ANRS 0789s PRINAVIH - Information for researchers

Study of the Prevalence of Transmitted HIV-1 Resistance, Viral Diversity, and Cluster Identification in Patients at the Time of HIV-1 Diagnosis

In brief	Investigator: Dr Marie-Laure CHAIX et Pr Diane DESCAMPS
	Structure/teams : Data controller (sponsor) : INSERM-ANRS MIE - Porjet Manager : Tounes SAISI Methodology and Management Centers (IPLESP) : - Lambert ASOUMOU (Director) - Clara AVERLANT (Project Manager) - Haithem BEN KAHLA (Data Manager) - Arbnor ZENUNI (Statistician)
	Start dates : September 2025 End date of research: September 2035
	Number of participants : the total planned sample size for this study is approximately 30,060 participants
	Research status: In progress
	Pathology: HIV-1
	Promotion: Inserm - ANRS MIE
The project	The PRINAVIH study aims to evaluate the prevalence of HIV-1 transmission with at least one antiretroviral resistance mutation, to analyze viral diversity, and to identify transmission clusters among participants at the time of their diagnosis. This is a national, multicenter study involving both retrospective and prospective data collection from all patients newly diagnosed with HIV, whether at the stage of primary infection or not. The study will be offered to all virology laboratories that participated in the most recent genotyping quality control of the ANRS MIE resistance group of virology/pharmacology network. The target population includes adults (≥18 years) who are naïve to any antiretroviral treatment (except for PrEP or PEP), for whom an HIV resistance genotype is available with amplification of at least the reverse transcriptase and protease regions, and who have not opposed participation. This surveillance project aims to: • Create a database of viral sequences obtained at the management of new patients in a single database under the sponsorship of ANRS-MIE. • Correlate the viral sequences with clinical and virological data collected in an eCRF under the responsibility of ANRS-MIE.

	This study will allow real-time monitoring of the circulation of resistant viruses and the identification of transmission clusters. The results will contribute to national and European HIV resistance surveillance and provide information to guide prevention strategies, targeted testing, and rapid management of infected individuals.
Latest news	Since 1999, ANRS MIE has established a system for monitoring transmitted resistance and viral diversity in participants at the time of their primary infection (annual surveillance, PRIMO study) and in treatment-naïve participants (every 4 years, ODYSSEE study) [1]–[6]. These studies show an overall stability of transmitted resistance, an increase in viral diversity, with a marked rise in non-B viruses and recombinant forms. An analysis of transmission clusters within these studies has shown that the proportion of participants included in clusters at the time of primary infection has increased over time, reaching up to 41% of participants for the period 2014–2016 [1]–[7]. The number and magnitude of recent transmission clusters in these studies underestimate the actual number of participants affected. For example, for the CRF94 transmission cluster, only 7 participants were actually captured in the PRIMO database out of 34 participants, including 13 at the primary infection stage, composing the cluster at the end of 2016 [10]. Despite this underestimation of the true importance of clusters, 39 large transmission clusters, including 4 to 14 participants each, can be identified in the PRIMO study. However, these studies currently present certain limitations, the main one being the incomplete capture of newly diagnosed cases. While this does not compromise the conduct or accuracy of their conclusions, it does not allow (i) an exact assessment of the importance of transmission clusters, which is largely underestimated as illustrated by CRF94, nor (ii) the identification of the main sites and hotspots of transmission that could be targeted by specific interventions.
Publication references	[1] M.-L. Chaix *et al.*, « Stable prevalence of genotypic drug resistance mutations but increase in non-B virus among participants with primary HIV-1 infection in France », *AIDS Lond. Engl.*, vol. 17, n° 18, p. 2635-2643, déc. 2003, doi: 10.1097/01.aids.0000088223.55968.1a. [2] M.-L. Chaix *et al.*, « Stable frequency of HIV-1 transmitted drug resistance in participants at the time of primary infection over 1996-2006 in France », *AIDS Lond. Engl.*, vol. 23, n° 6, p. 717-724, mars 2009, doi: 10.1097/QAD.0b013e328326ca77. [3] M.-L. Chaix *et al.*, « Increasing HIV-1 non-B subtype primary infections in participants in France and effect of HIV subtypes on virological and immunological responses to combined antiretroviral therapy », *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.*, vol. 56, n° 6, p. 880-887, mars 2013, doi: 10.1093/cid/cis999. [4] P. Frange *et al.*, « HIV-1 subtype B-infected MSM may have driven the spread of transmitted resistant strains in France in 2007-12: impact on susceptibility to first-line strategies », *J. Antimicrob. Chemother.*, vol. 70, n° 7, p. 2084-2089, juill. 2015, doi: 10.1093/jac/dkv049. [5] M.-L. Chaix *et al.*, « Increasing HIV-1 non-B subtype primary infections in participants in France and effect of HIV subtypes on virological and immunological

	responses to combined antiretroviral therapy », *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.*, vol. 56, n° 6, p. 880-887, mars 2013, doi: 10.1093/cid/cis999. [6] A. Chaillon *et al.*, « Spatiotemporal dynamics of HIV-1 transmission in France (1999-2014) and impact of targeted prevention strategies », *Retrovirology*, vol. 14, n° 1, p. 15, févr. 2017, doi: 10.1186/s12977-017-0339-4. [7] B. Visseaux *et al.*, « Surveillance of HIV-1 primary infections in France from 2014 to 2016: toward stable resistance, but higher diversity, clustering and virulence? », *J. Antimicrob. Chemother.*, vol. 75, n° 1, p. 183-193, 01 2020, doi: 10.1093/jac/dkz404.
Type of study	National, multicenter, retrospective and prospective study: Non-interventional clinical research, not subject to RIPH regulations
Main objectives	The primary objective of the study is to determine the frequency of transmission of viruses carrying at least one antiretroviral resistance mutation among all participants newly diagnosed with HIV-1.
Secondary objectives	1. Determine the frequency of resistance mutations for each therapeutic class (NRTI, NNRTI, PI, INSTI). 2. Determine the prevalence of viruses carrying resistance mutations to 0, 1, 2, 3, and 4 therapeutic classes. 3. Determine the prevalence of viruses susceptible to each of the recommended first-line antiretroviral combinations and to molecules used in PrEP/PEP. 4. Identify factors associated with the transmission of antiretroviral-resistant viruses. 5. Study the dissemination dynamics of different HIV subtypes across risk groups and geographic regions. 6. Identify new recombinant forms of HIV. 7. Detect clusters and transmission “hot spots” to inform and propose targeted prevention and care actions based on observed behaviors (e.g., posters, information stands, targeted messages on dating apps), improve access to testing and adapted prevention tools, and ensure rapid care in case of diagnosed infection. 8. Alert in case of an active transmission cluster to enable more targeted testing, prevention, and care interventions, and to contribute to the adaptation of prevention policies. 9. Contribute to European HIV antiretroviral resistance surveillance. Currently, individual resistance data are sent to the ECDC in an aggregated and disconnected format, due to the lack of a single database as proposed here, making cross-analysis impossible. Moreover, French resistance studies in chronically infected participants are performed only approximately every five years, preventing regular and rigorous comparisons with European data. The individual resistance data obtained in this project may be shared, after analysis by French researchers, with the

	ECDC database of new HIV diagnoses, currently transmitted via Santé Publique France.
Inclusion criteria	• Participant (male or female) aged 18 years or older. • Participant newly diagnosed at the laboratory, for whom mandatory reporting of HIV seropositivity must be made to Santé Publique France (SPF). • Participant naïve to all antiretroviral treatments (except for PrEP and/or PEP). • Participant with an available HIV resistance genotype, with amplification of at least the reverse transcriptase and protease regions.Participant who has not opposed participation in the study.
Non-inclusion criteria	• Participant who opposes the use of their data. • Participant already receiving antiretroviral treatment.
Primary endpoints	Proportion of participants with primary infection or treatment-naïve presenting a virus carrying at least one antiretroviral resistance mutation
Secondary endpoints	1. Proportion of participants with resistance mutations specific to each therapeutic class (NRTI, NNRTI, PI, INSTI). 2. Proportion of participants with resistance mutations to 0, 1, 2, 3, or 4 therapeutic classes. 3. Proportion of participants with viruses susceptible to recommended first-line treatment regimens and to molecules used in PrEP/PEP. 4. Analysis of epidemiological, clinical, and behavioral factors associated with the transmission of resistant strains (age, sex, mode of transmission, geographic origin, etc.). 5. Identification and classification of new recombinant forms. 6. Number and geographic location of detected transmission clusters. Identification of transmission “hot spots” according to risk groups and reported behaviors. 7. Time between detection of an active cluster and implementation of testing and prevention actions. Number of new infections diagnosed following targeted interventions around a cluster. 8. Integration of individual and resistance data into the European database of new HIV diagnoses. Comparison of resistance prevalences observed in France with those of other European countries.

Contents

A - Study methodology and type of data and/or samples collected

Data and samples collected	**Biotech libraries**	**NA**
	Data	• First two letters of the last name and first letter of the first name • Date of birth (month and year) • Country of birth • Sex • Date of first positive HIV serology • Date of the sample used for genotyping • Date of viral load measurement at inclusion • Plasma HIV RNA viral load value (copies/mL) at inclusion • CD4+ T-cell count closest to the viral load measurement date • Use of PrEP at the time of HIV diagnosis and date of last administration • Use of PEP at the time of HIV diagnosis and date of last administration • Inclusion number in the PRIMO ANRS-MIE CO06 cohort (for participants included in this cohort) • SmartGene identifier number (for laboratories using SmartGene) • Nucleotide and amino acid sequences of protease, reverse transcriptase, integrase, and envelope for laboratories not using SmartGene • Viral subtype • Pharmacological measurements if resistance mutations are present

Sampling schedule :

	Inclusion S0
Non opposition	x
Critères d'éligibilité	x
Examen clinique	x
Taux de CD4	x
ARN VIH plasmatique	x
Test génotypique de résistance	x