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# Susceptibility to lenacapavir, fostemsavir and broadly neutralizing antibodies in French primary HIV-1 infected patients in 2020–2023

Marie-Laure Chaix[1,2] | Laura Terracol[1] | Marie-Laure Nere[1] | Karl Stefic[3,4] | Caroline Lascoux-Combe[5] | Victoria Manda[5] | Pierre Sellier[5] | Sarah Maylin[1] | Jean-Michel Molina[2,5] | Geoffroy Liegeon[5] | Constance Delaugerre[1,2] | Maud Salmona[1,6]

[1]Laboratoire de virologie, Hôpital Saint-Louis, APHP, Paris, France

[2]INSERM, U944, Université Paris Cité, Paris, France

[3]INSERM, U1259, Université de Tours, Tours, France

[4]Laboratoire de Virologie, Centre Hospitalier Régional Universitaire de Tours, Tours, France

[5]Department of Maladies Infectieuses, Hôpital Saint-Louis-Lariboisière, Assistance Publique Hôpitaux de Paris, Paris, France

[6]INSERM, U976 Team INSIGHT, Université Paris Cité, Paris, France

**Correspondence**
Marie-Laure Chaix, Laboratoire de virologie, Hôpital Saint-Louis, APHP, Paris, France.
Email: marie-laure.chaix@aphp.fr

## Abstract

Surveillance studies of Transmitted Drug Resistance (TDR) are crucial in tracking the evolution of HIV epidemiology. Our aim was to investigate TDR to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs), as well as to new drugs: lenacapavir, fostemsavir. Predictive sensitivity was evaluated for maraviroc and broadly neutralizing antibodies (bNAbs) (zinlirvimab and teropavimab). Between 2020 and 2023, 85 people with HIV (PWH) were diagnosed with primary HIV-1 infection (PHI). Pol and env sequences were analyzed and TDR was characterized according to the French ANRS algorithm. The genotypic-based prediction of bNAbs sensitivity was based on HIV env amino acid signatures I108, I201, F353 for teropavimab and N325, N332, H330 for zinlirvimab. TDR to NRTIs, NNRTIs, PIs and INIs was evidenced in 8.2%, 12.9%, 4.7%, and 5.9% strains, respectively. Ten viruses were CXCR4/dual mix. All viruses were susceptible to lenacapavir (100%) and 52% harbored resistance to fostemsavir. The genotypic profile was associated with a predictive positive value (PPV) > 83% of susceptibility to both teropavimab and zinlirvimab for 23 viruses (31%), while 22 (29%) had a PPV between 62% and 75%, suggesting reduced susceptibility to both bNAbs as soon as primary infection. The surveillance of TDR evidenced at the time of PHI is important with regard to new strategies for HIV patients with virological failure and global implementation of PrEP using NRTI, INI such as recently approved injectable cabotegravir, and future long-acting drugs such as lenacapavir and bNAbs.

KEYWORDS

bNAbs (broadly neutralizing antibodies, drug resistance mutations, fostemsavir, HIV-1, primary infection, lenacapavir, teropavimab, zinlirvimab

## 1 | INTRODUCTION

Rapid access to care after HIV diagnosis and the widespread use of combination ART has resulted in a substantial reduction of HIV-related morbidity and mortality. Despite these improvements, the emergence and prevalence of drug associated resistance mutations poses a significant challenge, potentially compromising the efficacy of established antiretovirals (ARVs). HIV epidemiology is constantly evolving worldwide, and regular surveillance studies allow to monitor several important faces of the epidemic: emergence of TDR, HIV genetic diversity shifts or global transmission patterns. In France and in Europe, the emergence of TDR remains stable[1–5] between 10% and 12% of new infections, with a majority of mutations associated with resistance to nucleos(t)ide reverse transcriptase inhibitor (NRTI) and non-nucleosidic reverse transcriptase inhibitor (NNRTI), thus with a potential impact on combination ART based on first generation NNRTI. Thus, TDR are a major component of sentinel national surveillance networks worldwide as its evolution may lead to virological failures and compromise prevention strategies based on pre-exposure prophylaxis (PrEP).

The development of ART with novel mechanisms of action represents a significant leap forward in our ability to control HIV infection. Among these advancements, lenacapavir (capsid inhibitor), fostemsavir (attachment inhibitor), and broadly monoclonal antibodies (bNAbs) such as zinlirvimab (10-1074-LS) and teropavimab (3BNC117-LS) emerge as promising agents, each targeting different steps of the HIV lifecycle and offering new hope for people with HIV (PWH) harboring drug-resistant strains or those in need of more potent treatment options. Lenacapavir operates through a novel mechanism by targeting the HIV-1 capsid protein, which plays a crucial role in multiple steps of the viral lifecycle, including viral assembly, disassembly, and the nuclear import of the pre-integration complex. Fostemsavir is an attachment inhibitor that targets the gp120 subunit of the viral envelope glycoprotein, preventing the initial attachment of HIV-1 to the host CD4 + T cells. Zinlirvimab and teropavimab represent a class of bNAbs that targets distinct epitopes on the HIV-1 envelope, preventing the virus from binding to and entering host cells. Their broad neutralizing capacity makes them potent candidates for both treatment and prevention strategies in HIV management.

Here we investigated the resistance patterns to traditional ART classes—NRTIs, NNRTIs, protease inhibitors (PIs), and integrase strand transfer inhibitors (INIs)—as well as to new treatments such as the capsid (CA) inhibitor lenacapavir and entry inhibitors including maraviroc, fostemsavir, and bNAbs such as zinlirvimab and teropavimab, among PWH diagnosed between 2020 and 2023 at the time of primary HIV-1 infection (PHI).

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

Between 2020 and 2023, 85 PWH diagnosed at the time of PHI (infection less than 6 months) through our infectious disease department in Saint Louis and Lariboisière hospitals in Paris were consecutively included in the ANRS-MIE-PRIMO study.[1,2] Enrollment criteria were (i) a negative or indeterminate HIV ELISA associated with a positive p24 antigenemia or detectable plasma HIV RNA, (ii) a positive HIV ELISA with a western blot or immunoblot profile compatible with ongoing seroconversion (incomplete profile with absence of antibodies to pol proteins) or (iii) a negative test for HIV antibodies within 6 months before the positive HIV serology. This study is based on this retrospective cohort, with analyses performed on plasma stored at −80° and this was a non-interventional study involving the reuse of samples taken during care. All PWH were included in Nadis (Advanced Biological Laboratories, L-2550 Luxembourg, Luxembourg), an electronic medical record system, to gather data on people with HIV (PWH) (type 1 or 2), receiving care in French public hospitals. The cohort is registered on Clinical Trial.gov (NCT02898987), and all participants provided informed consent. The study was conducted in compliance with the principles of the Declaration of Helsinki, the Public Health Code, and the European Union General Data Protection Regulation.

### 2.2 | Genotypic resistance analysis

Genotypic resistance tests for NRTIs, NNRTIs, PIs and INIs were performed on plasma samples stored at −80° and collected before initiation of antiretroviral treatment using the consensus technique of the ANRS Resistance study group (www.hivfrenchresistance.org). Our laboratory participates in the annual ANRS quality control program.[6] Resistance to drugs was reanalyzed using the 2024 French ANRS algorithm v35 (www.hivfrenchresistance.org). RT sequences were used to determine subtype using BLAST tool and COMET.[7] HIV-1 genotropism was determined using Geno2Pheno algorithm (False positive rate [FPR] 10% for all subtype).

### 2.3 | Capsid and envelope analysis

RNA was extracted on the EasyMag automated extractor (Biomerieux, France). RT-PCR were performed using the ACCESS QUICK kit RT-PCR System (Promega) for the first amplification and the Q5 Hot Start High Fidelity DNA Polymerase (NEB, United Kingdom) for the nested PCR. *GAG* gene was sequenced using the consensus technique of the ANRS Resistance study group (www.hivfrenchresistance.org). Due to the length and the variability, *env* gene encoding gp120 was amplified and sequenced in two parts. For the first part R1 (539 nucleotides covering (AA position 71 to 250 of gp120), we designed outer primers (GP120-6206F1: AGAGCAGAAGAYAGTGGMAA, GP120-7028R1: TTCTTCTGCTAGACTGCCATT) and inner primers (6436-F2: CACATG CCTGTGTACCCACAG and GP120-6974-R2: TCCATGTGTRCATTG TACTGWGC). For the second part R2 (813 nucleotides covering AA position 260 of gp120 to AA 20 of gp41), we used outer primers (Env 779 F1: ACAGTACAATGYACACATGGA, Env 1695 R1: TGTTAAATG GYAGTCTAGCAGAA) and inner primers (828-F2: TGTTAAATG GYAGTCTAGCAGAA and env-1661-R2: CCCATAGTGCTTCCTGCTGY). Sequences were aligned and compared with the HIV HXB2 reference

sequence (GenBank reference: K03455;M38432) using Geneious R9 software.

### 2.4 | Analysis of capsid at lenacapavir resistance-associated positions

For capsid (CA) sequences, the presence of mutations at the eight CA positions associated with lenacapavir resistance were investigated,[8–10] (hivfrenchresistance.org and https://hivdb.stanford.edu/dr-summary/comments/CAI) and these included L56I, N57S, M66I, Q67H/K/N, K70H/R/N/S, N74D/H/K/S, A105T/S/E and T107A/C/N/S.

### 2.5 | Analysis of gp120 at fostemsavir resistance-associated positions

For fostemsavir, the presence of mutations at the positions S375H/I/M/N/T/Y, M426L/P, M434I/K, and M475I found to be associated with resistance was investigated.[11–15]

### 2.6 | Analysis of gp120 at genotypic signature predicting teropavimab and zinlirvim susceptibility

The positive predictive value (PPV) is defined as the probability that a sample with a given *ENV* genotype (based on amino acids or glycosylation site) is sensitive using the PhenoSense mAb DNA assay (Monogram Biosciences) to the antibody when that *ENV* genotype is present. Multiposition signatures with incremental increase in PPV were selected for the two antibodies to facilitate a full-range genotypic-based susceptibility assessment.

For teropavimab, we analyzed three genotypic signatures (gp120 AA: 108, 201, and 353) which predict phenotypic susceptibility with high specificity but reduced susceptibility[16,17] if isoleucine (I) is present at position 108 or 201 and phenylalaline (F) at position 353. Absence of these three signatures had a PPV to be sensitive of 75%. The presence I201, I201 + F353 or I108 + I201 + F353 was associated to a PPV of susceptibility of 78%, 84%, and 86%.

For zinlirvimab, we analyzed three signatures (gp120 AA: 325, 330, and 332)[16] defined by an aspartate acid (D) at position 325, an asparagine (N) at position 332, favoring a potential N-glycosylation site, and a histidine (H) at position 330. Absence of these three signatures had a PPV to be sensitive of 62%. The PPV was respectively 75%, 80%, and 83% for the presence of N332, N325 + N332 and N325 + N332 + H330.[17]

### 2.7 | Statistical analysis

Statistical and descriptive analyses were conducted using the R programming language, utilizing the gtsummary package. Appropriate statistical tests were employed, including Pearson's Chi-squared test, Fisher's exact test, and the Kruskal-Wallis test. A p-value of less than 0.05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Study population

Overall, 85 PWH were included in our study between January 2021 and March 2023. General characteristics of these 85 individuals are shown in Table 1. Median age was 33 years [IQR: 28–42]. PWH were mainly men (96%) having sex with men (MSM) (*n* = 72 [85%]). Most PWH (85%) were born in France. Median CD4 cell count, and plasma HIV-1 RNA were 467 cells/mm$^3$ [IQR: 345–608] and 5.50 $\log_{10}$ copies/ml [IQR: 4.68–6.59], respectively. Eleven (13%) PWH were on PrEP at the time of PHI. Among all included PWH 42%, 25%, and 33% harbored an HIV strain belonging to subtype B, CRF02_AG or other (HIV-1 group M lineages (3 A, 3 C, 1 BG, 1 CRF01_AE, 3 CRF06cpx, 1 CRF45cpx, 1 CRF60 BC, 6 F, 2 G and 5 complex recombinants with undetermined genotype (U)) respectively.

### 3.2 | Frequency of transmitted drug resistance to INTI, INNTI, IP, and INI

To assess the percentage of transmitted mutations conferring resistance to conventional ARVs, routine genotyping resistance tests were reanalyzed with the last 2023 ANRS algorithmv35. Resistance to NRTIs was found in 8.2% (7/85) with a mutation M184 I/V in six out of the

**TABLE 1** Demographic and clinic-virological patient characteristics (*n* = 85).

| | **Total** |
|---|---|
| **N** (%) | 85 (100) |
| **Age (years)** - *median [IQR]* | 33 [28–42] |
| **Men** - *n (%)* | 82 (96) |
| **Country of birth** - *n (%)* | |
| *France* | 71 (85) |
| *Other countries* | 13 (15) |
| *Unknown* | 1 |
| **Route of transmission** - *n (%)* | |
| *MSM* | 72 (85) |
| *HTS* | 4 (5) |
| *Other/unknown* | 9 (10) |
| **VL ($\log_{10}$ copies/mL)** - *median [IQR]* | 5.50 [4.68-6.59] |
| **CD4 (cells/mm$^3$)** – *median [IQR]* | 467 [345-608] |
| **Use of PrEP**– *n (%)* **Subtype** – *n (%)* | 11 (13) |
| *B* | 36 (42) |
| *CRF02_AG* | 21 (25) |
| *Other non-B* | 28 (33) |

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; HTS, heterosexual; VL, viral load.

seven cases. Among the 11 PWH who were on PrEP at the time of diagnosis, 6 (54.5%) selected M184V/I. Resistance to NNRTIs was 12.9% (11/85) with a majority of E138A ($n = 6$), and 5.9% (5/85) to INIs with one T97A and four E157Q, respectively. For PIs, only 4.7% (4/85) PWH had resistance to atazanavir/r with a pattern of polymorphic mutations 10 V, 16E, 60E, three of them were subtype F2. Twenty-five PWH were resistant to at least one ARV from one class and only two viruses were resistant to at least one ARV from two classes (Table 2).

### 3.3 | Frequency of resistance associated mutations (RAMs) to lenacapavir

Despite the frequency of non-B subtypes, capsid gene was amplified and sequenced for all 85 viruses. Only one PWH, homo/bisexual, originating from Ivory Coast harbored a CRF02_AG virus with a T107S mutation considered as a polymorphism with no impact on lenacapavir susceptibility[18] (Table 3, Figure 1).

### 3.4 | Frequency of RAMs to fostemsavir

Among the 73 viruses sequenced in the *env* gene, 35 (48%) had no mutation (Table 3, Figure 1). Among the 38 (52%) viruses with RAMs, four harbored two mutations: 375H + 475I (CRF01_AE), 375I + 434I (CRF06cpx), 375 T + 426 L ($n = 2$, one subtype B and one recombinant B/F1). Other viruses had only one mutation: 375 T in 19 cases, 375I in one case, 426 L in three cases, 434I in seven cases and 475I in four cases. Interestingly, among

**TABLE 2** Characteristics of patients with drug resistance mutation (DRM) to at least one antiretroviral (ARV).

| ID | Age | Sex | HIV-1 RNA (copies/ml) | CD4/ mm$^3$ | Subtype | Transmission group | Country of birth | DRM to at least one ARV | Genotropism | PrEP at the time of diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 26 | M | 304000 | 466 | CRF45_cpx | MSM | Martinique | NNRTI: 138 A | R5 | NO |
| 5 | 35 | M | 116000 | 490 | CRF06 | MSM | France | NRTI: 184I | NA | YES |
| 13 | 37 | F | 5140000 | 303 | A | Heterosexual | France | NNRTI: 98 G, 101E, 181 C, 190 A | X4 | NO |
| 14 | 49 | F | 4150000 | 61 | CRF02_AG | Heterosexual | Guinea | INI: 74 I, 157Q | R5 | NO |
| 15 | 35 | M | 191000 | 432 | B | MSM | France | NRTI: 184 V | R5 | YES |
| 24 | 21 | M | 1110000 | 464 | F2 | MSM | France | IP: 10 V, 16E, 60E | R5 | NO |
| 26 | 27 | M | 1400 | 568 | CRF02_AG | MSM | France | INI: 74 I, 157Q | NA | NO |
| 33 | 27 | M | 4340000 | 9 | B | MSM | France | NNRTI: 138 A | NA | NO |
| 34 | 30 | M | 34200 | 508 | CRF02_AG | MSM | France | NNRTI: 138 A | R5 | NO |
| 36 | 41 | M | 525000 | 365 | C | NA | NA | NNRTI: 98S | R5 | NO |
| 37 | 31 | M | 980000 | 307 | B | MSM | France | INI: 157Q | R5 | NA |
| 47 | 45 | M | 10000000 | 161 | CRF02_AG | MSM | Brazil | INI: 157Q | X4 | NO |
| 48 | 29 | M | 19100 | 725 | F2 | MSM | France | IP: 10 V, 16E, 60E | X4 | NO |
| 49 | 34 | M | 66900 | 381 | B | MSM | Salvador | NRTI: 184I | R5 | YES |
| 53 | 55 | F | 77600 | 229 | Recombinant cpx | Heterosexual | France | IP: 10 V, 16E, 60E + NNRTI: 103 N | R5 | NO |
| 55 | 25 | M | 4260000 | 635 | F2 | MSM | France | IP: 10 V, 16E, 60E | R5 | NO |
| 60 | 26 | M | 1230 | 997 | CRF02_AG | MSM | France | NNRTI: 138 A | X4 | NO |
| 68 | 46 | M | 48100 | 690 | B | MSM | France | NNRTI: 138 A | R5 | NO |
| 69 | 31 | M | 37300 | 903 | CRF06 | MSM | Italy | NRTI: 184I | R5 | YES |
| 72 | 64 | M | 145000 | 607 | CRF45_cpx | MSM | France | NNRTI: 138 A | R5 | NO |
| 73 | 26 | M | 433 | 1113 | B | MSM | France | NNRTI: 190E | R5 | NO |
| 75 | 39 | M | 15300 | 725 | B | MSM | Martinique | NRTI: 184 V | R5 | YES |
| 81 | 44 | M | 8640000 | 307 | B | MSM | France | NRTI: 215E + INI: 97 A | R5 | NO |
| 83 | 30 | M | 6930 | 608 | B | MSM | France | NRTI: 184 V | X4 | YES |
| 85 | 25 | M | 16300 | 1051 | CRF02_AG | MSM | France | NNRTI: 138 A | NA | NO |

*Note*: DRM reported are those associated with resistance to protease inhibitors, reverse transcriptase inhibitors and integrase inhibitors.
Abbreviations: F, female; M, male; MSM, men who have sex with men; NA, not available.

**TABLE 3** Frequency of resistance to lenacapavir, fostemsavir and susceptibility to teropavimab, zinlivirmab and maraviroc according to subtype B, CRF02_AG or another non-B subtype.

| Subtype | B *n* = 36 | CRF02_AG *n* = 22 | Other non-B *n* = 27 | *p*-value[a] |
|---|---|---|---|---|
| *Lenacapavir (n, %)* | | | | |
| Resistance | 0 (0%) | 0 (0%) | 0 (0%) | |
| No resistance | 36 (100%) | 22 (100%) | 27 (100%) | |
| *Teropavimab (n, %)* | | | | 0.10 |
| No signature or 1 mutation[b] | 16 (48%) | 4 (21%) | 12 (50%) | |
| 2[c] or 3 mutations[d] | 17 (52%) | 15 (79%) | 12 (50%) | |
| Unknown | 3 | 3 | 3 | |
| *Zinlirvimab (n, %)* | | | | 0.3 |
| No signature or 1 mutation[e] | 18 (56%) | 7 (37%) | 14 (58%) | |
| 2[f] or 3 mutations[g] | 14 (44%) | 12 (63%) | 10 (42%) | |
| Unknown | 4 | 3 | 3 | |
| *Fostemsavir (n, %)* | | | | <0.001 |
| Resistance | 25 (74%) | 9 (50%) | 4 (19%) | |
| No resistance | 9 (26%) | 9 (50%) | 17 (81%) | |
| Unknown | 2 | 4 | 6 | |
| *Tropism (n, %)* | | | | >0.9 |
| R5 | 26 (87%) | 15 (88%) | 19 (83%) | |
| R5/X4 | 4 (13%) | 2 (12%) | 4 (17%) | |
| Unknown | 6 | 5 | 4 | |

[a]Fisher's exact test; Pearson's Chi-squared test.
[b]I201.
[c]I201 + F353.
[d]I108 + I201 + F353.
[e]N332.
[f]N332 + D325.
[g]N332 + D325 + H330.

the 34 subtype B with available sequences, 25 (74%) were resistant to fostemsavir. Among the 18 CRF02_AG, 9 (50%) had fostemsavir RAMs. Among the 21 other non-B subtype, only 4 (19%) harbored resistant mutations (1 CRF01_AE, 1 CRF06cpx, 1 B/F1 and 1U), three of them with two RAMs. Analysis of fostemsavir resistance according to subtype revealed that subtype B had significantly more RAMs compared to non-B subtypes (*p* value < 0.001) (Table 3). Frequency of 375 T mutation was slightly higher in subtype B compared to non-B subtypes (38% (13/34) vs. 23% (9/39), *p* = 0.2).

## 3.5 | Suscpetibility to maraviroc

Among the 70 sequences available, 60 (86%) had a CCR5 genotropism (Figure 1). Ten (14%) viruses were CXCR4 or dual mix CCR5/CXCR4 with a FPR ranging between 1.70% and 7.8%. No association was found between fostemsavir resistance and susceptibility to maraviroc (*p* = 0.77 Fisher's exact test).

## 3.6 | Genotypic assessment for bNAbs

Among the 85 PWH, we obtained 76 sequences to predict the susceptibility to teropavimab (3BNC117-LS) and 75 sequences for zinlirvimab (10-1074-LS). For ease of interpretation, we grouped sequences presenting either one of the two phenotypes with the highest susceptibility PPV. For teropavimab, consistent with previous data,[16,17] I201, F353, and I108 in the HIV *env* were identified as single important positions for the prediction of suceptibility (Figure 1). Among the 76 viruses, 44 (58%) presented the highest PPV with the presence of I108, I201, and F353 (*n* = 42) or the association of I201 and F353 (*n* = 2), while 24 (32%) presented a single I201 with a PPV of 78%. Eight (10%) out of the 76 viruses had no signature mutations, associated with the lowest PPV of 75%.

For zinlirvimab, we evaluated the presence of a potential N-glycosylation site N-X-S/T in position 332 or the presence of D325 or H330. Among the 75 viruses, 36 (48%) presented a susceptibility PPV > 80% with the presence of combined N332, D325 and F353 (*n* = 35), or with the association of N332 and D325 (*n* = 1), while 11 (15%) presented only the N332 signature with a PPV of 75%. Twenty-eight (38%) out of the 75 viruses had no signature mutation with a PPV of 62%.

A total of 23 viruses (31%) had a PPV >83% for both teropavimab and zinlirvimab, which may suggest that they had good susceptibility to both monoclonal antibodies. Twenty-two viruses (29%) had a PPV between 62% and 75%, suggesting reduced susceptibility to both monoclonal antibodies as soon as primary infection. No correlation was found between subtype B, CRF02_AG and other non-B subtypes (Table 3).

## 3.7 | Cross resistance between entry inhibitors and monoclonal antibodies

No cross resistance was found between fostemsavir, maraviroc and the two monoclonal antibodies. However, we found a significant association between the presence of the 375 T mutation, conferring resistance to fostemsavir, and a lower positive predictive value for zinlirvimab (*p* = 0.024) (Table 4).

# 4 | DISCUSSION

To the best of our knowledge, this is the first report of resistance to ARV available in France for PWH detected at the time of primary infection. We analyzed TDR to NRTI, NNRTI, PI, and INI. In addition,

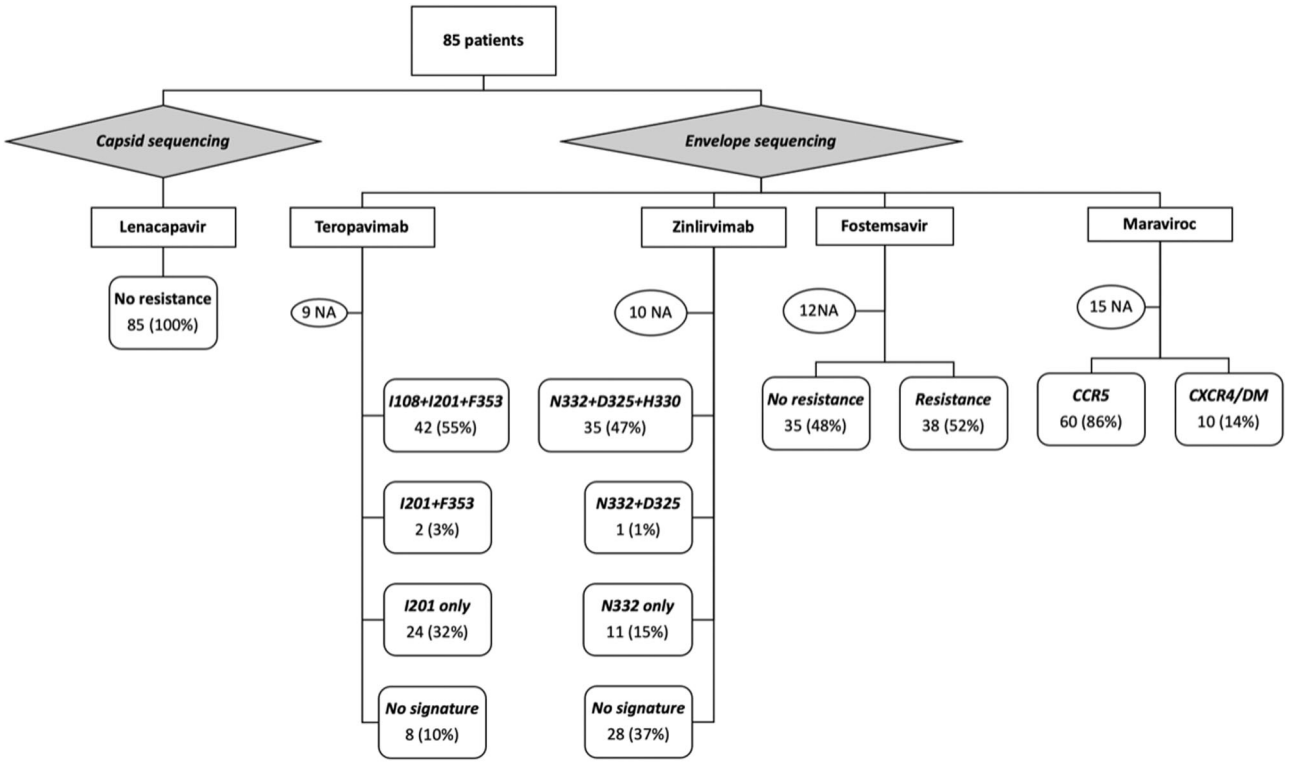


**FIGURE 1** Flow chart describing sequences of the capsid and the envelope for the 85 primary infected PWH. NA, not available.

**TABLE 4** Frequency of 375 T mutation according to monoclonal antibodies (teropavimab and zinlirvimab) and entry inhibitors (fostemsavir and maraviroc).

| 375 T mutation | No *n* = 51 | Yes *n* = 22 | *p*-value[a] |
|---|---|---|---|
| ***Teropavimab, n, %*** | | | 0.073 |
| 0 or 1 mutation | 25 (50) | 6 (27) | |
| 2 or 3 mutations | 25 (50) | 16 (73) | |
| Unknown | 1 | 0 | |
| ***Zinlirvimab, n, %*** | | | 0.024 |
| 0 or 1 mutation | 21 (42) | 15 (71) | |
| 2 or 3 mutations | 29 (58) | 6 (29) | |
| Unknown | 1 | 1 | |
| ***Fostemsavir, n, %*** | | | <0.001 |
| Resistance | 16 (31) | 22 (100) | |
| No resistance | 35 (69) | 0 (0) | |
| ***Genotropism, n, %*** | | | 0.4 |
| CCR5 | 40 (85) | 18 (95) | |
| CCR5/CXCR4 | 7 (15) | 1 (5) | |
| Unknown | 4 | 3 | |

[a]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test.

we analyzed resistance to maraviroc, to new compounds such as fostemsavir, lenacapavir and predictive susceptibility to two bNAbs (teropavimab and zinlirvimab). Among 85 PHI diagnosed in Paris in two sites from 2020 to 2023, overall TDR prevalence to at least one ARV from each usual class was 8.2% to NRTIs, 12.9% to NNRTIs, 5.9% to INIs and 4.7% to PIs. These prevalences are stable compared to previous survey in France in 2014–2016 [1] and in line with recent epidemiological European studies in PHI or naive PWH that reported TDR prevalence around 10%.[4,5]

Despite a high diversity, all primary infected PWH had a virus sensitive to lenacapavir, which guarantees its efficacy across a wide range of HIV-1 subtypes. This is concordant with the low prevalence of lenacapavir RAMs ( < 1%) previously described among ARV-naïve individuals and treatment-experienced PWH.[9] We identified one polymorphism at position 107 (T107S) in a CRF02_AG virus which is considered as a common polymorphism that occurs in previously untreated individuals (HIVdb Stanford). Nka et al., who evaluated lenacapavir RAMs according to clades among 2031 ARV-naïve individuals, showed an overall prevalence of 0.14% (0.05–0.44).[9] Of note, lenacapavir RAM with the highest variability was T107 (5.22%) and one subtype B virus harbored a T107S.[9] In a sub-study of the CAPELLA trial, nine PWH selected capsid RAMs.[18] Among them, only one had a T107S with no impact on lenacapavir susceptibility as the fold-change was 1.3 compared to wild type.

Our results confirm that TDR might not be of concern for the use of lenacapavir as PrEP.

As an attachment inhibitor, fostemsavir is active against CCR5-, CXCR4- and dual-tropic envelopes and against almost all HIV-1 subtypes tested, except for circulating recombinant form (CRF) 01_AE and group O viruses.[19–21] But the significant variability of HIV gp120 might be responsible for the natural emergence of substitutions at positions known to be associated with resistance to fostemsavir.[11] Previous studies on the susceptibility of clinical isolates in PBMCs to temsavir [22] showed that each subtype, and the population as a whole, exhibited a wide range of susceptibilities to temsavir. The presence of polymorphisms at AA positions 375, 426, 434, and 475 was evidenced in a small number of clinical isolates. Such mutations are known to alter the susceptibility of envelopes to temsavir.[11] As previously described, we found a double mutant (475I + 375H) in the only CRF01_AE of our study. As described by Zhou et al. mutation 426 L confers a reduction in susceptibility to fostemsavir with an $IC_{50}$ > 100 nM and an $IC_{50}$ > 10000 if an additional 375 T was selected.[11] This double mutant was found in a subtype B and a recombinant B/F1. For 434I or 475I substitutions, the fold change of the $IC_{50}$ was 59 and 9, respectively. Ray et al. reported a lack of virological response with a 8-day-course monotherapy of fostemsavir with the pattern 375 M + 434I.[14] In keeping with previous studies, 375 T was the most frequent AA substitutions but we find a higher frequency in subtype B (38% vs. 28.4%[23] and 17.7%[24]). The difference in prevalence between these studies may be due to the number of PWH included (34 in our study, 109 in Soulie et al. while Bouba et al. analyzed 1197 sequences from Los Alamos).[23,24] Furthermore, these three studies were not carried out at the same time at all. We included PWH infected between 2020 and 2023 while Soulie et al. included PWH infected before 2012.[23] Bouba et al. analyzed env sequences included in the Los Alamos database before 2019.[24] Neither of these two studies knows the duration of infection of PWH. As previously described, we cannot exclude a clear continuous and progressive enhanced resistance of HIV-1 to neutralization over time, providing evidence for an ongoing adaptation of the HIV-1 species to the humoral immunity of the human hosts over the course of the epidemic.[25] The contribution of S375 to fostemsavir resistance is controversial; although this mutation has appeared to contribute to phenotypic resistance to fostemsavir in some non-responders.[21,22] Moreover, in the BRIGHTE study, a virus with a 375 T had a baseline fold change at 16 which increased to >3300 at week 108 with an additional M426L.[26] Lataillade et al. described a range of $IC_{50}$ of 0.09 to 54 nM in case of 375 T at screening but a PWH with a baseline at a FC of 1.24 had a virological failure at week 40 with an additional 426 L and a FC of 547.[13] The presence of the 375 T mutation, even if it does not have a strong impact on susceptibility to fostemsavir, may possibly promote the selection of other mutations, thus making the virus more resistant.

For maraviroc, we found 14% of CXCR4 or dual mix-virus genotropism which is in line with previous studies in PHI PWH.[1] We found a slight increase of CXCR4 or dual mix-virus with DRM (5/10, 50%) compared to CCR5 virus with DRM (16/60, 27%) but this was not significant ($p = 0.2$).

Passive immunization is being considered with monoclonal antibodies that can neutralize a wide variety of HIV strains, known as bNAbs.[27,28] Across all bNAb clinical trials to date, treatment with one single bNAb was associated with the emergence of antibody-resistant viral variants.[29–33] To counteract escape mutations, recent trials have evolved to combination of bNAbs targeting different vulnerability sites on the envelope trimer such as the CD4-binding site and V3 glycan supersite. 3BNC117-LS (teropavimab), and 10-1074-LS, (zinlirvimab,) are representants of these two classes with the most advanced clinical data to date, LS being a Fc-modified version of each bNAbs with prolonged half-life. Indeed, several reports have indicated that this bNAbs combination was well tolerated and more effective in suppressing viremia than either of the antibodies alone.[34–37] Infusions of teropavimab and zinlirvimab during analytic treatment interruption maintained HIV-1 viral suppression in most participants with a strain that was susceptible to both teropavimab and zinlirvimab for up to 6 months in the study with the longest duration of repeated infusions.[37]

In early-stage clinical trials, the importance of screening for virus susceptibility to bNAbs has been evident, even in people who initiated ART during primary infection (i.e., low diversity viral reservoirs). No standard screening method exists to evaluate whether a viral population from a person living with HIV is sensitive to bNAbs. Several approaches have been proposed, but in general, a sequencing-based assessment would be preferred because of shorter turnaround and less laboratory requirements than a phenotypic-based assessment, and several genotyping-based assays have been used retrospectively to monitor pre-existing resistance.[29,30,32,33,36] Sequence predictions were, however, only used for zinlirvimab (a V3 glycan bNAb with well characterized escape mutations), as susceptibility to teropavimab (a CD4bs bNAb with many context-dependent escape mutations) is more complex.[29,31]

Zinlirvimab is an HIV Env V3 loop-targeting bNAb that interacts with the glycan attached on the potential N-glycosylation site (PNGS) at position 332 and binds the underlying 324 GDIR 327 motif [31,38–40] which mediates CCR5 binding. The clinical significance of this amino acid positions was demonstrated by Caskey et al.,[31] who observed that the two out of 19 PWH who had N332T and D325E mutations in 100% of their preinfusion plasma viruses, did not respond to zinlirvimab monotherapy. Sok et al. showed that the absence of the glycan on position 332 is associated with higher frequency of mutation at D325, R327, or H330 residues, which might affect bNAb neutralization.[39]

In our study of primary infected PWH, we reported thirty-six out of the 75 (48%) viruses presenting a PPV > 80% to be susceptible to zinlirvimab. In 2019, Mendoza et al. reported that 71% of pre-screened HIV-1-infected individuals on ART had 71% of susceptibility to zinlirvimab using phenotypic TZM-bl neutralization.[36] In a previous study on French primary infected PWH with subtype B viruses, 75% had a sensitive profile while only 17.5% had no signature,[25] which may be a consequence of HIV adaptation to immune system.[25,41] These findings raise concern of a growing resistance to this bNAb.

For teropavimab, in line with the complexity of the epitope for the class of CD4 binding site antibodies, a large set of single positions in the HIV env - that are important for susceptibility—was identified, including the previously described E102, I108, I201, A281, Y318, and F353.[17] Assembling multi-position HIV env signatures by combination of the single positions allows to generate HIV env signatures with PPVs for sucpetibility to teropavimab for subtype B viruses from 78% to 93%. With amino acids positions I108, I201 and F353, Selzer et al. reported PPV between 78% and 86%. In our study, we described 44 out of 76 (58%) viruses who presented the best PPV > 84% with the presence of at least I201 and F353. This is in line with Mendoza et al. who reported that 64% of the outgrowth viruses were sensitive to teropavimab.[36]

Regarding the bNAb combination, 33 (31%) strains had a PPV > 83% for teropavimab and zinlirvimab, which may suggest that they had good susceptibility to both monoclonal antibodies. Conversely, 22 viruses (29%) had a PPV between 62% and 75%, suggesting reduced susceptibility to both monoclonal antibodies as soon as primary infection. We did not find any difference between B and non-B subtypes. However, it is important to note that these predictions were primarily based on in vitro data with subtype B viruses, thus the result might vary with other subtypes due to genetic variability. In addition, the prediction used had a high PPV, and the absence of genotypic signature does not necessarily indicate resistance meaning that bNAbs may still be effective in that case. The generated data can help guide the usage of these antiviral agents in future clinical trials, including trial design related to target population and inclusion criteria. But more data are needed to improve the correlation of genotypic signatures, in vitro susceptibility and clinical efficacy of bNAbs, especially regarding non-B subtypes.

The surveillance of TDR found in PHI is important considering the global implementation of PrEP using NRTI but also INI with recent approval of injectable cabotegravir, and future long-acting drugs such as lenacapavir and bNAbs. While the prevalence of NRTI, NNRTI, INI and PI RAMs seems stable in European surveys, there has been reports of increasing resistance to bNAbs over time due to the natural adaptation of HIV-1 to human humoral response and genetic diversity.[41,42] This emphasizes the need to updated surveillance data on in vitro susceptibility to bNAbs of circulating strains.

Moreover, subcutaneous lenacapavir combined with teropavimab and zinlirvimab might provide a complete regimen with dosing every 6 months. In a phase 1b study, people with bNAb-sensitive HIV-1 who were virologically suppressed and on stable ART for at least 2 years were able to replace their baseline oral daily ART with the long-acting combination of subcutaneous lenacapavir, intravenous teropavimab, and one of two doses of intravenous zinlirvimab and maintain viral suppression for at least 26 weeks after one administration of the triple combination.[43] This study provided proof-of-concept that lenacapavir, teropavimab, and zinlirvimab could provide long-acting ART with twice yearly dosing for appropriately selected people with HIV. The efficacy and safety results support further clinical development of this combination that might provide an option for people who prefer less frequent dosing, have adherence challenges, suffer from stigma associated with daily oral pills, or are experiencing side-effects with current ART options.

## 5 | CONCLUSION

In conclusion, the rate of NRTI, NNRTI, IP, and INI resistance mutations in primary infected subjects remained stable in France. Despite a high diversity, all PWH were sensitive virus to lenacapavir. Thirty-eight (52%) viruses had a reduced susceptibility to fostemsavir. Twenty-three viruses (31%) had a PPV > 83% for both teropavimab and zinlirvimab, which may suggest that they had good suscpetibility to the two bNAbs. The surveillance of TDR found in PHI is important with regard to new strategies for HIV PWH with virological failure and global implementation of PrEP using NRTI but also INI with the recent approval of injectable cabotegravir, and future long-acting drugs such as lenacapavir and bNAbs.

## AUTHOR CONTRIBUTIONS

**Laura Terracol:** Investigation, formal analysis, writing original draft, review and editing. **Marie-Laure Nere:** Investigation, formal analysis, data curation. **Karl Stefic:** Formal analysis, writing—review and editing. **Caroline Lascoux-Combe:** Investigation, writing—review and editing. **Pierre Sellier**: Investigation, writing—review and editing. **Sarah Maylin:** Investigation, writing—review and editing. **Jean-Michel Molina**: Investigation, writing—review and editing. **Geoffroy Liegeon**: Investigation, writing—review and editing. **Constance Delaugerre**: Conceptualization, Investigation, writing—review and editing. **Marie-Laure Chaix**: Conceptualization, resources, formal analysis, supervision, writing original draft, writing—review and editing. **Maud Salmona:** Conceptualization, data curation, statistic, formal analysis, supervision, writing—review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Karl Stefic* http://orcid.org/0000-0002-9686-9194
*Sarah Maylin* http://orcid.org/0000-0002-0991-4381
*Maud Salmona* http://orcid.org/0000-0001-7985-6132

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