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Letter to the Editor
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Lenacapavir: Advancing HIV Control Requires Resistance Vigilance and Equitable Access

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Dear Editor,

Lenacapavir is a first-in-class long-acting capsid inhibitor emerging as a potent tool in both treatment and prevention strategies of HIV-1 infections. It can maintain therapeutic plasma levels for nearly six months after a single subcutaneous injection. It offers clinical utility for heavily treatment-experienced individuals and is also being explored for use in pre-exposure prophylaxis (PrEP) [1–4].

Clinical trials, such as CAPELLA and CALIBRATE, have shown promising results. In one prevention study, none of the 2,134 participants in the lenacapavir arm acquired HIV, while infections occurred in comparator groups receiving F/TAF or F/TDF [5]. In treatment settings, lenacapavir led to significant viral load reductions and CD4 count improvements in patients with multidrug-resistant HIV-1, with over 80% achieving viral suppression by week 26 [6].

While there has been progress, two major concerns remain: the threats posed by resistance management and restricted access to treatment and medicine. Lenacapavir has a relatively low barrier to resistance. Capsid mutations, such as Q67H, N74D, and M66I, have already been observed in both clinical and in vitro studies [7–10]. Structural studies show these mutations disrupt inhibitor binding through conformational or electrostatic interference [11]. Furthermore, the prolonged pharmacokinetic “tail” of lenacapavir, during which subtherapeutic concentrations persist for weeks or months, may encourage viral replication and resistance if adherence is compromised [12]. Scaling global resistance monitoring using established systems such as the WHO's HIVDR Surveillance, PEPFAR-supported labs, and IAS-coordinated resistance cohorts is crucial for promptly detecting and responding to emerging mutations. Equally important is the inclusion of inexpensive resistance testing into distribution plans, especially in low-resource, high-burden areas.

The development of next-generation capsid inhibitors with improved resistance profiles should be prioritized to address current limitations. Promising approaches to overcome resistance associated with known mutations such as Q67H and N74D include efforts by NIH-funded pipelines and collaborations with corporate partners (e.g., ViiV Healthcare, Gilead Sciences) [11].

Equitable access remains another pressing challenge. Although lenacapavir’s annual cost exceeds $20,000 USD per patient [13], academic modeling and MSF Access Campaign analyses estimate production costs to be under $100 per year. This pricing disparity renders lenacapavir inaccessible to the very regions most burdened by HIV. Furthermore, restrictive licensing that excludes several low- and middle-income countries exacerbates inequities [14]. Addressing cost-related barriers through pricing reforms and expanded voluntary licensing agreements is critical to achieving equitable access.

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Research must also extend to underrepresented populations, including pregnant individuals, people of reproductive potential, adolescents, and those with renal or hepatic impairment, to ensure safe and effective use across diverse clinical settings [15].

In conclusion, lenacapavir marks a revolution in HIV pharmacotherapy, which will completely shift the paradigm of treatment and prevention of HIV. Still, its effects will remain limited unless there are parallel investments in access expansion and resistance reduction. The worldwide reaction to HIV has reached a crossroads. Shall we let innovation exacerbate inequalities, or will we use it to democratize healthcare and address treatment gaps? Policymakers, funders, and the international HIV community have to act forcefully to guarantee that this breakthrough benefits everyone who needs it, not just a chosen few.

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