Lenacapavir-associated drug resistance: implications for scaling up long-acting HIV pre-exposure prophylaxis

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Although drug resistance could emerge if lenacapavir is initiated during undiagnosed acute infection or if infection occurs during the drug's pharmacokinetic tail, these cases will not compromise the effectiveness of WHO-recommended therapies, as there is no cross-resistance between lenacapavir and other licensed antiretroviral drugs. Lenacapavir pre-exposure prophylaxis (PrEP) is also unlikely to drive population-level lenacapavir resistance given the rarity of breakthrough infections and the reduced replication capacity of most lenacapavir-resistant variants, which most likely reduces their transmission potential. Conversely, the risk of acquiring lenacapavir-resistant HIV-1 while receiving lenacapavir PrEP is likely to remain extremely low, as lenacapavir-associated drug-resistance mutations are rare among individuals without previous lenacapavir exposure, and widespread use of lenacapavir-based regimens remains years away. Nonetheless, as the number of lenacapavir PrEP programmes increase, surveillance for emerging lenacapavir resistance should also be implemented.

Introduction

WHO estimates that approximately 40 million people were living with HIV in 2023, with 1·3 million people newly acquiring HIV that year.[1] These new infections were estimated to be globally distributed across the six WHO regions as follows: 640 000 people in Africa, 160 000 in the Americas, 160 000 in Europe, 140 000 in the Western Pacific, 120 000 in South-East Asia, and 67 000 in the Eastern Mediterranean. To end HIV as a public health threat, UNAIDS adopted 95-95-95 targets for HIV testing, treatment, and viral suppression in 2021, and established the target of 21·2 million people at substantial risk of HIV using pre-exposure prophylaxis (PrEP) by 2025.[2]

Oral PrEP substantially reduces the risk of acquiring HIV-1, with an estimated 99% risk reduction for sexual transmission when used as recommended.[3] Tenofovir disoproxil fumarate in combination with emtricitabine is highly effective as PrEP across diverse populations. However, the global uptake of PrEP remains far below target, with only 3·5 million people using PrEP at least once in 2023.[2] Moreover, adherence to PrEP, which is essential for effectiveness, remains a major challenge.[3]

Advances in long-acting PrEP offer a promising alternative to increase adherence. In 2021, the HPTN-083 and HPTN-084 trials[4,5] showed that intramuscular injection of long-acting cabotegravir every 2 months was more effective than tenofovir disoproxil fumarate–emtricitabine in preventing HIV infection in populations at high-risk, at least partly due to poor adherence to tenofovir disoproxil fumarate–emtricitabine. In 2024, the PURPOSE-1 and PURPOSE-2 trials[6,7] evaluated the efficacy of the novel capsid inhibitor lenacapavir, a long-acting drug administered every six months via subcutaneous injection. In PURPOSE-1—which enrolled adolescent girls and young women in South Africa and Uganda—lenacapavir recipients had an HIV-1 acquisition rate of 0 per 100 person-years (95% CI 0·00–0·19; p<0·001), compared with 1·69 per 100 person-years for those receiving tenofovir disoproxil fumarate–emtricitabine (95% CI 0·96–2·74; p<0·001).[6] Similarly, in PURPOSE-2—which enrolled men who have sex with men, transgender women, transgender men, and non-binary people—lenacapavir recipients had an HIV-1 acquisition rate of 0·1 per 100 person-years (95% CI 0·01–0·37; p=0·002), which was significantly lower than the 0·93 per 100 person-years observed in the tenofovir disoproxil fumarate–emtricitabine group (95% CI 0·43–1·77; p=0·002).[7] A phase 1 study in people without HIV has shown that an intramuscular lenacapavir formulation, given once yearly, maintains plasma drug concentrations that exceed those observed with subcutaneous injections every 6 months.[8]

Although both lenacapavir and the long-acting formulation of cabotegravir have been shown to be safe and effective PrEP products, lenacapavir offers several advantages over cabotegravir from a public health perspective. First, and most importantly, individuals who develop virological breakthrough while receiving long-acting injectable cabotegravir often acquire integrase strand transfer inhibitor (INSTI)-associated drug-resistance mutations that confer cross-resistance to dolutegravir, the mainstay of current first-line antiretroviral therapy (ART). In HPTN-083,[4] ten of 16 individuals with a first positive HIV-1 test within 6 months of receiving long-acting injectable cabotegravir had a major dolutegravir-associated resistance mutation.[9] By contrast, individuals who develop virological breakthrough and capsid inhibitor resistance while receiving lenacapavir PrEP do not develop cross-resistance to any of the current WHO-recommended ART regimens. Second, lenacapavir's twice-yearly subcutaneous injections require fewer resources and reduce the risk of administration errors compared with the intramuscular injections required for cabotegravir every 2 months.

Long-acting PrEP (in any form), however, is associated with logistical implementation challenges. Moreover,

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despite the marked efficacy of long-acting PrEP, the risk of virological breakthrough and emergent drug resistance is unlikely to be completely eliminated. In this Viewpoint, we review what is known about lenacapavir-associated drug resistance and the significance of this knowledge for scaling up of lenacapavir PrEP, particularly in resource-limited settings.

Lenacapavir resistance

Lenacapavir inhibits HIV-1 replication by disrupting the assembly and disassembly of the viral capsid. The capsid assembles into a cone-shaped core of approximately 250 hexamers and 12 pentamers. Lenacapavir binds to a conserved interface between capsid monomers, interfering with protein–protein interactions crucial to both early and late stages of virus replication.[10] During the early stages of viral replication, the core facilitates reverse transcription, uncoating, and nuclear import of viral DNA. During late stages of replication, the capsid subunits participate in viral assembly and maturation. The inhibition of the early viral replication processes by lenacapavir likely underlies its effectiveness as a PrEP agent by preventing viral integration into host DNA, therefore blocking established infection. Lenacapavir is active at subnanomolar concentrations against all HIV-1 subtypes and shows no cross-resistance with other approved antiretroviral drugs.[10]

Mutations at seven positions have been identified, either through in vitro passage experiments or among the approximately 20 patients who did not attain an undetectable viral load when receiving a lenacapavir-containing regimen:[7,10–14] Leu56Ile; Met66Ile; Gln67His, Gln67Lys, or Gln67Asn; Lys70His, Lys70Asn, Lys70Arg, or Lys70Ser; Asn74Asp, Asn74His, Asn74Lys, or Asn74Ser; Ala105Thr or Ala105Ser; and Thr107Asn, Thr107Ala, or Thr107Cys (table 1). Among these mutations, Met66Ile, Gln67His, and Asn74Asp are the most commonly observed lenacapavir-associated resistance mutations and can occur alone or in combination with other lenacapavir-associated resistance mutations. Conversely, mutations at codon positions 70, 105, and 107 have only been identified in combination with other lenacapavir-associated resistance mutations, although Lys70His and Lys70Asn alone confer marked reductions in susceptibility (table 2). Leu56Ile has only been selected in vitro.[10]

Met66Ile is associated with over 1000-fold reduction in lenacapavir susceptibility and a reduction to 1–5% in replication capacity of wild-type viruses (table 2).[10,14–16] High-resolution x-ray structure of capsids containing Met66Ile has shown that this mutation induces steric hindrance to lenacapavir, substantially reducing its binding affinity.[17] Analysis of replication intermediates found that Met66Ile reduces HIV-1 replication capacity by impairing nuclear import.[17] The CAPELLA trial[11] evaluated viral load changes in participants with multidrug-resistant HIV-1 who received lenacapavir with an optimised background antiretroviral regimen. Met66Ile usually emerged initially as a standalone mutation;[11,14] however, at later timepoints, Met66Ile was consistently accompanied by additional lenacapavir-associated resistance mutations that, in some cases, partially increased viral replication capacity up to 24% (table 1).[14]

Gln67His alone is associated with a six-fold reduction in lenacapavir susceptibility as a result of reduced binding affinity,[18] resulting in no significant reduction in replication capacity.[10,14–16] Gln67His has been reported in combination with each of the other lenacapavir-associated resistance mutations and, in this context, might be associated with a more than hundred-fold reduction in susceptibility (table 2).[10,14–16] Gln67Lys and Gln67Asn, both of which have been reported only in combination with other mutations, have not been studied for their individual effects on lenacapavir susceptibility.

	Type of lecanapavir-based therapy	Drug-resistance mutation pattern*
Kelley et al (2025; PURPOSE-2)[7]	Pre-exposure prophylaxis	Asn74Asp (week 9); Asn74Asp (week 22)
Gupta et al (2023; CALIBRATE)[12]	Tenofovir alafenamide, emtricitabine, and lenacapavir	Gln67His (week 54); Gln67His and Lys70Arg (week 10)
Margot et al (2025; CAPELLA)[14]	Heavily treated individuals receiving a health-care provider optimised background antiretroviral therapy regimen	Met66Met/Ile (week 4) followed by Met66Ile and Ala105Thr (week 26); Met66Met/Ile, Gln67Gln/His/Lys/Asn, Lys70Lys/Arg, and Thr107Thr/Cys (week 4); Met66Ile and Thr107Ala (week 4); Met66Met/Ile and Lys70Lys/Asn/Arg/Ser (week 4) followed by Lys70Asn/Ser and Asn74Asn/His (week 10); Gln67His and Lys70Arg (week 4); Met66Ile, Asn74Asp, and Ala105Thr (week 10) followed by Met66Ile, Gln67Gln/His, Asn74Asp, and Ala105Thr (week 22); Lys70His, Ala105Ala/Ser/Thr, and Thr107Thr/Asn (week 10) followed by Gln67Lys and Lys70His (week 52); Met66Ile (week 26) followed by Met66Ile, Asn74Asp, and Ala105Thr (week 52); Gln67Gln/His (week 52); Asn74Asp (week 72); Lys70His and Asn74Lys (week 78); Gln67His, Lys70Arg, and Thr107Thr/Asn (week 78); Gln67His (week 88); Gln67His, Lys70Arg, and Ala105Ala/Thr (week 88)
Margot et al (2022)[15]	Phase 1b dose-ranging monotherapy	Gln67Gln/His (day 10); Gln67His (day 10)

*The day or week at which the drug-resistance mutation was first detected is indicated in parentheses. Each mutation is represented by the three-letter code of the consensus amino acid, the amino acid position within the HIV-1 capsid, and the three-letter code of the amino acid that emerged after receiving the lenacapavir-containing regimen.

Table 1: **Patterns of lenacapavir-associated capsid drug-resistance mutations in clinical trials**

	Fold-reduced susceptibility (median)*	Replication capacity (median)
Low (2–9-fold)		
Gln67His	6	78%
Lys70Arg	1	10%
Ala105Thr	3	57%
Thr107Asn	4	32%
Intermediate (10–49-fold)		
Asn74Asp	17	49%
Lys70Asn	24	7%
Gln67His and Lys70Arg	18	63%
Gln67Hi and Asn74Ser	32	34%
High (50–249-fold)		
Lys70His	154	10%
Gln67His and Ala107Asn	62	41%
Gln67His, Lys70Arg, and Thr107Ser	66	109%
Very high (≥250-fold)†		
Met66Ile‡	>1000	4%
Gln67His and Asn74Asp	>1000	30%

Data are median fold-reduced susceptibility or median replication capacity. All isolates shown were site-directed mutants tested using the Monogram PhenoSense Assay.[15,16] Each mutation is represented by the three-letter code of the consensus amino acid, the amino acid position within the HIV-1 capsid, and the three-letter code of the mutated amino acid. *Results for Gln67His, Asn74Asp, Gln67His plus Lys7Arg, and Met66Ile were obtained on 2, 3, 2, and 4 isolates, respectively. †For some isolates, the fold-reduced susceptibility was reported to be more than 869. These results were converted to greater than 1000. ‡Five isolates with Met66Ile plus Gln67His, Met66Ile plus Asn74Asp, Met66Ile plus Ala105Thr, Met66Ile plus Thr107Ser, and Met66Ile plus Gln67His and Lys70Arg are not shown. Each of these five isolates had a fold-reduced susceptibility of greater than 1000 and a replication capacity of 1–24%. Leu56Ile, which was reported only during in vitro selection experiments, had a fold-reduced susceptibility of 204 and a replication capacity of 9%.[10] Clinical isolates with Thr107Ala and Thr107Ser displayed 0·6-fold and 1·3-fold reduced lenacapavir susceptibility, respectively.[14]

Table 2: **Phenotypic effects of commonly occurring patterns of lenacapavir-associated capsid drug-resistance mutations**

Lys70 mutations usually occur in combination with mutations at positions 66, 67, and 74. Lys70Asn and Lys70His mutations reduce lenacapavir susceptibility by 24-fold and 154-fold, respectively.[10,16] Lys70Arg alone has minimal effect on lenacapavir susceptibility, but does contribute to resistance when occurring with Gln67His (table 2). Lys70Ser, which has been reported only in combination with other mutations at this position, has not been studied for its effect on lenacapavir susceptibility.

Asn74Asp has been observed alone in two breakthrough cases in the PURPOSE-2 PrEP trial[7] and in one case report of an individual receiving functional lenacapavir monotherapy.[13] In two CAPELLA trial participants, Asn74Asp occurred in combination with other lenacapavir-associated resistance mutations. Asn74Asp reduces lenacapavir susceptibility by approximately 20-fold and is associated with a replication capacity of about 50%.[10,14–16] X-ray crystallography has shown that Asn74Asp reduces hydrogen bonding to lenacapavir and introduces electrostatic repulsion, weakening lenacapavir binding.[18] Asn74His and Asn74Lys, both of which have been reported only in combination with other mutations, have not been studied for their individual effects on lenacapavir susceptibility.

Each of the lenacapavir-associated drug-resistance positions are highly conserved in isolates from lenacapavir-naive individuals, irrespective of previous exposure to ART.[19–23] Among those mutations associated with reduced lenacapavir susceptibility, only Gln67His has a prevalence in lenacapavir-naive individuals of 0·1% or more (appendix p 1). Notably, around two-thirds of lenacapavir-naive individuals with Gln67His have CRF01_AE viruses, corresponding to a prevalence of about 0·5% in this clade.[21,22]

See **Online** for appendix

Preliminary clinical data provide insight into the genetic barrier to lenacapavir resistance. Lenacapavir-associated resistance mutations were seen in two of six participants in the CALIBRATE trial[12] and in 14 of 27 participants in the CAPELLA trial,[11] with confirmed virological failure, suggesting that lenacapavir's genetic barrier to resistance is lower than that of second-generation INSTIs and pharmacologically boosted protease inhibitors, but not as low as that of non-nucleoside reverse transcriptase inhibitors. The low barrier is further supported by the emergence of mutations associated with high-level reductions in lenacapavir susceptibility within 4–10 weeks in seven CAPELLA trial participants (table 1). However, extrapolating the risk of lenacapavir resistance from the CAPELLA trial is challenging, as many participants were receiving few additional active drugs—a situation that has become increasingly uncommon in people treated for HIV-1. Although seven of 14 CAPELLA participants with emergent lenacapavir resistance reached virological resuppression (largely due to resumed adherence to their optimised background regimen or a change in regimen),[14] the significance of these cases remains uncertain given their anecdotal and heterogeneous nature.

Potential risks and consequences of PrEP-associated lenacapavir resistance

Systematic reviews have highlighted the preference for long-acting PrEP among many populations at risk for HIV-1.[24] In a modelling study evaluating the potential use of lenacapavir for PrEP, achieving approximately 32–40% coverage of populations at increased risk was estimated to avert 12·3% of HIV-1 infections in South Africa, 17·0% in Zimbabwe, and 18·0% in western Kenya over a ten-year period of implementation compared with the reference scenario of oral PrEP alone.[25] Plans to widely implement lenacapavir-associated PrEP in low-income and middle-income countries, however, are likely to face meaningful implementation challenges and higher risk of breakthrough infection and drug resistance than those observed in the PURPOSE-1 and PURPOSE-2 trials.

Four scenarios lead to drug resistance in people taking PrEP who acquire HIV-1: (1) PrEP initiation during undiagnosed HIV-1 infection; (2) infection followed by

acquired HIV-1 drug resistance as a result of suboptimal adherence; (3) infection followed by acquired HIV-1 drug resistance despite optimal adherence; and (4) infection with an HIV-1 strain that is already resistant to the drugs used in the PrEP regimen (transmitted drug resistance). Among individuals receiving oral PrEP with tenofovir disoproxil fumarate–emtricitabine, the first two scenarios appear to be the most common.[26] Although long-acting injectable cabotegravir PrEP is more efficacious than tenofovir disoproxil fumarate–emtricitabine, rare instances of the third scenario have been reported.[9] HIV-1 infection in the context of long-acting injectable cabotegravir PrEP has been associated with long-acting early viral inhibition syndrome, whereby acute HIV-1 infection and emergence of INSTI resistance present atypically and diagnosis might be delayed due to low HIV-1 viral load and diminished or delayed seroconversion.[9]

Although the risk of HIV infection occurring during PrEP and emergent lenacapavir resistance was extremely low in the PURPOSE trials, the risk will likely be higher when lenacapavir PrEP is scaled up. Breakthrough infections among those who start lenacapavir during an undiagnosed acute infection might occur more often in settings where less sensitive testing approaches are used due to resource constraints. Infection followed by acquired HIV-1 drug resistance as a result of suboptimal adherence might occur among those who experience delays outside of the recommended 4-week dosing window or who discontinue lenacapavir without transitioning to another form of PrEP.

The PURPOSE-1 and PURPOSE-2 trials have shown that breakthrough infections despite on-time lenacapavir injections will likely be exceedingly rare. Additionally, breakthrough infections resulting from transmitted drug resistance are also likely to be exceedingly rare due to the near complete absence of lenacapavir-associated resistance mutations in lenacapavir-naive individuals. However, this possibility might increase in the future should lenacapavir-based regimens become widely used for HIV-1 treatment.

Despite population-level benefits of lenacapavir PREP for HIV-1 prevention, integration of long-acting PrEP into existing health-care systems in resource-limited settings will present challenges. Implementation will require addressing service delivery logistics for a provider-administered injectable, adequate training to administer the injections and manage side-effects, and strategies to ensure on-time injections. Additionally, once lenacapavir-based long-acting PrEP programmes are initiated, maintaining continuity is crucial, as interruptions could increase the risk of late breakthrough infections and resistance emergence. To mitigate this risk, contingency plans should be in place to transition lenacapavir recipients to oral PrEP if needed.

A recent analysis of data from the PURPOSE-1 trial by the WHO Guidelines Development Group[6] concluded that lenacapavir is safe in pregnancy, as rates of negative pregnancy outcomes were similar between 193 people who were pregnant receiving lenacapavir and 98 people receiving tenofovir disoproxil fumarate–emtricitabine. Another topic of ongoing study is obtaining a better understanding of lenacapavir's pharmacokinetic profile. Although lenacapavir undergoes minimal metabolism, it is a substrate for CYP3A4, UGT1A1, and P-glycoprotein. Therefore, the concentrations of lenacapavir might be affected by inducers of these enzymes.[27]

Should lenacapavir become widely adopted for long-acting HIV-1 treatment in the future, potentially in combination with long-acting injectable cabotegravir or broadly neutralising antibodies,[28] lenacapavir-associated resistance mutations arising from PrEP breakthrough infections could theoretically affect future treatment options. However, the benefits of expanding lenacapavir for PrEP are expected to outweigh this risk, especially since lenacapavir-containing regimens are years away from widespread availability, particularly in resource-limited settings. Furthermore, current evidence suggests that lenacapavir PrEP is unlikely to contribute meaningfully to population-level lenacapavir resistance, given the anticipated rarity of breakthrough infections and the reduced replication capacity associated with most known lenacapavir-associated resistance mutations. Mutations with reduced replication capacity are more likely than those without reduced replication capacity to be out-competed by wild-type revertant mutations in the absence of selective drug pressure, which limits the potential for sustained transmission.[29,30]

Although genotypic resistance testing might not be available for all individuals who acquire HIV-1 during lenacapavir prophylaxis, population-level drug-resistance surveillance should be conducted for those acquiring HIV while lenacapavir concentrations are within the therapeutic range or in the early tail phase when concentrations remain sufficient to select for lenacapavir-associated resistance mutations. WHO is currently developing recommendations for the creation of surveillance programmes at sites administering long-acting PrEP and at ART clinics to establish the proportion of people with incident infections who have received a long-acting injectable regimen within the preceding 12 months.

Conclusion

To date, infection with an HIV-1 strain already resistant to lenacapavir is highly unlikely due to the extremely low prevalence of lenacapavir-associated resistance mutations. Drug resistance might emerge in individuals receiving lenacapavir PrEP if they initiate prophylaxis during an undiagnosed acute HIV-1 infection or if they acquired HIV during the drug's pharmacokinetic tail phase. However, the emergence of lenacapavir-associated resistance mutations, in what are likely to be rare cases of breakthrough infection, will not compromise the effectiveness of currently WHO-recommended first-line,

second-line, or third-line therapies, as there is no cross-resistance between lenacapavir and other recommended antiretroviral drugs. This landscape might change if long-acting lenacapavir-based regimens are approved in the future for the treatment of HIV-1. Surveillance programmes can help estimate the prevalence of lenacapavir-associated resistance mutations by monitoring the prevalence and trends over time of lenacapavir resistance among individuals testing positive for HIV-1 while receiving lenacapavir PrEP.

Contributors

GvZ, MRJ, and RWS conceived the project. RWS reviewed and summarised the published literature on lenacapavir resistance. GvZ, MP, H-MAS, MRJ, and RWS drafted the manuscript. CO, JMS, SMM, MV, RK, UMP, and MR edited the drafts of the manuscript.

Declaration of interests

RWS received honoraria for lectures from Gilead Sciences and ViiV Healthcare in 2022. GvZ received honoraria for a lecture from ThermoFisher. JMS received honoraria for participating in advisory boards for Merck, Gilead Sciences, GlaxoSmithKline, ViiV Healthcare, Moderna, and Pfizer; speaker fees from Merck, Gilead Sciences, GlaxoSmithKline, and ViiV Healthcare; and consulting fees from Teva, GlaxoSmithKline, and ViiV Healthcare. RK received honoraria for a lecture from ThermoFisher. UMP received consulting fees from Merck and honoraria for a lecture from ThermoFisher. SMM received grant funding from Merck and ViiV Healthcare paid to her institution. All other authors declare no competing interests.

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