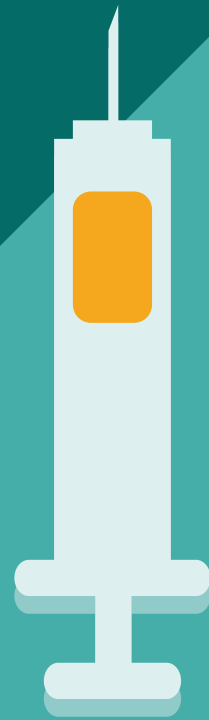


Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis



Web Annex F. Lenacapavir-associated drug resistance:
implications for scaling up long-acting PrEP



World Health
Organization

Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis

**Web Annex F. Lenacapavir-associated drug resistance:
implications for scaling up long-acting PrEP**



**World Health
Organization**

Some rights reserved. This work is available under the [CC BY-NC-SA 3.0 IGO](#) licence.

Suggested citation. van Zyl G, Prochazka M, Schmidt HM, Rodolph M, Jordan MR, Shafer RW. Web Annex F. Lenacapavir-associated drug resistance: implications for scaling up long-acting PrEP. In: Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. <https://doi.org/10.2471/B09481>

The named authors alone are responsible for the views expressed in this publication.

This publication forms part of the WHO document entitled *Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP)*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).



Lenacapavir-associated drug resistance: implications for scaling up long-acting PrEP

Authors: Gert van Zyl,¹ Mateo Prochazka,² Heather-Marie Ann Schmidt,^{2,3} Michelle Rodolph,² Michael R Jordan⁴ and Robert W. Shafer⁵

1. Stellenbosch University
2. Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, World Health Organization
3. United Nations Joint Programme on HIV/AIDS
4. Tufts University
5. Stanford University

Abstract

Twice-yearly subcutaneous lenacapavir (LEN) injections have demonstrated high efficacy in preventing HIV-1 acquisition in people at risk. Given the promise of LEN for pre-exposure prophylaxis (PrEP), coordinated efforts are underway to scale up LEN PrEP worldwide. We summarize published data on the risks, genetic mechanisms and implications of LEN resistance for a successful LEN PrEP rollout. The likelihood of acquiring an HIV-1 strain already resistant to LEN is extremely low, as LEN-associated drug resistance mutations are rare among individuals who have never received LEN. Although drug resistance could emerge if LEN is initiated during undiagnosed acute HIV-1 infection or if infection occurs during the drug's pharmacokinetic tail, such cases will not compromise the efficacy of the World Health Organization's currently recommended first-, second- or third-line therapies, as there is no cross-resistance between LEN and other antiretroviral drugs. Additionally, most LEN-associated resistance mutations reduce viral replication capacity, limiting their transmission potential. Given the rarity of breakthrough infections, LEN PrEP is unlikely to significantly drive population-level LEN resistance. Nonetheless, current HIV-1 drug-resistance surveillance programmes should expand to monitor the emergence of LEN-associated resistance mutations occurring in populations in which LEN PrEP is administered.

**Department of Global HIV, Hepatitis
and Sexually Transmitted Infections
Programmes**

World Health Organization
Avenue Appia 20
1211 Geneva
Switzerland

www.who.int