RÉPUBLIQUE FRANÇAISE
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SYMPOSIUM OMS – ANRS MIE

AFRAVIH - 17 avril 2024, 17h15 - 18h45

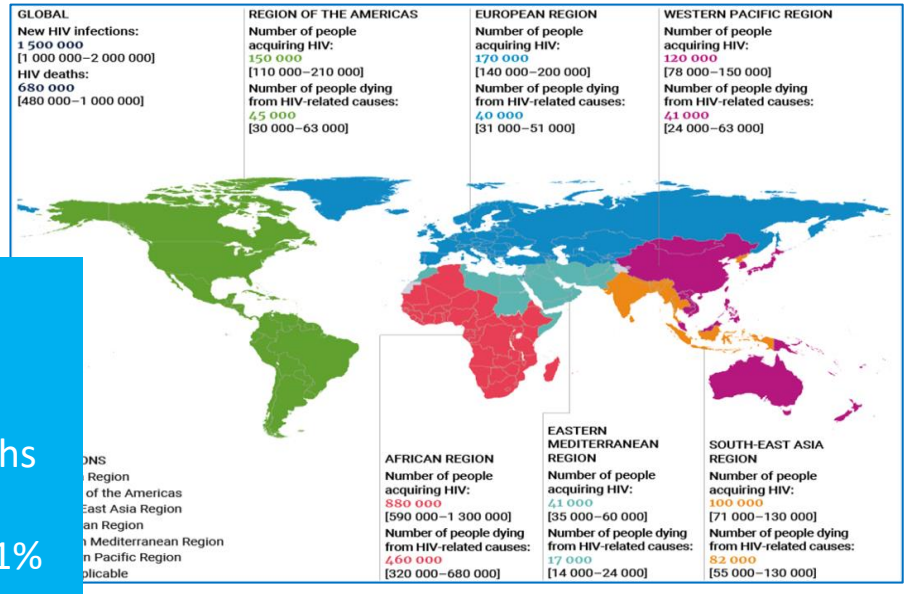
Perspectives de recherche thérapeutique sur VIH/Sida (et Hepatite/IST) en Afrique

Meg Doherty, MD, MPH, PhD
Director Global HIV, Hepatitis and STI Programmes, WHO

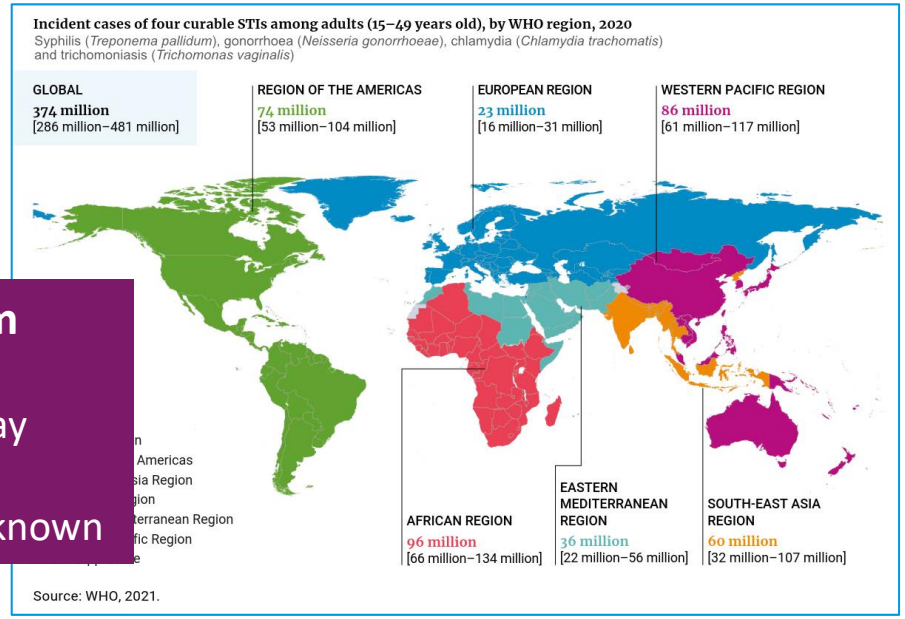
Global HIV, Hepatitis and STI

Different but intersecting epidemiologies that affect the most vulnerable

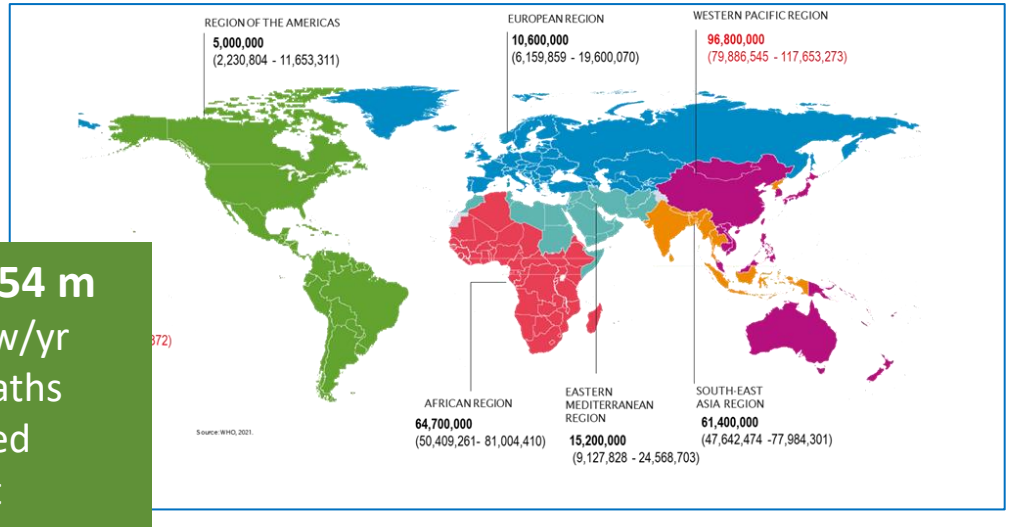
HIV -> 39 m
1.3m new infections/yr
630,000 deaths
29 m on ART
86% /76% /71%



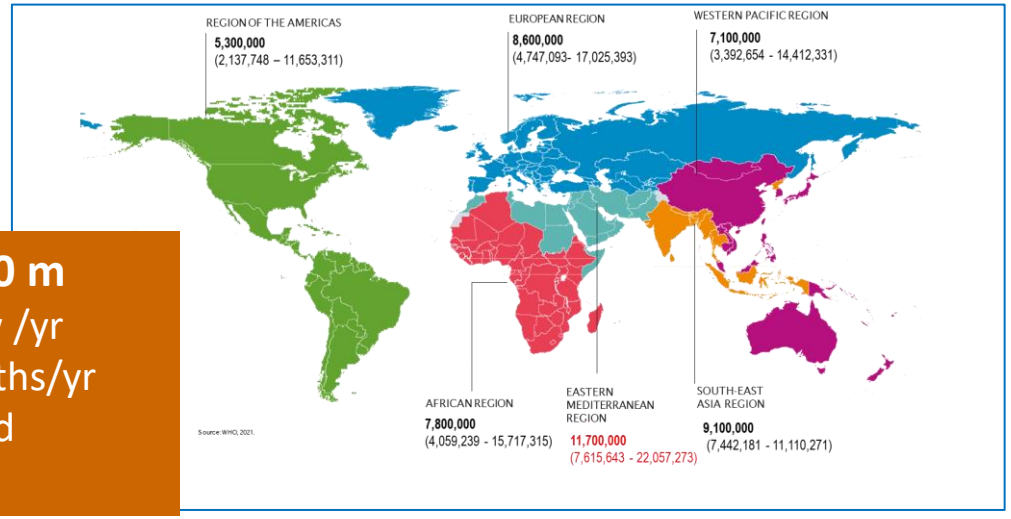
STI -> 374 m
1.0 m new infections/Day
Testing & Txt coverage unknown



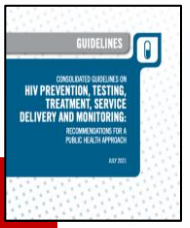
HBV-> 254 m
1.2 m new/yr
1.1 m deaths
13% tested
3% on txt



HCV -> 50 m
1.0 m new /yr
242 K deaths/yr
36% tested
20% txt



WHO Consolidated HIV Guidelines



Chapter 2 – Testing & diagnosis

- Point-of-care tests for diagnosing HIV infection among children younger than 18 months
  April 2020
- Consolidated guidelines on HIV testing services for a changing epidemic
  27 November 2019
- ★ **New:** POC infant diagnosis

Chapter 3 – HIV Prevention

- A framework for voluntary medical male circumcision
  15 July 2016
- ★ **New:** Dapivirine vaginal ring

Chapter 4 – HIV treatment and monitoring

- Update of recommendations on first- and second-line antiretroviral regimens
  22 July 2019
- Transitioning to an optimal paediatric ARV formulary: implementation considerations
  19 July 2018
- ★ **New:** POC viral load and treatment algorithm

Chapter 5 – Co-morbidities

- Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV
  1 April 2020
- Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children
  1 March 2018
- ★ **New:** TB HIV
- Cervical cancer prevention

Chapter 6 – Service Delivery

- Maintaining and improving quality of care within HIV clinical services
  22 July 2019
- ★ **New:** Service delivery recommendations

Chapter 7 – Toxicity, HIVDR, M&E

- Consolidated guidelines on person-centred HIV patient monitoring and case surveillance
  20 June 2017
- Tackling HIV drug resistance: trends, guidelines and global action
  20 July 2017
- Consolidated HIV strategic information guidelines: Driving impact through programme monitoring and management
  April 2020

- Updated Recommendations on First-line and second-line antiretroviral regimens and post-exposure prophylaxis and on early infant diagnosis of HIV
  27 December 2018
- Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations
  1 July 2016 – **update End of 2021**
- Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy
  20 July 2017

World Health Organization

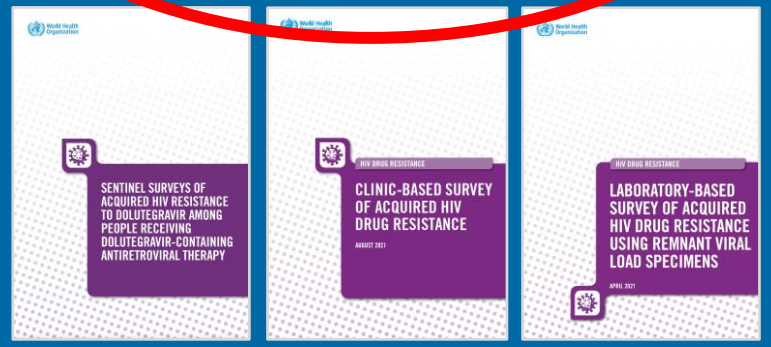
Adult ARV treatment: Questions that still need to be answered

Priority topic	Opportunities and Challenges
Consolidation of TLD transition in LMICs	• Address gender inequity to DTG observed in some countries • Long term safety (body weight gain, metabolic syndrome) • INSTI Resistance (strengthen HIVDR monitoring)
DRV/r in 2nd and 3rd line regimens	• Would be better promote DRV/r in 2nd line or maintain it as a preferred option for 3rd line?
Role of TAF (expanded use in some subpopulations)	• Long term safety need more studies (body weight gain, dyslipidaemia and other emerging AEs) • TB/HIV - do we need TAF dose adjustment if using rifampin? • TDF-TAF transition in stable patients (all patients or only specific groups?)
Role of dual therapy (including injectable long acting drugs and emerging classes) in LMIC context	• Limited data on long term safety and resistance risk (WHO monitoring tools developed) • Limited data on use in LMIC context • How to implement (operational research) • Should LAIs be promoted as a complementary option to oral regimens in some situations or should replace current oral ARV framework?

Acquired HIV drug resistance surveillance

- DTG resistance has been described in a few ART-naïve people failing first-line DTG-based ART.
- DTG resistance can emerge among people with previous exposure to first-generation INSTI (with comparatively lower genetic barriers to the selection of drug resistance) or when used as DTG monotherapy.
- **Recent evidence from ART programmes from sub-Saharan Africa suggests that DTG resistance can emerge in people taking DTG-containing regimens in the medium to long term.**
- Nearly one in four persons diagnosed with HIV after receiving CAB-LA PrEP may have cross-resistance to dolutegravir before treatment initiation.

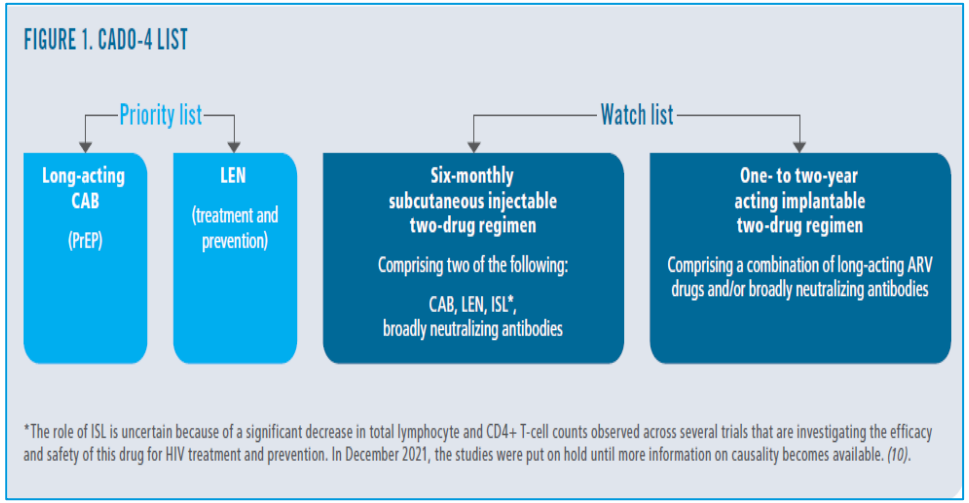
WHO recommends that surveillance of HIV drug resistance should accompany the scale-up of DTG-containing ART and CAB-LA PrEP in HIV programmes.

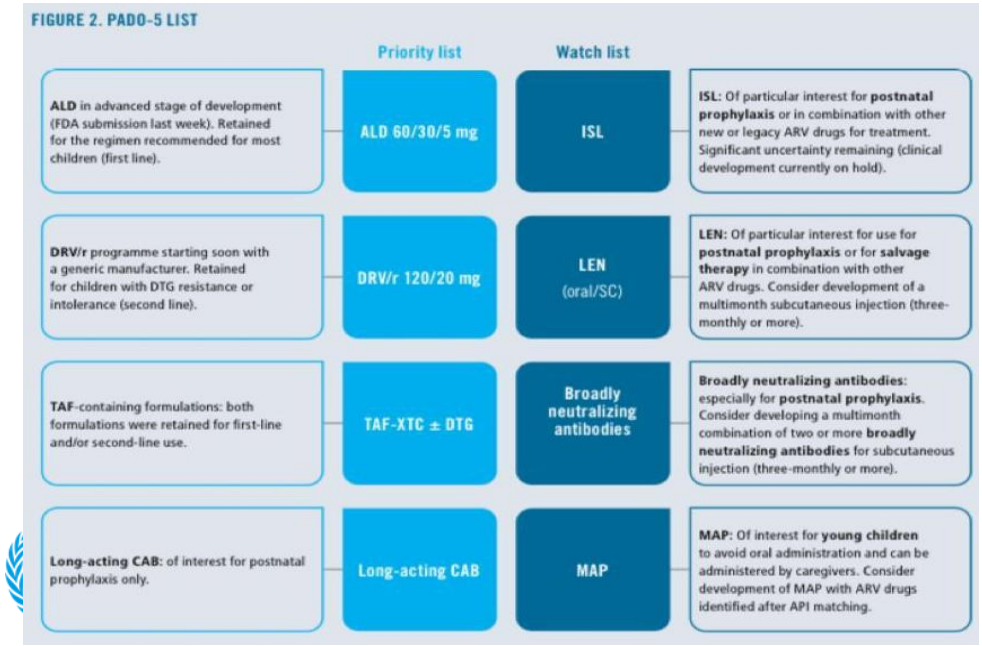


https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment/hiv-drug-resistance/hiv-drug-resistance-surveillance/surveillance-of-acquired-hiv-drug-resistance-in-populations-receiving-art

- Lübke N, Jensen B, Hüttig F, Feldt T, Walker A, Thielen A et al. Failure of dolutegravir first-line ART with selection of virus carrying R263K and G118R. N Engl J Med. 2019;381:887–9.
- Rhee SY, Grant PM, Tzou PL, Barrow G, Harrigan PR, Ioannidis JPA et al. A systematic review of the genetic mechanisms of dolutegravir resistance. J Antimicrob Chemother. 2019;74:3135–49.
- van Oosterhout JJ, Chipungu C, Nkhoma L, Kanise H, Hosseinipour MC, Sagno JB et al. Dolutegravir resistance in Malawi's national HIV treatment program. Open Forum Infect Dis. 2022;9:ofac148.
- Ahluwalia AK, Inzaule S, Baggaley RC, Vitoria M, Schaefer R, Schmidt HA, et al. Characterization of dolutegravir drug resistance in persons diagnosed with HIV after exposure to long-acting injectable cabotegravir for preexposure prophylaxis. AIDS (London, England). 2022;36(13):1897-8.

WHO priority lists of new ARVs (CADO & PADO lists)





WHO, 2022

Expected Changes with Long-Acting ART

New Modalities

New modalities for treatment, including injectables and other long-acting products like pills and implants

Service Delivery Changes

Changes in how HIV treatment is delivered, with potential changes needed to DSD models

Sequencing Complexity

Dissolution of rigid therapy lines; HCWs to use clinical history to determine future options

Client Choice

Increased focus on client choice across treatment regimens and formulations

CHAI, 2023

- Interchangeability and transition between oral and injecting regimens
- Implementation science on delivery of LA formulations in LMICs
- Safety data of LA drugs in pregnancy
- Toxicity monitoring and DR surveillance of LA drugs
- Use of LAs as PEP and in salvage regimens

New Long-acting formulations

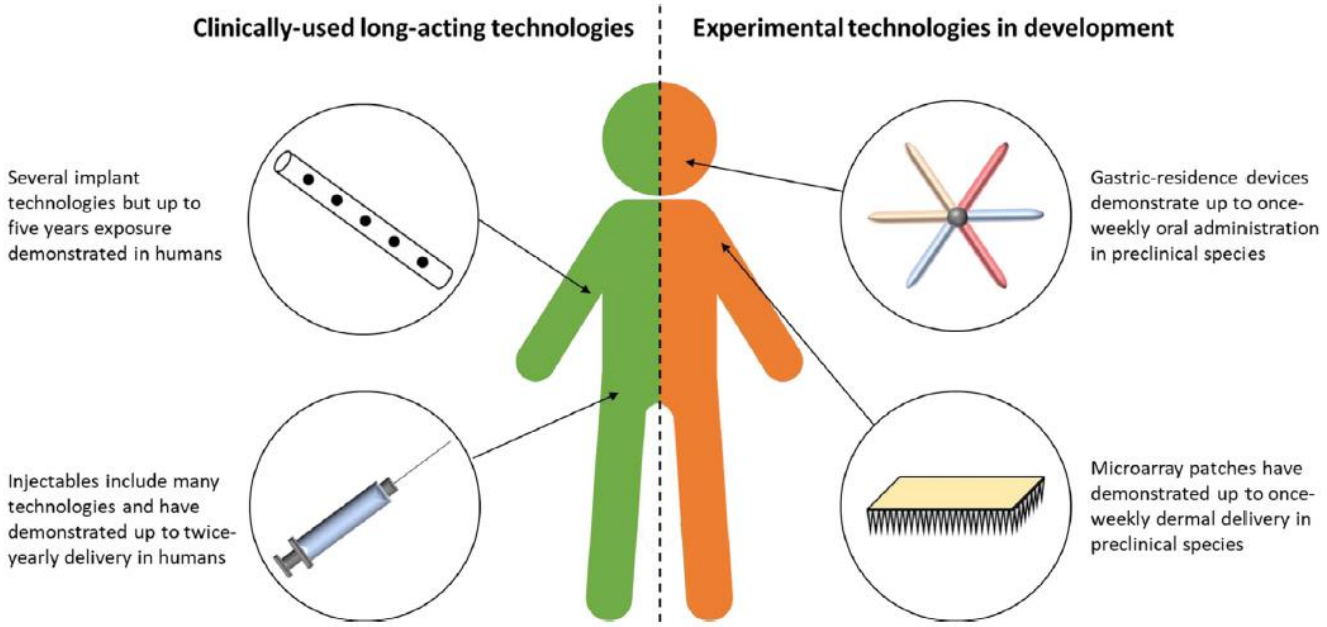


Fig. 1. Examples of long-acting and extended-release drug delivery technologies in preclinical and clinical development for the treatment and prevention of human deficiency virus (HIV) infection.

AIDS

Articles & Issues | For Authors | Journal Info

BASIC SCIENCE: CONCISE COMMUNICATION

A novel formulation enabled transformation of 3-HIV drugs tenofovir–lamivudine–dolutegravir from short-acting to long-acting all-in-one injectable

Perazzolo, Simone[a]; Stephen, Zachary R.[a]; Eguchi, Masa[a]; Xu, Xiaolin[a]; Delle Fratte, Rachele[a]; Collier, Ann C.[b]; Melvin, Ann J.[c]; Ho, Rodney J.Y.[a,d]

Author Information

AIDS 37(14):p 2131-2136, November 15, 2023. | DOI: 10.1097/QAD.0000000000003706

Abstract

Objective:

To develop an injectable dosage form of the daily oral HIV drugs, tenofovir (T), lamivudine (L), and dolutegravir (D), creating a single, complete, all-in-one TLD 3-drug-combination that demonstrates long-acting pharmacokinetics.

Design:

Using drug-combination-nanoparticle (DcNP) technology to stabilize multiple HIV drugs, the 3-HIV drugs TLD, with disparate physical-chemical properties, are stabilized and assembled with lipid-excipients to form *TLD-in-DcNP*. *TLD-in-DcNP* is verified to be stable and suitable for subcutaneous administration. To characterize the plasma time-courses and PBMC concentrations for all 3 drugs, single subcutaneous injections of *TLD-in-DcNP* were given to nonhuman primates (NHP, *M. nemestrina*).

Results:

Following single-dose *TLD-in-DcNP*, all drugs exhibited long-acting profiles in NHP plasma with levels that persisted for 4 weeks above predicted viral-effective concentrations for TLD in combination. Times-to-peak were within 24 hr in all NHP for all drugs. Compared to a free-soluble TLD, *TLD-in-DcNP* provided exposure enhancement and extended duration 7.0-, 2.1-, and 20-fold as *AUC* boost and 10-, 8.3-, and 5.9-fold as half-life extension. Additionally, DcNP may provide more drug exposure in cells than plasma with PBMC-to-plasma drug ratios exceeding one, suggesting cell-targeted drug-combination delivery.

Conclusions:

This study confirms that TLD with disparate properties can be made stable by DcNP to enable TLD concentrations of 4 weeks in NHP. Study results highlighted the potential of *TLD-in-DcNP* as a convenient all-in-one, complete HIV long-acting product for clinical development.

World Health Organization

Example of long-acting ART combinations under evaluation or in clinical use

Frequency	LA regimen	Modality	Study phase
Daily	LEN + BIC	oral	Phase II/III
Daily	ISL + DOR	oral	Phase III
Weekly	ISL + LEN	oral	Phase II
Monthly	TLD (in DcNP)	injectable	Pre-clinical
Every 2 months	CAB + RPV	injectable	Approved (implementation studies)
Every 4-6 months	CAB400 + RPV	injectable	Phase I
Every 4-6 months	CAB400 + N6-LS	injectable	Phase I
Every 6 months	LEN + Teropavimab/Zimlirvimab	injectable	Phase II

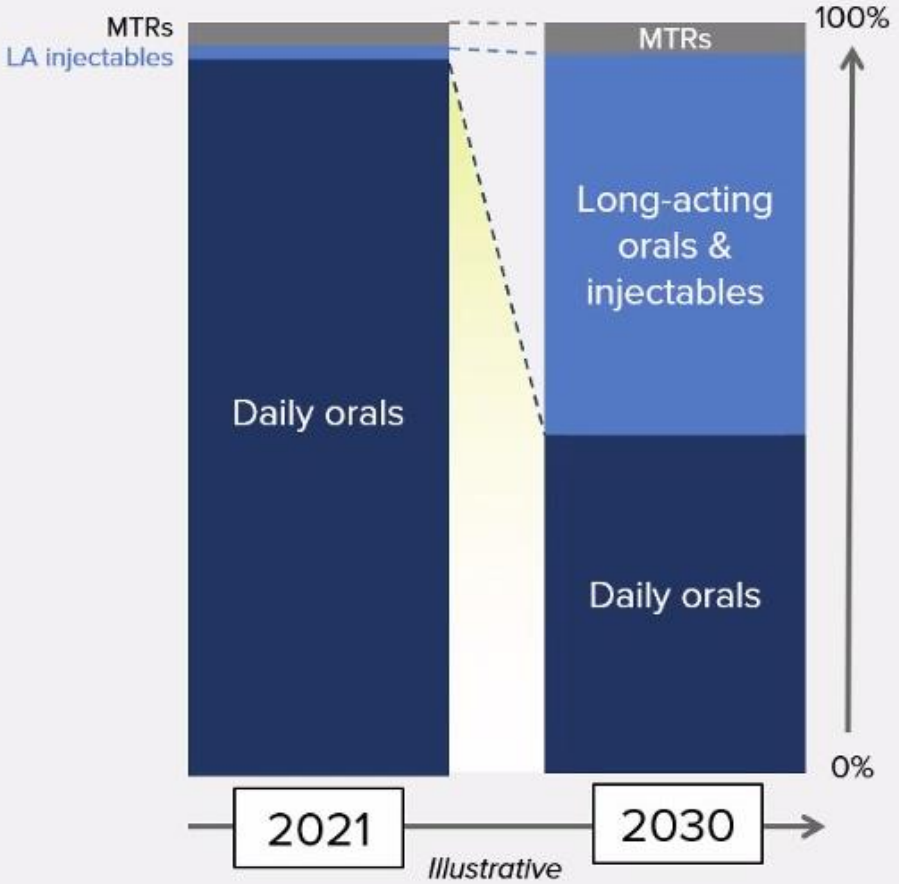
World Health Organization

What about LEN + CAB for treatment

- Not studied because orginators do not work together
- Need to overcome these barriers

Diverse pipeline of HIV long-acting treatment options

Modality	Frequency	Backbone		Partner
Oral	Once-daily	Lenacapavir	+	**Bictegravir** Phase 2/3 combo
	1 week	Lenacapavir	+	**INSTI oral** Phase 1
		Lenacapavir	+	**NNRTI** Phase 1
		Lenacapavir	+	**Islatravir** Phase 2[1]
Injectable	3 months	Lenacapavir	+	**INSTI inj.** Phase 1
		Lenacapavir	+	**NRTI** Pre-IND
	6 months	Lenacapavir	+	**INSTI 1** Pre-IND
		Lenacapavir	+	**INSTI 2** Pre-IND
		Lenacapavir	+	**2 bNAbs** Phase 2



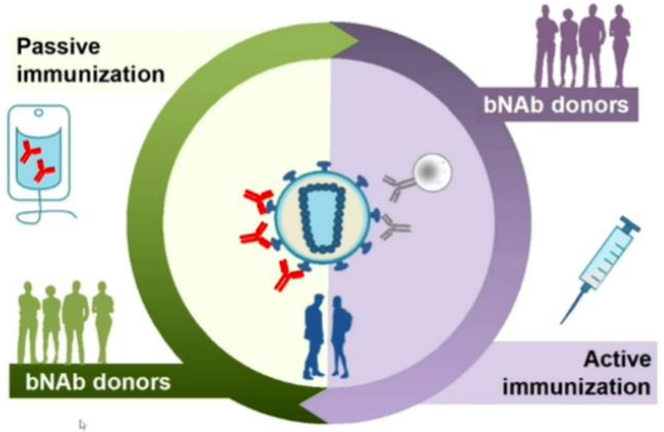
Note: **The combinations and dosing regimens shown are investigational and are not approved by any regulatory authority for any use; their safety and efficacy are not established. Merck's islatravir is an investigational agent and is not approved by any regulatory authority for any use; its safety and efficacy are not established. 1. Lenacapavir + Islatravir oral combo is expected to commence in 1H 2023**. bNab: broadly neutralising antibody; IND: investigational new drug; INSTI: integrase strand transfer inhibitor; LA: long-acting; MTR: multi-tablet regimen; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; POC: proof of concept. Gilead. Data on file.

Approaches to integrate long acting ARVs into clinic and programmatic framework – Areas for research

Major areas	Key challenges in transitioning to current LAIs	Major concerns	Potential approaches with future LAIs
Clinical/ Pharmacological (regimens)	• "pK tail" • Drug interactions • Polypharmacy • Pharmacogenetics • Changes in physiologic status	• Subtherapeutic levels (reduced efficacy, resistance risk), • Need of lead in / dose escalation/adjustments • management of toxicities	• Use of prodrugs • Multiple implants with different dosages ("tunneled" /reservoir in style implants, • Biodegradable implants • LA oral formulations (particularly for elderly patients) • TDM
Acceptability (formulations)	• Injection site pain • Size/ visibility of implants • Management of adverse events	• Adherence • Stigma • Values and preferences of HCWs /patients	• SC injections, microneedles (microarray patches), • Implants (synergies with contraceptives/other disease treatments - neuropsychiatric disorders), • Nano formulations (low volumes) • Implementation studies in more diverse settings
Operational (logistics for stock, drug application and patient follow up)	• Service/programme SOPs changes from an oral to injectable treatment platform • Cost-effectiveness/ cost savings (high cost)	• Inejction supply costs • stock/ refrigeration needs, • HCW training needs, • service visit schedules, waste disposal	• Use of non-traditional health care models (pharmacies, minute clinics, community-based organizations, mobile vans, home visits), • Extension of dose intervals • Heat stable formulations all components of the regimen, • Biosafety measures with needles and syringes

BNAbs and HIV Vaccines

Broadly neutralizing antibodies continue to be a major focus of vaccine design strategies



Many passive bNAb immunization prevention trials in progress, and at CROI

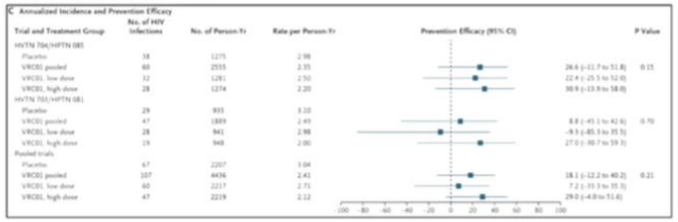
- Novel combinations / cocktails
- Routes of administration (IV vs subQ, hyaluronidase)
- Adults *and* infants
- Probing the vaccinal effect (CD8 immunity after bNAb administration)
- Exploring Fc effector function in passive immunization

Efficacy Trials of VRC01 Antibody to Prevent HIV acquisition: The AMP Studies


ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

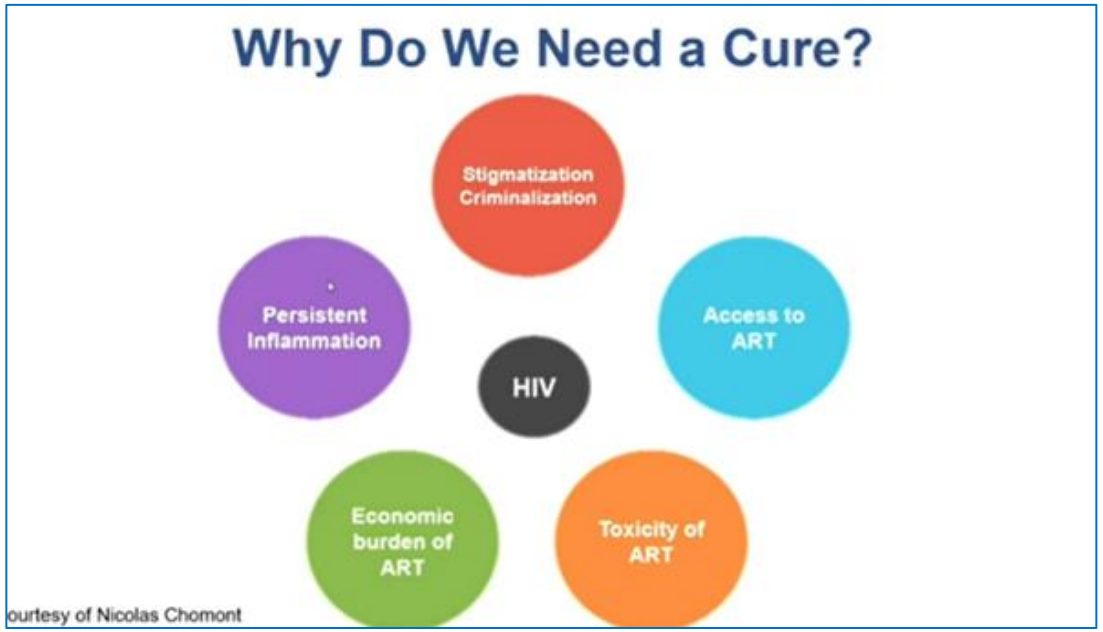
No overall prevention efficacy in either trial, but….



New technologies enabling bNAb development

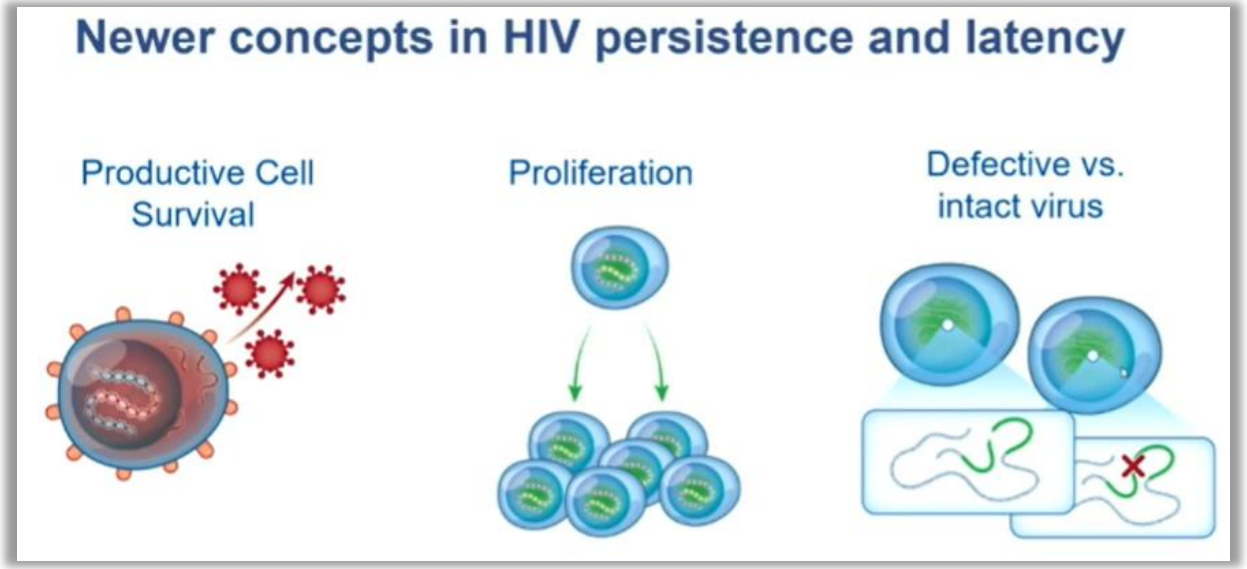
- While promising initial results have been obtained for initiation of bnAb induction, an efficacious regimen will require **sequential immunizations to drive bnAb potency and breadth.**
- An efficacious HIV vaccine will likely require induction of bnAbs targeting ***multiple (perhaps 3) Env epitopes, and this will likely require simultaneous administration of immunogens targeting the induction of multiple bnAb specificities.***

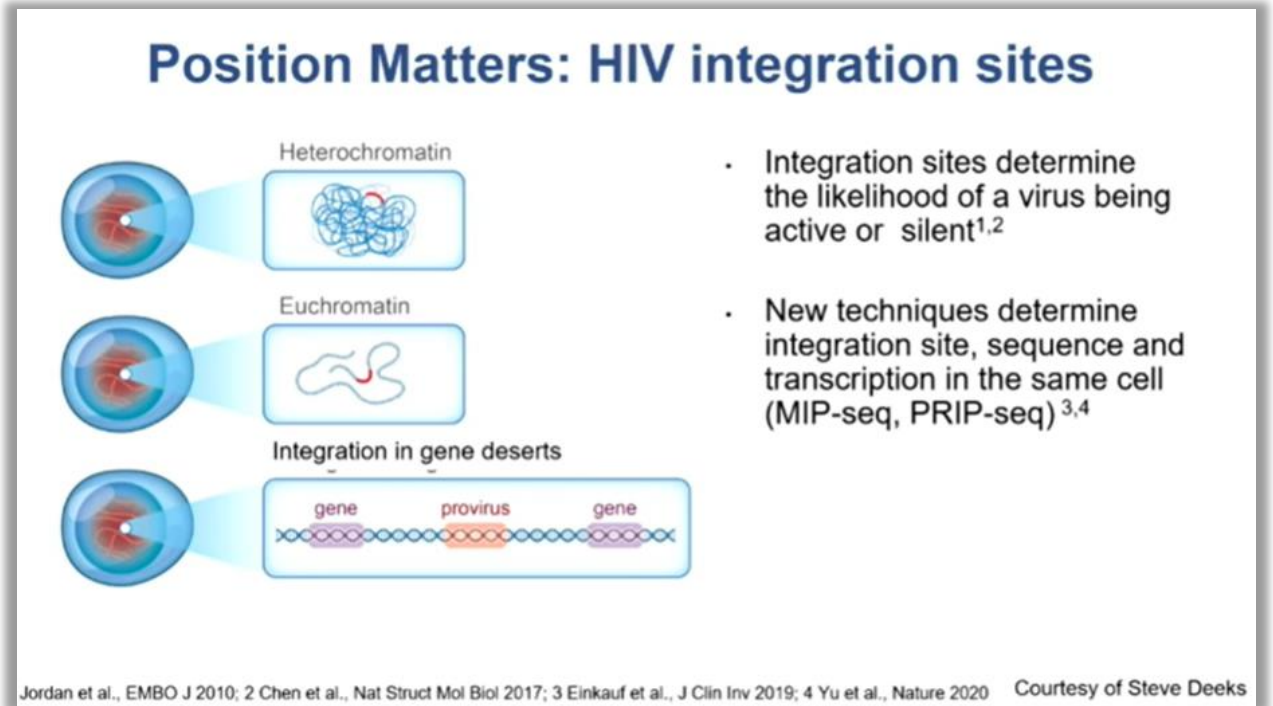
HIV Cure



If We Cannot Eradicate or Control, Can We "Block and Lock?"

World Health Organization



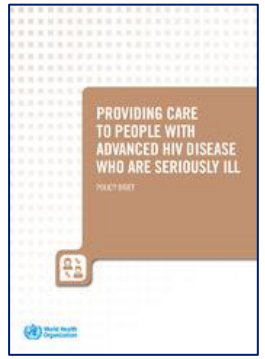


Advanced HIV Disease (AHD)

Innovations to Keep People Alive

- New single high dose of L-amphotericin induction for Cryptococcal Meningitis
- Updated guidance for cryptococcal meningitis and leishmaniasis
- WHO expert consultation on severe bacterial infections
- WHO Policy brief on caring for individuals who are seriously unwell

- **AHD Research Landscape released on 19 Jan 2024**
  - Advocating for access to CD4 POC testing due to anticipated global shortfall
  - How to better deliver the package
  - Use of Azithromycin for severe bacterial infections and AMR
  - Other cause of death (fungal infections)



WHO guidance on oral PrEP and PEP for HIV

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Pre-exposure prophylaxis (PrEP)

2015. Daily Oral PrEP containing **tenofovir** as an additional prevention choice for people at substantial risk of HIV infection

2019. Event-driven PrEP for MSM

2021. Dapivirine vaginal ring as an additional prevention choice for women at substantial risk of HIV infection

2022 Event-driven PrEP for ALL men (updated)

2022. Long acting injectable cabotegravir (CAB-LA) as an additional prevention choice for people at substantial risk of HIV infection

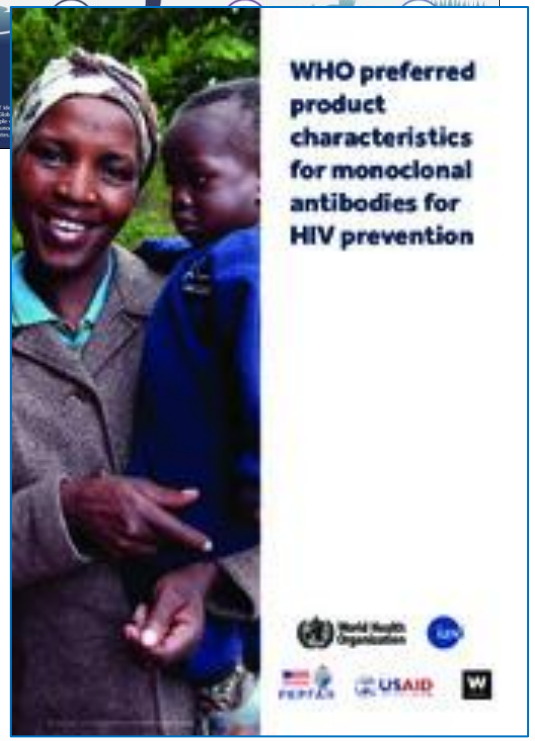
Post-exposure prophylaxis (PEP)

Three ARV drug regimen is *preferred* (same as 1st line ART)

WHO guidance guidelines in 2024 to look at simplifying delivery & expanding access to PEP in community settings

WHO actions for future LA-PrEP

- **Lenacapavir**
  - Results for Purpose 1 (women) Q3 2024; Purpose 2 (men) Q4 2024
  - Assuming results are favorable, WHO will consider guidance
- **DPP**
  - Combined TDF/FTC + COC
  - No need for guideline since WHO already has guidance on both products
  - Generic company currently doing BE study to submit for PQ inclusion
- **MK-8527**
  - Phase 2a
  - Oral pill delivered 1x/month
- **mAbs**
  - In partnership with IVB and IAVI
  - WHO preferred product characteristics for monoclonal antibodies for HIV prevention
- **4m injectable CAB (phase 1)**
  - Data to be presented at CROI



Data introducing our next generation of potential ultra long-acting medicines for HIV: ViiV Healthcare will share findings from a phase I study evaluating different formulations of cabotegravir and their potential for dosing every four months. The ongoing, open-label, single-dose, dose-escalation phase I study in 70 healthy adults assessed both the 200 mg/mL formulation of cabotegravir in combination with recombinant human hyaluronidase PH20 (rHuPH20), as well as a new formulation of cabotegravir (CAB-ULA) administered by itself.[1] Researchers will share safety and pharmacokinetic findings from both ultra long-acting approaches and their potential for future clinical development.

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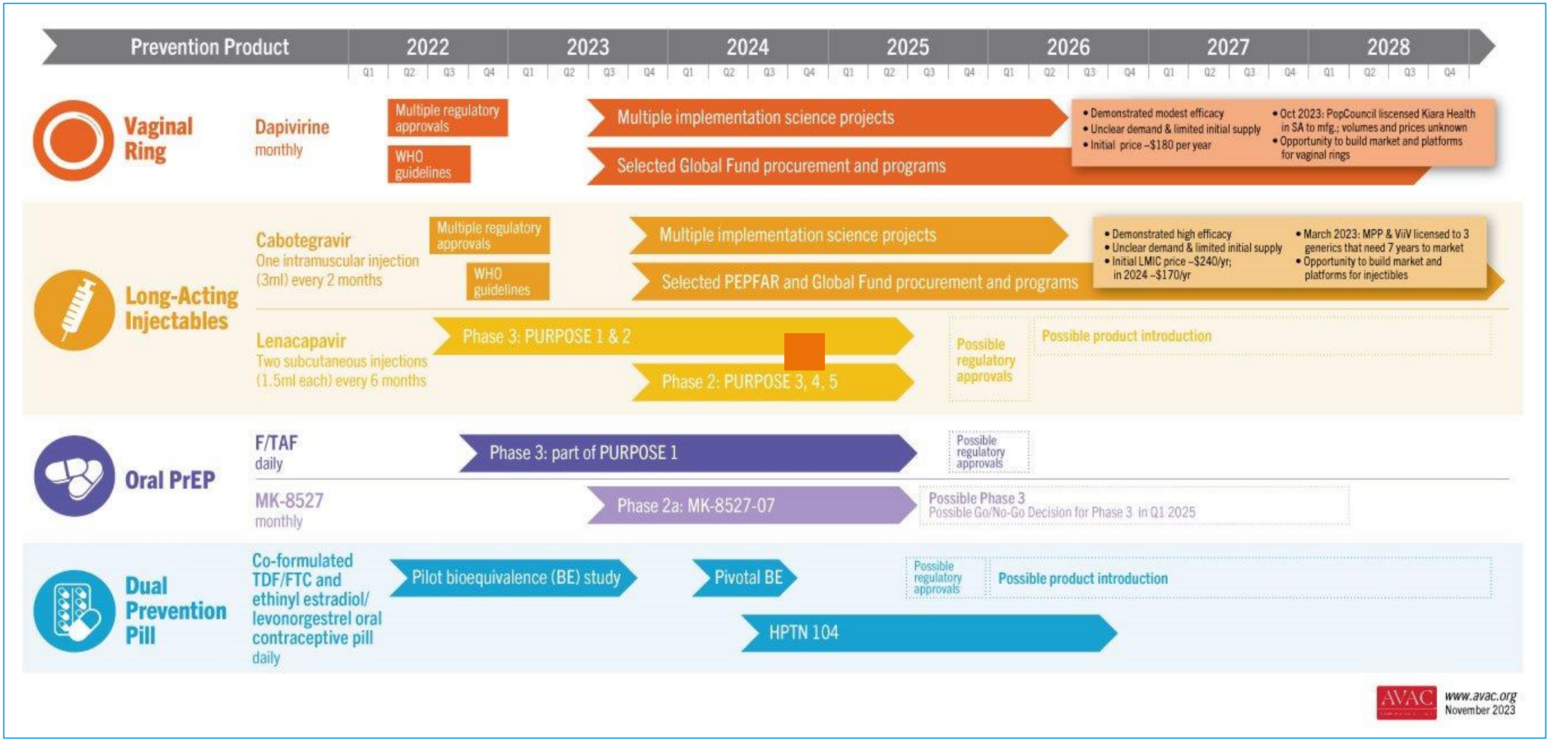
PrEP product pipeline



Defining the scope for addressing stigma and discrimination in health services

Internal WHO

- ✓ HWF
- ✓ GER
- ✓ MSD
- ✓ MCHA
- ✓ SRHR
- ✓ IHS
- ✓ TFNM

External

- ✓PLHIV networks
- ✓KP networks
- ✓Implementers
- ✓HCW professional bodies
- ✓UN partners including UNAIDS
- ✓Other Partners (LSHTM, CDC, BMGF, IAS, RTI etc)

* Note: Have expanded this informal working group to other key stakeholders since March 2023

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Technical Brief
Community and Expert Feedback

- Despite 40 years of research on S&D, still have difficulty changing views and perceptions
- Research into social & behavioral change to address S&D is still needed

Most important ways to address HIV-related stigma and discrimination

- Amplify examples of good practice
- Provide training tools and curricula to enhance medical education
- Support attention to stigma and discrimination in community led monitoring
- Provide job aid(s) and practical resources for a clinical setting

How research / brief should be used

- Guide national health policies
- Inform clinical policies and standard operating procedures
- Review and update in-service training for healthcare professionals
- Review and inform workplace policies and practices

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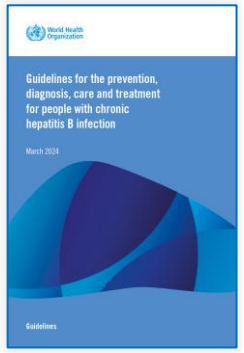
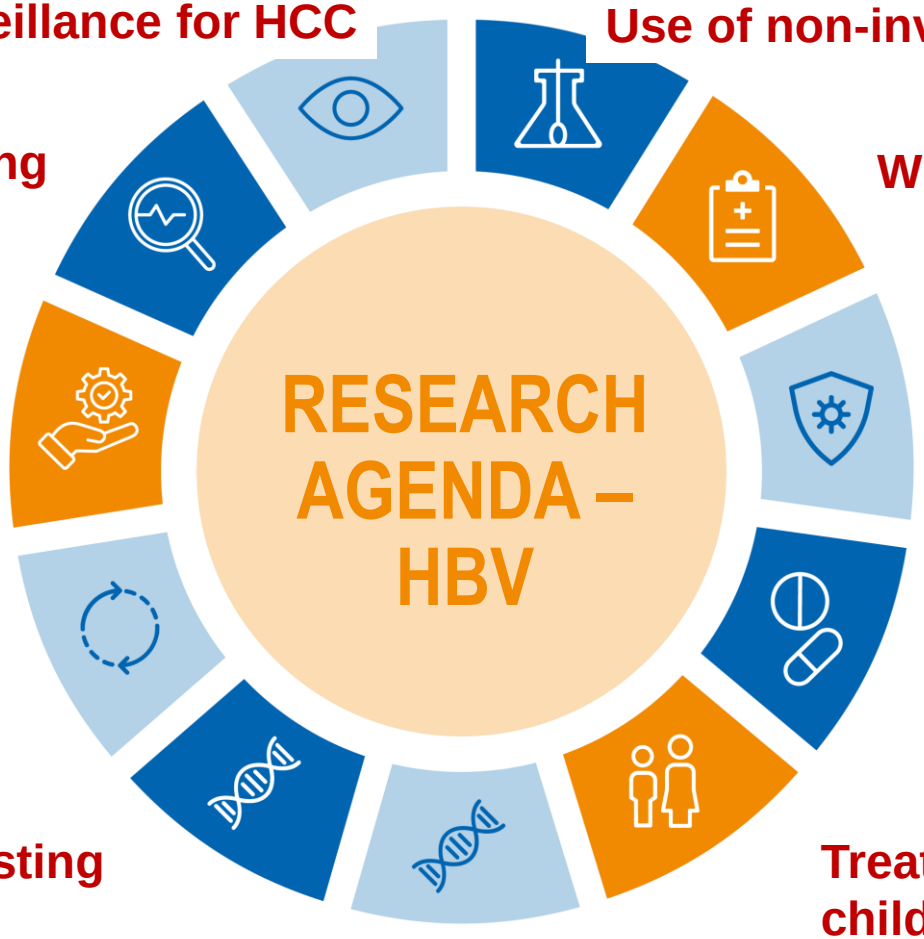
Hepatitis B – Research Agenda





Surveillance for HCC

Use of non-invasive tests

Monitoring

Who to treat

Simplified service delivery

First-line antiviral regimens

Delta testing:
Who to test and how to test

Use of antiviral prophylaxis for PMTCT

Reflex HBV DNA testing

Treatment of adolescents and children

Point-of-care HBV DNA testing

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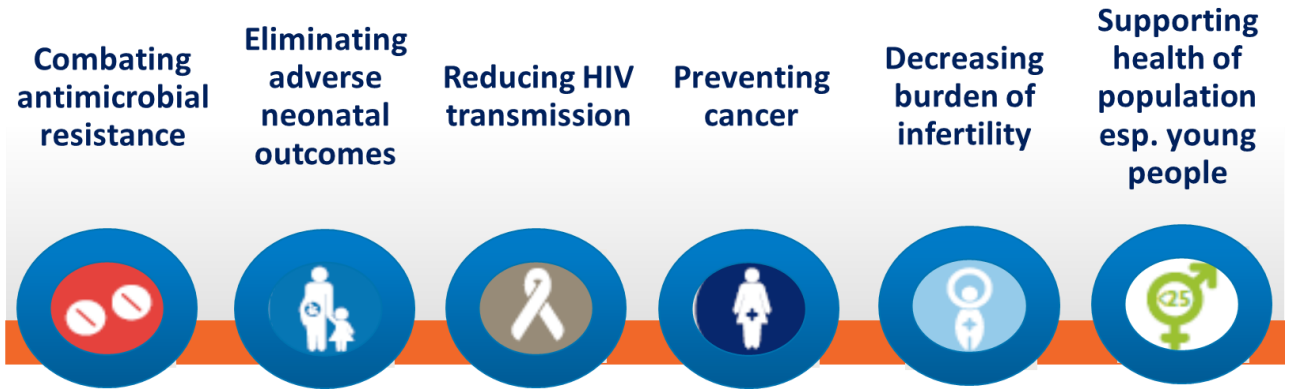
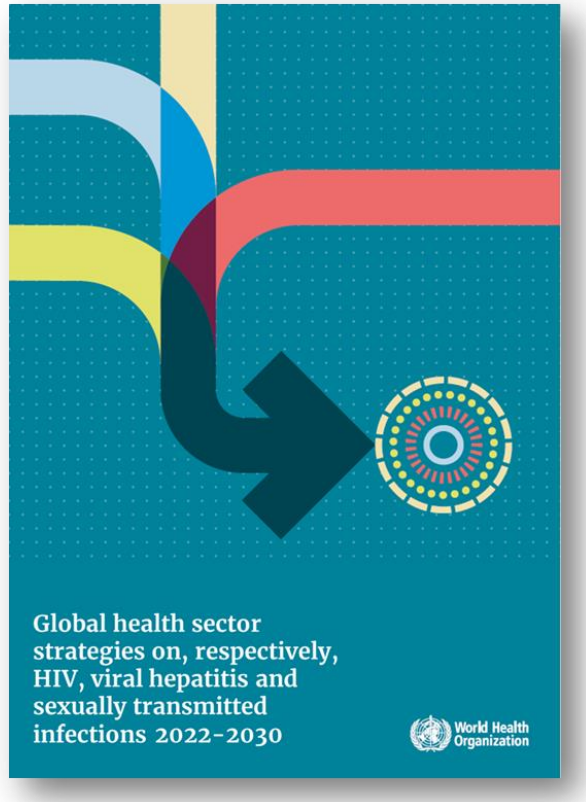
Global STI strategy challenges and new innovations

- Many challenges in reaching STI Strategy targets
- While efforts are redoubled to improve scale-up of existing interventions…





- …the **Strategy also calls for new innovations that might enhance existing efforts or address specific gaps**

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WHO global STI research prioritization

Aim: Developing a set of STI research priorities to guide future funding and focus for the most critical research:

- ✓ to address gaps in STI prevention, management, control
- ✓ to inform STI guidelines, programmes, and policies

1. Proposal of STI research areas — SURVEY 1 — Sept-Oct 2022
2. Consolidation of STI research areas — Nov 2022-Jan 2023
3. Scoring of STI research areas — SURVEY 2 — Apr-May 2023
4. Analysis and ranking — Jun-Jul 2023
5. Incorporation of final input — Jul-Oct 2023

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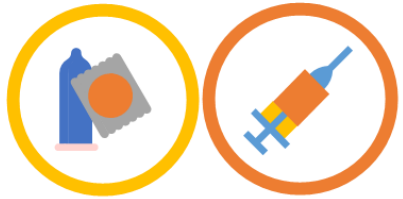
The top global STI research priorities areas by research domain

Diagnosis

- **Low-cost, rapid STI point-of-care tests**
  - Ng and Ct infection
  - Active vs past syphilis
  - AMR for Ng and Mg
- **Implementation science on STI testing**
  - Syphilis screening
  - Ng, Ct, Tv screening
  - STI symptoms
  - Self-sampling/testing
- **Multiplex platforms** for testing STI syndromes



Prevention

- **Multipurpose prevention technologies** for STIs & pregnancy +/- HIV
- **STI vaccines**
  - Ng infection
  - HSV infection
  - Syphilis
  - Ct infection
- **Communication** strategies to increase STI awareness
- **STI screening** and adverse **pregnancy** outcomes

Management

- **Therapies for AMR Ng** infection
- **Alternatives to benzathine penicillin** for syphilis
- STI **partner management** strategies
- **Management** options: congenital and other **syphilis** complications

Epidemiology

- **Prevalence and incidence of infection**
  - Syphilis
  - Ng and Ct
- STI **healthcare-seeking** behavior
- Epidemiology of **AMR** & treatment failures
- **Burden of disease outcomes** due to STIs
  - Ng/Ct, e.g. infertility
  - Syphilis outcomes

In Summary: Most urgent research priorities for WHO

HIV:

1. **Long acting antiretrovirals**: assessing the strategic use for prevention and treatment – whether injectable or oral; assure ART pipeline
2. **Advanced HIV disease**: assessment of the research and development pipeline
3. **Broadly neutralising antibodies (bNAbs)**: Possible role in treatment and prevention, and in particular in **Post-Natal Prophylaxis**
4. **HIV Vaccine & Cure research**: Horizon scanning & assessment of LMIC readiness
5. **Cohort monitoring:** HIV observational cohorts (notably https://www.iedea.org/) to assess clinical challenges in the HIV response, toxicity
6. **Implementation Science**: science of service delivery for HIV & NCD / momorbidity integration, Sustainability & Stigma & Discrimination; how to scale paediatric case finding and treatment

World Health Organization

In Summary: Most urgent research priorities for WHO

Hepatitis B, C and D:

1. Evidence of **HCV treatment in pregnancy and children** 3 years and above ; PMTCT
2. **HCV Prevention: R&D** pipeline for Hepatitis C vaccines (mRNA vaccines, nanoparticle-based delivery of HCV immunization etc.)
3. **Improved technologies for case finding and diagnosis:** HCV self-testing and integrated viral hepatitis diagnostics platforms. R&D of novel HBV biomarkers such as hepatitis B core-related antigen (HBcrAg) & HCV core antigen as a rapid diagnostics technology.
4. **Innovative therapeutics:** R&D long-acting therapies for hepatitis B and C and Hepatitis-B cure to promote elimination of viral hepatitis as a public health threat
5. **Hepatitis Delta:** Assessment of the research and development pipeline of improved testing and diagnostics option (including and RDT for HDV serology) and the emerging treatment options
6. **Timely birth dose vaccine of HBV:** implementation research & optimized formulations (including without controlled temperature chain)
7. **Biomarker surveys for hepatitis B and C as part of Country HIV impact assessment**

World Health Organization

In Summary: Most urgent research priorities for WHO

STI:

1. **R&D of new gonorrhoea treatment (End to End - development, clinical trials and early introduction)** Developed target product profile (TTP) for new gonorrhoea treatment, inputs in the Phase 3 clinical trial for Zoliflodacin as well as modeling and prevalence surveys on positioning zoliflodacin; future work (proposal to EU) on increasing access to zoliflodacin and antibiotic stewardship and monitoring patterns of AMR resistance to ceftriaxone and when to use zoliflodacin
2. STI diagnostics and new POCT for STIs – development of target product profile for POCT ; landscape analysis of STI diagnosis; facilitate development of new POCT for gonorrhoea to support antibiotic stewardship; inputs in accessing the diagnostic accuracy of new POCT for gonorrhoea; modeling and surveys to access how to position new POCT in gonorrhoeae and chlamydial infections
3. **STI vaccine –** PCC for gonorrhoea **and** HSV; work with SRH, NIH and IVB to support vaccine development.
4. **Prevalence surveys** in STIs and STI estimations

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