

# Yeztugo<sup>®</sup> (lenacapavir)

## Mechanism of Action

This document is in response to your request for information regarding Yeztugo<sup>®</sup> (lenacapavir [LEN]) and its mechanism of action.

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**The full indication, important safety information, and boxed warning are available at: [www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo\\_pi](http://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi).**

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## Product Labeling<sup>1</sup>

### Mechanism of Action

LEN is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Surface plasmon resonance sensorgrams showed dose-dependent and saturable binding of LEN to cross-linked wild-type capsid hexamer with an equilibrium binding constant ( $K_D$ ) of 1.4 nM. LEN inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).

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## Available Data on Mechanism of Action of LEN for PrEP

LEN is a first-in-class capsid inhibitor that disrupts multiple stages in the HIV replication cycle. While the exact mechanism of action for LEN's preventative effects has not been directly studied, it is likely the inhibition of early replication after HIV-1 exposure. The prophylactic efficacy of a long-acting capsid inhibitor has been demonstrated in proof-of-concept SHIV non-human primate challenge models.<sup>2-5</sup>

LEN binds directly between capsid protein subunits and inhibits 3 essential steps of the viral lifecycle: Capsid-mediated nuclear uptake of HIV proviral DNA, virus assembly and release, and capsid core formation which results in an abnormal, non-infectious capsid structure.<sup>6-8</sup>

1. LEN interferes with capsid mediated nuclear uptake by blocking nuclear import proteins for binding to capsid.
2. Viral assembly and release are inhibited by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits.

3. When LEN binds to hexamers in the later stage of the viral lifecycle before the capsid core is formed, the polymerization process is accelerated which leads to uncontrolled and disorganized structures.
4. This results in an abnormal, non-infectious capsid structure.

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## References

1. Enclosed, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.
2. Bekerman E, Yant SR, VanderVeen L, et al. Long-acting lenacapavir acts as an effective preexposure prophylaxis in a rectal SHIV challenge macaque model. *J Clin Invest*. 2023;133(16).
3. Bekerman E, Hansen D, Lu B, et al. Long-acting Capsid Inhibitor Effective as PrEP Against Vaginal SHIV Transmission in Macaques [Presentation]. Paper presented at: 11th International Aids Society (IAS) Conference on HIV Science Virtual; 18-21 July, 2021.
4. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature*. 2020.
5. Bester SM, Wei G, Zhao H, et al. Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. *Science*. 2020;370(6514):360-364.
6. Cihlar T. Lenacapavir (GS-6207): The First Clinically Active Long-Lasting Inhibitor of HIV Capsid [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; 06-10 March, 2021.
7. Muller B. Track me, if you can - the journey of the HIV-1 capsid through the cell [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; 06-10 March, 2021.
8. Ganser-Pornillos B. Visualization of HIV-1 Capsid-Dependent Replication in vitro [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; 06-10 March, 2021.

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## Abbreviations

LEN=lenacapavir

PrEP=pre-exposure  
prophylaxis

SHIV=simian-human  
immunodeficiency virus

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## Product Label

For the full indication, important safety information, and boxed warning, please refer to the Yeztugo US Prescribing Information available at:

[www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo\\_pi](http://www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi).

## Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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