cost adds a higher share to the overhead rate.

Who pays for the HIV/AIDS package?

The government agency that asked for expressions of interest, that issued an RFP, and that signed a contract agreement with a private construction company is ultimately paying for all the goods and services included in the contract. That agency does so on behalf of its government, and that government has undertaken the project on behalf of its citizens, the presumed major beneficiaries of the implementation of the project. In many low-income countries, a donor, such as one of the international financial institutions, shares the cost and reduces the burden on taxpayers. The HIV/AIDS package is a 'good buy' if the benefits, received by the workers and the larger community of citizens in which they live, in the form of a lowered risk of disease, exceed the costs of providing the package. Since reducing the risks of HIV/AIDS is a global public good, the intangible benefits of such spending may spill over an even larger geographical area to a global population.

The government agency may incur additional costs to monitor performance by contractors to assure that they implement the agreed interventions. Alternatively, the agency may delegate this responsibility to a department of the Ministry of Health or National AIDS Control Program. Compliance with contracts, laws and regulations varies between countries; poorer countries and those more affected by HIV/AIDS may pose serious challenges in the public effort to monitor and enforce compliance. The costs presented in Table 1 make no effort to estimate such costs.

Option 2
Seek government or donor technical support to provide the basic or expanded package at no cost to the project

Despite the advantages that accrue from pursuit of Option 1, there may be resistance to associating a "health objective" so closely with a "hard sector" activity in infrastructure improvement. In that circumstance, a multi-sectoral approach by a National AIDS committee or health ministry could guarantee provision of the HIV/AIDS package at its own expense. The government agency building the project would then not bear the burden of these added services. The national AIDS committee might secure donor support to finance the package. In India, for example, the Bill and Melinda Gates Foundation has earmarked US$100 million to be applied to prevention activities among mobile populations. Some of these funds could finance interventions with construction workers. NGOs could use their own resources to offer services at construction work sites without the support of the government contracting agency. Implementation may be uncertain. In the World Bank assisted Chad/Cameroon pipeline project, most HIV/AIDS services were financed and provided under terms of a separate International Development Association (IDA) loan to the governments in question [6]. Another example is the port rehabilitation project in Cambodia financed by Japan Bank for International Cooperation (JBIC), in which technical assistance interventions for HIV/AIDS prevention were provided for construction workers.

Supervision of service delivery by a national AIDS control agency might also help avoid the serious risk that private contractors might attempt to use HIV/AIDS testing as a means to avoid employment of HIV positive persons, or even to dismiss them. Such actions are unlawful in almost all countries facing the HIV/AIDS pandemic. Without public supervision by authorities determined to protect workers' rights, the risks of violation may be great. Thus this second approach may merit special consideration in environments that could fail to protect workers' rights.

Option 3
No change from current practice

Construction workers will incur larger incidence of HIV/AIDS than would occur if the HIV/AIDS package were to be provided at their workplace. These workers will eventually require higher medical treatment costs. They

may also risk transmitting the disease to a spouse or other partner when they return home (this mode of transmission has been a major cause of the spread of the disease in sub-Saharan Africa). These costs may be a burden on the workers' own families or on governments in the geographical areas to which they return after concluding construction work.

In the course of informal discussions with representatives of governments receiving loans, contractors implementing projects, and interested bilateral donors, UN agencies and NGOs, one finds few knowledgeable people satisfied with the status quo (Option 3). Most would agree with these points:

– the costs expected from these interventions are modest when compared to contractor obligations to provide safety, insurance against work-related injury, housing, safe water and waste removal, and basic first aid in case of injury, as well as referral to appropriate medical services for all on-site workers; and,

– the rate of return from implementation of these actions yields a high ratio of benefits to costs by lowering medical costs and increasing the working life of those who avoid illness and death from AIDS.

Contractors will accept inclusion of such services in bidding documents if they do not detract from the focus on productive work and provided that they do not reduce expected profit.

Would the net benefits of these eight interventions compensate for the added costs?

This key question is difficult to answer. The benefits from avoiding the spread of HIV/AIDS lie in the future. What may transpire with and without the proposed interventions to prevent, care for and treat the results of this disease requires some degree of speculation. Studies in Thailand and Brazil suggest that the internal rates of return on HIV/AIDS prevention investments range from at least 12 percent to more likely near 50 percent because of savings in medical costs and increased output generated by workers who do not otherwise become disabled and die [7]. There have been no comparable cost-benefit analyses for the specific interventions proposed here. It may be safe to say, however, that the low cost, compared to both aggregate wages and to the total project cost, supports the conclusion that making these investments has a high probability of yielding a very positive return.

Advantages of financing by contractors

Success in the fight against HIV/AIDS will ultimately depend on securing sustainable means of financing essential interventions. For families that can afford to pay, the purchase of condoms for prevention and medical care in the event of infection and onset of illness can proceed without a role for government or employers. For low-income workers, however, some alternative means of financing services needs to be secured. Public financing of health care services through social security systems has worked well in Latin America but is far less developed in other low- and middle-income regions of the world. Contracts for infrastructure construction can be written to be inclusive of HIV/AIDS services. Workers then need not face an out-of-pocket expense for those services.

Sources of resistance

Contractors in the informal sector may be reluctant to include HIV/AIDS prevention and care in a non-wage benefits package. Such interventions can raise costs. Managers may argue that HIV/AIDS prevention must be handled as part of overall Government labor legislation and policy. In no case, some argue, should specific requirements of this kind be specified by international donors or financing organizations.

The workforce may be uncomfortable with any open discussions of HIV/AIDS. They might reject any interventions on grounds that they violate privacy and cause discrimination and stigma. Managers express concern about sensitivity of workers who may be uneducated and unaccustomed to discuss matters concerning HIV/AIDS prevention.

On balance, however, changes in labor (and other) legislation to incorporate HIV/AIDS interventions for prevention and care, or inclusion of HIV/AIDS related clauses in bidding documents for major public infrastructure projects, could be acceptable to contractors. Contractors on major publicly financed projects must already provide a range of non-wage benefits and services for workers and their families.

How important is the construction workplace in the fight against HIV/AIDS?

UNAIDS estimates that the cost of workplace interventions constitutes eight percent of required prevention spending [4]. Construction workers, even if all formal and informal sector participants could be covered by contract-funded HIV/AIDS services, would use only one to two percent of total HIV/AIDS resources[2]. The amounts actually covered would be considerably less in most countries because so many informal sector construction workers are not covered by contracts or labor legislation requiring provision of HIV/AIDS (or any other non-wage benefits) services.

Despite this small quantitative impact, financing by contract requirement could nonetheless serve as the cutting edge for new, enlightened policies. Major infrastructure projects affect many more people than the workers who build them. They often have a high profile, particularly when implemented in major population centers as with urban road construction, ports, and underground railways. Experience with such projects can serve to demonstrate the feasibility of this alternative mode of financing. That experience can also demonstrate that workers may react positively to free-to-the-user services if properly integrated in a larger context of worker safety and health.

Advantages of financing by social health insurance

Where there are adequate labor legislation and social security systems, contractor financing of HIV/AIDS services could be covered automatically as part of legislation. Ministries of labor may need to revise regulations to assure inclusion of HIV/AIDS services. They may also need to assure compliance with laws and regulations. Generally, such overarching legal provisions would be preferable to specific terms and conditions written into contract agreements that cover only specific projects and interventions. The experience of major countries in the LAC region that have funded HIV/AIDS prevention, care, and treatment through social security, deserves

2. Calculated as follows: 0.07 of workers x 0.08 of prevention spending x 0.67 of combined prevention, care and treatment spending = 0.004 of all HIV/AIDS spending allocated to worker prevention spending. Spending on care and treatment is three-quarters of prevention spending at low prevalence levels and three times prevention spending at high prevalence levels. The share of all required HIV/AIDS spending allocated to all construction workers would thus sum to under 0.5% in low prevalence settings, and 2% in high prevalence settings.

study, and possible adoption, by countries in other regions. In governments with Ministries of Finance barely able to balance their budgets, any source of financing aside from tax-based revenues can help ease the sense of fiscal crisis.

Summary comments

The infrastructure construction workplace offers several strategic advantages as a place to offer a full range of HIV/AIDS prevention, care, and treatment interventions. This mobile population of workers constitutes a key group of young, at-risk candidates for peer counseling, voluntary testing and counseling, treatment of STIs, and condom distribution. For those in need of care and treatment, the workplace also offers an environment that can be free of stigma, provided that the HIV/AIDS health services are integrated into the health care and emergency medical support contracted with an NGO or government health service provider. Financing can occur as a component of total project costs and need not exceed a modest share includable among general overheads. Where social health insurance prevails, public policy need only assure that HIV/AIDS prevention, care and treatment are part of services available to all.

Major infrastructure projects employ a fraction of the seven percent of all workers employed in construction trades. Money spent on this group would constitute less than two percent of all required HIV/AIDS spending. But because such projects have high visibility, and are often associated with major donor assistance, they can constitute the cutting edge opening the way for sustainable financing of essential HIV/AIDS interventions across all groups.

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HIV/AIDS Affected Households: Status and Temporal Impacts

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Key words: impact; households;
measure; costs; affected.

Abstract

Micro studies, sectoral approaches and macro-models have tried to explain the implications of HIV/AIDS for the economy. These various approaches lead to a complex picture of the relationship between HIV/AIDS and economics. The objective of this article is to clarify the consequences of the epidemic by focusing on one social structure, the household, and by classifying the impacts according to status and temporal dimensions.

The main result of this paper is that, due to the multiplicity of impacts, the definition of what is traditionally considered as an affected household is not valid any more. Part of the status impacts and all the temporal impacts are experienced by households traditionally considered as non-affected. As a consequence, the restrictive definition of an affected household could lead to the underestimation of the cost of HIV/AIDS and to inappropriate policies.

Résumé

Trois niveaux d'analyse – études microéconomiques, sectorielles et macroéconomiques – se sont attachés à la relation entre Sida et économie. De ces différentes approches, ressort une image complexe des implications de l'épidémie sur les agents économiques et sur la production de richesse. Cet article tente

de clarifier les conséquences du sida sur l'économie en s'attachant à une structure socio-économique, le ménage, et en ordonnant les impacts du virus, d'une part, selon le changement de statut qu'ils entraînent pour les membres du ménage et, d'autre part, selon leurs caractéristiques temporelles.

La principale conclusion de ce travail est de mettre en évidence une nécessaire extension du concept de ménage affecté par l'impact de l'épidémie. La prise en compte de certains impacts liés au statut des individus au sein des ménages ainsi que la totalité des coûts temporels suggère qu'il serait pertinent d'inclure certains ménages aujourd'hui dits « non-affectés » dans la catégorie des ménages « affectés ». Une définition trop étroite de qui sont les agents affectés pourrait être à l'origine d'une sous-estimation de l'impact de l'infection à VIH et de la mise en place de politiques inappropriées.

Introduction

Many public health experts as well as non-governmental organizations share a common dissatisfaction with current economic analyses of the impacts of HIV/AIDS which are often viewed as only reflecting a limited part of the picture [1]. On the other hand, the diversity of economic approaches – microeconomic, sectoral and macroeconomic – creates a complex image of the relationship between the disease and development. These criticisms are mainly due to the failure of economic research on HIV/AIDS to incorporate a wide range of impacts and to consider as affected structures only groups of agents that experience illness or death due to HIV/AIDS. One way to shed light on the impacts of HIV/AIDS and to confirm – or otherwise – that the global cost is underestimated is to use a methodology which focuses on one social structure, namely the household, and which brings together the impacts found in the economic literature on HIV/AIDS under explicit headings. In this paper, impacts are organized under status and temporal dimensions. The status dimension refers to the impacts due to a change in the status of the members of the household, while the temporal dimension deals with the dynamic or chronic characteristics of the implications of HIV/AIDS.

The main result of this paper is to highlight the existence of three profiles of "affected" households that share common status or temporal impacts. It is not only households that experience illness or death due to HIV/AIDS that are "affected", but also households that are involved in the life of an affected household or households and that change their economic decisions as a result of the presence of the epidemic in their environment. Consequently, the definition of what is traditionally called an affected household can no longer be used.

Even if the consequences of the epidemic on the profiles are difficult to measure, their existence can explain part of the potential underestimation and questions the relevance of mitigating policies that focus on limited impacts and on the original profile of "affected" households.

I
THE COMPLEX IMAGE OF THE IMPACT OF HIV/AIDS ON DEVELOPMENT

Microeconomic, sectoral and macroeconomic approaches

The literature on the consequences of HIV/AIDS on the economy has been based on three different approaches. Micro-studies have described the consequences of the epidemic on a certain social structure or on specific agents, typically firms, governments, households, orphans, women etc. For example, a longitudinal sero-epidemiological study conducted in the Rakai district (Uganda) between 1989 and 1992, has provided information on ownership of durable goods of affected and non-affected households. In the survey, a significant decline in resources in HIV/AIDS affected households was observed over the period, whereas the economic status of non-affected households did not change [2].

Sectoral approaches have tried to assess the costs and benefits of alternative prevention and care of HIV/AIDS. For example, for the period 2000-2005, the costs of four treatment intervention scenarios in South Africa have been evaluated. The first two simulations assessed that if 25% and 75% of all pregnant women and infants living with HIV/AIDS received antiretroviral prophylaxis, such policies would cost respectively 1.8 and 5.5 million US$. In the third scenario in which all pregnant women received the prophylaxis treatment, irrespective of their serostatus, the global cost would reach 52 million US$. The last scenario concerns the impact of triple-combination antiretroviral treatment on 25% of the adults living with HIV/AIDS, excluding pregnant women: it estimated a global cost of 19 billion US$ [3].

Finally, macro-models have tried to measure the overall impact of the epidemic on economic development. Those models evaluate the percentage points of growth lost through the presence of HIV/AIDS. For South Africa, a recent model calculated that the difference between the real growth rate in the no AIDS scenario and the AIDS scenario will reach a maximum value of 2.6% in 2008 [4].

Even if these approaches appear quite different, they do share common limitations. The objective here is not to carry out another review of the literature [5], or to list all the limitations of each approach, but rather to highlight selected common problems.

Common limitations to the three levels of evaluation

First, there is a lack of consensus on the best way to model or understand each approach. Micro-studies on HIV/AIDS do not agree for example on the best sampling method: recruitment via health care services, recruitment via tests on a random sample of the general population, or recruitment via community-based organizations, non-governmental organizations and community leaders [6]. With regard to macro-models, there are as many theoretical frameworks as there are studies. For example, some estimates are based on the Solow growth theory [7], others use a computable general equilibrium model [4] or supply/demand frameworks [8].

Secondly, this lack of consensus is partly due to the lack of data and to the fact that barriers to research are enhanced by parameters such as information on the serostatus or the stage of the epidemic at national and individual levels in this country. Consequently, each approach tries to build models or procedures that use available data. The need for nationally representative surveys of HIV prevalence in particular is at the centre of this preoccupation. In South Africa, the Nelson Mandela Human Sciences Research Council (HSRC) study of HIV/AIDS is the first household survey that assesses several levels of prevalence – by sex, age, community or province, and also social information – awareness of HIV/AIDS serostatus, sexual behaviour or socio-cultural context – at the national level [9].

Thirdly, each level of analysis has failed to take into account the conclusions of the other levels of research. In particular the constraints of macro-modelling do not allow all the impacts that have been described in depth at the micro or sectoral levels to be aggregated effectively. This is true in particular for long-term effects or psychological impacts of the epidemic. Typically, even if recent micro-studies have assessed the dangers of not giving appropriate care to children, especially orphans [10], no macro-economic model has been designed to incorporate the future consequences on growth of this vulnerable population. Consequently, it is acknowledged that the impact of HIV/AIDS might be underestimated.

Lastly, the research on the economics of HIV/AIDS has failed to use recent relevant economic tools to assess the impact. One example could be the growing

interest in the role of information on economic decisions. Individuals who know their serostatus will not behave the same way as individuals who do not. Similarly, individuals who know they can be treated are likely to make different economic decisions from individuals who are unaware of the existence of this treatment or whose access to treatment has been refused or is impossible. Consequently, the literature on rational expectations should be used to improve the analysis of the impact of HIV/AIDS at the microeconomic level as well as at the macroeconomic level.

Typology of the impacts in the literature

From these common major limitations, several problems of conceptualization emerge when one tries to collect the different impacts and to clarify the complex picture of the interactions between development and the epidemic. In order to understand this better, we will focus on the household as a specific social structure facing specific impacts.

The first issue concerns the relevant typology for classifying costs. Some authors do not always choose to classify the impacts, and list them putting emphasis on one aspect or one member of the household [2]. Others do classify them by focusing both on the origins of the impact – morbidity or mortality [7], and on the nature of the impacts – indirect or direct. The first typology is useful to understand the epidemic and its characteristics, but can appear redundant as some impacts, such as the care of the nuclear family of a worker living with HIV/AIDS, are due to both morbidity and mortality. The second distinction appeared at the early stages of the economic research on HIV/AIDS and defined direct costs as costs for medical and funeral expenditures, and indirect costs as those due to the impact of the illness on productivity [11].

Although useful, this typology has failed to incorporate the whole range of costs related to the epidemic, and research on the impact on households has focused on the short term impacts and on those that are most easily measured in financial terms. More recently, new terms have been introduced such as "decreased investments in productive activities, education and savings" [12], "other impacts" [13], "intergenerational impacts" [10] or "indirect differed costs" [14]. However, explicit definitions of these new categories of costs have often been missing.

The last limitation of the available typologies refers to the basic definition of the impact. Fifteen years of economic research on HIV/AIDS has led to the conclusion that this disease cannot be considered as a sharp shock but as a continuum between a sharp shock and slow and profound changes [15]. In the

literature, the distinction between these short run shocks and their consequences is not always highlighted. Typically, migration can be considered in some articles as an impact of the epidemic and in others as a coping strategy to mitigate the growing costs of the epidemic [16]. This creates confusion about what a sharp impact is, what a coping strategy is and what the overall consequences on wealth are.

Proposing a typology of impacts of HIV/AIDS on households is not a sterile exercise. The limitations due both to the existence of different levels of research and to the lack of typology could explain the suspected underestimation of the impact of HIV/AIDS on households and more generally on development.

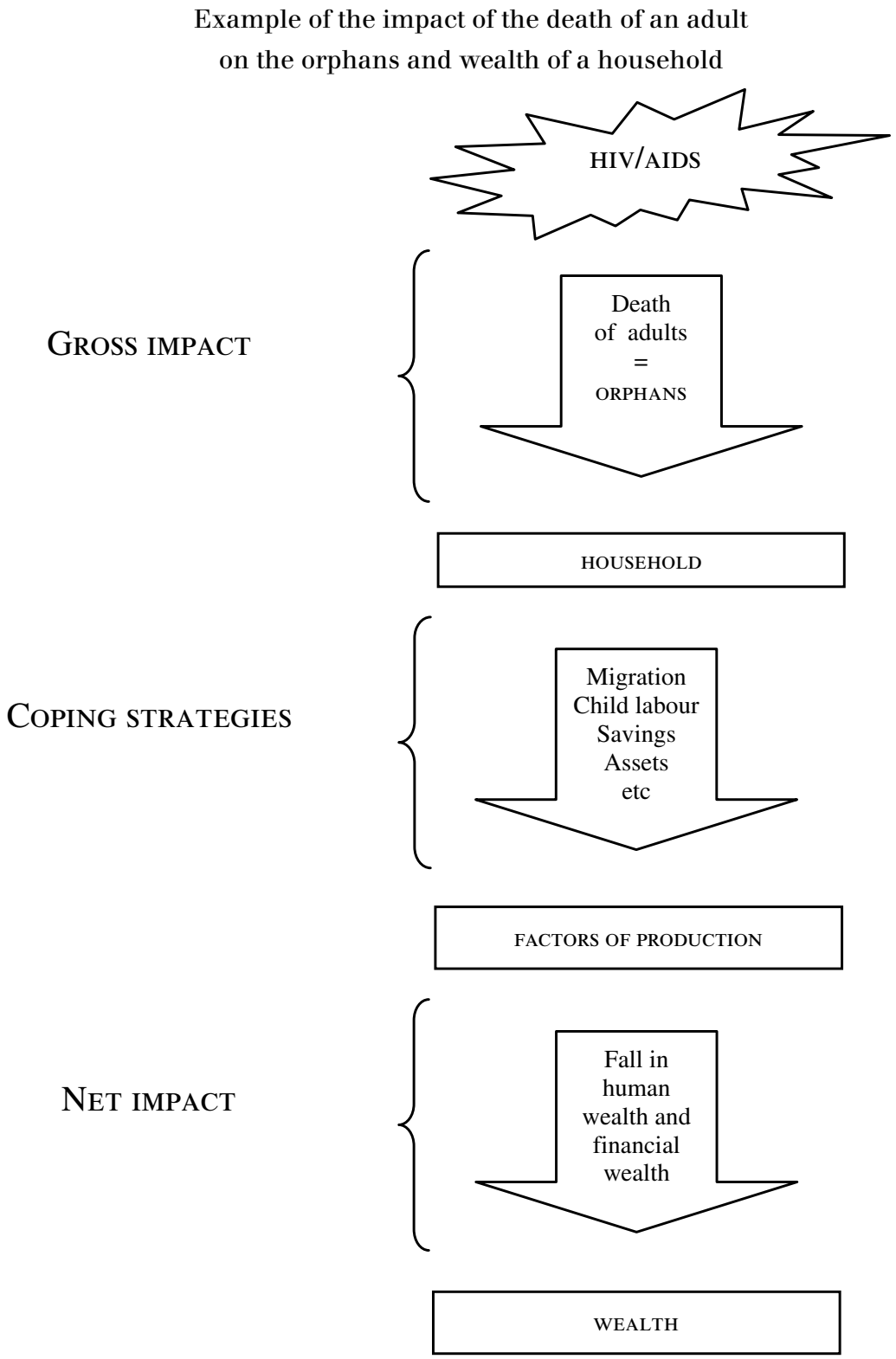
II
A SOLUTION TO CLARIFY THE COMPLEX PICTURE: STATUS AND TEMPORAL DIMENSIONS OF THE IMPACTS

Gross impact, coping strategy and net impact

The first conceptual proposition concerns the definition of what an impact is, or rather on which type of impact the emphasis should be put. In order to choose the relevant impacts for analysis, the chain of implications from the immediate impact to the loss of wealth of the household is shown in Figure 1. This figure presents three stages in the continuum of any impact. The first is what is called here gross impacts of HIV/AIDS on the household. Gross impacts are prime consequences of the epidemic before any change in the strategy of the household to mitigate them. Responding to these costs, the members of the household will adapt their economic behaviour to "cope": coping strategies correspond to the second stage of the continuum. Several "economic" coping strategies can be listed, including migration, child labour, sale of assets, use of savings etc. [16] These strategies will result in changes in the factors of production that are likely to affect the wealth of the household. The interaction between factors of production and wealth is the last stage of the chain. The terminal change in the wealth of the household is then called the net impact. In this paper, the analysis will focus on a range of gross impacts.

The distinction between the three stages is not always obvious, in particular certain costs could be defined as gross impacts or coping strategies. Care, for example, will not be considered here as a coping strategy: the members of the household living with HIV/AIDS need care and this care cannot be negotiated or planned.

Figure 1: Gross impact, coping strategies and net impact of HIV/AIDS on households



Consequently, we consider here that a distinction must be made between care – that could be considered at the same level as medical costs – and the other "coping strategies" such as sales of assets.

For a better understanding, the gross impacts can be differentiated according to status and temporal dimensions. Such differentiation will allow our proposed alternative typology to overcome some existing limitations of the current classification based on the distinction between direct and indirect costs.

Status and temporal dimensions of the impacts

The status dimension refers to the change in the status of the members of the household as a consequence of HIV/AIDS. This idea comes from the evidence that some of the impacts are due to a change in the status of the members of the household living with HIV/AIDS, whereas others are due to a change in the status of the members of the same household who are not living with HIV/AIDS. The first point refers to the transition of the members living with HIV/AIDS from having the status of a productive or active member to one of being ill and finally deceased. The second point refers to a transition from the active status of the members that are not living with HIV/AIDS to that of a care-giver then to the status of dependant - a widow or orphan. Consequently the status characteristic has two values: change in status of the members living with HIV/AIDS and change in the status of the other members of the household. Even if this aspect is more documented today, with the distinction for example between the impacts on individuals or households and the impacts on dependants, orphans and the elderly [15], the separate analysis of the different members of the community confuses the overall implications of the disease.

The temporal dimension refers to impacts considered as either "dynamic" or "chronic" These terms were given preference over the use of the traditional distinction "short run/long run" in order to put the emphasis on the fact that no cost due to HIV/AIDS is static: all the implications have long run consequences. What distinguishes dynamic from chronic impacts in the long run is whether or not the causal chain presented in Figure 1 will be repeated. On the one hand, by dynamic we mean an impact that creates a shock in the short run and leads to consequences in the long run through coping strategies or public policies – or absence of such actions. Chronic effects on the other hand are impacts that correspond to permanent dynamic shocks in the economy as explained in Figure 2. Such a distinction was made to separate impacts such as actual health expenditures from the anticipation of those expenditures.

Figure 2: Dynamic and chronic impacts of HIV/AIDS

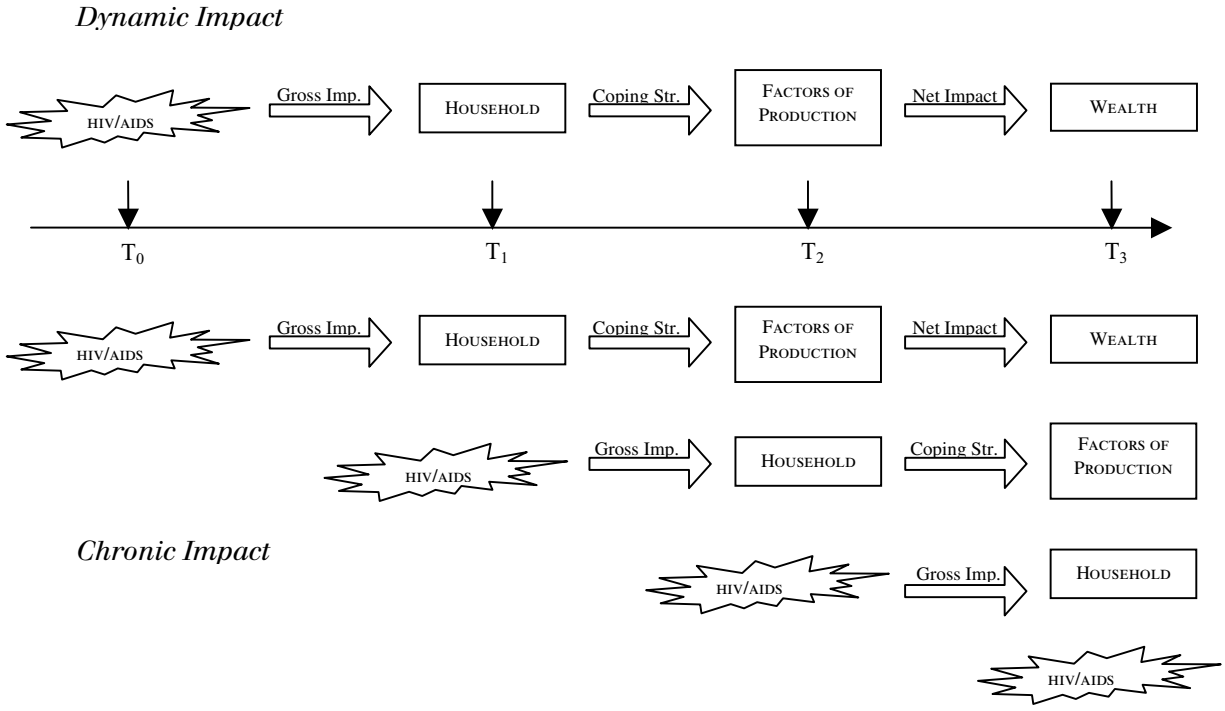
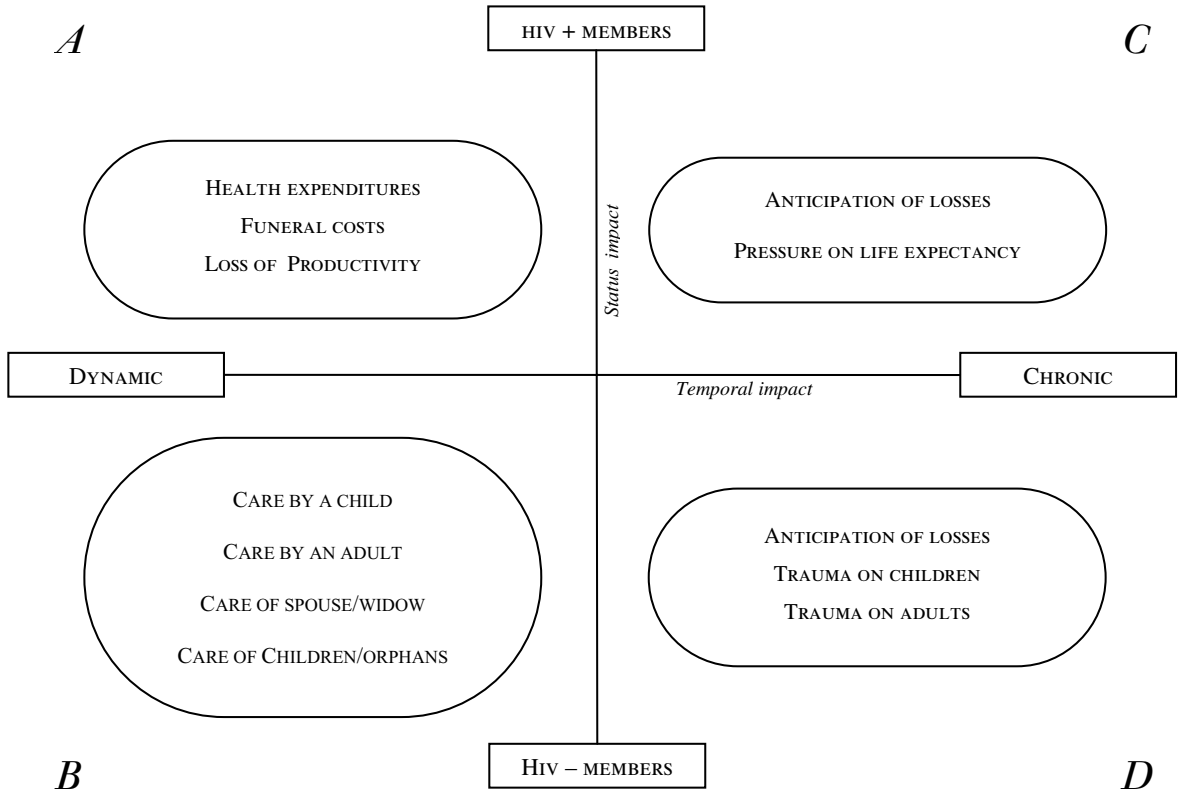


Figure 3: Status and temporal impacts of HIV/AIDS on households



The first impact is a sharp shock that in itself, as a gross impact, influences wealth during a specific period – the period of the disease – and in the long run influences decisions through coping strategies and the consequences of those strategies. In contrast to actual health expenditures, anticipation of health expenditures, as a gross impact, will alter any economic decision in the future and will lead to appropriate permanent coping strategies which are different from those due to actual health expenditures. The coping strategy to meet health expenditures could be to sell assets, while the anticipation of costs could lead to permanent restrictions in consumption in order to pay for those potential future expenditures.

The impacts chosen and their classification under status and temporal dimensions are presented in Figure 3. Four groups of impacts collect costs that share the same status and temporal characteristics.

III
ALTERNATIVE REPRESENTATION OF THE IMPACTS OF HIV/AIDS ON HOUSEHOLDS

Dynamic impacts due to a change in the status of the members living with HIV/AIDS

In group A, health expenditures and funeral costs are "direct costs", whereas loss of income due to the fall in productivity of the members living with HIV/AIDS is usually considered as an "indirect cost". Health expenditures include medical care and transport costs. Health costs can represent a significant percentage of the household income: in different parts of South Africa, 771 HIV/AIDS affected households surveyed spent on average a third of their income on health-related expenses, whereas the national average household expenditure on heath care is 4% per year [17].

Funeral costs do not refer to the cost of the funeral itself: HIV/AIDS does not change this value, given that everyone will die one day. The implicit cost of HIV/AIDS relates on the one hand to the repetition of funeral costs or participation in funeral costs, and on the other hand to the fact that the deceased passed away sooner than in the absence of the epidemic: the sooner the death occurs, the less time to save for funeral costs, the higher the relative cost of funeral. The cost of the funeral for the 771 South African affected households previously mentioned represented on average four times the total monthly

income. 55% of these households had paid for a funeral the previous year. Concerning the loss of income, two thirds of the households in the same study experienced a fall in their income [17].

These costs are considered as dynamic as they are gross impacts that change one economic variable – income – in the short run and set in motion a mechanism of coping strategies that will impact the household's wealth in the long run. These costs depend largely on the relationship of the members of the household living with HIV/AIDS with the rest of the household. They will be higher for the head of the household than for other members, for a worker than for an unemployed member, for a young person than for an elderly one, for an adult than for a child.

Dynamic impacts due to a change in the status of the other members

In group B, the impacts concern the care of the members living with HIV/AIDS by other members, while they are still alive, and the care of their nuclear family by other individuals during their illness and after their death. For example, in the previously mentioned household study in South Africa, in 40% of households, caregivers had to take time off from work and other income generating activities or school [17]. The clear distinction between adults and children is necessary to show the divergent consequences of this impact on the resources of the household in the long run. Concerning care given at home, an adult who stops working significantly lowers the financial wealth of the household in the short run, whereas when a child is withdrawn from school the human wealth of the household in the long run is negatively affected.

As a consequence, the seronegative members change their status to care-givers or to dependants. These terms imply that the person living with HIV/AIDS in the household was a worker with children. Obviously this is a simplified version of reality. As shown in box A, these impacts will depend on the relationship of the members living with HIV/AIDS with the other members. They are also dynamic impacts.

Chronic impacts

Groups C and D represent gross impacts seldom taken into account in the economic literature. Anticipation of losses, pressure on life expectancy, trauma on adults and children are immeasurable on a direct level and need new tools adapted to the economic analysis of the epidemic.

Anticipation of losses and the pressure on life expectancy mean that in countries where the epidemic is generalized and where the burden of the disease is widely understood and visualised, rational members of affected households will anticipate the expenditures due to morbidity as well as mortality and change their vision of the future. As a consequence, these households are likely to change their economic behaviour incorporating potential future costs and a potential reduction of their productive lives.

The economic impact of trauma on adults and children refers to the undetermined effect of the disease on the motivation to cumulate financial wealth – in the case of an adult – and human capital wealth – in the case of children – in an environment of illness and death. In the Raikai district of Uganda, orphaned children were found to be conscious of the difference in quality of life before and after the death of their parents, to suffer from depression and, most of them were still angry about their parents'death, in particular when cared by relatives other than widowed parents or grand-parents [18]. Obviously, this psychological sensitivity will influence their present ability to succeed at school, and their future as members of the society and economy of their country. Economic behaviour such as educational or savings choices will be disrupted.

Even if today these costs are given more importance and mentioned in surveys, they are not modelled in economic terms. As they disturb each periodical decision in the long run, they can be classified as chronic impacts. Group C presents costs that are due to the anticipation of costs as a result of a change in the status of the person living with HIV/AIDS in the household. Group D concerns the other members of the household.

IV
CONSEQUENCES ON THE EVALUATION OF THE IMPACT OF HIV/AIDS

What is an "affected" household?

The term "affected household" refers to two issues. The first deals with the definition of household and its association with close concepts such as the nuclear family, extended family or community, and is not specific to HIV/AIDS studies. The second concerns what constitutes an HIV/AIDS-affected structure or agent. Even though these issues are not independent, we have chosen to use the conventional definition of a household as a person or group of persons sharing the same dwelling, the same income and expenditures. We will focus on

the issue of the definition of what constitutes an HIV/AIDS-affected household in economic terms. Questioning the terms used to describe the interactions between individuals or groups of individuals and HIV/AIDS is not new. Susceptible, vulnerable, infected, afflicted, affected individuals are some of the terms that shed light on the evolution of the knowledge of the epidemic, as well as on the emergence of more appropriate terminology [15, 19]. The objective here is to draw a parallel between the groups of impacts described in Figure 3 and the number of households that could be partly or fully affected by them. Indeed, three categories of households will face different levels of costs.

The first group of households is obviously those that have been considered as affected in previous research, *i.e.* households that experience illness or death of one (or more) of their members due to HIV/AIDS. The overall impact of the epidemic for each of these households corresponds to the sum of all the costs (groups A, B, C and D) defined previously.

A second group of households experiencing costs due to HIV/AIDS includes other individuals who do not belong to the household of a person living with HIV/AIDS but provide care to a sick person or take care of the nuclear family of a deceased person. Consequently, the costs listed in groups B and D are those experienced by these other households who may also change their economic behaviour. This extra group of affected households could be defined as those that have strong personal or social relationships with the households that directly experience illness or death due to HIV/AIDS. They intervene in the lives of an affected household, providing emotional, financial and social transfers. In this case also, the interaction with individuals directly suffering from HIV/AIDS-related diseases can alter their vision of the future and lead to anticipation of potential future costs and pressure on life expectancy. These observations have been verified in the case of households fostering children: they suffer from a reduction of their income, investment as well as human capital accumulation. In Uganda, investigations on the long term welfare of AIDS foster children have observed that receiving a foster child impacts not only on consumption but also on capital accumulation in the households who receive the child but have not been directly affected. In particular, adding a foster child reduced investment by between 0.59 and 0.51 percentage points when the overall investment in the sample was only 2.2% [20].

A last group of households can be added to the overall impact by taking into account the temporal characteristics of the costs. Taking a country where the epidemic is generalized and the impacts are publicly known, it is likely that some of the agents who are unaware of their serostatus but believe that

they have a high probability of experiencing the consequences of HIV/AIDS in the future will have a subjective approach to the impacts of the disease that will also affect their behaviour. They will turn objective variables - such as life expectancy or future productivity - into subjective ones. These agents will anticipate part of the costs and alter their vision of the future. They could be defined as households that experience changes in their behaviour due to the presence of HIV/AIDS in their environment. In South Africa, assuming that the population as a whole would change its consumption decisions as a consequence of the fall in the average national life expectancy due to HIV/AIDS, a simulation revealed that the savings rate in 2015 would be at least 5 percentage points lower than it would have been in the absence of the epidemic [21].

Undervaluation of the impact of HIV/AIDS and inappropriate policies?

The division of the population into several groups sharing similar costs would improve the global impact of HIV/AIDS on households. More specifically, a population of N households ranked from 1 to N can be divided into four segments: the first households, n1, experience illness or death due to HIV/AIDS; the following households, n2-n1, intervene in the life of the affected households; the following ones, n3-n2, experience a pressure of HIV/AIDS on their economic behaviour even though they are not involved in the life of an affected household; the remaining ones, N-n3, do not share the concerns of the rest of the population and do not alter their economic behaviour in the presence of a general epidemic. Consequently, the overall measure of the epidemic should be modelled as the sum of the costs A – for the households ranked from 1 to n1 –, the impacts listed in group B – experienced by the first n2 households –, and the costs C and D – for the n3 first households.

The confrontation of selected impact characteristics with the issue of what constitutes a household affected by HIV/AIDS clearly suggests that the economic impact of HIV/AIDS actually affects a larger number of households than that estimated using traditional models. In particular, macroeconomic models essentially measure the A costs for the first households, n1, and seldom simulate scenarios in the long run. Such an approach would support the theory of an underestimation of the implications of HIV/AIDS and motivate further research in that field.

The issue now is to confront different household profiles and different types of impact to anti-HIV/AIDS policies that are designed for just one class

of impacts – those listed in group A – and one profile – households that experience death or illness due to HIV/AIDS. With regard to coping strategies, very little is known about how households that intervene in the life of affected households mitigate the costs due to these emotional, financial and social transfers. Obviously nothing is known about the remaining households that could change their economic behaviour even if they are not directly involved in affected households. Similarly, national and local policies to fight against HIV/AIDS do not consider the long term effects and the range of the population that is effectively affected. They do not take into account the costs listed as groups B, C and D in affected households, and they are even less adapted to the other profiles of "affected" households highlighted here.

Even if the typology is useful, two difficulties emerge from this conceptual work on the impacts of HIV/AIDS on households. The first is the need to identify segments of the population with regard to their links with the virus, while current microeconomic studies are struggling even to identify affected households. The second is to propose mitigating policies that would take into account all the impacts and population profiles, while current policies are struggling just to mitigate the direct and indirect impacts on affected households.

Conclusion

The aims of the typology of impacts classified under status and temporal characteristics are to clarify the image of the relationship between HIV/AIDS and development and to provide arguments for the debate on the potential underestimation of this relationship. Four groups of impacts and three profiles of households that should be considered as affected by HIV/AIDS have been highlighted. The argument here is to show that, among these groups of impacts, only one group is currently measured and the costs of the epidemic are assessed for only one household profile. Consequently, even if this approach does not provide the relative magnitude of the impacts and does not give answers to how the population profiles could be identified in practice, it confirms the threat of a larger burden on development due to the HIV/AIDS epidemic.

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AIDS and Economic Growth in Africa: a Critical Assessment of the 'Base-Case Scenario' Approach

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Key words: AIDS; impact; macrodynamics; human capital; macroeconomic policy; endogenous growth model.

Abstract

The literature dealing with the issue of the macroeconomic impact of AIDS can be presented in several ways: by differentiating the studies according to the channels they use (section 1), or by differentiating the studies according to the development models that they use (section 2). We can then attempt to construct a "model" which synthesises these different approaches, thus enabling a comparative study of the means of forecasting the impact of AIDS in a developing economy (section 3). The result of this work is that, by considering a multiplicity of productivity variables as potential engines of development (such as human capital, public spending, etc.), endogenous growth models produce more valuable and precise assessments of an epidemiological crisis such as AIDS in developing countries. For example, we highlight a non-linearity and the risks of the persisting effect of the AIDS crisis on development, which would not be demonstrated by an exogenous growth model based solely on the idea of a "catching-up effect" established with regards to the permanent Gross Domestic Product (GDP) target level of the Solowian permanent regime.

Résumé

On peut présenter la littérature sur la question de l'impact macroéconomique du sida de plusieurs manières : en différenciant les études par les canaux qu'elles sollicitent (section 1), en différenciant les études par les modèles du

développement qu'elles utilisent (section 2). On peut ensuite tenter de construire un « modèle » qui synthétise ces différentes approches, autorisant de ce fait une étude comparée des outils de prospective de l'impact du sida dans une économie en développement (section 3). Le résultat de ce travail est que les modèles de croissance endogène, en multipliant les variables de productivité comme moteurs potentiels du développement, produisent des diagnostics à la fois plus riches et plus précis d'un choc épidémiologique tel que le sida dans les pays en développement. Par exemple, nous faisons apparaître une non-linéarité et le risque d'un effet persistant du choc du sida sur le développement, chose que ne pouvait faire apparaître un modèle de croissance exogène, basé uniquement sur une idée de « retard » par rapport à un niveau cible de régime permanent.

Introduction

AIDS is a terrible crisis, not only on a human level, but also on an economic level. Certain economists have understood this, for as early as the beginning of the 1990s they attempted to evaluate the economic impact of the epidemic: the impact appeared to be globally responsible for a reduction in the economic growth rate of one percentage point (*cf. infra)*, with evaluations mainly considering the Gross Domestic Product (GDP) growth rate in countries affected by an epidemiological shock of HIV prevalence above 10%. The starting point for our own work is that these evaluations of growth reduction seem quite limited and that new evaluations are required: on the one hand, the relatively early date of the studies means that certain effects of AIDS on long-term economic behaviour are overlooked; on the other hand, the evaluation models used can be improved by systematically taking into account existing phenomena of productive complementarities (synergy) in the accumulation of productivity factors of the national economy (the different forms of "human capital" entering the production function, for example); these phenomena have notably been highlighted by the theory of endogenous growth and seem to have been underestimated in previous research on the economic impact of AIDS.

The literature on the macroeconomic impact of AIDS can be presented in several ways: by differentiating the studies according to the specific impact investigated (section 1), or according to the development models that they use (section 2). Finally, constructing a "model" which synthesises the different approaches will allow a comparative study of the means of forecasting the

impact of AIDS in developing economies and a more valid assessment of the impact of AIDS on these economies (section 3).

I
THE "IMPACT" APPROACH

At a macroeconomic level, the accumulation of wealth and the development of the economy could be negatively affected by a reduction in the average productivity of the country (reduction in life expectancy and alteration of the productivity of workers), but also by the increase in healthcare expenditure which "diverts" national resources from their long-term allocation. However, in the short run, healthcare expenditure is positively accounted in the GDP. To gain a clearer picture, we have applied a standard classification: direct cost / indirect cost, adding a supplementary category, deferred indirect cost [1].

Three impacts

Direct costs: These costs include medical expenditure linked to HIV/AIDS: treatment of opportunistic diseases as well as the possible use of antiretroviral drugs (ARVs), remuneration and training of medical and administrative personnel, spending on hospital infrastructure, monitoring and safety of blood transfusions, costs of preventive interventions, and costs of scientific and medical research (sometimes including the costs of prevention). In countries where there is some form of public health insurance and/or redistribution policy benefiting the poorest sections of the population, we can expect an increase in the tax rate to cover this increase in health expenditures. In Africa, these costs, said to be direct, will mainly be represented at a personal level (household income) by extra withdrawal from a 'net surplus after consumption' which is already excessively limited. The economic impact of AIDS will thus be felt mainly via *savings*, with the following mechanism:

AIDS Ÿ treatment Ÿ decrease in savings Ÿ lower accumulation of capital.

However, in many studies, this impact remains limited, as this "equation" is only true if AIDS incurs (costly) treatment. In the opposite case (illness not

treated or treated by traditional methods[1], which is frequently the case in Africa), the economic effects of AIDS as a reduction in savings remain limited[2].

Indirect costs: A person who develops AIDS experiences a reduction in his productive capacity, as he regularly falls ill. The reduction in his work capacity means a reduction in household resources if the victim has family responsibilities. For the poorest, this reduction is particularly hard to bear as opportunistic diseases increase the spending required on household healthcare (direct costs). In this case, the macroeconomic impact of AIDS is thus analysed through its impact on the labour supply, with the following mechanism:

AIDS Ÿ invalidity Ÿ reduction in labour participation.

In concrete terms, the consequences of AIDS on the productive system differ according to the production sectors: agriculture, transport, mining, manufacturing, the public sector. It appears indeed that analysis of the impact varies widely according to assumptions about the prevalence of HIV/AIDS in the different labour sectors, and about the possible susceptibility of the sectors in terms of labour flow, depending on their strategic importance for development. Some professional activities are more sensitive than others to epidemiological transmission of HIV, either for behavioural reasons (for example in the transport sector where employees, such as truck-drivers, are often a long way from home) or for reasons of exposure (for example, employees in the health sector). Another differentiating effect which causes concern is that in West Africa the prevalence of the disease is sometimes greater in skilled workers (for cultural reasons, also linked to the urban way of life[3]). The public sector, with a concentration of skilled workers, could be particularly affected, especially the education

1. Traditional methods are not cost free (symbolic sacrifice and travel expenses for example), but they cause minor *official* disbursements (visible in official statistics).

2. ...without counting the Malthusian effects: the demographic crisis (negative) can paradoxically play a favourable role for the economy measured by the per capita variable (of survivors); this argument recurs in the more precise study of the "impact" of AIDS in the Solow model. It is in this way that certain studies, such as that of Martha Ainsworth and Mead Over [2], insist on the "human cost" of AIDS, with numerous deaths, whilst admitting a relatively limited "economic cost". See also the model developed by Cuddington and Hancock [3].

3. …rather than rural for the less skilled employees (peasant workers). In the context of African economies, there are two important (linked) dualisms: urban / rural (agricultural), and skilled work / non-skilled work; a third, formal sector / informal sector could also be taken into account. See Cuddington and Hancock [3], Kambou, Devarajan and Over [4] and the studies conducted by the IIASA [5].

sector: according to UNESCO, AIDS is the main cause of mortality among teaching staff in Côte d'Ivoire[4]. In general, the premature death of an employee leads to the loss of know-how which can no longer serve production or be transmitted. Therefore, even before a more detailed analysis of family strategies for access to education[5], there already appears in the analysis by sector the important question of the effects of AIDS on "human capital", today considered as *the boosting factor* of economic and social development (see section 3 for an extensive use of "human capital" in a growth model [6]).

Deferred indirect costs: In the absence of external aid, the reduction in resources linked to AIDS could have even more significant deferred effects, as it risks modifying the productive structure of the household, notably its "educative" function. The spouse who is not ill (which would seem a highly unlikely situation) or 'not yet ill' will devote more time to work and less to the education of the children. The children themselves are sometimes diverted from their schooling and are forced to work; the "production detour" entailed in access to schooling would seem too costly in light of the financial emergency confronting the household[6]. Deaths are also costly; the funeral rites can last for several days, necessitating *de facto* a prolonged interruption of work for the entire family. There remains the problem of the surviving children of the deceased. Who will provide for the needs of these orphans? Who will raise them and educate them? Generally speaking, a worrying characteristic of the Aids crisis is its consequence on the accumulation-transmission of human capital throughout society: in other words, the quality of labour will not be assured in the long run.

All of these considerations, to which may be added an analysis of the age-pyramid of the population and its distortion due to AIDS (even more "hollowed out" in developing countries in the short run [7]), converge on the idea that AIDS affects:

1) in the short run, the *quantity* ratio: active-able to work / total population in the economy;

4. For the whole of Africa (not exclusively West Africa or Côte d'Ivoire), the debate on the AIDS-prevalence for skilled/unskilled workers is not clear. This question requires careful investigation by specialists. But it is not a crucial point for our own macro-dynamics approach, as in the long run the absence of creation-transmission of skill (differed indirect costs) is more important than this short term destruction.

5. See below, the category "deferred indirect costs".

6. Families often withdraw their daughters from school to take care of their sick parents or to fulfil other family responsibilities, thus compromising the education and future prospects of these young girls. In Swaziland, school enrolment has dropped by 36% due to AIDS, according to UNAIDS-WHO (*cf. The facts on the AIDS epidemic*, UNAIDS-WHO, December 2001).

ii) in the long run, the quality of work supplied by the representative worker (the human capital effect).

Below, we will discuss the dual effect, quantitative (short-term) and qualitative (long-term), of AIDS on African economies.

Some evaluations

Different studies have been conducted to attempt to measure the economic consequences of HIV/AIDS in terms of GNP points lost. The main studies supply comparable figures for the African economies. On average, the authors forecast a one-point reduction in the growth rate of national wealth[7]. These studies are based on an *ad hoc* modelling of the economy, allowing a comparative approach: that is, a comparison between a "base-case scenario" (without AIDS) and the actual economy (with AIDS). The study conducted by Bonnel (2000) provides an econometric estimation which endeavours to link the growth rate to the prevalence rate by screening other explanatory factors such as the institutional environment, physical capital and human capital. This estimation of African economies used data collected between 1990 and 1997.

Table 1: Link between growth, life expectancy and the prevalence rate

Rate of prevalence	Reduction in the rate of per capita growth (1)	Years of life expectancy lost (2)
5%	-0.6	4.7
10%	-0.8	9.4
15%	-1	14.1
20%	-1.2	18.8
30%	-1.4	28.2

Sources: (1): R. Bonnel [8]. (2): calculations by Touzé and Ventelou [1] using data from the US Census Bureau, Population Reference Bureau, and WHO.

7. The impact on the per capita GDP may appear less significant for the simple reason that AIDS reduces above all the size of the population, which represents a "positive" shock in the Malthusian context.

Table 2: Reduction in GNP attributable to HIV/AIDS

Country	Average reduction in GNP (in annual growth points)	Period	Year	Sources/ authors
30 sub-Saharan African countries	[0.8; 1.4]	1990-2025	1992	Over (1992) [9]
Cameroon	2	1987-1991	1992	Kambou *et al.* (1992) [4]
Zambia	[1; 2]	1993-2000	1993	Forgy (1993) [10]
Tanzania	[0.8; 1.4]	1991-2010	1991	Cuddington (1992) [11]
Kenya	1.5	1996-2005	1996	Hancock *et al.* (1996) [12]
Mozambique	1	1997-2020	2001	Wils *et al.* (2001) [13]

Source: estimations collected by Touzé and Ventelou [1] using the cited articles; the intervals relate to the size of the impact according to the scenarios studied. A similar but more extensive table appears in Barnett and Whiteside [14], p 286-7.

In general (and despite a terrible human cost), these studies provide a "diagnosis" of a crisis which will remain on a relatively limited economic scale[8]. First of all, it should be recalled that healthcare expenditure (like military expenditure) is included in the GDP: in the immediate context, there is a positive accounting effect, even if later it could be thought that this expenditure, re-directed towards emergency health-care, might hinder a balanced process of development. Next, it should be noted that more often than not these evaluations overlook "deferred indirect" effects (the transmission and accumulation of "capital", both physical and human). In general, the problem of the aforementioned studies is that they do not offer a valid analysis in the long term: such analyses can only claim to be genuinely valid for a period of 5 to 10 years. This could be justified at the beginning of the 90s, as it was difficult to forecast exactly "the input" of the model over time, *i.e.* the epidemiological crisis. Furthermore, the studies

8. A notable exception is that of Barnett and Blaikie [15], who speak of AIDS as a "*long wave"* disaster on the same scale as global warming, insofar as the "major effects were already in play well before the extent of the crisis was known" and "no existing answer can be applied".

are generally weak with regard to one of the first two channels cited earlier. In the long run, they neglect the possible interactions between the two (complementary) channels.

Indeed, the literature tends to neglect the analysis of the long-term effects of the crisis, and especially its impact on the accumulation of both physical and human capital. Thus, for these two variables, the impact exists and the risks are significant.

Physical capital (direct cost): the sums devoted to treatment are diverted from their productive allocations (savings and private investment; public investment). As we have seen, the effect is sometimes considered in the studies, but is often minimised due to a limited time horizon and to additional assumptions regarding Africa: low savings (constraint of indebtedness) and low productive investment.

Human capital (indirect cost): this effect is rarely evoked and in practice is not quantified in macroeconomic dynamics[9]: on the one hand, as noted in the studies, AIDS reduces the productivity of the population, notably that of the skilled population, when there is a marked "dualism" for this type of work, while on the other hand it reduces the accumulation and transmission of skills (transmission via the family if the head of the family dies, via school if the teaching staff die; and the children, for their part, work at an earlier age due to the death of the head of the family).

And what if there were cumulative effects of these two variables? (*i.e.* the reciprocal relationship of human capital and physical capital during their formation process, and the need experienced by the poorest countries to develop these two engines of development concurrently?). We will return to this question in section 3, in which we give a brief explanation of the apparent paradox between the conventional forecasts of a limited aggregated impact, and the huge impact already measured at microeconomic levels (on businesses and households). For the moment, we can summarise our approach in the following way:

9. Certain studies include a 'skilled workers / unskilled workers' differential [5], but few effects on the *accumulation* of skilled work. Only Theresa M. Ndongko [16] insists on the reduction of the expected future level of qualifications due to the fall in school attendance, but she does not measure it.

Table 3: Breakdown of the costs of HIV/AIDS

	Very poor countries	Developing countries	Rich countries
Direct costs (1)	+	++	++
Indirect costs (2)	+++	++	+
Deferred costs (3)	+++	++	+
Prevention (4)	+	++	++++

(Hypothetical table[10]: + weak; ++high; +++ very high)

1. These costs include medical expenditure linked to HIV/AIDS: treatment; remuneration of medical and administrative personnel; spending on hospital infrastructures; blood transfusion monitoring and safety; scientific research.

2. These costs include all immediate negative economic effects caused by the epidemic: reduction in productivity through the increase in morbidity, reduction in life expectancy (social and psychological damage).

3. These costs represent a profound loss of the development mechanisms due to a lack of accumulation of physical and human capital. They are noticeable in the long term.

4. These costs concern expenditure linked to informing the population about the disease and the practice of safe sex (use of condoms).

This table, both hypothetical and intuitive, summarises the idea of a differentiated impact of AIDS for the poorest countries. In contrast to rich countries, which are less affected and at the same time capable of a certain flexibility in their response to the disaster ("dualisms", *e.g.* skilled work v. unskilled work, are less marked and the strategies for accumulating productive assets less constrained), the poorest countries will in all probability be confronted by extremely high deferred costs[11]. These remain invisible.

II
THE "STANDARD GROWTH MODEL" APPROACH

Before studying a more general model, it is important to present some relatively standard considerations regarding the long-term economic development analysis

10. See Touzé and Ventelou [1].

11. The main idea is that the development mechanisms of the poorest countries are fragile, and that a shock such as AIDS could have an enormous impact, not only on the current level of activity, but on the future development path of the country. Barnett and Whiteside [14] have used the term "susceptibility" to characterise this fragility.

models. Two major types of growth model can be distinguished: traditional models, with decreasing factorial returns, analysing growth as a process of catching up a target level determined by the scarcity of resources; and models with constant returns, also called "models of endogenous growth", which seek in their analyses to constantly push back the resource scarcity frontier.

The impact of AIDS in an exogenous growth model: the Solowian framework

Traditional growth models study the relationship between the process of accumulation of capital and growth. They are characterised by a dynamic equation, called the Solow relation [17]:

$$\dot{k}_t = s f(k_t, \phi) - n k_t$$

with k_t the capital per capita, $\dot{k}_t$ its derivative in relation to time, s the rate of savings in the economy, ϕ a term of productivity, $f(k_t, \phi)$ per-capita production. This equation means that the net formation of capital per capita is equal to per-capita savings ($s f(k_t, \phi)$), less the share which serves to endow the new generations with capital ($n k$). The dynamics of the model result from the characteristics of the production function of the economy. What are these characteristics? Firstly, at a macroeconomic level, we generally assume that the production function presents constant returns to scale in its two arguments: capital and labour. This means that, *potentially*, the economy can reproduce itself identically from one period to the next, thus allowing extensive growth. Furthermore, as companies are constantly in search of efficient productive combinations and as these always contain capital and labour, this means that the production function is quasi-concave. This notably implies that the marginal productivity of factors (factorial returns) are decreasing and therefore that the production function per capita is a concave function of capital per capita.

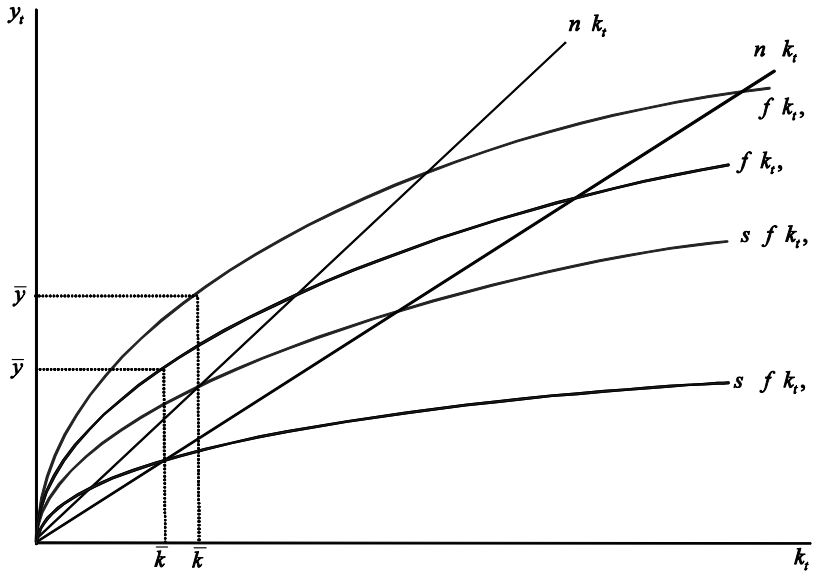
In this framework, it is the relative scarcity of production factors which limits the growth process. As the only residual scarce factor is labour, it is precisely the dynamics of the population which will determine the dynamics of national income, possibly adjusted by the productivity growth rate (advances in knowledge). Capital per capita will evolve progressively to attain the target level in a steady-state regime, where the growth rate of both income and capital is equal to the growth rate of the population, again, as noted above, possibly increased by an exogenous productivity trend facilitated by

technological progress. Short-term growth is thus perceived as a process of catching up a target level determined by the scarce resources, whilst in the long term it is based on exogenous data and depends on neither the savings rate nor the growth rate of the population, and even less on other economic behaviour such as the choice of healthcare and education.

In such a context, what will the impact of the AIDS epidemic be on the dynamics of growth? It is necessary to consider the impact of AIDS on the parameters of the model[12]. We will identify three effects, which can be represented in the equation and the following graph, with κ representing the epidemiological crisis:

$$\dot{k}_t \mid s(\kappa) f / k_t, \phi(\kappa) 04\, n(\kappa) k_t$$

Figure 1: Impact of AIDS on growth: the traditional approach



– With regard to the population growth rate (n), we can logically assume that this will fall, even if we cannot exclude the fact that households modify their reproductive behaviour to compensate for the increased mortality. In the Solow model, this reduction in the growth rate of the population will have a counter-intuitive effect. Indeed, by reducing the demographic pressure on savings ($n\ k$), the fall in the population growth rate will tend to increase the

12. We consider here an immediate impact. In practice, the modification of the parameters of the model will be progressive, according to the epidemiological model characterising the rate of prevalence.

capital per capita and will thus accelerate the growth of per-capita national income in transitional regime; this effect will then disappear in the steady-state regime. With regard to the growth of total income, the effect will be indeterminate in transitional regime (in the catch-up phase, $k \prod \overline{k}$), as the per capita income increases more quickly, while population growth is slower. In steady-state regime ($k = \overline{k}$), the growth of total income is weaker.

– With regard to the savings rate, two effects acting in the same direction can be noted. First, the increase in healthcare expenditure reduces the amount of resources available for savings and thus reduces per-capita savings. Second, according to the theory of the choice of savings in the life-cycle model with uncertain lifespan [18], an increase in the risk of dying reinforces the preference for the present and diminishes expected wealth, thus tending to reduce the rate of savings[13]. In the Solow model, this reduction in the savings rate leads to a lower capital per capita product in the steady-state regime. It also reduces growth in the transitional regime. In the steady-state regime, it will have no effect on the growth of national income or of per-capita income.

– Finally, the AIDS epidemic certainly has a negative impact on labour productivity (absenteeism, fatigue, etc.), entailing a reduction in per capita production. This reduction leads to a fall in capital per capita for the permanent regime and thus a fall in growth in the transitory regime. However, in the permanent regime, the productivity growth rate remains exogenous and thus has no impact on the long-term growth of national income and national per-capita income.

In the final analysis, in the Solowian framework, the impact of the AIDS epidemic on capital per capita in a permanent regime is theoretically indeterminate since it is the sum of three effects, one positive and two negative. Only empirical quantification of these different effects can allow a conclusion to be drawn one way or the other. Furthermore, we note that the long-term growth rate of the economy is not affected, other than by demographic effects. We may nevertheless ask ourselves if studies analysing the impact of the AIDS epidemic on growth using the Solow model will not automatically lead to qualified

13. The inter-temporal choice is also sensitive to the institutional context. For a detailed study of the comparative statics of the model of inter-temporal choice with an uncertain life span, see Drouhin [19].

conclusions due to the very structure of the model, notably as a result of the exogeneity of productivity growth. What happens if, for example, the productivity trend (human capital) and the savings rate (physical capital) both react in a cumulative manner, ϕ and s being linked by microeconomic choices? The risk is seeing the development of negative synergies between the two variables in times of crisis, calling into question current assessments based on the hypothesis of separate effects.

The evolution of growth theory during the past twenty years has consisted of developing the Solow model to make long-term productivity development depend on the economic decisions of agents[14]. It is precisely the aim of the so-called endogenous growth theories to establish a new analytical framework giving a better description of agents behaviour, notably with regard to their choice of accumulation of factors, henceforth referred to as being of productivity, rather than of production (those already identified). In particular, the introduction of knowledge as an economic good or of knowledge embedded in the economic agents (human capital) is likely to counteract the effect of the relative scarcity of the labour factor on growth[15]. The growth rate of the economy will thus be determined endogenously by the decisions of interacting economic agents. In such a context, the AIDS epidemic can have much more marked consequences in terms of growth, as it will interact with decisions about healthcare and the accumulation of human capital, and thus on the growth rate of the economy.

The comparative statics which we have just evoked in the Solow model (and which assumed a study of the impact on economic variables decided individually: ϕ, s and n) can thus be improved by considering:

– genuinely endogenous dynamics of labour productivity;

– the possibility that, in addition to the effect of changes in labour productivity, the other key variables of development (savings rate, demographic structure, etc.) interact – not only additively – in the face of the crisis, and do so *via* the microeconomic choices of the decentralised agents.

By increasing the variables of productivity as potential engines of development, the endogenous growth models produce assessments of epidemiological crises, such as AIDS in developing countries, which are potentially both more useful and more precise. For example, in the following section, we will see the appearance

14. And thus also on the institutional context where they are taken.

15. In other words, as certain factors which can be taken together appear with a non-decreasing return in the macroeconomic production function, there are no longer any scarce factors [20].

of non-linearity and the risk of the persisting effect of the AIDS crisis on development, a fact that an exogenous growth model could not take into account because it remains based on the idea of "catching-up" in relation to the target level of a single permanent regime. In an endogenous model, there are several permanent regimes, and a possibility of divergence rather than convergence.

The impact of demography in an AK-type endogenous growth model

In an endogenous growth model, the productivity of factors of production, notably that of labour (ϕ_t), is linked to the evolution of the different variables of the economy. In its most simple formulation, labour productivity is assumed to have a linear relationship with the stock of available capital: this relationship can be expressed as $\phi_t = \bar{\phi}_t K_t$, where $\bar{\phi}_t$ is a residual and exogenous parameter of productivity growth. Using a Cobb-Douglas production function, national production also becomes a linear function of the stock of capital:

$$Y_t = F(K_t, \phi_t L_t) = (L_t \bar{\phi}_t)^{1-\zeta} (K_t).$$

This formulation brings us back to the model called "AK", $Y_t = A_t K_t$ where $A_t = L_t \bar{\phi}_t^{1-\zeta}$. The technique employed here is not that of constant returns to scale (Solow model) but of crossing, and the marginal productivity of capital is no longer a decreasing function of the stock of capital. Indeed, the accumulation of capital indirectly (via its effects on ϕ) produces gains in global productivity of factors which are sufficient to compensate for the decrease in the marginal productivity of capital. However, the marginal productivity of labour remains a decreasing function of the number of workers.

The dynamics of capital accumulation is described by the following equation:

$$K_{t+1} = K_t + s_t K_t L_t \bar{\phi}_t^{1-\zeta} - K_t.$$

where s_t is the savings rate. The growth rate of the capital stock is calculated as follows:

$$\frac{K_{t+1} - K_t}{K_t} = s_t \bar{\phi}_t L_t^{1-\zeta}.$$

This equation demonstrates that the size of the active population influences the growth rate of the capital stock: this is "productive synergy" which can be explained by the fact that the gains in global productivity of the factors caused by the accumulation of capital become greater as the size of the active population increases: "the positive externality" is shared by a larger number of workers which reduces its impact. The parameter $/14\zeta 0$ measures the elasticity of the growth rate to population size.

The growth rate of per-capita production can also be calculated:

$$\frac{\div Y_t / L_t}{Y_{t41} / L_{t41}} \cdot \frac{\div A_t}{A_{t41}} 2 \frac{\div K_t}{K_{t41}} 4 \frac{\div L_t}{L_{t41}} .$$

Insofar as the growth rate of the global productivity of capital can be approached in the following way: $\frac{\div A_t}{A_{t41}} \cdot /14\zeta 0 \left(\frac{\div \bar{\phi}_t}{\bar{\phi}_{t41}} 2 \frac{\div L_t}{L_{t41}} \right)$, it is possible to deduce the growth rate of per capita income as the sum of three effects:

$$\frac{\div Y_t / L_t}{Y_{t41} / L_{t41}} \cdot s_t \left(\bar{\phi}_t \left(L_t 0^{4\zeta} 2 /14\zeta 0 \left(\frac{\div \bar{\phi}_t}{\bar{\phi}_{t41}} \right) \right) 4\zeta \left(\frac{\div L_t}{L_{t41}} \right) \right) .$$

The first term refers to the growth rate of the capital stock. The other two effects form a weighted average between the increase in the exogenous component of productivity (favourable to the growth of per-capita income) and the relative variation of the active population (unfavourable Malthusian effect).

Following a single variation of the active population, we encounter the Malthusian effect characteristic of the Solow model. The latter appears as a transitional crisis in the form $4\zeta \left(\frac{\div L_t}{L_{t41}} \right)$: the decrease in the active population initially indicates an increase in the growth of production per capita. Nevertheless, for reasons of productive synergy (a hypothesis contained in the AK model), a larger population is favourable to a high growth rate of per capita income. Thus, with a capital elasticity coefficient equal to 0.3, a permanent reduction of 10% in the size of the population represents a transitional 3-point increase in the growth rate of per-capita income followed by a permanent reduction of 7% in the level of the growth rate (*cf.* elasticity of the growth rate

of the capital stock to population size). For example, if the level of the long-term endogenous growth rate is 5%, we observe a temporary increase (Malthusian effect) of +3 points (at the moment of the crisis, the growth rate reaches 8%) accompanied by a permanent reduction of 0.35 points (from the moment of the crisis to the "end of time" the growth rate is reduced to 4.65%). In the space of 10 periods, the "synergy" effect becomes preponderant and the level of production is thus definitively lower in relation to its initial course before the crisis.

III
A COMPREHENSIVE MODEL.

Discussion on the choice of a model

Faced with those multiplicity of effects, our own work firstly seeks to synthesise the different approaches, with the initial objective of better evaluating the relative importance of each of the impacts, and also with a view to obtaining and quantifying their possible resonance effects when the accumulation profiles of several factors overlap.

The work thus aims to take into consideration both the different channels of impacts and the different models. To summarise its structure, the best solution is to list the effects (the "channels") and to indicate which variable will be affected first by the crisis.

CHANNEL	VARIABLE OF THE MODEL	TIME HORIZON
Rate of participation (*quantitative* effect of AIDS on the labour supply)	*L*/*N*, share of the total labour force effectively able of working	Short
Productivity of workers (*qualitative* effects of AIDS on the labour supply)	*H*, "human capital"	Long
Rate of public investment	*D*, productive public spending	Long
Private investment	*K*, physical capital accumulated in the short term (possible financial imbalance of the national economy)	Short
Rate of private savings	*K*, physical capital available in the long term (economy financially balanced: endogenous interest rate)	Long

With the following macroeconomic production function:

$$Y \mid F(K,L,D,H) \mid K^{\zeta}(L.H)^{\eta}(D)^{\theta}$$

To present a phenomenon of endogenous growth, the production function should be characterised by the constraint: $\zeta 2 \eta 2 \theta \mid 1$. We should note that it is still possible to observe and compare this type of model with the forecasts of an exogenous growth model, by assuming the alternative hypothesis: $\zeta 2 \eta 2 \theta \{ 1$.

In the appendix, we present the microeconomic specificities of the model: choice for *H*, choice for *K*, choice for *D*. These variables are "endogenised" by the microeconomic choices and are thus possibly linked to each other (to simplify, we note that each variable depends on income *Y*). We also note κ, the epidemiological state of the population. Any increase in κ represents a deterioration in the health status of the population[16].

$$Y(\kappa) \mid (K(Y,\kappa))^{\zeta}(L(Y,\kappa).H(Y,\kappa))^{\eta}(D(Y,\kappa))^{14\zeta 4\eta}$$

This equation will serve to analyse the effect of the crisis on the macroeconomic income of a country. We should note that, in comparison with the Solow model, a separate analysis of the different impacts (per isolated variable) is not possible directly, as the cumulative effects passing via *Y* and the endogenous loop would not be taken into account. It is necessary to resolve the model first.

A result: epidemiological trap and threshold effect

Leaving aside the numerical and calculable applications of the model (we confine ourselves here to an analytical resolution), we can first simplify the general model presented in the appendix in order to explain as clearly as possible what is referred to as the risk of an "epidemiological trap". For the case which concerns us (demonstrating a trap), we can, without losing any generality, reduce the model to two factors of production:

16. Here, we will analyse the increase in κ as the "AIDS crisis". However, the same reasoning can be applied to any pandemic which affects both the virtual prognosis and the capacity to work: tuberculosis, malaria, yellow fever, etc.

$$Y = K^{\zeta} \left[h \left(\kappa, x^{4} \right) L \right]^{1-\zeta}$$

– With h the level of individual human (health) capital of workers, we obtain $h_{\kappa} < 0$ (AIDS destroys human capital) and $h_{x^4} > 0$ (human capital can be constituted and reconstituted thanks to healthcare expenditure x).

– We also assume that:

$$L = \left(1 - \kappa \right) \left(1 - g \left(x^{4} \right) \right) N$$

The number of agents L effectively able to work in an economy with N potential workers is affected by AIDS: the factor κ has a negative effect on the ratio L/N (active/total population). However, we can possibly restore the labour capacity by using healthcare x: the logarithmic function g provides the size of this restoration. We assume $g' > 0$, $g'' < 0$, with $g(0) = 0$ and $g(+\infty) = g^{*} < 1$.

Two "health effects" are present: a qualitative effect (AIDS affects the productivity of workers via human capital, h) and a quantitative effect (AIDS has a short-term effect on the ratio *active/total population*, $\kappa(1-g)$).

We establish a very simple expression of health expenditure:

$$x = \varsigma y$$

and a human capital formation function which is just as simple:

$$h = x^{4} - \lambda \kappa^{4}$$

with $\lambda(\kappa)$ a measure of the impact of AIDS on the state of individual health: $\lambda' > 0$.

These two functions can be justified by more complex 'microeconomics', but the important element is the strong direction of the variation of the functions (see appendix for more details).

Based on the assumption of the profit maximisation of firms, the productive capital stock can be written as a proportion of national income:

$K = \frac{\zeta / 1 4 \mu 0}{r} Y$, with σ the taxation rate of firms.

We can thus very simply derive the growth rate of national per-capita income:

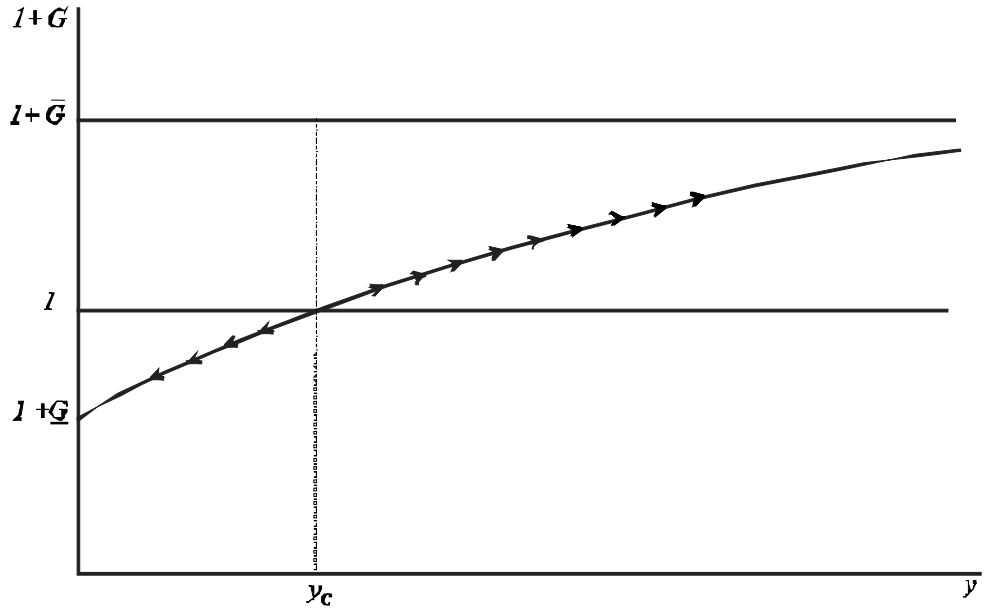
$$1 2 G = \frac{y}{y^4} = B / \kappa^4, \kappa, \sigma, y^4 0$$

where: $B / \kappa^4, \kappa, \sigma, y^4 0 = \varsigma 1 / \kappa^4 0 / 1 4 \kappa / 1 4 g / \varsigma y^4 000 \left(\frac{\zeta / 1 4 \mu 0}{r} \right)^{\frac{\zeta}{1 4 \zeta}}$

The growth rate of the economy G is therefore an increasing function of the already attained per-capita national income (y^-), varying between a maximum value $\overline{G}$ and a minimum value $\underline{G}$.

Here, we wish to stress a particularly interesting case which is likely to modify noticeably the manner in which we envisage the impact of AIDS on the growth of the economy: when $\underline{G}$ and $\overline{G}$ are situated on either side of the value *one*, we notice the appearance of a threshold effect[17].

Figure 2: Growth and the threshold effect



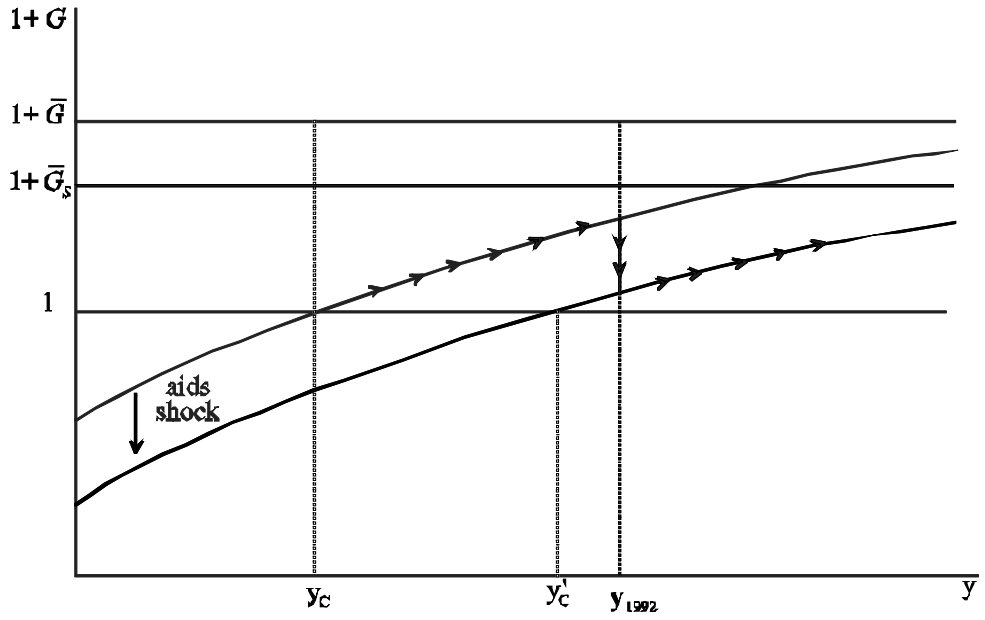
17. We should stress that this case corresponds to realistic values of the parameters. Numeric measurement of the complete model presented in the appendix is currently being carried out for Côte d'Ivoire.

For an epidemiological state of the population, κ, and for a given level of health expenditure ς, a threshold y_C exists, below which the growth rate of per-capita national income is negative. The "withdrawal" caused by the disease and a poor level of health on the factors of productivity of the economy are too serious to allow the latter to reproduce identically. However, above this threshold, the economy provides sufficient resources to undertake a process of self-maintained cumulative growth (benefiting from the regular provision of human capital parallel to the accumulation of physical capital). In this model, an underdevelopment trap appears which we may qualify as an epidemiological trap.

What are the effects of the AIDS epidemic in this analysis framework? The increase in κ shifts the growth rate curve downwards, mechanically raising the critical threshold for per capita national income below which the growth process is inversed. For countries initially experiencing growth, there are two possible scenarios.

In the first scenario, which we qualify as "depressive", the threshold y_C, although raised, remains below the current level of per capita national income at the moment of the crisis. Here, the growth rate of the economy will be lower for all future periods. In particular it will converge on a permanent regime rate below that which would have been possible in the absence of the epidemic.

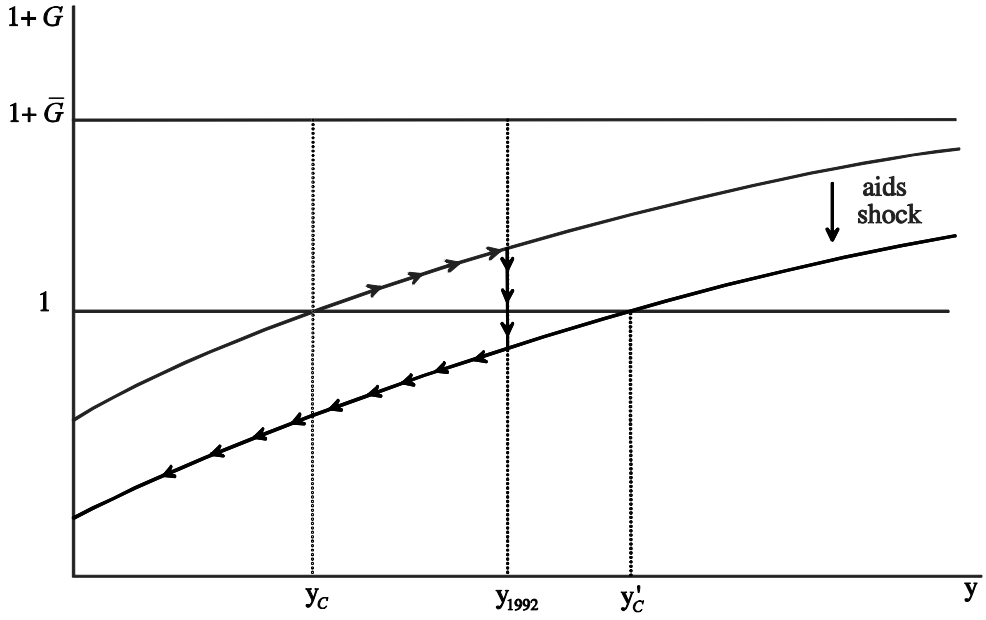
Figure 3: The depressive scenario



This scenario, which concerns the countries which are more advanced in their development process and/or where the epidemiological impact remains limited, provides a vision of the impact of the AIDS epidemic which, although significant, remains a case of a differential in the growth rate. Growth slows down, but the process of growth itself is not fundamentally altered in its essential mechanisms.

The second scenario, which we qualify as "catastrophic" in the etymological sense of the word, is quite different. In this scenario, which concerns countries which are still at the very beginning of their development process and/or where the AIDS epidemic has reached significant proportions, the AIDS crisis will increase the critical threshold y_C above the per-capita national income level existing at the moment of the epidemiological crisis. A bifurcation is thus produced. The process of growth stops and the economy begins to regress. At a basic level, economic agents modify their long-term prospects (stationary equilibrium has changed) and the entire economy heads towards a reverse low equilibrium (characterised by a growth rate level of $1+\underline{G}$).

Figure 4: The catastrophic scenario



Our model strongly emphasises that not all countries are affected by the epidemic in the same way. If the AIDS crisis radically modifies the dynamics of the economy, it would be a serious mistake to take an approach which limits itself to measuring the distances between the growth rate curves for the "base-case scenario" (before the AIDS crisis) and the growth rate curve after the crisis, as it would overlook the bifurcation. In other words, the comparison would be made with a base-case scenario ("no-AIDS") which already (incorrectly) includes the impact of the crisis! In the catastrophic scenario, the question is no longer how long it will take to reach a given level of development. What is at stake is quite simply the potential loss of any opportunity for further economic development in the countries concerned (in the absence, of course, of positive counter-shocks, such as massive technological transfers, notably in the medical domain; see below, ARV programmes).

Taking into account this possibility noticeably modifies the analyses of health policies which can be implemented. The coefficient ς, *i.e.* the proportion of per capita national income devoted to healthcare expenditure is the variable which allows the partial compensation of the impact of the AIDS epidemic. The increase in healthcare spending acts not only on the rate of participation (quantitative effect) but also on productivity through human capital (qualitative effect). It must nevertheless be stressed that no level of healthcare spending exists which would totally cancel the effect of the disease on growth, for two reasons. The first results from medical technology which, in the current state of knowledge, does not allow the consequences of the disease to be "repaired in their entirety". This first reason is presented in our model by means of the function $g(\varsigma y^4)$ which is bounded at a level g^* which is strictly below 1. The second reason, which is more fundamentally economic, results from the necessity, in the absence of external aid, to finance this supplementary healthcare spending. In our simplified model, where there is no other public spending, we can simply consider that the tax levied at a rate of σ serves to finance healthcare spending: $\sigma | \varsigma$. If we adopt the maximisation of the growth rate of the economy as a criterion of well-being, we will have an optimum level of healthcare spending $\hat{\varsigma}$, taking into account the opportunity cost of public funds. The effect of healthcare spending can thus be illustrated graphically. For all values $\varsigma \{ \hat{\varsigma}$, the increase in healthcare spending allows the growth rate curve to be "lifted", thus softening the economic effect of the AIDS crisis. However, for higher values of ς, the effect of the tax deduction for healthcare spending on the accumulation of factors of

productivity becomes too significant and does more than cancel the beneficial effects of the latter. Graphically, this increase in ς is represented by a fall in the growth rate curve. It should be added that any increase which might, as an ethical argument, tend dogmatically to refuse the existence of this optimum ς would commit a grave error of reasoning. The growth of the economy is the only sustainable means of increasing healthcare spending. In this domain, as in many others, the choice of economic policy is also an inter-temporal trade-off. However, it is quite obvious to us that the effective ς practised by developing countries is still well below the threshold level ($\varsigma \{ \hat{\varsigma}$) and that a progression margin is obviously desirable for healthcare spending in order to lift the growth curve and remove the risks of an epidemiological trap.

Furthermore, we wish to stress that our model also supplies an argument justifying the increase of healthcare spending above $\hat{\varsigma}$, provided that this spending is financed by international transfers. Indeed, if we consider the catastrophic scenario and we choose healthcare spending which maximises the growth rate, taking into account the AIDS crisis, there is nothing to say that this maximum rate might not, despite everything, be negative! In this situation, since any increase in healthcare spending financed by internal resources would reduce the growth rate, only international transfers financing the over-spending on health would allow the bifurcation of the economy to be avoided and the growth process to be maintained. Of course, this over-spending would only be transitional, as once the per capita GDP is pushed above the critical threshold, the country would be in a position to finance its health policy itself.

By putting forward the possibility of an epidemiological trap, we provide arguments which highlight the particularity of the effect of the AIDS epidemic on the least developed countries (or on the most affected low – and medium – income countries) in their development process; a particularity which requires public policy measures which are themselves particular. To be precise, our argument, essentially based on a macro-dynamic analysis, offers strong support for therapeutic ARV programmes: the outcome of such programmes could be, as an emergency policy, to remove the epidemiological trap (and, as a positive spin-off, to re-validate the linear prognostics delivered by the classic models of forecasting!).

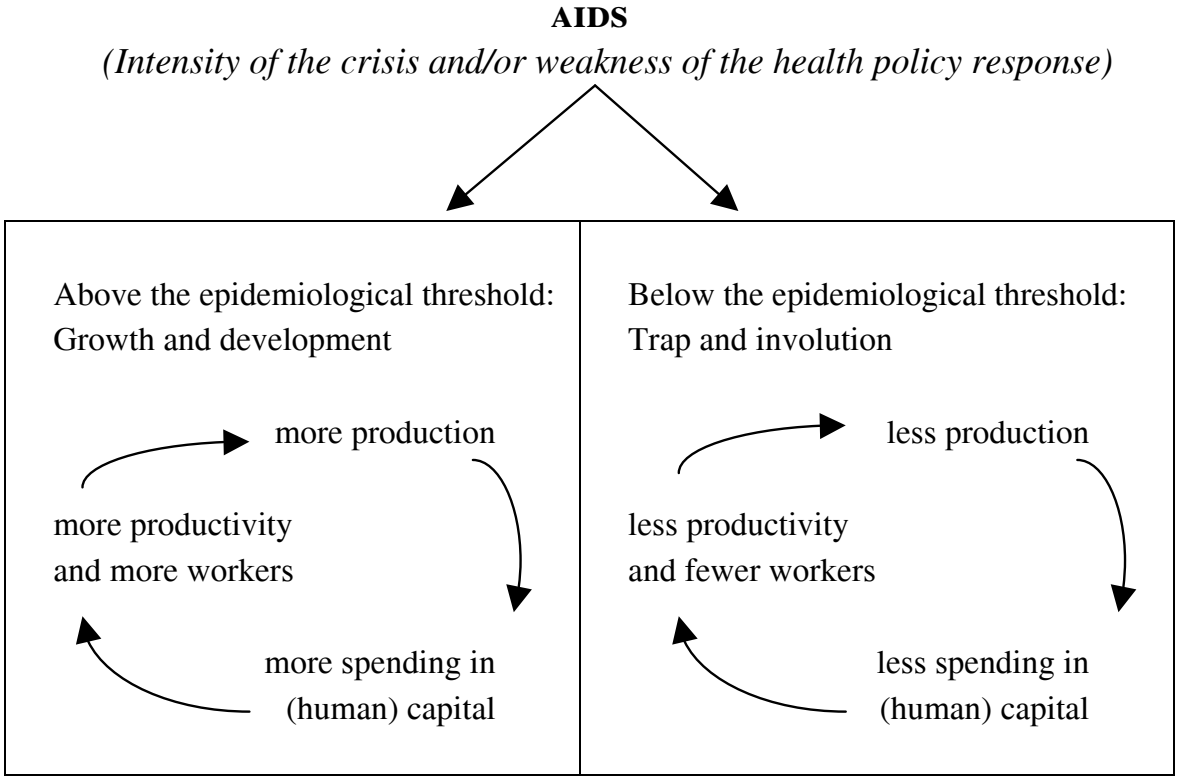
Conclusion

The simplified model in section III was based on two crucial assumptions:

I) AIDS has a short-term impact on a flow variable (the flow of potential workers available and able to effectively work at a specific time *t* in the economy);

II) AIDS has a long-term impact on a stock variable (human capital, *i.e.* the stock of the workers' state of health or education). Integrating these two impacts in a coherent production model, is sufficient to reverse the standard prognostic based on a relatively linear evolution of the economies. An involution trap appears, corresponding to a modification of the long-term growth regime of the economy (the equilibrium which we aim for):

Figure 5: Economic Impact of AIDS: two paths for the economy



The quantifications of the macroeconomic impact of AIDS on developing countries are only in the early stages. The sensitivity of the studies to the structural models used for forecasting is a delicate point. Notably the appearance of threshold effects and bifurcations calls into question the prognostics based on economies which are developing much more regularly. Thus, by using forecasting terminology, it would appear that the base-case scenario, *i.e.* the

virtual evolution of the economy for a supposed zero crisis, is totally disrupted, after a bifurcation, by the crisis itself. This phenomenon invalidates the impact quantifications based on comparisons by linear approximation. Economic behaviour, incorporating the shift of the long-term equilibrium due to the crisis (the bifurcation), is already altered[18], making the use of the base-case scenario futile, or at the very least misleading.

APPENDIX
COMPLETE PRESENTATION OF THE MODEL

Production function and behaviour of firms

The production function describes a technology with constant returns to scale and includes four arguments: the stock of physical capital K, the number of workers L, productive public spending D and the stock of human capital H. It is expressed as:

$$Y \mid F(K,L,D,H) \mid K^{\zeta}(L.H)^{\eta}(D)^{14\zeta 4\eta}$$

We assume that firms maximise their profit. In the optimum situation, the private factors of production are remunerated at their marginal productivities. This gives:

$$(14\mu)\frac{\in Y}{\in K} \mid r \heartsuit (14\mu)\zeta\frac{Y}{K} \mid r$$
$$(14\mu)\frac{\in Y}{\in L} \mid w \heartsuit (14\mu)\eta\frac{Y}{L} \mid w$$

Notes: H and D behaviour will be determined respectively by households and the government. L is given by a population dynamic which is altered by AIDS, for a total population of N individuals. These demographic dynamics are described by:

$$\frac{L}{N} \mid 14\kappa(14\, g(x^4));$$

18. This argument is similar to that evoked in the "Lucas criticism" [21] of econometric models.

with κ AIDS crisis, and $g(x)$ a "reparation function" of the ability of AIDS sufferers to work through healthcare spending (x in t-1). We stipulate the following restrictions:

$$g_x^{'} \} 0 \text{ et } 0 \{ g(x) \{ 1.$$

Programme and behaviour of the different types of household

We consider two types of household: the workers-employees and the capitalists-rentiers.

Behaviour of workers-employees

Employees do not save. We consider the plan of an extended family, of which a proportion *L/N* works (the different families are affected identically by the disease). There are *F* families and *N/F* is the number of individuals in the household.

Decisions about household consumption rest on a choice between consumption of everyday goods and consumption of health goods. Health demands are influenced by the morbidity of the family. The function $l(\kappa)$ influences the state of family health: we have $e \mid x.l(\kappa)$ with the restrictions: $l_{\kappa}^{'} \{ 0, \quad \text{et} \quad l(1) \mid 0$. The programme of maximisation of a household is expressed:

$$Max[U(c,e)] \mid Max[(\tau.c^{\lambda} 2\ \psi e^{\lambda})^{\frac{\nu}{\lambda}}]$$
$$sc:(N/F)c 2\ p(N/F)x \mid w(L/F) 2\ T/F$$

We use *w* as the wage rate, *T* transfers, *p* the price of health/education goods, *x* the private quantities of health/education goods consumed, *e* the state of health/education.

The stock of human capital evolves following the rule: $H^2 \mid e 2\ \iota H$. *e* is a flow of consumption of health and/or educational goods, which accumulates on the stock of human capital *H.* This stock *H* will itself be used as an individual indicator of the quality of labour. This effect can "capture" both a health-capital effect and the restoring of this capital-health by healthcare spending, and an education effect.

We find:

$$\frac{\tau c^{\lambda 41}}{\psi e^{\lambda 41}.l(\kappa)} \mid \frac{1}{p}$$
$$c 2\ px \mid w(L/N) 2\ T/N$$

and the function of health status demands is written:

$$e \mid \frac{w(L/N)\,2\,T/N}{\frac{p}{l(\kappa)}\,2\,(\frac{\tau}{\psi})^{\frac{1}{14\lambda}}.(\frac{p}{l(\kappa)})^{\frac{1}{14\lambda}}}$$

Behaviour of the capitalists-rentiers (endogenous saving)

The capitalists have a consumption/ savings choice. They seek to maximise their inter-temporal welfare. The programme is written:

$$W \mid \; Max[U(c)\,2\,\frac{14\,\kappa}{12\,R}W^{2}]$$

$$sc:c \mid \; rk\,4\,(k^{2}\,4\,k)\,2\,rb\,4\,(b^{2}\,4\,b)\,2\,\phi$$

where r is the rate of return on the world capital market (assumption of a small open economy), k is the accumulation of national assets, b foreign asset holdings. The programme gives in log form (for example) the following profile of inter-temporal consumption:

$$\frac{c^{2}}{c} \mid \; \frac{14\,\kappa}{12\,R}(12\,r)$$

"Behaviour" of the State

The functions of the State are limited to financing public expenditure (D^{2}) with a tax rate (σ) on added value (Y), and which is only productive for the period that follows, as well as subsidising healthcare spending on a flat-rate basis (T), but this spending can also be assimilated to the financing of a collective health infrastructure:

$$\mu Y \mid \; D^{2}\,2\,T$$

Major lines of resolution of the model

Based on the production function, $Y = (K)^{\zeta}(L.H)^{\eta}(D)^{1-\zeta-\eta}$, we can substitute the stock of capital by $K = \frac{\zeta(1-\mu)}{r}Y$, the number of workers by $L = (1-\kappa(1-g(x^4)))N$, the stock of human capital by $H^2 = e^2 \iota H$ and productive public spending by $D^2 = \mu Y - T$.

We thus find:

$$Y = (\frac{\zeta(1-\mu)}{r})^{\zeta/1-\zeta}[N.(1-\kappa(1-g(\frac{e^4}{l(\kappa^4)}))).(e^4 - \iota H^4)]^{\eta/1-\zeta}(\mu Y^4 - T^4)^{(1-\zeta-\eta)/1-\zeta}$$

We note that *Y* is a function of delayed variables (Y^4 and κ^4). We could thus very simply calculate the GDP of the period (and the GDP growth rate) with the help of numeric simulations.

By recalling the demand function of the state of health calculated below:

$$e^4 = \frac{w^4(L^4/N^4)-T^4/N^4}{\frac{p^4}{l(\kappa^4)}-(\frac{\tau}{\psi})^{\frac{1}{1-\lambda}}.(\frac{p^4}{l(\kappa^4)})^{\frac{1}{1-\lambda}}},$$

we highlight some interesting results to be commented upon. With regard to the question of public choice (*T* for example), we note the trade-off on *D versus H* (accumulation of *e*), fundamentally regulated by the production elasticity of the two factors.

Note 1: a priori, an under-estimation by the public decision-maker of the coefficient η (elasticity of production to human capital) biases the public choice to the detriment of *H* and health/education spending.

Note 2: a perverse effect*:* when (κ) increases*,* the number of workers falls and the public choice on *H* could also be biased downwards.

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HIV/AIDS, Human Development and the Coming Epidemic in the Balkans, Baltic, Russian Federation and the CIS

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Key words: HIV/AIDS; CIS; socio-economic impact; human development.

Abstract

HIV/AIDS affects human development. The United Nations has developed this concept most elaborately. Although useful as an advocacy tool it does not adequately capture the effects of a long wave event like an HIV/AIDS epidemic. The CIS (Commonwealth of Independent States), Russian Federation, Balkans and Baltic States are diverse and they face an impending epidemic. In some states, 1% of the adult population is HIV-infected, suggesting a "generalised" epidemic. Further epidemic growth will mean that excess morbidity and mortality may soon affect health, education and governance activities. Comparison with Botswana shows how rapidly these effects can appear. This chapter considers some of the conceptual and theoretical challenges to measuring the impact of such an event.

Résumé

Le VIH affecte le développement humain. Les Nations Unies ont minutieusement élaboré ce concept qui reste cependant un outil plus utile pour plaider une cause que pour rendre compte des effets à long terme d'un événement tel que l'épidémie de VIH/sida. La Communauté des Etats Indépendants (CIS), la Fédération de Russie, les Balkans et les Etats baltes sont dans des situations

très diversifiées et ils font face à une épidémie imminente. Dans certains pays, 1% de la population adulte est séropositive au VIH, ce qui constitue une épidémie "généralisée". Une accélération de l'épidémie dans le futur et l'augmentation de la morbidité et la mortalité associées vont affecter la santé, l'éducation et même la bonne gouvernance des Etats. L'exemple du Botswana montre avec quelle rapidité ces effets peuvent apparaître. Cet article analyse certaines des questions conceptuelles et thématiques posées par l'évaluation de l'impact de cette épidémie.

Introduction

This is the third decade of the global HIV/AIDS pandemic. The magnitude and long-term nature of the pandemic and its severe impact on societies and economies are indisputable and raise issues for social sciences. In a sub-Saharan population of 642 million people[1], UNAIDS estimate just under 30 million are living with HIV/AIDS. A cumulative total of 12-14 million people have died in the past 10 years. If each death has affected the lives of five survivors – orphans, spouses, parents—the lives of at least 200 million people have been directly affected by the epidemic. These effects will last for decades. Adult HIV/AIDS prevalence rates of 10% to 20% are common in many African countries, and Botswana, Lesotho and Swaziland are close to 40%. Such figures signify the epidemic is affecting each and every rural and urban household. Within ten years, the largest numbers of infections (not the largest percentage infected) in any country will be in India or China[2]. Current estimates of numbers of HIV-infected persons in the former range between 3.5 and 6 million. In the latter, around 10 million people may be infected. In Russia and the CIS[3], HIV/AIDS epidemics were, until recently, driven mainly by intravenous drug-use. In some countries, epidemics are now generalised. Adult infection rates are around 1% in three countries: Russia, Ukraine, Estonia. "Low" levels such as these were seen between 10 and 20 years ago in Africa. That is the planning horizon within which social scientists, politicians and policy makers must think in relation to these countries, many of which are insecure and unstable and some of which are about to accede to the European Union. The time

1. World Bank: *World Development Report 2000-01: Attacking Poverty*. Washington: World Bank and Oxford University Press, p. 275, Table 1.

2. Estimates from UNAIDS.

3. For purposes of contextualisation, in some cases data are also presented for Eastern Europe given the contiguity of the area.

perspective is in fact longer, as "impact" of the epidemic will continue for many more decades [4].

I
HUMAN DEVELOPMENT AND EPIDEMIC COST

What precisely do we mean by "impact"? An answer to this question directs attention to a number of normally unrelated areas of social science thought and suggests the following issues:

1) a discussion of the concept of "cost"[5] as traditionally used in social sciences;

2) the possibility of using insights from hedonic psychology [1] and economics [2] to examine the relationship between impact and its effects on social and economic reproduction [6];

3) the discourse of "responsibility" – which might be defined as social and cultural recognition and moral interpretation of the relation between cause and effect [5-7]. This latter concept has received relatively little recent examination in the social sciences. The major exception has been S. Cohen [8][7].

Here we limit ourselves to:

— presenting some recent data about the situation in the CIS and its region;

— exploring the limitations of the Human Development Index as a mechanism for reflecting the impact of the HIV/AIDS epidemic;

— considering what further conceptual and theoretical work is necessary to assess the ideas of cost and impact.

4. Professor Roy Anderson of Imperial College, London, has suggested in an unpublished paper that the full wave amplitude of the epidemic and its impacts may extend to 120 years.

5. Which has come down to economic discourses such as cost effectiveness or cost benefit.

6. The precise definition departs from Bourdieu and Passeron [3] and succeeding work rather than from the literature on "social capital", Putnam *et al.* [4].

7. There are also interesting insights to be gained from the work of Heidegger.

II
THE HIV/AIDS EPIDEMIC IN THE CIS, RUSSIAN FEDERATION, THE BALTIC, THE BALKANS[8]

This region has the fastest-growing epidemic in the history of the global epidemic. The number of new HIV infections is rising steeply. In Russia, reported diagnoses have doubled annually since 1998. A conservative estimate puts the number of people living with HIV at least 4 times higher than the reported figures, quickly approaching an HIV prevalence rate of 1% in the adult population. In October 2000, the Director of the Federal AIDS Centre estimated that the true number of infections was six to 10 times higher than the number of notified cases [9].

The HIV crisis is escalating in other countries. In Estonia new reported HIV infections jumped from 12 in 1999 to 1,474 by the end of 2001; in Latvia the incidence jumped from 25 cases in 1997 to 807 cases in 2001. The epidemic is getting worse in Kazakhstan. After the first outbreak of HIV in 1997, 1,175 HIV infections were reported in 2001. Rapid spread is reported in Kyrgyzstan, Tajikistan, Uzbekistan, Azerbaijan and Georgia. With an adult HIV prevalence rate of 1%, Ukraine remains the most seriously affected country.

The current situation is summarised as follows:

– one country (Russia) accounts for close to 70% of all infections in the region;

– two countries (Russia and Ukraine) make up some 95% of all infections in the region;

– adult infection rates are around 1% in three countries: Russia, Ukraine, Estonia;

– infection rates between 0.2% and 0.4% are found in Belarus, Moldova, Latvia;

– prevalence is at or lower than 0.1% in 17 out of the 23 countries;

– Poland has a considerable number of infections, but a low adult infection rate;

– Russia plus Ukraine shift the region-wide average adult infection rate to 8 times the average of the other countries.

Can we conclude then that this is a Russian, a Ukrainian or an Estonian problem? Experience shows that such responses are unhelpful. They are rather part of general denial. Certainly, the epidemic is worse today in Russia, Ukraine and Estonia than elsewhere in the region. But we must remember that

8. This summary is informed by a document prepared by Dr Henning Mikkelsen of UNAIDS to whom thanks are due.

what we know about the epidemic depends on the reporting system in place in each country. Reporting systems and political engagement with this issue vary. The conditions for a large and destructive epidemic are ripe across the whole region and no country is immune. This could be a major epidemic on the threshold of the European Union (EU) and should be of interest to politicians and policy makers in the EU.

III
THE BALKANS, BALTIC, RUSSIA AND THE CIS AS A RISK ENVIRONMENT

Literature on infectious disease epidemics has focused on risk behaviours. Here we introduce another term, risk environment [10, 11]. This concept shifts emphasis from individuals'behaviours to characteristics of the social, cultural and economic environment which make individual behaviours more or less risky. This entire region is a "risk environment" for the following reasons.

Superimposition of long wave events

Societies in this region are in transition. Some are moving towards a new order; others, particularly in South East Europe, the Caucasus and Central Asia, continue to experience social disorder and even war; most exhibit low levels of social cohesion, as well as increased income and wealth inequalities.

Endemic poverty means that there is significant unemployment in the young generation in Central Asia. Forty percent of that population is under 18.

There is a strong possibility, and in many countries this must be seen as a high probability, that the long wave event of the transition is now superimposed by another long wave event – an HIV/AIDS epidemic.

Superimposition of these two long wave events poses unique problems of human development.

Population Dynamics

a. Russia's population is shrinking, and Central Asia's population is growing: Turkmenistan's growth rate is around 3.8% per year.

b. Populations are moving from rural to urban areas.

HIV/AIDS will interact with this dynamic and will have implications for responses. In states such as Russia, Ukraine and Belarus where population is shrinking, the epidemic's effects on population could spur politicians to act. In contrast, societies which perceive themselves to have growing populations, as in parts of Central Asia, may consider that the epidemic, while tragic, is of little structural importance.

IV
HIV/AIDS AND HUMAN DEVELOPMENT
THE IDEA OF HUMAN DEVELOPMENT

The notion of human development can be traced to early periods in human history and is found in many cultures and religions throughout the world. Until the end of the 19th century, many writings in economics were concerned with the broader development of human lives as well as with the creation of wealth. During the 20th century, this approach gave way to concentration on the creation of wealth and an emphasis on economic growth to the exclusion of other aspects of human development. Gross Domestic Product (GDP) per capita became the focus of economic and social policy. At some periods it became the main proxy measure of "development". This was particularly the case in the USSR.

The modern idea of human development, characteristic of the United Nations Development Programme (UNDP), tries to go beyond GDP alone to arrive at a more pragmatic balance between growth of wealth, environmental sustainability and people's need to be full participants in the lives of their societies. It tries to recognise that these goals should be achieved in relation to widely varying cultural and national traditions. The Human Development Reports and the Human Development Index (HDI) attempt to measure progress on several dimensions. This enables national politicians to see how they are doing in relation to other countries; and individuals and groups of citizens to make some judgement of how well their governments are doing on their behalf.

The 1990 Human Development Report [12] defined human development as 'the process of enlarging people's choices'This complex of ideas has been influenced by the concept of "capabilities" [13], a perspective focusing on the opportunities for choice which are open to people, thus linking how far people are able to exercise those choices in terms of their entitlements to the concept of a risk environment. "People's choices" mean different things. Above all, "choice" occurs in a social and economic context. It is not only about individual

decisions. Our individuality depends on the conditions in which we lead our lives. Choices may be very large indeed. They are certainly dynamic – they change as our opinions alter and differ according to our position in society, in relation to key social and economic characteristics such as age, gender, ethnicity, social status, education, and beliefs.

What types of choices are we concerned with when we talk about "human development"? Irrespective of the level of wealth or development of a country, some basic choices appear to be constant across human groups. People want to lead long and healthy lives, to be educated and have access to resources for a decent standard of living. These choices are basic in the sense that without them other choices, equally valued, are unavailable. Other choices include political, economic, social and cultural freedoms, human rights, self-esteem, and opportunities for being creative and productive.

The components of human development

Human development has four components:

1) the creation of human capabilities – improved health, knowledge and skills so that people can increase their productivity and fully participate in income generation and remunerative employment;

2) the elimination of barriers to economic and political opportunities, enabling people to have equal access to and benefit from opportunities;

3) the people's full participation in decisions and processes affecting their lives;

4) the sustainability [14] of the development process. Here:

> – human development is sustainable if the present generation can earn its living without compromising the ability of future generations to do the same and vice versa;
>
> – livelihoods of present and future generations are compromised if development does not allow all people, men and women, to participate. When women are excluded from social, economic and decision-making processes, development is rendered fragile and inequitable.

Thus – with the addition of the concept of risk environment – many links can be made between process sustainability, human rights and the effects of an HIV/AIDS epidemic.

Environment and sustainability

Another way of measuring sustainability is to ask the question "is economic growth or a rise in per capita GDP in the short run achieved by reducing environmental capital?" If the answer is "yes" and such short-term gains reduce the future rate of economic growth, then economic growth is environmentally unsustainable.

Trade-offs must be made. Political judgements are necessary. There is always the possibility that livelihoods of present and future generations could be compromised. Economic growth may be achieved by undermining human capital. Today it is widely believed that we must ensure that economic growth develops human capital. However, extreme concern for environmental protection might neglect the need for people to survive through intensive use of the environment. In this situation, environmental protection at the expense of survival is morally wrong and politically unacceptable. We must strike a balance between environmental sustainability and human sustainability. Compromising situations may arise where there is either an absence of economic policies to avoid macroeconomic disequilibrium or where formulaic macro-economic policies are imposed regardless of local circumstances. While good economic policies are essential for any economy to function properly, to raise per capita income and to improve human development, the wrong choices can result in dramatic losses of people's quality of life, their health and the conditions for the development of the next generations. HIV/AIDS threatens health, life expectancy and the entire development project.

V
BEARING HIV/AIDS IN MIND

The Russian Federation and CIS are experiencing economic, social and political "transitions". They are in parallel confronting an epidemic of HIV/AIDS. This has numerous implications for both human capital and the effectiveness of macro-economic policies as well as, in an advanced epidemic, the possibility of effective governance. HIV/AIDS affects human capital as premature illness and death waste the investment that society has put into training people. Illness and death among people aged 15-50 who would usually make the fewest demands on health and other caring services imposes an unexpected cost on society.

The effects of HIV/AIDS on the economy of the Russian federation

It has been estimated that in the Russian Federation even a low level epidemic will have adverse effects on economic performance [16]. In 2002, the chief economist of the World Bank's Moscow office, said:

"HIV is a time bomb. As HIV spreads through society, the economy suffers from a decline in the workforce while enormous health-care costs eat up money that is desperately needed for investment in industry and infrastructure As a result, if current transmission rates slow down and 2.32 million people become HIV positive by 2010, gross domestic product would be depressed by 0.15 percent, according to the World Bank's optimistic scenario. But the conservatively pessimistic scenario indicates that if 5.25 million people become HIV positive, a staggering 4.14 percent would be shaved off GDP. [Even 1 percent] does matter in a country that needs very high growth rates to catch up to other countries." [16]

Because it affects mature age adults, the morbidity and mortality associated with an HIV/AIDS epidemic also affects the unpaid, non-market economic activities – what can be called socially reproductive labour [11]. These activities – child rearing, community participation, self-provisioning through agricultural or pastoral work – do not enter into economic calculations of the effects on the macro-economy. Loss of such activities must be assumed to have important effects on human development. Such activities may be conceptualised through the idea of a relational good [17] – final consumption goods (valued for themselves) and/or intermediate goods, where certain social relations may facilitate co-operation and trust, recognising that social relations can be a source of value in themselves [18]. These ideas have implications for our thinking about social and economic impacts of events on capacities for social and economic reproduction.

VI
HUMAN DEVELOPMENT IN THE CIS, BALTIC, SOUTH AND SOUTH EAST EUROPE REGION OF EURASIA

In 1999, the mean Human Development Index (HDI) for those countries of the region for which data were available was 0.753 – putting them collectively into the category of "medium human development". A number of countries – the Czech Republic, Lithuania, Poland and Slovakia – fell into the high human development group, while the majority were in the medium range (Table 1).

Table 1: The human development index and its components for the CIS, the Balkans and the Baltic states

Countries	*Human Development Index*				*GDP Per Capita (ppp US$)**	*Life expectancy at birth* (YEARS)		*Adult literacy rate* (% AGE 15 AND ABOVE)
	1985	**1990**	**1995**	**1999**	**1999**	**1970-75**	**1995-2000**	**1999**
Albania	0.689	0.700	0.701	0.725	3,189	67.7	72.8	84.0
Armenia	---	---	---	0.745	2,215	72.5	72.4	98.3
Azerbaijan	---	---	---	0.738	2,850	69.0	71.0	97.0
Belarus	---	0.808	0.774	0.782	6,876	71.5	68.5	99.0
Bosnia-Herzegovina	N.A.	N.A.	N.A.	N.A.	N.A.	---	73.3	N.A.
Czech-Republic	---	0.833	0.841	0.844	13,018	70.1	74.3	99.0
Georgia	---	---	---	0.742	2,431	69.2	72.7	99.6
Kazakhstan	---	---	---	0.742	4,951	64.4	64.1	99.0
Kosovo	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	
Kyrgyzstan	---	---	---	0.707	2,573	63.1	66.9	97.0
Latvia	0.801	0.803	0.761	0.791	6,264	70.1	69.6	99.8
Lithuania	---	0.814	0.780	0.803	6,656	71.3	71.4	99.5
Moldova	---	0.758	0.704	0.699	2,037	64.8	66.6	98.7
Poland	---	0.790	0.807	0.828	8,450	70.5	72.8	99.7
Romania	0.793	0.775	0.771	0.772	6,041	69.2	69.8	98.0
Russia	0.826	0.823	0.778	0.775	7,473	69.7	66.1	99.5
Slovakia	0.811	0.818	0.816	0.831	10,591	70.0	72.8	99.0
Tajikistan	---	---	---	0.660	1,031	63.4	67.2	99.1
Turkmenistan	---	---	----	0.730	3,347	60.7	65.4	98.0
Ukraine	---	0.793	0.744	0.742	3,458	70.1	68.1	99.6
Uzbekistan	---	0.693	0.683	0.698	2,251	64.2	68.3	88.5
Yugoslavia	N.A.	N.A.	N.A.	N.A.	N.A.	---	72.2	N.A.

*Source: Human Development Report, 2001. N.A.: not available; *: PPP: purchasing-power parity.*

All of these countries face challenges to their efforts to achieve better lives for their citizens. Most confront transition from the Soviet system to some form of market economy and increasing pressures of globalisation. There are additional challenges. One group (Estonia, Latvia, Lithuania, Poland, Czechoslovakia, Hungary, Slovenia, Slovakia, Romania, and Bulgaria) is moving rapidly toward accession to the European Union with attendant requirements for stricter control of state spending and rapid development of representative institutions. Another group is troubled by unresolved and serious tensions and/or border disputes (Georgia, Armenia, Kosovo, Bosnia-Herzegovina, Moldova). Some countries show evidence of rapidly growing epidemics of HIV/AIDS which threaten to explode into the general population. All of them face a potentially serious HIV/AIDS epidemic.

VII
WHAT WE KNOW ABOUT HIV/AIDS AND HUMAN DEVELOPMENT

While the global HIV/AIDS epidemic began somewhere towards the end of the 70s, it is surprising that we have limited understanding of its effects on human development. The international community has development goals. In 1997 the Development Assistance Committee of the OECD (Organisation for Economic Co-operation and Development) articulated a set of global and international development goals. These are supposed to be ambitious but realisable[9].

Such targets have influenced the public stances of most of the major donor agencies.

Attacking poverty is the goal that resonates best with donors and in their policies. The World Bank articulated its 'poverty reduction policy'in 1998 and in 2000 began its Development Report with the statement:

"Poverty amid plenty is the world's greatest challenge. We at the Bank have made it our mission to fight poverty with passion and professionalism, putting it at the centre of all the work we do. And we have recognised that successful development requires a comprehensive, multi-faceted, and properly integrated mandate" [19].

The practice, assumptions and goals of "development" must take account of the HIV/AIDS epidemic. The consequences of HIV/AIDS are only just coming on to the international development agenda as anything other than health problems. The global scale of the epidemic and the possible regional consequences mean that it is a major multi-sectoral issue for human development.

The overarching international goal for human development is poverty reduction. The 2000/2001 World Development Report "seeks to expand the understanding of poverty and its causes and sets out actions to create a world free of poverty in all its dimensions" [19]. Since 1996 there has been a slight decrease in the percentage of the global population living in poverty but the absolute number has risen (Table 2). There are wide disparities between regions and within countries. Table 3 shows the percentage of people in the region with which this chapter is concerned living at or below a poverty line of $4 per day.

9. These goals were revisited and reissued by the UN following the Millennium Summit of the United Nations on the theme "The role of the United Nations in the twenty-first century" held in New York from 6-8 September 2000.

Table 2: Global population living on less than US$1 a day

	1987	1990	1993	1996	1998
People (Million)	1,183.2	1,276.4	1,304.3	1,190.6	1,198.9
Share of population (percent)	28.3	29	28.1	24.5	24

Source: World Bank 2001.

Table 3: Percentage of regional populations living on or below US$4 a day

Country	*Population below income poverty line, percentage on or below US$4 per day 1993-1995 (1990 PPP US$)**
Albania	N.A.
Armenia	N.A.
Azerbaijan	N.A.
Belarus	22
Czech	<1
Georgia	N.A.
Kazakhstan	65
Kosovo	N.A.
Kyrgystan	88
Latvia	22
Lithuania	30
Moldova	66
FYR Macedonia	N.A.
Poland	20
Romania	59
Russia	50
Slovakia	<1
Tajikistan	N.A.
Turkmenistan	61
Ukraine	63
Uzbekistan	63
Yugoslavia	N.A.

Source: UNDP, Human Development Report. Making New Technologies. Work for Human Development. New York: Oxford University Press, p. 152-53.
N.A.: not available. * Data refers to most recent years.

There is growing evidence that HIV/AIDS spreads more rapidly where there is poverty, grossly unequal distribution of income and wealth, unequal gender relations, unsustainable livelihoods, large scale population movement and civil disorder [20, 21, 11]. In these circumstances, poverty assists the spread of HIV, and the resulting illness pushes people into poverty or makes it harder for them to escape from it. Thus low levels of human development encourage the spread of the epidemic and low levels of human development make it more difficult to respond to the epidemic or to its effects on human development. Put very simply: it seems certain that poverty contributes to HIV/AIDS epidemics and AIDS contributes to poverty, but we do not know very much about the complex pathways of the relationship.

As development is about more than Gross Domestic Product, so poverty is about more that financial deprivation. This was recognised by the UNDP in 1990. The first Human Development Report opened with the statement:

"The real wealth of a nation is its people. And the purpose of development is to create an enabling environment for people to enjoy long, healthy and creative lives. This simple but powerful truth is too often forgotten in the pursuit of material and financial wealth" [12].

One of the most measurable ways that we see the effect of AIDS on Human Development is through mortality rates. Adults and many infants and children are dying prematurely. This impact is measured in the HDI though the life expectancy component. Because the epidemic is still in comparatively early stages in most countries of the region, we must look outside of the region to see the effects of an HIV/AIDS epidemic. We should recall that in many parts of Africa the progression from a few initial cases of infection to a large scale heterosexually driven epidemic took only a decade. While the epidemic in the Balkans, Baltic and the CIS is for the moment often characterised as driven by intravenous drug use (IDU), this may soon change in many countries. The transition to a generalised epidemic outside of these core groups may have occurred already in Russia, Belarus and Ukraine where IDUs are not solely isolated and marginalised groups but also schoolchildren residing in their parental homes. While this point may be debated for political and presentational reasons[10], for the moment it is only safe and possible to conclude that we do not know and thus that it is necessary to act as though we are confronting a generalised epidemic with consequent effects on society and economy.

10. For example because of sensitivities in countries soon to accede to the EU.

Table 4 shows how AIDS mortality has affected both life expectancy and HDI scores and rankings for selected countries.

Table 4: Life expectancy and place in the HDI (selected countries)

	1996 Report (1993 data)		*1997 Report (1994 data)*		*2000 Report (1998 data)*	
	Life Expect.	*HDI (Rank)*	*Life Expect.*	*HDI (Rank)*	*Life Expect.*	*HDI (Rank)*
Cambodia	51.9	0.325 (156)	52.4	0.348 (153)	53.5	0.512 (136)
Thailand	69.2	0.832 (52)	69.5	0.833 (59)	68.9	0.745 (76)
Botswana	65	0.741 (71)	52.3	0.673 (97)	46.2	0.593 (122)
Côte d'Ivoire	50.9	0.357 (147)	52.1	0.368 (145)	46.9	0.420 (154)
Kenya	55.5	0.473 (128)	53.6	0.463 (134)	51.3	0.508 (138)
Malawi	45.5	0.321 (157)	41.1	0.320 (161)	39.5	0.385 (163)
South Africa	63.2	0.649 (100)	63.7	0.716 (90)	53.2	0.697 (103)
Zimbabwe	53.4	0.534 (124)	49.0	0.513 (129)	43.5	0.555 (130)
Zambia	48.6	0.411 (136)	42.6	0.369 (143)	40.5	0.420 (153)
Haiti	56.8	0.359 (145)	54.4	0.338 (156)	54.0	0.440 (150)

Source: United Nations, HDR's 1996, 1997, 1998, 1999 and 2000.

VIII
BOTSWANA –AN IMAGE OF THE FUTURE, A LESSON TO BE LEARNED?

Botswana is in Southern Africa. It is a middle income country with large mineral resources, a long history of stable government and social provision for many of its citizens. HIV prevalence among adults is now close to 40%. Its GDP per capita in 1999 was higher than that of 16 of the countries in the CIS, the Balkans and the Baltic region of Eurasia. The effect of the HIV/AIDS epidemic on Botswana is significant and important for what it suggests to us about the potential for this epidemic to harm the economic and social life – the level of human development – in the Eurasian region.

In 1996, Botswana's HDI was 0.741 and it occupied 71st position in the world ranking of Human Development. By 1997 when HIV/AIDS was first taken into account in calculation of the HDI, the country's position fell from 71st to 122nd. Even Thailand – a country that has an HDI comparable to those of the countries of this region at 0.757 [22] and where serious efforts have been made to bring the epidemic under control has been affected. Life expectancy has fallen slightly, contributing to the fall from 52nd to 76th place in HDI

rankings. Table 5 shows the HDI score of most of the countries of concern to this chapter for two years, 1995 and 1999, together with their GDP per capita in 1999. It shows the same information for Botswana.

Table 5: HDI scores 1995 and 1999 for countries from this region compared with Botswana

Country	*HDI Score 1995*	*HDI Score 1999*	*GDP per capita (PPP US$) 1999*
Albania	0.701	0.725	3,189
Armenia	N.A.	0.745	2,215
Azerbaijan	N.A.	0.738	2,850
Belarus	0.774	0.782	6,876
Botswana	0.621	0.577	6,872
Bulgaria	0.775	0.772	5,071
Czech	0.841	0.844	13,018
Estonia	N.A.	0.812	8,355
Georgia	N.A.	0.742	2,431
Hungary	0.807	0.829	11,430
Kazakhstan	N.A.	0.742	4,951
Kosovo	N.A.	N.A.	N.A.
Kyrgystan	N.A.	0.707	2,573
Latvia	0.761	0.791	6,264
Lithuania	0.780	0.803	6,656
FYR Macedonia	N.A.	0.766	4,651
Moldova	0.704	0.699	2,037
Poland	0.807	0.828	8,450
Romania	0.771	0.772	6,041
Russia	0.778	0.775	7,473
Slovakia	0.816	0.831	10,951
Slovenia	0.850	0.874	15,977
Tajikistan	N.A.	0.660	1,031
Turkmenistan	N.A.	0.738	3,347
Ukraine	0.744	0.742	3,458
Uzbekistan	0.683	0.698	2,251
Yugoslavia	N.A.	N.A.	N.A.

Source: Human Development Report 2001, p. 145-8; 141-4.

In many cases, the years 1995-99 saw countries improving their HDI. This was so even in the face of enormous difficulties. Most countries increased their HDI marginally or remained static. Four countries – Moldova, the Russian Federation, Bulgaria and Ukraine saw small falls. In contrast, Botswana, with relatively high GDP per capita, high value mineral exports, stable government, low levels of corruption and a long history of civil order, registered a decline. This was precisely the result of the effects of HIV/AIDS-related deaths on life

expectancy. Before HIV/AIDS life expectancy was 60.3 years: in 2001 it was 41.9 years – a loss of 18 years of life expectancy. Table 6 shows this process in a longer perspective – 1975 to 1999. We see that Botswana follows a clear trajectory of improving human development from 1975 until 1995 – in fact its HDI reached 0.741 in 1996. Then it declined. This is what HIV/AIDS can do in practice to human development.

Table 6: Human Development and HIV/AIDS: Botswana – a middle wealth country with a big HIV/AIDS epidemic

Year	1975	1980	1985	1990	1995	1999
HDI Score	0.495	0.558	0.615	0.654	0.621	0.577

IX
WHAT HAPPENS TO HUMAN DEVELOPMENT IF LIFE EXPECTANCY IS REDUCED?

How might changes in life expectancy affect the HDI of countries in this region? Table 7 shows the effects of reductions in life expectancy by 1, 2, 5 and 10 years for most of the countries for which data were available. Reduction in life expectancy by one or two years does not seem to make a great difference to the HDI. Reduction by five years does make a difference – and such reductions, as in the case of Botswana, would be year on year and cumulative rather than a one time event. But could such large changes in life expectancy really occur in this region; after all, Botswana is in Africa, which is very different from the CIS, the Baltic and the Balkans? In fact, such changes can happen and they have happened. The transition that has occurred in this region since 1989 has resulted in some significant reductions in life expectancy in the region. These are shown in Table 1.

Adverse changes have taken place in five countries – Armenia, Belarus, Kazakhstan, Russia and Ukraine. For the most part these are a matter of a few decimal points. But even this is undesirable given that citizens and politicians expect year on year increases. However, in three cases – representing very large populations – the decrease has been significant: Russians have lost 3.6 years of life expectancy, Belarussians have lost three years of life expectancy and Ukrainians have lost two years of life expectancy (and in each case, more is lost by men than by women). In total these three countries have a population of about 207 million people.

Table 7: The effect of declining life expectancy on the HDI of selected countries

Countries	*Human Development Index (HDI)*	*HDI- 1 years life expectancy*	*HDI- 2 years life expectancy*	*HDI- 5 years life expectancy*	*HDI- 10 years life expectancy*
Albania	0.726	0.720	0.714	0.698	0.670
Armenia	0.743	0.734	0.732	0.716	0.688
Azerbaijan	0.736	0.730	0.724	0.708	0.680
Belarus	0.785	0.779	0.774	0.757	0.729
Bosnia-Herzegovina	0.268	0.263	0.257	0.241	0.213
Czech-Republic	0.841	0.835	0.829	0.813	0.785
Georgia	0.738	0.734	0.727	0.711	0.683
Kazakhstan	0.741	0.735	0.729	0.713	0.685
Kosovo	---	---	---	---	---
Kyrgystan	0.703	0.697	0.692	0.675	0.647
Latvia	0.788	0.782	0.777	0.760	0.732
Lithuania	0.801	0.796	0.790	0.773	0.746
Moldova	0.698	0.692	0.687	0.670	0.642
Poland	0.826	0.820	0.814	0.798	0.770
Romania	0.769	0.763	0.758	0.741	0.713
Russia	0.775	0.769	0.764	0.747	0.719
Slovakia	0.829	0.823	0.818	0.801	0.773
Tajikistan	0.658	0.652	0.647	0.630	0.602
Turkmenistan	0.758	0.752	0.747	0.730	0.702
Ukraine	0.743	0.737	0.732	0.715	0.687
Uzbekistan	0.694	0.688	0.683	0.666	0.638
Yugoslavia	---	----	----	----	----

Source: HDI estimates rounded to 3 decimal points.

X
HIV/AIDS AND HUMAN DEVELOPMENT: THE REAL COST WHO IS MEASURING AND WHAT ARE THEY MEASURING?

In the absence of life, other indicators are irrelevant. AIDS causes premature death and means that international, national, and personal development goals and aspirations are not achievable. These deaths appear at the aggregate level as decreased life expectancy and increased infant and child mortality. It is difficult to assess the degree to which the effect of HIV/AIDS is felt beyond these limited indicators because of the following issues:

1) indicators are based on the demographic event of death! AIDS deaths are preceded by a period of long, debilitating and unpleasant illness. This is not reflected in the available gross indicators;

2) the disease has unexpected and long term consequences: enrolment in primary education decreases because parents cannot afford to send children to school. Child labour is needed at home. Teachers are sick or have died so there is no school. So we see that the epidemic affects human capital stocks and increases child mortality in the next generation – mothers'levels of education are a good predictor of this;

3) loss of people in their prime years may impact upon the structures of government and the possibility of effective government;

4) we have minimal insight into the effects of the epidemic on processes of social and economic reproduction at the household, community or national levels – and do not really understand how to approach this important problem.

Thus, it must be stated clearly that although we are in the third decade of this epidemic there remains little appreciation of what HIV/AIDS means for development targets. Indicators do not pick up the impact of the disease, because they are based on historical data and take no account of current and future impact.

Even with existing data it is not clear what is and is not included. It is important that national statistical services engage with this issue and begin to consider "with" and "without" scenarios when making projections, and in particular when planning health, education and human resource services. Yet, even that will not capture the full extent of impact. Much conceptual work is required before that becomes possible.

HIV/AIDS is a long wave event. Its effects on human development go on for many years, perhaps as long as a century. Impacts are complex and self-reinforcing.

They are slow but inexorable once they begin. They are also eminently deniable as more pressing issues take priority in the long queue of day-to-day political pressures.

Thus it is of the highest importance that politicians and policy makers in this region and elsewhere see that HIV/AIDS is not:

– something which is happening "out there", but is here;

– something that will happen in the future – but is with us now;

– solely a medical problem – it affects our well-being and welfare and thus many aspects of human development;

– a disease of those who are in some way considered socially undesirable – but a disease which could affect anybody who is sexually active or who is born to a mother who is infected;

– something we can put away to deal with later – action now can save resources and human suffering not so far down the line.

It is vital that professional social scientists see this as a major challenge. The social sciences must now progressively elaborate the conceptual and theoretical apparatuses to better comprehend the complex long-term impact of this epidemic.

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Expanding Access to Antiretroviral Therapies in Chile: Economic and Financial Issues for Patients and the Health System

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Key words: Chile; financing; scaling up;
health system; health insurance; HIV/AIDS care.

Abstract

Chile's experience of scaling-up access to antiretroviral treatment (ART) is relevant to identify main problems related to such a process and to assess their consequences for the patients and their caregivers as well as for the health system. Two data sources are used: a quantitative survey of people living with HIV/AIDS (PLWA) (12/2000-03/2001) and two series of structured interviews with key actors of the Chilean Health System (mid-2001 and mid-2002). The main results concern:

1) criteria for accessing ART in a context of limited resources: apart from medical criteria, socioeconomic factors introduce a significant bias in the selection of patients;

2) the transfer from private to public health system: due to better cover, 30% patients switched to the Public Health System before accessing ART;

3) the financial burden for patients: patients have to use different strategies in order to access ART, including paying for treatment out-of-pocket and taking out loans;

4) distribution of ART: due to the complexity of the distribution process, stocks frequently run out, with consequences on the patients' health status and the quality of work in the health centers, as well as creating tension among the various health institutions involved.

Lessons drawn from the Chilean experience should be useful for other countries with intermediate levels of development and HIV/AIDS prevalence which have a well-established health system.

Résumé

L'expérience du Chili en matière d'élargissement de l'accès aux antirétroviraux (ARV) permet d'identifier les problèmes liés à un tel processus et d'évaluer leurs conséquences à la fois pour les patients et leur entourage et pour le système de santé. Deux sources de données sont utilisées : une enquête quantitative auprès des personnes vivant avec le VIH/sida (12/2000-03/2001) et deux séries d'entretiens semi-structurés auprès des acteurs clés du système de santé chilien (mi 2001 et mi 2002). Les principaux résultats ont trait :

1) aux critères d'accès aux ARV : dans un contexte de ressources limitées ; à côté des critères médicaux, les facteurs socio-économiques constituent un biais significatif dans la sélection des personnes qui ont accès aux traitements ;

2) aux migrations de patients des systèmes privés vers le système public de santé : du fait d'une meilleure couverture, 30 % des patients ont changé de système avant d'avoir accès aux ARV ;

3) à la charge financière pour les patients : les patients mobilisent différentes stratégies pour accéder aux traitements, depuis l'achat sur leurs propres ressources jusqu'à l'endettement ;

4) à la distribution des ARV : du fait de la complexité du processus de distribution, de nombreuses ruptures de stock se sont produites, menaçant la santé des patients et la qualité du travail dans les services, et créant des tensions entre les acteurs du système de soins.

Les leçons tirées de l'expérience chilienne doivent être utiles aux autres pays à niveau intermédiaire de développement économique et d'épidémie qui disposent d'un système de santé bien organisé.

Introduction

As the epidemic in Chile is relatively limited, the country's experience of Antiretroviral Therapies (ART) delivery in the public health sector, especially in the initial period of scaling up access to ART (1998-2001), constitutes a good example of the difficulties that many countries will have to face when implementing such a process.

These difficulties are related to two main features:

– first, the scarcity of resources in the Public Health System (PHS) that limits its ability to offer public subsidies for ART cover for all medically eligible patients;

– second, the presence of a mixed health system combining public and private health insurance[1] but where the private sector does not provide cover for ART expenditures.

These features pose a serious challenge to the public health system (PHS) that has to respond alone to the HIV/AIDS pandemic with an insufficient budget.

The main goal of this paper is to describe the Chilean experience in improving the accessibility to ART, in order to identify the problems more clearly and to assess the consequences both for patients and their caregivers and for the health system. The paper will specifically study 4 key issues:

1) the selection of the patients having access to ART in a context of limited resources;

2) the transfer of the patients from the private system to the PHS;

3) the financial burden for patients;

4) the impact of expanding ART on the current organization of ART distribution.

Lessons from the Chilean experience should be useful not only for the Chilean health authorities in their efforts to develop evidence-based interventions to fight HIV/AIDS, but also for other countries of Latin-America, Eastern Europe and Asia that may share similar epidemiological, economic and social characteristics.

Background

With a Gross Domestic Product (GDP) per capita of US$4,289 [1] in 2001, Chile is an intermediate country in terms of economic development with a relatively low public health expenditure that accounted for 2.4% of the GDP (US$65 billion) in the same year [2].

The Chilean health system is funded by a monthly contribution of 7% of the workers' income[2]. Individuals are free to choose between the private and the public insurance health system[3]. Those in a precarious economic situation and people over 65 are covered by the PHS free of charge.

1. And a countrywide network of public and private providers.

2. An additional budget may be allocated by the State to the PHS in order to fund specific programs, such as ART drugs.

3. Ability to pay is the barrier to access since co-payment in the private system may rise to 40%. When registered with the PHS, people may choose to get part of their health care from the network of private providers.

In 2001, the Public Health System (FONASA) covered 67.4% of the whole population [3]. The remainder was covered either by the private-for-profit sector (Isapres) (19%) [4] or by other population-specific not-for-profit insurance systems such as the Defense insurance (Capredena) [5].

Private schemes do not fund drug-related expenses, including ART. Except in cases of hospitalization, people in need of ART who are insured in the private sector will either have to pay drug-related expenses themselves, or move from the private to the PHS.

Since the first cases of HIV/AIDS were detected in the country in the mid-80s, HIV/AIDS has become a major source of concern for the Chilean health authorities. On the one hand, the pace at which the pandemic is evolving has serious medical and social consequences, while on the other hand, HIV/AIDS treatment puts heavy financial pressure on the health system as well as on the patients and their caregivers [6].

Between 1984 and 2001, the total number of reported AIDS cases in Chile was 4,646 individuals [7]. During the same period, 5,228 non-AIDS HIV infected cases were reported. In 1999, the incidence rate of AIDS was 4.1 per 100,000. In 2002, UNAIDS estimated the number of people living with HIV/AIDS (PLWA) in Chile at some 21,000 individuals, with a prevalence rate of 0.3% among the adult population [8].

Chile thus appears to be an intermediate country both in terms of the level of the HIV/AIDS epidemic and of economic development.

A landmark in the national strategy to fight HIV/AIDS in Chile was the creation in 1990 of the National Commission on HIV/AIDS (Conasida). This Commission is a technical unit of the Chilean Ministry of Health (Minsal) responsible for providing a coherent social response to the HIV/AIDS pandemic in the country [7]. Amongst other responsibilities, Conasida allocates the resources available to provide access to ART to individuals registered in the PHS who may require it. But the problem is the same as in many other countries of the region: available public financial resources are often insufficient to cover the needs.

In 1993, Zidovudine (ZDV)[4] was the first antiretroviral drug offered to patients registered in the PHS. With a total cost of less than US$300,000, there was 100% cover of ZDV needs at the time. The situation in terms of ART cover has changed under the pressure of two factors. First, the course of the pandemic has increased the number of patients requiring ART, and

4. The trademark of ZDV is AZT.

second, new expensive molecules have to be used in order to improve significantly the clinical status of patients and to cope with therapeutic failures.

In 1996, Conasida started to supply ZDV in combination with 3TC. However, while the public budget available for ART in 1997 was US$1.5 million, the standard bi-therapy in Latin America (AZT+3TC) was estimated to cost US$4,800 per year [9]. Thus, with such a limited budget the PHS would have been able to fund around 300 patients while the expected number of patients in need of treatment at the time was certainly much higher (according to Conasida, the number of AIDS patients in 1996 was 422).

The clinical and biological successes following the introduction of highly active antiretroviral therapies (HAART) in 1996 exacerbated this situation by imposing new standards for the treatment of HIV-infection. The year 2000 was a milestone in the effort to take into account these new clinical standards and to improve the level of access to ART in the Chilean PHS. At that time, national therapeutic guidelines for the PHS distinguished 3 categories of patients:

– no use of ART was recommended for patients with low probability of progression: asymptomatic, CD4 count >500cc/mm^3 and viral load < 10,000/ml;

– for patients with intermediate probability of progression: asymptomatic; CD4 count <350 mm^3 and viral load <30,000 ml, prescription of a bitherapy was recommended and HAART was also recommended provided that the patient was able to pay for the third additional drug in the combination;

– HAART was recommended for patients with high probability of progression: symptomatic; CD4 count <350 mm^3 and viral load >30,000 ml: prescription of a tritherapy.

On the basis of these criteria, 750 bitherapies and 750 tritherapies were provided to PHS patients, representing approximately 46% of the estimated needs [10]. This improvement in access to ART was partly due to Chile's participation as one of the four pilot countries[5] in the UNAIDS Drug Access Initiative (DAI) [11]. With the support of the United Nations Development Program (UNDP), who agreed to be the official ART importer, DAI allowed a dramatic reduction of the import-taxes on ART. Such tax cuts represented savings of approximately 21% on the price of ART provided to PHS patients [12].

Nevertheless, HAART were, and remain, very expensive and the ressources insufficient to provide a 100% access. In 2000, the public budget available for ART reached US$6.5 million. The situation remained approximately the same until 2001.

5. Other countries were: Côte d'Ivoire, Uganda and Vietnam.

Because of the risks of therapeutic failures and the development of resistant strains, physicians soon became reluctant to prescribe bitherapies. Patients had to procure the third molecule themselves: either through other public or non-profit institutions (Municipalities, NGOs, Foundations), or from their own or their family's resources, on the private market or even on the informal market [13].

Since 2001, Chile's participation in the new UNAIDS Accelerated Initiative to Access to ART has enabled the health authorities to successfully negotiate prices for ART with industry, obtaining an average reduction of 50% [8, 12]. In 2002, 2,600 ART were provided, representing 86% of the patients meeting the national guidelines criteria followed by the PHS. The main factors contributing to this increase in cover were the new lower prices and a 33% increase of the public budget for ART. Finally, the level of cover is expected to rise to 3,600 ART in the first half of 2003, and when the extra-resources from the Global Fund to Fight AIDS, Tuberculosis and Malaria[6] become available, 4,200 treatments will be distributed, approaching the goal of 100% cover. It is worth pointing out that so far no antiretroviral generics have been used in the Chilean PHS [14].

In summary, Chile's access to ART at the very beginning of the century was that of a country with significantly expanding access but still with insufficient resources to afford universal ART cover. We analyzed the consequences of this increased but limited access, both for the persons living with HIV/AIDS and for the health system. We focused on 4 main issues:

– first, how patients were selected for access to ART: in a context of limited resources the selection process raises questions of equity that need to be explored in order to develop interventions aimed at reducing the social and economic inequalities that may result from such a process;

– second, to what extent PLWA not-covered (or poorly covered) by the private system have moved to the PHS: as the private insurance programs do not cover for ART, patients get better access to ART if they register with the PHS. Such a phenomenon could undermine the long-term sustainability of the public policy for access to ART;

– third, how the health-related financial burden on patients has evolved within the new context of access to ART: most PLWA are in a precarious

6. Thanks to a multi-sector project presented by a partnership including the health authorities and representatives of the patients. The funding of this project is US$ 36 million over a five year period. Nevertheless, the Global Fund project has been approved only for the first two years (US$13 million). After that, continuity will depend on the evaluation and availability of funds from the Global Fund.

socio-economic situation [15], and due to the limited resources of the PHS, they are often asked to contribute substantially to the purchase of their treatment. This could jeopardize the patient's long-term follow-up treatment;

– fourth, what are the individual and organizational consequences of ART supplies running out related to scaling up access? This issue challenges the management of the ART distribution process in the PHS.

III
METHODS

To answer these questions, two different data sources from the Evaluation of the Chilean UNAIDS Drug Access Initiative[7] were used: one quantitative and the other qualitative[8].

Quantitative survey of PLWA

The first data source is a survey of public sector patients that was carried out between December 2000 and March 2001. The survey was of PLWA in six public hospitals in the Metropolitan District of Santiago and two in the vth District of Valparaiso. These eight hospitals treat over 70% of national PHS patients. Participants were randomly selected from the hospital databases of HIV/AIDS patients on the basis of 1 out of 3. People were approached and informed of the survey by a member of the medical or nursing staff in the hospital department, and when the person consented to participate, he or she was interviewed by a member of the research team.

In-depth data about the patients' sociological, economic and psychological characteristics were obtained by means of a face-to-face questionnaire. It included questions on the following topics: current ART treatment, changes in the social security system, level of health expenditures, sources of ART funding.

7. In Spanish, the Chilean participation in this UNAIDS-Initiative is called Iniciativa ONU-SIDA-CONASIDA para Facilitar el Acceso a los Antiretrovirales. The evaluation of this initiative was funded by the ANRS (French National Agency for Aids Research) on behalf of UNAIDS and in collaboration with Conasida and the Chilean Health Ministry.

8. Combination of both methods is particularly appropriate to study complex interventions such as expanding ART cover in a developing country. While the quantitative techniques are relevant to studying the main tendencies and the statistical relationships between different variables, the qualitative techniques allow more in depth insight into the underlying relationships of the phenomena studied and contribute to implementing actions intended to address the issues [16, 17].

Biological data, in particular CD4 counts, were obtained from medical files. Biological data going back more than 6 months before the survey were not taken into consideration.

Data were treated with EPI-Info and SAS and the unit of analysis was the patient.

Semi-structured interviews with key-actors

The second source of data was two sets of semi-structured interviews with key-players involved in HIV/AIDS [18]. These were aimed at highlighting the key players' roles and perceptions regarding the issues of the study [19]. In this type of survey, the criterion allowing adequate analysis of the data is saturation. It requires getting a sufficiently representative sample of key actors involved in the fight against HIV/AIDS to cover the whole range of opinions. The quotations used in the Results section are not anecdotal since they reflect convergent arguments expressed by various interviewees; they complement the interpretation of the statistical survey.

Two settings were represented in the sample:

– three large urban centers with high HIV prevalence (Santiago, Valparaiso and Viña del Mar);

– two small urban areas with low HIV prevalence (Valdivia and Osorno).

The interviews were carried out in July 2001 and August 2002, a previous round of interviews having been completed during the pre-implementation phase in late 1999 [12]. As the 2002 round of interviews was aimed at updating the earlier information, only a subset of these organizations was selected to participate.

Overall, the organizations and institutions selected were as follows:

– 5 central institutions: Conasida, Fonasa, UNDP, Cenabast[9], and, ISP[10]; with a total of 18 persons interviewed (12 in 2001 and 6 in 2002);

– 9 health centers: seven in large urban areas and two in small urban areas; with a total of 28 persons interviewed (22 in 2001 and 6 in 2002);

9. Cenabast is an autonomous public body in charge of grouping purchases of drugs and medical equipment for the public health centres. Before the involvement of UNDP in purchasing ART, Cenabast was in charge of the purchase and distribution of ART. Cenabast was included only in the 2001 round of interviews.

10. The Institute of Public Health (ISP) is in charge of controlling the quality of imported ART and the viral load kits. As a biological laboratory, ISP is currently the national reference laboratory for the HIV tests. ISP was included only in the 2001 round of interviews.

– 4 pharmaceutical companies: Glaxo-Smith-Klein, Merk-Sharp&Dohme, Boehringer[11] and Roche; with a total of 9 persons interviewed (6 in 2001 and 3 in 2002);

– 5 patient organizations: Vivo positivo (the federation of PLWA organizations) and four local patient organizations; with a total of 10 persons interviewed (5 in 2001 and 2002).

The mean time of the interviews was 35 minutes and more than one thousand pages of transcriptions were produced.

Data were treated with QSR-NUD*IST discourse analysis software package; the unit of analysis was the key-players involved in the health system.

IV
RESULTS

Description of the population of PLWA (quantitative survey)

929 persons were selected for the survey. 50 could not be contacted and 80 refused to participate. 799 persons completed the questionnaire (answer rate = 85.5%).

Overall, 20% of respondents were women (N = 160); 80% were men (N = 639), including 481 homo/bisexual men (60%). Mean age was 36.6 years (sd = 9.5). 22.5% were under 30 (N = 180) and 30.4% were over 40 (N = 242).

CD4 counts taken within the last 6 months were available for 672 persons. There was no statistical difference between people with and without CD4 counts for demographic and socio-economic factors (gender, age, sexual identity, family per capita income, marital status, schooling, membership of a voluntary organization, employment). Mean CD4 count was 257.7 (sd = 200.3).

The proportion of individuals having access to ART in the sample was 62.5% (N = 499). 44% had been on ART for less than one year (N = 180). This proportion of people on ART is higher than the 46% cover in the PHS estimated by CONASIDA at the time. This relative overrepresentation of individuals receiving ART is probably related to the recruitment in large hospitals of major urban areas. These areas are known to have higher rates of HIV prevalence [7], and probably deal with a larger number of individuals in more advanced stages of the disease.

11. Only in the 2001 round of interviews.

Access to ART

Patients eligible for ART must be registered with the PHS and meet the medical criteria defined in the national guidelines. But as long as there is no full cover, some individuals will not receive ART even when their medical condition requires it.

The health centers have to define their own additional criteria, resulting in a wide variety of approaches in selecting the patients who receive ART. These criteria may include the length of time on the hospital waiting list, lifestyle, social support, socioeconomic situation (*i.e.* the ability to pay for a third molecule), and sometimes random selection by lottery. The quotations below, from the semi-structured interviews, illustrate the diversity of approaches that exist in the various health centers:

> […] *At that point (when it is time to choose) we are God and the Devil. God for those who get the therapy and the Devil for the others… As I cannot choose because one patient is nicer or has blue or brown eyes or is big or small… Then (I choose) by the order of arrival.* (Key informer: physician, small urban area, 2001-free translation).

> […] *To choose between two individuals with the same urgency for treatment, we consider who is expected to be more adherent, who is more motivated by the therapy, who has better support from their family network, and who is not an alcoholic or drug addict.* (Key informer: physician, major urban area, 2001-free translation).

> […] *Once the criterion of being affiliated to the public system is met, there are some 50% of the patients left… How to decide who will get ART and who will not? We choose to not discriminate by sex, age or lifestyle, so facing the same clinical needs it will be a lottery that will decide who will receive the ART.* (Key informer: physician, major urban area, 2001- free translation).

Some interviewees expressed concern about the fact that informal networks may favor an individual and give him/her access to ART before another with the same indication for treatment and medical need.

> […] *Also there is the issue of the pitutos (relationships)… I entered the system because of who I know… At that point I told the physician I will come back…*

Even if I have to talk with the president… I won't move and if you don't treat me I will find another hospital… I won't die without a fight. (Key informer: patients' advocate, major urban area, 2001 -free translation).

From the quantitative survey [Table 1], we compared individuals with and without ART. Then we took into account that the category 'without ART' is heterogeneous, as it refers to both clinical and biological criteria, and therefore includes both people not in need of ART and people in need of ART but without access. In order to reduce the heterogeneity, we focused on the individuals medically eligible for ART according to the national guidelines and compared them with people under treatment. As relevant data on viral loads and clinical status were not available, we used CD4 counts to separate the people without ART into two categories of people 'in need of ART':

– group 1 (N = 163): people without ART and with a CD4 count under 350 (threshold at which a patient is considered to present a high probability of disease progression, according to the national therapeutic guidelines);

– group 2 (N = 96): people without ART and with a CD4 count under 200 (threshold at which there is a world-wide consensus among experts that immediate ART initiation is essential [20]).

Comparison of people with ART and people without ART

Individuals without ART are significantly younger than individuals with ART. There is no relationship between access to ART and gender or sexual identity.

Mean CD4 count is significantly lower for ART-treated patients. This result probably reflects the relatively recent access to ART for a large proportion of the sample: mean CD4 for people with access to ART within the last year (44% of people with ART) is 185.

Access to ART is also positively correlated with socioeconomic and behavioral factors: people with monthly family income per capita of more than US$100 are more often treated with ART. Conversely, people not treated with ART are more frequently alcohol and drug users.

*Table 1: Characteristics of people with and without ARV treatment**

	With ART	Without ART	Without ART and CD4<350 *(Group 1)*	Without ART and CD4 <200 *(Group 2)*
	N = 499	N = 300	N = 163	N = 96
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Age	37.8 (9.3)	34.7 (9.5) p<0.001	35.8 (9.1) p<0.02	36 (8.4) NS
CD4 (N = 672)	238 (184) (N = 425)	291 (222) (N = 247)	162 (106)	86 (64)
	%	%	%	%
Women	21	17	18	17
Homosexual men	59	62	62	59
Family Income per capita < 100 US$	45.1	54.3 p<0.01	53.8 p<0.05	58.5 p<0.02
Member of voluntary organization	24.7	24.4 NS	21.5 NS	20.8 p<0.02
Alcohol consumption (at least once a month)	46.1	54.7 p<0.02	51.5 NS	44.8 NS
Drug consumption last month	10.2	15 p<0.05	14.1 NS	13.5 NS

* Each comparison is with column 1 (with ART).

Comparison of people with ART and people 'in need of ART'

People 'in need of ART' are younger than people with ART. The difference is significant for Group 1.

Behavioral variables (alcohol and drug consumption) are not significantly different between people with ART and people in need of ART (Groups 1 and 2).

Conversely, economic and social support variables are significant: the proportion of people with low family income per capita is significantly higher in the 2 groups of people 'in need of ART' than in the group of treated patients. Belonging to an AIDS voluntary organization is more frequent among persons with treatment; the difference is significant for Group 2.

Thus our data provide evidence that in addition to medical criteria, socioeconomic factors introduce a significant bias in selecting patients for access to ART [21, 22].

Transfer from the private to public health system

Table 2 documents the phenomenon of transfer from the private health system to the PHS for patients with HIV/AIDS once they have been informed of their serological status.

This phenomenon is far from being anecdotal: among the 794 individuals who answered the questionnaire, 29% (n = 233) declared that they had moved from the private to the public system. The proportion was even higher for people with ART (32 vs 25%), but the difference was not statistically significant.

Table 2: Transfer from the private to the public health system following notification of diagnosis of HIV-infection

	WITH ART	WITHOUT ART	TOTAL
DID NOT CHANGE SYSTEM	314 (63%)	202 (68%)	516 (65%)
CHANGED SYSTEM	157 (32%)	76 (25%)	233 (29%)
NOT CONCERNED	24 (5%)	21 (7%)	45 (6%)
TOTAL	495 (100%)	299 (100%)	794

Reasons for such transfers were documented for 206 individuals:

- 55% (n = 125) perceived that they would have better health cover in the public health system;
- 22% (n = 50) could no longer afford the cost of their insurance premiums;
- 8% (n = 18) were obliged to transfer in order to have access to the support of a private or public foundation;
- 6% (n = 13) were explicitly excluded from their private insurance program because of their HIV serostatus.

These results raise the issue of the sustainability of the public supply of ART, especially if the epidemic continues to grow. To what extent such an issue could undermine the process of universal access to ART is nevertheless difficult to assess due to the absence of relevant data on the number of HIV/AIDS patients in the private sector. In addition, they highlight the private sector's lack of involvement in the fight against AIDS.

Financial burden to the patients and their caregivers

Table 3 shows the magnitude of the financial burden reported by PLWA in the questionnaire.

While the mean monthly health expenditure for patients treated with ART is US$98, it is only US$33 for patients without access to ART. The difference is highly significant. Persons treated with ART declared monthly health expenditures of over US$84 in more than 40% of the cases. This proportion fell to 20% for the non-treated individuals. On the other hand, only 26% of individuals treated with ART declared monthly health expenses of US$17 or less, against 42% for the non-treated individuals. These differences are statistically significant.

Thirty two per cent of individuals treated with ART (N = 159) said they had taken out a loan in order to cover their health budget, against 22% of non-treated individuals (N = 62)[12]. The difference is significant.

Table 3: Individual health expenses and indebtedness

	WITHOUT ART	WITH ART	
Monthly health expenses (means)	US$33 (SD = 38; N = 285)	US$98 (SD = 104; N = 485)	P<0.01
Proportion of individuals with health expenses < US$17 (10,000 pesos)	42%	26%	P<0.02
Proportion of individuals with health expenses of US$17-84 (10,000-50,000 pesos)	38%	32%	
Proportion of individuals with health expenses of > US$84 (50,000 pesos)	20%	42%	
Proportion of patients having contracted a debt in order to cover their health expenses	22%	32%	P<0.00

NOTE: US$ OF 2001 (1US$ = 526 CHILEAN PESOS).

Main reasons for such differences in health expenses and loans between people with and without ART are the following:

– first, in 2000 a large proportion of patients treated with bitherapy were asked to provide the third molecule to complete their treatment;

12. Given the precarious socioeconomic status of most patients, different mechanisms are used to meet the health expenses. These mechanisms include contracting mainly short-term debts with family and friends, but also mid- and long-term debts when they have access to the credit market (credit cards, consumer credits, etc.)

> […] *The bitherapies we prescribe are prescribed on the condition that the patients, with or without our support, are able to obtain the other molecules elsewhere…* (Key informant: Physician, major urban area, 2001.)

– second, access to ART was partially determined by the time that individuals spent on the waiting list: when they finally had access, their health status could have become more serious, incurring higher health expenses;

– third, due to occasional breakdown in the distribution of ART, some patients may have been forced to obtain their ART themselves on the formal or the informal private market.

> […] *Besides, there is the dramatic case of persons who due to their precarious economic conditions sell their ART, as it is a transaction good: if they don't have pesos for food, they sell it on the market and they can eat.* (Key informer: patients' advocate, major urban area, 2001-free translation)[13].

Both the survey and the semi-structured interviews identified the following sources of funding for ART: the PHS, clinical trials, municipalities, some other non-profit sources (foundations, NGOs), and the patients' family and caregivers. Of the 499 individuals receiving ART in our sample, the type of treatment was documented for 495 (91 under bitherapy and 404 tri- or quadri-therapy).

Overall 73% (n = 362) were fully covered by the PHS: 96% for people with bitherapies (n = 97) and 69% for people with tri/quadritherapies (n = 275).

The distribution of funding sources among the individuals not fully covered by the PHS was the following:

- 8% (n = 40) from a mix of public, non-profit and protocol sources (10% of tri/quadritherapies and 1% of bitherapies);
- 17% (n = 86) from a mix of private and public sources (21% of tri/quadritherapies and 2% of bitherapies);
- and only 1% (n = 3) from an exclusive private source.

Municipalities were involved in the full or partial funding of drugs for 25 individuals (5%); other non profit sources (foundations, NGOs), for 19 (4%). Eight people (2%) participated in clinical trials, and consequently they received their drugs from the protocol sponsors.

13. The phenomenon of the informal market is not yet well-documented but many key actors of the Chilean health system interviewed in the framework of the research have acknowledged its reality [13]. In the quantitative survey, 13.5 per cent of people treated with ART said they had been obliged to buy drugs from other patients at least once because the health center was out of stock (n=67).

Finally, 89 individuals (18% of people with ART) had to pay costs for accessing ART out of their own pocket.

Distribution of ART

Access to ART is not only an issue of availability of financial resources but also involves the organization of the drug distribution process. In the perspective of scaling up access to ART, any dysfunction of this process may have a negative impact on the patients' health status, and even for public health in the event of the spread of resistant viral strains.

Due to the high number of possible therapeutic combinations and the need for a continuous supply of each drug, the antiretroviral schemes are especially difficult to manage.

These issues require the health authorities to optimize efficiency of the distribution process. As shown in figure 1, this process is complex due to the diversity of the actors involved and their interrelationships. Seven main actors are involved:

– Conasida: evaluates the needs, defines the purchasing strategy, negotiates prices with industry and coordinates the whole process;

– Fonasa (PHS): funds drug purchases;

– UNDP: plays an intermediary role in the purchase of ART allowing a tax exemption for imported ART;

– pharmaceutical companies: provide and distribute drugs at the local level (Health services or health centers), following the instructions of Conasida;

– National Institute of Public Health (ISP): controls the quality of the imported drugs;

– regional health services: coordinate the distribution to the hospitals;

– hospitals (health centers): assess local needs and, of course, provide ART to the patients.

The usual time between evaluation of the needs by Conasida and distribution of ART to the patients in the health centers is 3 months.

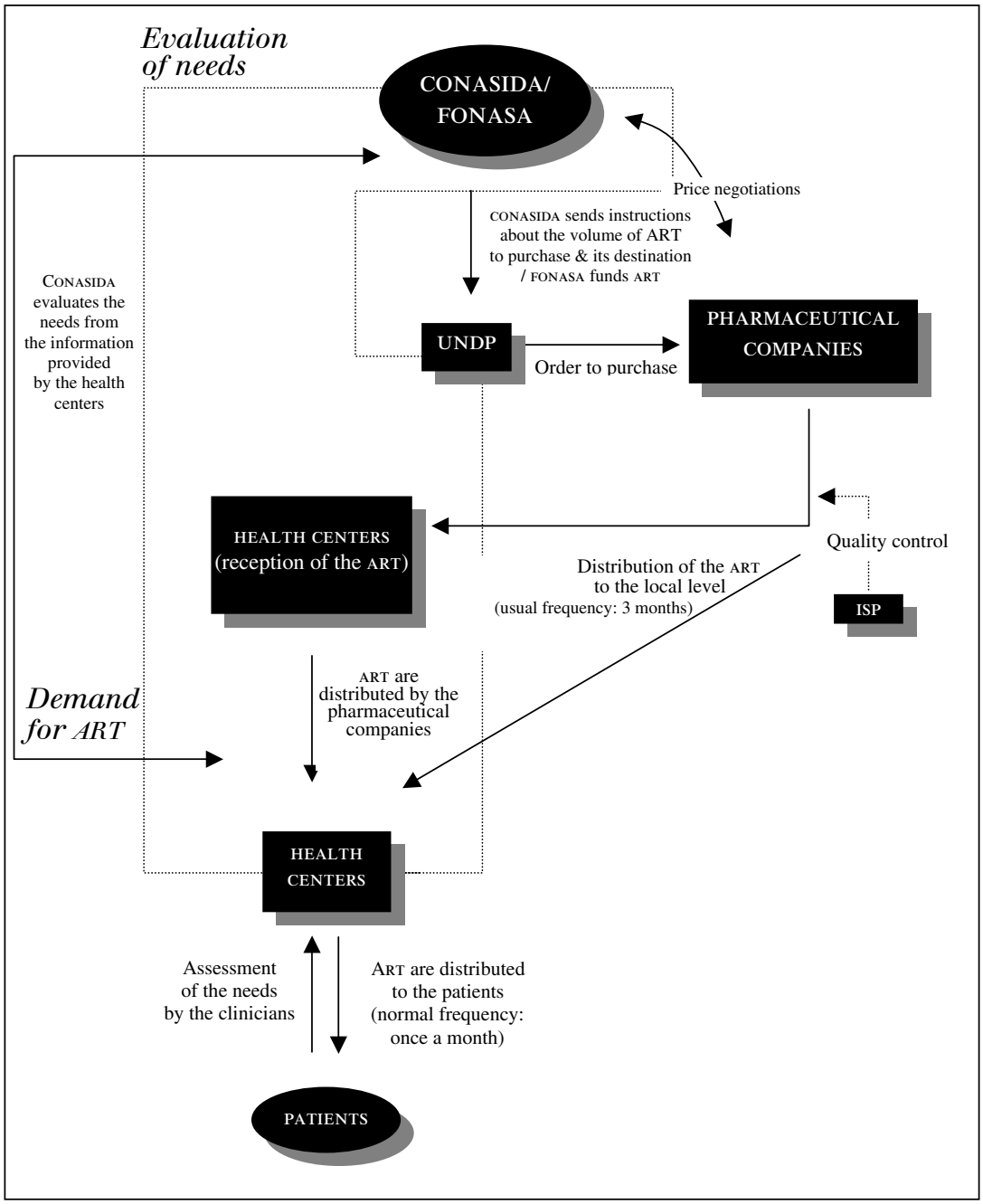
Problems may obviously arise at each step of this process. For instance, an insufficient access to viral loads and CD4 tests will challenge the ability to carry out accurate medical assessment of the patients' status; the lack of human resources will undermine the quality of the data transmitted to Conasida and will prevent an accurate assessment of the needs.

Such planning problems have occasionally led to purchases of drugs close to their expiry date. Lack of coordination also results in extra delays and in conflicts between the public health authorities and the industry: for example,

when the local branch of a company is not able to fulfill the demand due to the short deadline of the purchase order (incompatible with the rigid supply requirements of the company's headquarters). Any such mismanagement may lead to supply problems.

> […] *(supply problems) have occurred five times in the last year… Now we have a lot of cooperation from patients… when you explain to them that we have not received any AZT they understand better.* (Key informer: pharmacist 2001).

Figure 1: The process of distribution of ART



In the survey, 52 persons (10.4%) with ART declared that they had been forced to give up their treatments at least once because the drugs were not available at their hospitals.

The consequences of such situations were documented in the semi-structured interviews. They concern the patients and the different actors and players involved in the distribution process.

For patients, the consequences of running out of stock are financial (due to unexpected expenses), work-related (due to absenteeism) and health-related (anxiety, stress and risk of therapeutic failures)

> *We have had this problem (supply problems) twice this year… It is a mess because we give the patients 5 caps for 5 days when the usual doses are monthly… So, they have to come back more often to the hospital, they have to spend more money on transport… (also) they become stressed and even desperate, they tell you that if it (the ART) does not arrive they will stop the therapy… it happened for instance with Combivir.* (Key informer: Physician 2002).

In some extreme cases, supply problems may even lead to interruptions in the patient's treatment.

For the health centers the consequences of disruptions concern the quality and quantity of work (increase in the work-load, diverting time from patient care to administrative duties, deterioration of the work atmosphere), stress and burn-out (coping with patient frustration and dealing with bureaucracy).

> […] *It is very stressful and I have a difficult time because of Conasida but I know that I will eventually be lucky and I will obtain what I need… But it is painful and difficult… Everything is in the hands of the professionals (at the health center)… I waste hours that I could be using on the other many tasks I have.* (Key informer: pharmacist, major urban area, 2002 – free translation).

For the different institutions and organizations involved in the ART distribution process, the consequences of running out of stock are potential tension, conflicts and a deterioration of the atmosphere of trust.

> […] *Of course, it (the ART) arrives bit by bit and it's a disaster… We never know when to expect it (the ART), Conasida blames the industry that doesn't deliver on time, the industry blames Conasida claiming that they don't pay.* (Key informer: physician major urban area, 2001-free translation).

Conclusion

When examining the Chilean experience it appears that even in a country with a relatively low epidemic and an intermediate level of development, the economic and organizational consequences of scaling up access to ART are far from minor at both the individual and the community level. While some of the consequences regard the limited covering of needs, others concern the access expansion process itself.

First of all, because of a lack of resources, there is probably no satisfactory way of selecting patients for ART treatment among those who meet the clinical and biological criteria. Nevertheless, our data clearly show that access to ART is dependent on socioeconomic factors. We do not know if these factors are used as a priori criteria, but the reference to patients adherence as a selection criteria is likely to include such socioeconomic factors. Such a criterion should be removed: it has been clearly demonstrated that patient adherence is a dynamic process that cannot be predicted reliably solely on the basis of a few a priori patient characteristics [23]. In order to decrease inequalities in access to ART in countries involved in a scaling-up process, it would be preferable to define the conditions of access better, either by strengthening biomedical criteria, or by prioritizing some specific sub-groups of the population.

Secondly, the lack of resources imposes a significant financial burden on a large proportion of the PLWA, especially those having to pay for the third molecule themselves, while only bitherapy is funded by the PHS. Thus, these conditions affect individual health status and equity.

Financial constraints could be a factor in stopping treatment either temporarily or even permanently. In other countries, it has been proved that disruption of the patient's financial resources was the main obstacle to adherence to ART adherence [24].

As Evans [25] has clearly shown, any form of co-payment reduces the health system's ability to redistribute financial resources. On the one hand, the more a system is funded by co-payments rather than taxes, the less it is able to redistribute from poor to rich individuals and achieve an equitable distribution. On the other hand, the more a system is funded by co-payments rather than by state-financed health insurance premiums, the less it is able to dissociate the risks related to the illness from the ability to pay and to redistribute resources from healthy to sick individuals.

Thirdly, the move of patients from the private health system to the PHS may undermine the sustainability of a policy aimed at improving access to ART if: the HIV pandemic continues to increase at the same pace; and/or the PHS experiences difficulties in maintaining an adequate level of funding.

Obviously, as long as the for-profit private sector does not accept a fair share of the collective responsibility to fight HIV/AIDS by including cover for out-patient ART treatment in insurance schemes, the long-term sustainability of the public strategy will continue to be challenged. This latter issue is currently under debate in the framework of the Chilean health reform[14]. Another approach for strengthening the involvement of the private sector would be to give it the possibility of acquiring ART at the same reduced prices as the PHS.

Finally, the success of scaling up access to ART will depend not only on financial issues but also on issues regarding the organization of the health system itself, especially the drug distribution process. Due to the complexity of this process, supply problems may occur, especially in a context of limited resources. The recent Chilean experience provides a good example. In order to improve the process, four main issues have been addressed, concerning:

1) management of information: implementation of an online information system allowing patient needs to be monitored in real time;

2) improvement of the medical decision-making process: creation of an advisory committee to manage the prescription of ART and therapeutic changes;

3) improvement of the coordination and planning of the negotiation process with companies: design of a yearly programmed schedule for the purchase of ART and of a fixed calendar of negotiation rounds with the industry;

4) reduction of the number of stakeholders in order to raise the efficiency of the process: substitution of the artificial mechanism of drug purchasing involving the UNDP by a permanent tax exemption for the purchase of ART[15]. Such a measure would not only improve the ART distribution process, but would also bring about a 21 percent price reduction.

Recently, the Chilean situation in terms of access to ART has evolved significantly. Today, the needs are almost completely met, and in the near

14. The Chilean health reform project (AUGE) proposes universal health care protection for 56 health problems, including HIV/AIDS, accounting for most causes of death in Chile with explicit guarantees concerning waiting list times, level of co-payment, and quality of care standards.

15. In Chile, a law on catastrophic diseases has been a subject of recent debate. One issue is the exemption of import taxes on drugs for catastrophic diseases such as HIV/AIDS.

future, implementation of the Chilean health reform project (AUGE)'s proposals, predicting the inclusion of HIV/AIDS as one of the 56 national health priorities with universal and comprehensive cover in the country, will bring even further improvements[16]. This dramatic expansion of access to ART will of course improve the health status of patients and probably, at least in the short- and mid-term, reduce the global HIV-related health expenditures due to a decrease in the number of hospitalizations, as has been documented in the case of Brazil [26]. Expansion of ART cover will also reduce the negative effects induced by partial cover: socioeconomic inequalities in access to treatment and risk of disrupting treatment due to lack of individual resources.

Success in effectively maintaining this strategy of universal cover will further depend on the appropriateness of the needs assessment, on the involvement of the private sector, on the efficiency of the distribution process and, above all, on the ability of the PHS to mobilize funds. Mobilization of national funds will be the key to substituting in the mid-term those recently obtained from the Global Fund to Fight AIDS, Malaria and Tuberculosis and also to sustaining future therapeutic guidelines regarding new generations of more expensive ART.

16. Auge proposals will be of benefit to patients registered in the private as well as in the public system and will include out-patient care and hospitalization.

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Analysis of HIV/AIDS Expenditures in Senegal: from Pilot Project to National Program

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Key words: Senegal; antiretroviral treatments; HIV/AIDS; cost; funding; public spending.

Abstract

This paper describes and analyzes the financial resources devoted to combating HIV/AIDS in Senegal, distinguishing between state resources and foreign aid. The funding of antiretroviral drugs is a special focus of attention. The results show that the development of actions in the field of HIV/AIDS has not led to massive absorption of Health Ministry resources to the detriment of other health care priorities. Public spending has been sufficient to ensure that dependency on foreign aid is comparable to that of the nation's overall health budget. The costs of treatment (antiretroviral drugs, reagents and certain drugs for opportunistic infections) have increased relative to other activities (especially prevention) but remain below 40%. An ambitious program designed to decentralize patient management is planned for 2003-2006, with the support of new funds (World Bank, Global Fund to Fight AIDS, Tuberculosis, and Malaria, etc.). This upscaling will probably profoundly modify the distribution of spending, relative to both State budgets and the funding structure.

Résumé

Ce texte décrit et analyse les ressources financières consacrées à la lutte contre le sida au Sénégal, en distinguant les ressources mobilisées par l'État,

de celles provenant de l'aide extérieure ; une attention particulière est portée sur le financement des médicaments antirétroviraux. Les résultats présentés montrent que le développement des activités VIH/sida n'a pas entraîné un captage massif des ressources du ministère de la Santé, aux dépens d'autres programmes de santé. Le niveau des dépenses publiques engagées a permis de maintenir un degré de dépendance vis-à-vis de l'aide extérieure comparable à celui de l'ensemble du budget de santé du pays. La part des dépenses liées à la prise en charge thérapeutique (médicaments antirétroviraux, infections opportunistes et réactifs) par rapport aux autres activités de la lutte (notamment la prévention) a augmenté mais est resté inférieure à 40 %. Un ambitieux programme de décentralisation de la prise en charge thérapeutique est planifié pour les années 2003-2006, avec l'appui de nouveaux financements (Banque Mondiale, Fonds Global), ce changement d'échelle entraînera probablement une profonde modification dans la répartition des dépenses, dans leur place relative au sein des budgets de l'État et dans la structure des financements.

Introduction

In view of the catastrophic spread of HIV/AIDS through Africa, the persistently low prevalence observed in Senegal (about 1.4% of the adult population) is often attributed to successful public health initiatives [1-3]. Since 1998, a pilot antiretroviral treatment program – one of the first African programs of this type – has demonstrated the feasibility and efficacy of such interventions, and has bolstered the reputation of the Senegalese "success story". Activities targeting HIV/AIDS received major funding from both the State and foreign donors. Funds from various sources are now set to increase substantially with the aim of reinforcing prevention campaigns and offering access to antiretroviral treatments (ARV) throughout Senegal.

Meanwhile, however, the Senegalese economy continues to deteriorate. In July 2000, Senegal was added to the list of heavily indebted poor countries; the national debt, already 77% of Gross Domestic Product (GDP), continues to grow [4]. Average per capita GDP is estimated at US$545 (1996-1998) [5], and 65% of the population live below the poverty line (defined as 392 FCFA[1] per day per adult-equivalent) [5]. The public health situation is critical in many respects: the infantile and infantile-juvenile mortality rates are respectively 70 and 145.3 per 1000 (year 2000), the maternal mortality rate is 510 per

1. Francs CFA (100 FCFA = 0,15 €).

100,000 live births (year 2000) [6], and the estimated vaccine coverage rate, based on the Extended Vaccination Program, is 42% [7].

The contrast between the size of Senegal's financial commitment to combat AIDS and the many other health emergencies confronting this country has kindled a heated debate on the optimal distribution of available resources: what place should be given to the fight against AIDS relative to other health priorities [8, 9], and how should funds devoted to HIV/AIDS be distributed between prevention and treatment [10]? In a country with what is considered to be a low prevalence, and where the total number of HIV-seropositive persons is still relatively small (75,000 in 2002), what share of available human and financial resources is devoted to fighting AIDS? Is the choice to fund an extension of the ARV treatment program compromising other public health interventions that would benefit far larger populations? And will the Senegalese experience risk, sooner or later, becoming a victim of its own success, absorbing a growing part of the country's financial and health infrastructure capacities?

It is too early to assess the precise impact of the different components of the current AIDS program, but it is nonetheless useful to examine the share of available resources devoted to each component by the Senegalese health authorities and foreign donors. The importance given to fighting AIDS relative to other public health priorities is sometimes overestimated because of its strong media impact. Conversely, at the same time, there is a tendency to underestimate these resources, because some spending that is more or less directly linked to HIV/AIDS management is not always taken into account.

After describing the aims and obstacles of this funding analysis of the fight against AIDS in Senegal, we offer a synthesis of the resources devoted to it by the State and foreign donors, focusing particularly on ARV financing. Finally, 2003 being a watershed year in the fight against AIDS in Senegal, we examine likely future spending trends.

I
AIMS OF THE ANALYSIS

Analysis of the literature

Many teams have studied the impact of AIDS on the health care sector in African countries [11] and the cost-efficiency of the different possible actions [12]. Models have been developed to forecast future needs [13]. In contrast, few analyses have focused on actual public spending on the fight

against AIDS in Africa. Studies conducted in Thailand, Tanzania and Côte d'Ivoire [14] have compared funding by the private and public sectors, and the distribution of funds between curative and preventive actions. These studies provided comparative data on State funding of programs targeting AIDS relative to other health concerns. Finally, other studies have compared annual spending by foreign donors and national governments [15]. However, all these studies were done before 1996, *i.e.* before the arrival of antiretroviral treatments in the relevant countries.

UNAIDS has undertaken global analyses of national spending and funds promised by the principal foreign donors [16]. Some recent surveys, in Vietnam for example, analyzed the aid offered by the different foreign donors [17]. However, in the numerous evaluations of public health spending in African countries, including Senegal's most recent done in 1999 [18], the functional analysis grouped together the different levels and types of intervention but did not break down spending according to strategic priorities.

Conditions of the analysis

Analyses of public AIDS expenditures are more important than ever before, but are also becoming more difficult. The international "aid market" in this area has grown significantly. The increasing number of donors and operators (projects, NGOs, private sector initiatives, etc.) has made the situation more complex. Striking gaps between promised investment and actual spending are frequent in this increasingly mediatized field. Complex funding operations, and especially joint funding projects, increase the risk that the same donation will be counted twice. Furthermore, institutional reforms (multisector approaches, decentralization, etc.), budgetary changes (*e.g.* the new Senegalese nomenclature adopted in 2002) and more global approaches (budgetary aid, sectorial approach, Sector-Wide Approach) make it even more difficult to analyze spending on a specific health problem. In Senegal, the steady growth of the Fonds de Dotation pour la Décentralisation (FDD, Decentralization Endowment Fund) further hinders analyses based on central budget documents.

In contrast, the program-based approach adopted by the health authorities facilitates health spending analyses in Senegal. After lengthy discussions with all its partners, the Health Ministry launched a Programme National de Développement Sanitaire (PNDS) for the period 1998-2007. An Integrated Health Development Program (Programme de Développement Intégré de la Santé – PDIS) covers the first five years of the PNDS [19] and groups together

the different funding sources (State, population, local government, and foreign donors). A public spending review has already analyzed the baseline situation (1998-1999), and a new one is being prepared for 2003. It will set the groundwork for the second PDIS (2003-2005) and fix objectives for 2015 (and even 2025!). These documents provide useful points of comparison when analyzing the proportion of total Senegalese health spending devoted to AIDS.

Limitations of the analysis

We were only able to analyze funds transiting via PNLS (*Programme National de Lutte contre le Sida*/National AIDS Program) within the framework of the Strategic AIDS Program. Some foreign donors (especially NGOs) sponsor projects directly, but the vast majority of foreign aid is recorded by the Health Ministry. These data do not underestimate the place of NGOs, because almost all active local NGOs in Senegal receive foreign aid. A detailed analysis of each NGO's expenditures would be very useful to compare their interventions. But such a study would necessitate a specific survey covering a very large number of stakeholders and is outside the scope of the present study.

Only a part of all research spending is centralized by the Health Ministry. A study of institutions that fund AIDS research (French National Agency for AIDS Research-ANRS, Centers for Disease Control, European Commission, Institut de Recherche pour le Développement, etc.) would yield not only an estimate of total spending, but also the fractions that specifically benefit Senegal versus the scientific community as a whole. And while research sometimes provides supplementary resources, it can represent an added burden for a particular program.

State spending on patients with HIV/AIDS is distributed among a variety of public structures. Because of the limited information system developed in these facilities, only by studying the mean costs per structure can one measure the human and financial resources dedicated to managing a particular patient sample. Moreover, it is impossible to determine the total number of seropositive patients (diagnosed and undiagnosed) who have developed opportunistic diseases and to measure the precise proportion of AIDS spending attributed to them.

Patients themselves pay for some of these costs in Senegal. Cohort studies of treated patients [20] have previously estimated the mean cost of prescriptions for opportunistic diseases (600 to 3,500 FCFA per month according to the disease), examinations (1,200 FCFA per month) and hospitalization (15,000 FCFA per event). Information is lacking on the health status of

seropositive persons and on how often they seek medical care. However, based on surveys of recourse to care [21], total spending on the estimated 75,000 HIV-seropositive Senegalese persons no doubt reaches several hundred million FCFA. It should also be noted that further large sums of money that would theoretically be necessary are not spent by households, for lack of sufficient income.

In Senegal, the public sector only accounts for about half of all national health spending [22] which itself only represents 4.5% of GNP (US$23 per capita per year). The spending analyzed here is therefore just the "tip of the iceberg", and funding requirements must be interpreted within this general context. Spending by individual households can of course be influenced by public policies, especially those concerning drug prices and payment. However, this analysis will be limited to spending over which the Senegalese health authorities have more direct control and are able to make strategic choices (whatever the origin of available funds).

II
STATE SPENDING

Budgetary follow-up

Until 2000, public spending on AIDS was recorded as part of the Health Ministry budget, partly under the fight against sexually transmitted diseases (122 million FCFA for functional costs) and partly under the Social Hygiene Institute (75 million FCFA for salary costs). Other spending was dispersed among the different health care structures, such as the Blood Transfusion Center. It is difficult to estimate how much of these individual budgets were devoted to combating AIDS. As some AIDS-related activities are integrated (especially in the countryside, where they are becoming increasingly important), part of the functioning and salary budgets (and even the cost of equipment use) of many other structures (National Supply Pharmacy, laboratories, hospitals, dispensaries, etc.), and services (regions and districts) can be devoted to the fight against AIDS.

In 2001 a National AIDS Program (PNLS) was attributed 575 million FCFA in the national operating costs budget. The majority of salary costs are now included in the Health Department budget. In 2003, PNLS became the Division de Lutte contre le Sida (DLS). Salary and functioning costs were integrated into those of the Health Department.

In 2002, the *Conseil National de Lutte contre le Sida* (CNLS) was created under the authority of the Prime Minister. The budget of the Executive Secretariat (SENLS) is therefore no longer managed by the Health Ministry. Moreover, the multisectorial nature of the fight against AIDS requires that several ministries other than the Health Ministry must also set aside certain resources for this purpose. "Budgetary authorizations for health purposes" already existed in the armed forces (4.3 million FCFA in 1999), the Ministry of the Interior (174 million FCFA) and the Ministry of Education (73 million FCFA). The new program also seeks to involve the Ministries of Family, Youth and Employment, among others. These ministries have not, however, created specific budgets.

A proportion of State spending is also imputed to the Consolidated Investment Budget (BCI). In 2002, 180 million FCFA was budgeted for PNLS (mainly to combat STDs), to which 500 million FCFA was added for the AIDS/Drugs Program.

Changes in funding distribution

It is therefore difficult to provide a precise summary table of total spending on AIDS. However, based on the PNLS budget, it can be estimated that public funding of this program rose from 400 to 2,475 million FCFA over the last five years.

Table 1: Evolution of operational budgets

Millions FCFA

	1998	1999	2000	2001	2002
State Budget	267 000	295 600	321 300	373 900	419 700
Health budget	18 444	20 643	23 280	25 821	30 912
PNLS-State	400	500	550	1 300	2 475
ISAARV	250	250	300	600	975
Health/State	6.9%	7.0%	7.3%	6.9%	7.4%
PNLS/Health	2.2%	2.4%	2.4%	5.0%	8.0%
ISAARV/PNLS	62.5%	50.0%	54.5%	46.2%	39.4%

Source/Finance Law, PDIS, PNLS.

During the same period, the proportion of the health budget allotted to PNLS rose from 2.2% to 8%. This increase is even larger in real terms, as total health spending also increased to meet the authorities' objectives for 2003: more than 9% of the Ordinary Expenditures Budget *(Budget des Dépenses Ordinaires)* was allotted to health (although with a slightly different method of calculation from that used in Table 1). In real terms the health budget increased by more than 20% in 2002, while the PNLS budget doubled. At the same time, spending on other health priorities also greatly increased. Hence, it is difficult to pretend that HIV/AIDS spending has occurred to the detriment of other health concerns.

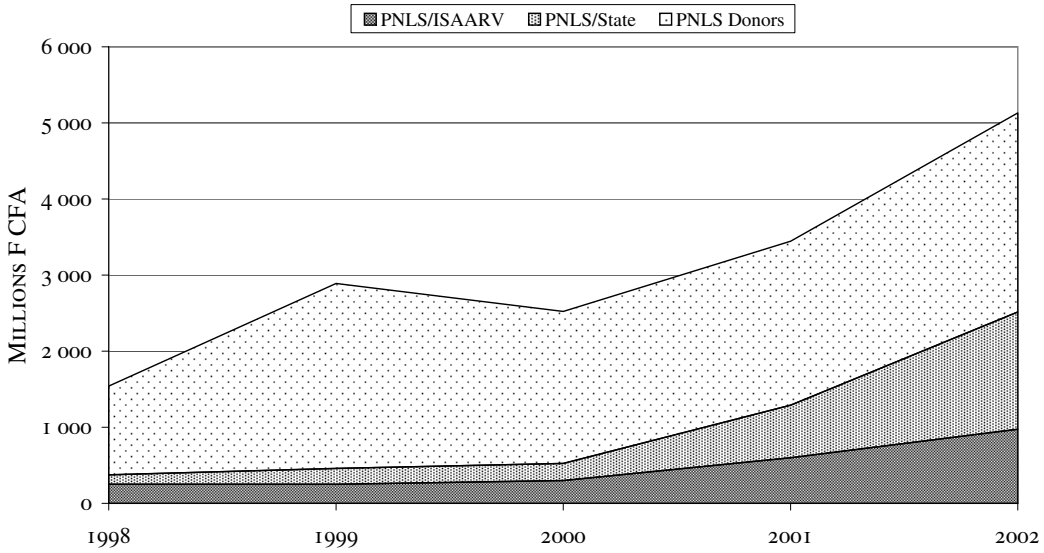
This increase in the PNLS budget is not solely explained by increases in ARV and reagent purchases, which are key ISAARV(*Initiative sénégalaise d'accès aux antirétroviraux* – Senegalese Antiretrovirals Access Initiative) expenditures still fully met by the State. Despite a tripling of purchases in three years, the share of ISAARV in the National AIDS Program declined from 62.5% to less than 40%. The Program's other activities therefore increased in parallel, and were publicly funded.

The PNLS operational budget remains large relative to other programs (835 million FCFA was budgeted to PEV (*Programme élargi de vaccination* – Expanding program on immunization) in 2002 for vaccines) and also relative to grants to districts (about 5 million FCFA annually on average) and regional hospitals (about 150 million FCFA). These comparisons offer a basic picture of the order of spending, as they obviously concern very different operations. These structures'own resources, and foreign aid for programs, must also be taken into account.

III
FOREIGN AID

Like other programs, PNLS has received funds from foreign donors (Figure 1).

Figure 1: PNLS financing



Foreign aid, which was already high in 1998, increased in 1999. This funding source stabilized in 2000, and the increase in foreign aid now parallels that in national funding.

Comparison of AIDS funding with total health spending

Senegal is a moderate-income country (GNP US$545 per capita). It continues to receive large amounts of foreign aid, although the trend is currently downwards. Public development funding corresponded to 8.1% of GDP in 2000, *i.e.* US$37.5 per capita [23]. The health sector received 12.6% of all international aid granted to Senegal in 2000, a major increase over 1999 (8%).

In this general context of health prioritization by the Senegalese authorities and international donors, it is interesting to compare AIDS funding with total health spending. PDIS summary accounts show that the health sector receives about half its funds from national and local government (Table 2A).

Table 2: PNLS and overall health sectorfunding sources

	1998	1999	2000	2001
A. Total health spending				
FOREIGN DONORS	23%	33%	37%	34%
POPULATION	15%	12%	12%	15%
NATIONAL / LOCAL GOVERNMENT	62%	56%	51%	51%
B. PNLS spending				
FOREIGN DONORS	75.4%	83.9%	78.9%	62.1%
POPULATION	0.4%	0.3%	1.0%	1.0%
STATE	24.3%	15.9%	20.7%	37.2%

Sources: PNLS and PDIS.

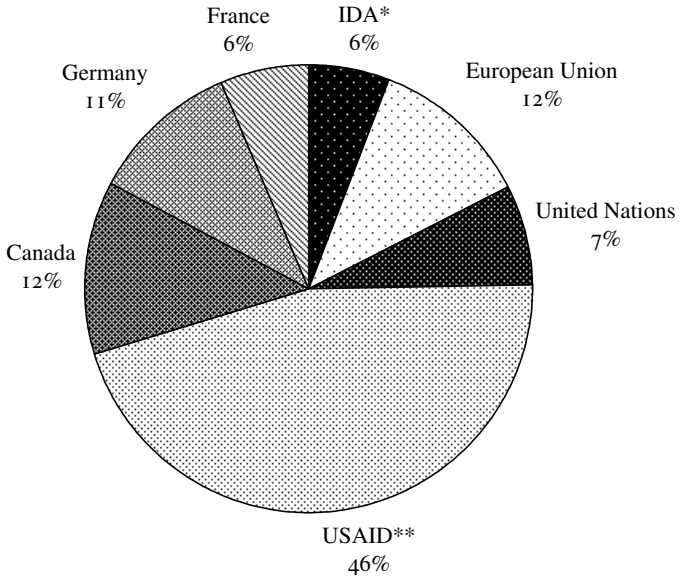
PNLS funding (Table 2B) thus appears to be more dependent than the overall health sector on foreign donors (62% of total spending), although this discrepancy became less marked between 1998 and 2001. Indeed, the part represented by foreign aid in PNLS spending decreased, whereas it increased as a part of overall health spending. This clearly shows that the fight against AIDS in Senegal is not artificially sustained by foreign aid.

The specific nature of PNLS funding (which explains the difference between the two tables) is related to the financial contribution of the population. This contribution is far higher in the health sector as a whole, with the general application of payment systems (often to the detriment of treatment accessibility). In contrast, the only household contribution to PNLS funding is the amount paid by patients for their treatment within the ISAARV program (or for the sale of ARV outside the program, by Fann Hospital pharmacy [24]). These sums remain modest, although they have increased in recent years. The receipts, which now total 85 million FCFA, have not yet been used.

Funding sources

Most foreign funding received by PNLS comes from bilateral aid, mainly from the United States (Figure 2). A few other countries, such as Canada, Germany and France, account for most of the rest.

Figure 2: Budget spending by PNLS 1998-2001



*International Development Agency (World Bank).
**US Agency for International Development.

Multilateral aid comes mainly from the European Union (EU). United Nations funding comes from several different institutions (WHO, UNDP, UNICEF, FNUAP and UNAIDS). The following table compares foreign aid for the fight against AIDS with total aid received by the Senegalese health sector (Table 3).

Table 3: Pledged aid, by donor; 1998-2001

Millions FCFA

	Overall Health sector	PNLS	PNLS/Health
IDA	16,030	414	2.58%
EU	2,761	829	30.03%
United Nations	6,755	514	7.61%
USAID	14,371	3,268	22.74%
Canada	900	882	98.00%
Germany	1,821	778	42.71%
France	6,144	452	7.36%
Others	24,924	0	0.00%
TOTAL	73,707	7,137	9.68%

Sources PDIS, PNLS.

Canada devotes almost all its aid to combating HIV/AIDS. PNLS receives about one-quarter (or sometimes one-third) of the aid provided by the main foreign donors, such as USAID, Germany and the European Union. In contrast, many other foreign donors make little or no contribution to the fight against AIDS. On the whole, 9.7% of foreign aid is devoted to the PNLS operational budget, representing a sum similar to that allotted to PNLS in the state budget. Contrary to the impression created by the visibility and concomitance of AIDS projects, foreign aid to Senegal has so far not been particularly targeted at AIDS.

While the proportion of international aid pledges actually disbursed is often low in Senegal (only 47.7% of aid pledged for the entire health sector), the proportion received by PNLS is relatively high (80% on average), despite strong variations among projects and foreign donors. For example, from 1998 to 2001, the average execution rate of EU-sponsored AIDS projects was only 67%. By comparison, the execution rate of publicly funded PNLS projects was about 90%.

Distribution according to the type of spending

The distribution according to the type of spending also varies according to the funding source (Table 4).

Table 4: Actual PNLS spending in 1998-2001

	State	Foreign aid	Total
Investment	1.5%	12%	10%
Operations	94%	72%	78%
Salaries	4.5%	16%	13%
Total	94%	100%	100%

Source: PNLS.

Most PNLS spending is devoted to operations (excluding salaries) which represented 78% of all funding received. This is particularly the case of state funding, as salaries for PNLS personnel (a dozen staff, including 6 doctors) are not taken into account. The 36 million FCFA spent each year on salaries allow the recruitment of contractual technicians within the framework of

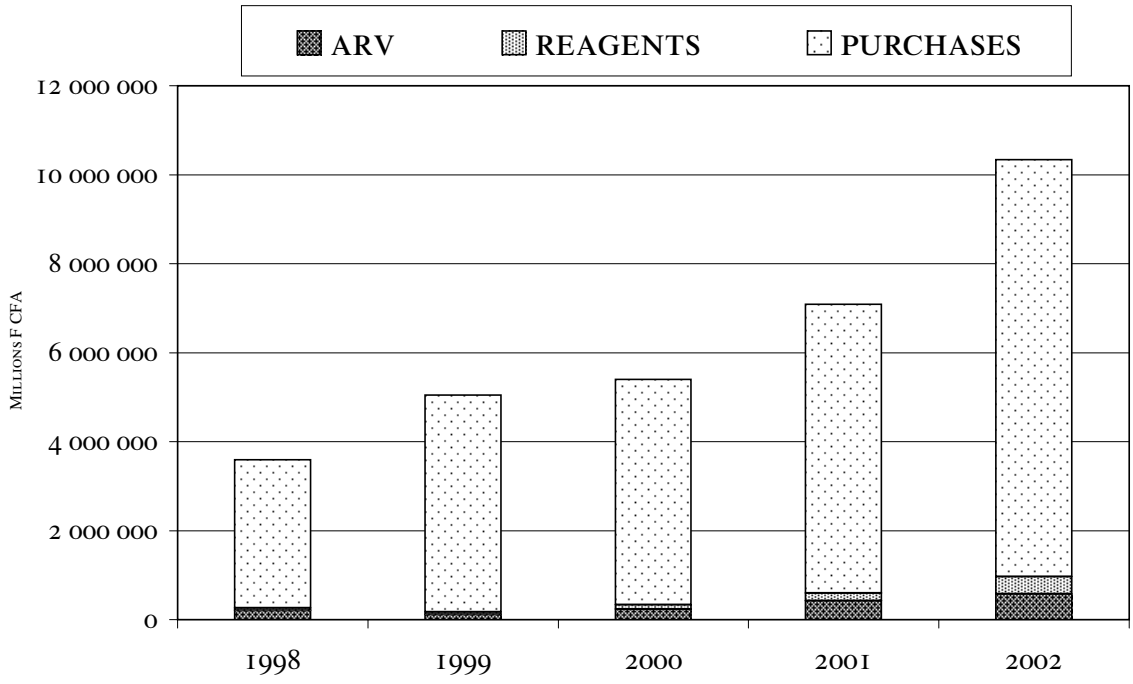
projects. In contrast, international donors pay for salary costs (16%). They also devote a relatively large part of their aid to investments (12%), although so far this has mainly been limited to office equipment. Vehicle purchases are not included in these data, being part of the Health Ministry budget.

It would be interesting to analyze the distribution of funds according to the type of activity (transfusion safety; Information, Education, Communication [IEC]; STD, etc.) and operator (NGOs, programs, decentralized structures), but we do not yet have access to operational tools (such as strategic plans) for the years in question. We therefore limit this analysis to purchases of antiretroviral drugs.

IV
PURCHASES OF ARV AND REAGENTS

Since 2000 the Pharmacie Nationale d'Approvisionnement (PNA - National Supply Pharmacy) has exerted an effective monopoly on ARV importation (including for the private sector, which is supplied within the "out-of-program" framework). Purchases of ARV have grown significantly, but not as rapidly as total PNA purchases (Figure 3).

Figure 3: Evolution of PNA purchases



The increase in PNA purchases in 2002 was due to the creation of a 6-month strategic stock of all products. PNA is also taking over a growing proportion of vaccine purchases. In 2002, ARV and reagents represented 10% of all PNA orders. Total annual purchases rose from 261 to 969 million FCFA between 1998 and 2002. The price cuts negotiated with suppliers in 2000 did not slow this progression. Almost all orders were placed with patent holders. Only one "test" order was placed with a generics manufacturer, in 2002 (for 38 million FCFA, *i.e.* 3% of the year's orders).

But PNA still plays a limited role in the national drug supply chain, its turnover representing only 8.4% of the overall pharmaceutical sector. In Senegal, half of all national health spending (about US$23 per year per inhabitant) takes place in the private sector, and 90% of household spending is devoted to buying drugs from the private sector or the "informal" market. ARV therefore constitutes only 0.3% of the overall pharmaceuticals market. Although this share has increased considerably, pharmaceutical companies' chief concerns are their patents' rights and public image.

Since the PNA will likely transform into an autonomous public establishment, its role in the ARV supply chain must be discussed. For the moment, 80% of PNA receipts come from direct purchases by health care structures (through cost recovery). Following decentralization, some structures will deal more with the private sector. Does this mean PNA should specialize in supplying drugs of "public interest" (vaccines, ARVs, etc.) and be funded mainly by the State? One drawback is that this might carry a risk of cash-flow problems due to inadequate debt recovery. Or, on the contrary, with the development of AIDS management on the periphery of the private sector, should the drug supply circuit be opened up to the private sector? Ultimately, what impact would this have on the continuity of price control, quality assurance and availability?

V
EVOLUTION BETWEEN 2003 AND 2006

2003 is a watershed year in the fight against AIDS in Senegal, with major institutional reorganization (creation of CNLS and SENLS) and the release of new funds, especially by the World Bank (Multi-Country HIV-AIDS Program, MAP) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

"The watershed year"

In 2003, it is also planned to significantly develop ISAARV decentralization and to launch new activities such as voluntary screening centers. This change in the scale of actions against HIV/AIDS translates into a large increase in resources, as listed in the first-year budget of the new strategic plan (Table 5)

Table 5: Provisional budgets of PNLS then DLS (division de lutte contre le sida)

Millions FCFA

	PNLS 2002	DLS 2003	VARIATION
ISAARV State	975	1,428	46%
ISAARV Donors	0	3,131	
Total ISAARV	975	4,559	368%
State Program	2,475	3,418	38%
Foreign aid	2,617	6,585	152%
Total Program	5,092	10,003	96%
Total Health Ministry	30,912	35,343	14%

ISAARV/Program	19%	46%
Donors/Program	51%	66%
Program/Ministry	8%	10%

Thus, between 2002 and 2003, the Program's total budget has doubled, from 5 to 10 billion FCFA, while the ISAARV budget has been multiplied 4.6-fold, and the share of ISAARV in PNLS has risen from 19% to 46%. Foreign aid now meets two-thirds of the ISAARV budget. Public funding of ISAARV increased by only 46%.

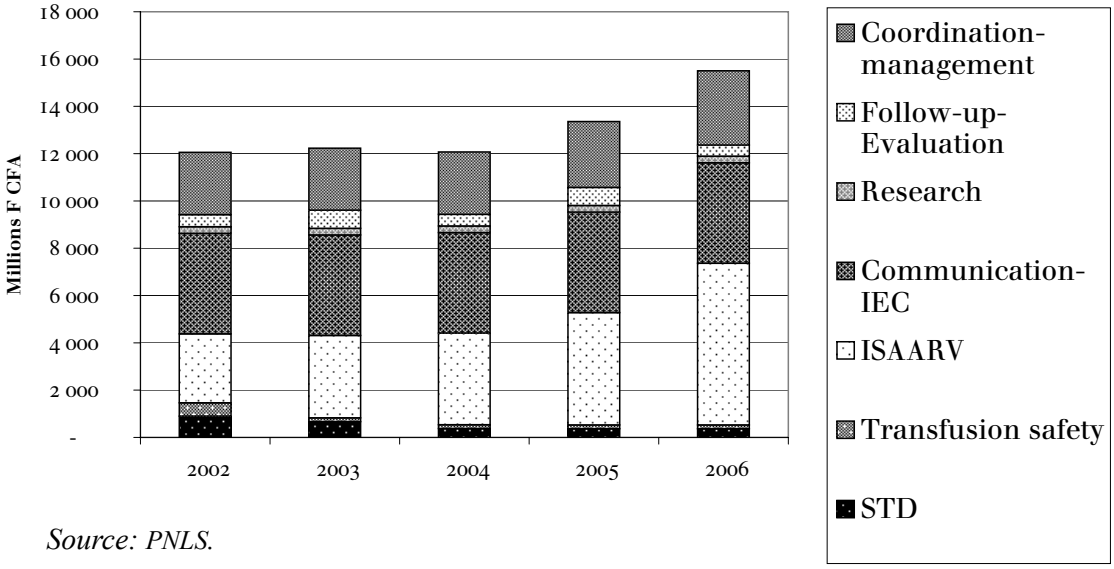
The State budget for other items of the Program showed similar growth (38%), but the contribution of foreign aid has considerably increased here, too. Globally, the program represents a reasonable part of the Health Ministry budget (10% instead of 8%), but dependence on foreign aid has increased (66%).

This increase in total resources has thus been accompanied by a change in the distribution of funding sources. The Program has not only seen an increase in its budget but also a change of philosophy, which is most evident with regard to the distribution of resources according to the type of activity.

Five-year forecasts according to the type of activity

It is also interesting to analyze mid-term estimates based on the strategic plan of the CNLS (Figure 4). This plan was to cover the period 2002-2006 but, because of delays in foreign aid, a shift of about a year is anticipated.

Figure 4: Budget of the strategic HIV/AIDS plan



Source: PNLS.

After major transformations linked to this new plan's implementation, its total resources and their distribution will evolve more gradually. The total budget will be stable for the first three years and then increase slightly. The largest share of available resources will be equally devoted to the two main items (IEC and ISAARV). From 2004 onwards the ISAARV budget will exceed the IEC budget, but, in absolute terms, spending on IEC will not fall. Thus, the increase in the Program's total budget during the last two years can be attributed to the extension of patient management.

Funds reserved for STDs and transfusion safety will decline, but part of these activities will be gradually integrated into existing structures. The research budget is modest, but significant resources will be devoted to follow-up and evaluation. "Coordination and management" will receive a large share, in order to ensure that the expansion of activities, and especially their decentralization, takes place in favorable conditions. This part of the budget will cover unforeseen contingencies related to organizational problems. Indeed, during the period concerned, this budget will remain relatively stable despite the expansion of the program, and this implies the need for major gains in efficiency and productivity.

Funding of the strategic plan

For the 5-year period, the program will cost nearly 65 billion FCFA. Existing funds cover 81% of this sum (53 billion FCFA).

Table 6: Strategic plan, 2002-2006

Millions F CFA

Funding source	Current budget	%
State	7,150	13.5%
United Nations	692	1.3%
GFATM	8,300	15.7%
IDA	21,647	40.9%
HIPC Initiative*	5,000	9.4%
EU	855	1.6%
USAID	4,167	7.9%
Germany	3,000	5.7%
Canada	1,064	2.0%
France	1,050	2.0%
GSK**	36	0.1%
Total	**52,961**	**100%**

* Heavily Indebted Poor Countries Initiative.
** Glaxo Smith Kline.

The share of state funding, which was 37% in 2002 and 34% in 2003, will fall to 13.5% for the entire period of the plan. These figures are solely indicative, because state commitments are not fixed mid-term, but are voted each year.

Long-standing foreign donors to the National AIDS Program continue to finance the plan, but the distribution is appreciably modified and far more concentrated. The World Bank will finance 41% of the plan, but in the form of loans (IDA), compared to the previous 4 years when 96% of foreign aid came in the form of donations. It is somewhat paradoxical that the program should be financed through both a substantial increase in debt and debt relief. It is true that in Senegal, these latter resources (HIPC Initiative funds, which represent nearly 10% of the total budget) still depend on negotiations with the IMF.

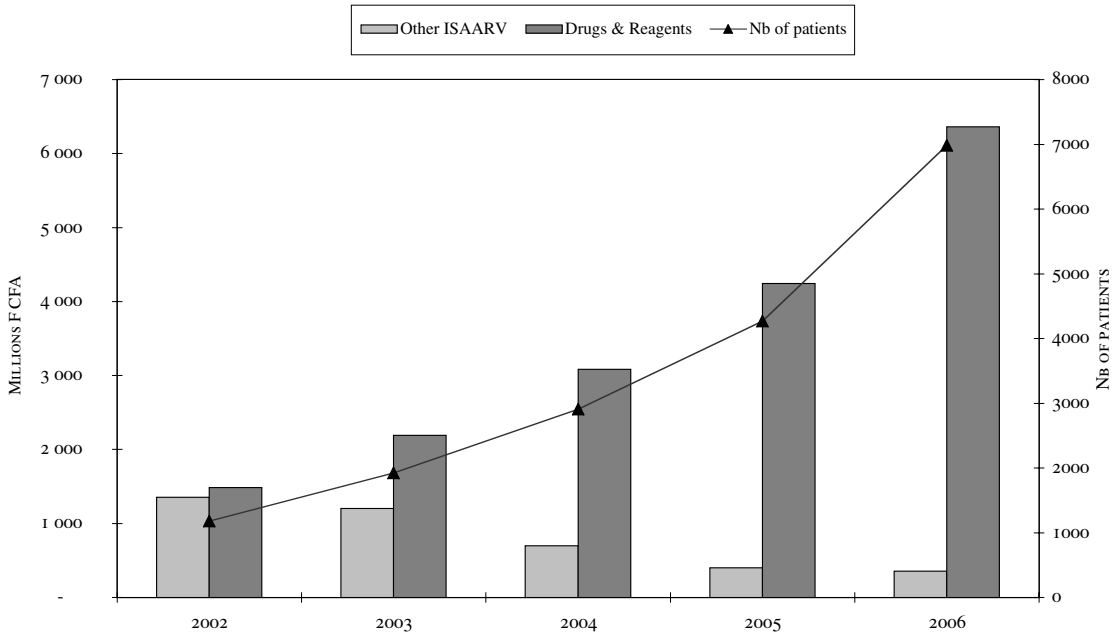
A new donor, the GFATM, now provides almost 16% of funds. Aid from all other foreign donors has appreciably decreased in relative value. But the

average annual funding by France and Germany has increased considerably compared with the previous period (two-fold and three-fold, respectively). Canada and the United Nations will maintain their funding at stable levels in absolute values, while the contribution of the European Union is shrinking.

Development of ISAARV

Patient management is a major feature of the new plan and, as such, warrants special attention. The share of ISAARV will increase significantly, because it is planned to gradually expand treatment from 1,177 patients to 6,982 patients, *i.e.* a year-to-year increase of more than 50%. As an estimated 15,000 persons in Senegal qualify for treatment from a medical standpoint, the program would only meet half the theoretical needs. The objective is nonetheless ambitious, and explains the relative increase in the pharmaceuticals budget (Figure 5).

Figure 5: Evolution of the provisionnal budget for 2002 to 2006



The pharmaceuticals budget also comprises a growing proportion of drugs for opportunistic diseases. During the first years of the plan, half the ISAARV budget will be devoted to investments (computers, diagnostic devices, refurbishment of health care centers) and to training, which is necessary for successful decentralization. Gradually, the bulk of the budget will be devoted to purchasing the drugs required to meet the growth in demand as the program expands.

However, the decline in both the relative and absolute value of other ISAARV expenditures is potentially worrisome. Major funding will probably be required for on-the-job training and equipment maintenance. Despite the multiple funding sources, peripheral structures may not be able, within such a short time span, to support these services at the same level of technical quality and administrative efficiency.

Regarding the funding of ARVs, reagents and certain drugs for opportunistic infections (OI), estimated needs, although significant, are more or less covered (Table 7).

Table 7: provisional budget, 2002-2006
Millions F CFA

	ARV	**Reagents**	**Drugs for OI**
STATE	2,575	3,700	225
IDA	3,087	182	–
HIPC INITIATIVE	5,000	–	–
GFATM	1,500	365	–
FRANCE	283.5	44	50
EU	–	9.5	14.6
WHO	7	–	–
GSK	–	6	–
TOTAL ACQUIRED	12,452.5	4,306.5	289.6
TOTAL REQUIRED	12,575.9	4,780.1	499

As HIPC Initiative funding is uncertain, the World Bank is the principal funding source for ARV purchases (budget of three billion FCFA). The State finances a similar amount but also pays for the bulk of reagents (budget of 3.7 billion F CFA). This provisional public spending is considerably higher than that represented by current drug purchases by the Health Ministry.

These budgets are based on a yearly ARV treatment cost of US$700 to 1000 per patient, which is itself based on prices negotiated with pharmaceutical firms in 2000. This cost could potentially be halved by the use of generics, although this would require changes in the habits of Senegalese health care professionals, and also a generic supply chain.

The organization and management of drug purchases may also become a key problem. Total ARV and reagent orders are scheduled to increase to more than 6 billion F CFA in 2006, *i.e.* almost half current total orders by the National Supply Pharmacy. Will PNA be in a position to control the supply and distribution of products required for the program while fulfilling its other roles? The place of ARV in the Senegalese drug market will also change radically, posing new challenges for the private drug distribution sector.

Conclusion

Many previous economic analyses have focused on the unit cost of treating HIV-seropositive patients or on costs per avoided infection [25]. Because of the low prevalence and the relatively small number of patients requiring treatment, these unit costs appear far higher in Senegal than those of other health care interventions (before even attempting to measure the impact of the different types of intervention). Adopting a different perspective, we attempted to measure the global cost of an HIV/AIDS program, to estimate what proportion of Senegal's overall health spending is devoted to combating AIDS, and to determine whether spending on AIDS compromises other health priorities.

Our results show that the growth of HIV/AIDS programs has not massively absorbed the resources available to the Senegalese Health Ministry. Indeed, the growth of spending on the National AIDS Program remained relatively under control until 2002. In addition, the national effort on AIDS, and on all other health sectors, has been reinforced. The AIDS program has probably had a "mobilizing" effect, especially in terms of prevention. Public spending has ensured that dependence on foreign aid remains at a reasonable level. This relative independence is also ensured by the diversity of external funding sources. The fight against AIDS has attracted a variety of funds that are not always fungible and therefore readily attributable to other health actions. Yet the fight against AIDS does not seem to have received special status relative to other health care priorities.

Cost-efficiency analyses of the different possible actions on HIV/AIDS haves led some authors to propose focusing on prevention and to consider treatment as "experimental" pending the success of prevention programs [10]. However, it is difficult to define a "satisfactory" level of prevention and debatable whether such a level could be reached without expanding treatment simultaneously. Senegalese experience in coming years may throw light on this discussion. For the time being, it seems that treatment has not expanded to the detriment of prevention, at least as regards funding. However, analysis

of the impact, positive or negative, of the treatment of seropositive persons on a country's overall health care system is a far more complex task.

The Senegalese experience has already led the national health authorities and foreign donors to propose a far more ambitious strategic plan for the coming years. This plan does not simply represent a change of scale but also implies a profound modification in the distribution of spending, in its relative place within the different state budgets, and in the funding structure. It is of course difficult to anticipate the chances of success of this strategic plan in light of previous experience, because the challenges are of a different order. They include the training of health care personnel, the administrative capacities of the different services, the place of the private sector, and the degree of dependency on foreign aid. The philosophy of intervention has changed in many areas (especially financial considerations). The implementation of this program must be closely monitored (and budgeted). Foreign donors will be required to adapt their funding pragmatically to foster a more gradual and progressive evolution, perhaps not as rapid as currently anticipated, in the face of these new stakes.

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