

Lenacapavir - A Novel Capsid Inhibitor

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Disclosures

No conflicts of interest or relationships to disclose.

Lenacapavir

- **Type of Medication**
 - First-in-class HIV capsid inhibitor
- **Proposed Indication**
 - Resubmitted new drug application to U.S. FDA on July 2, 2022
 - For heavily treated persons with multi-drug resistance
- **Preparations**
 - Oral (daily and weekly)
 - Long-acting subcutaneous injection (every 6 months)
- **Resistance**
 - No overlapping resistance with other FDA-approved HIV therapies

*Resubmission addressed vial glass compatibility problem with new vials made of aluminosilicate glass

Lenacapavir

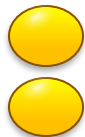
Lenacapavir Dosing Schedule

Day 1



600 mg

Day 2



600 mg

Day 8



300 mg

Day 15



927 mg

6 months



927 mg

6 months



927 mg

6 months



927 mg



Oral lenacapavir 300 mg



Subcutaneous lenacapavir 463.5 mg

Lenacapavir: Mechanism of Action

What is HIV Capsid?

HIV Cross Section

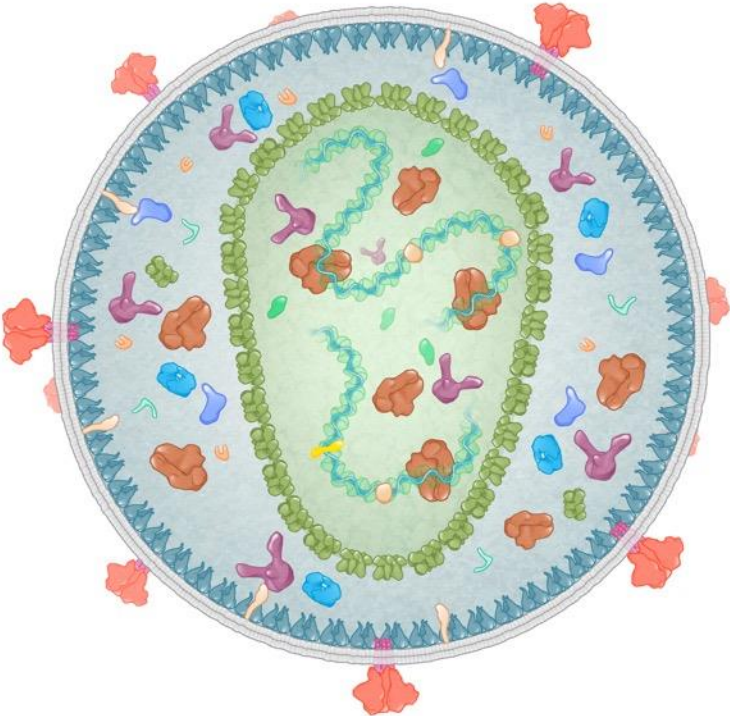
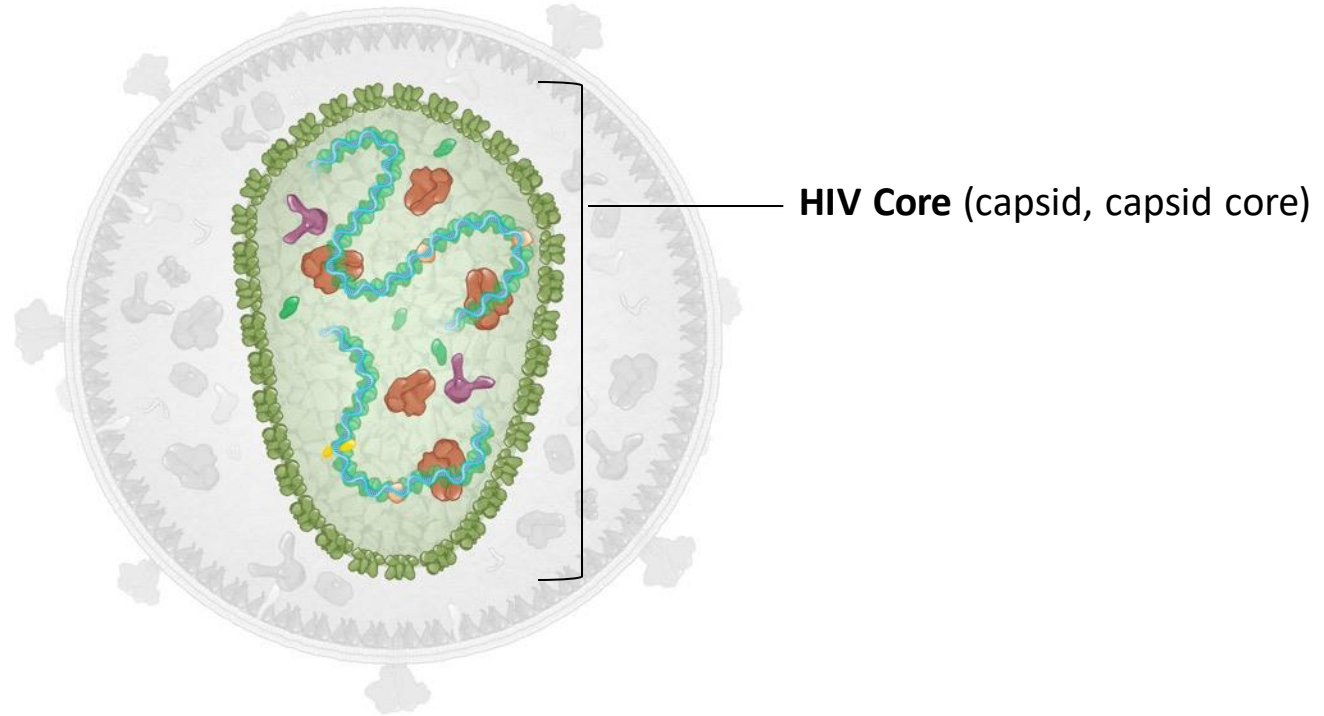
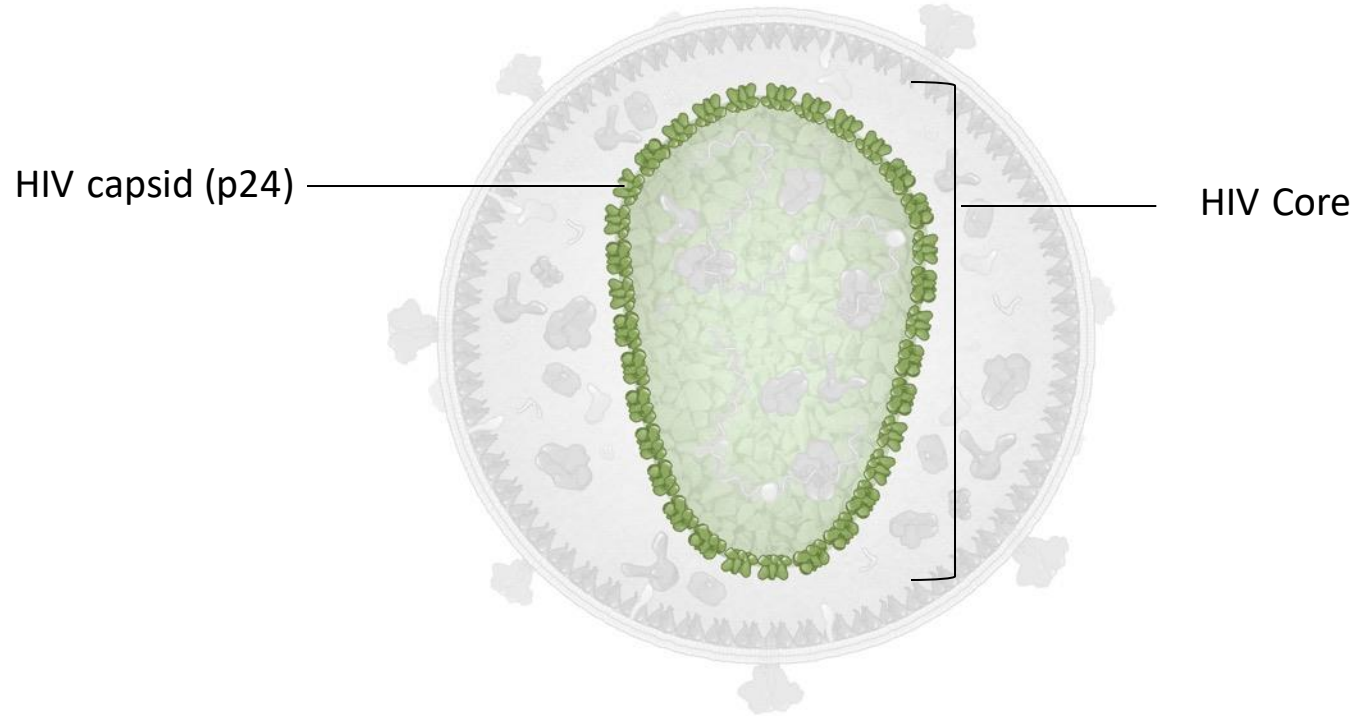


Illustration: Cognition Studio, Inc. and David H. Spach, MD

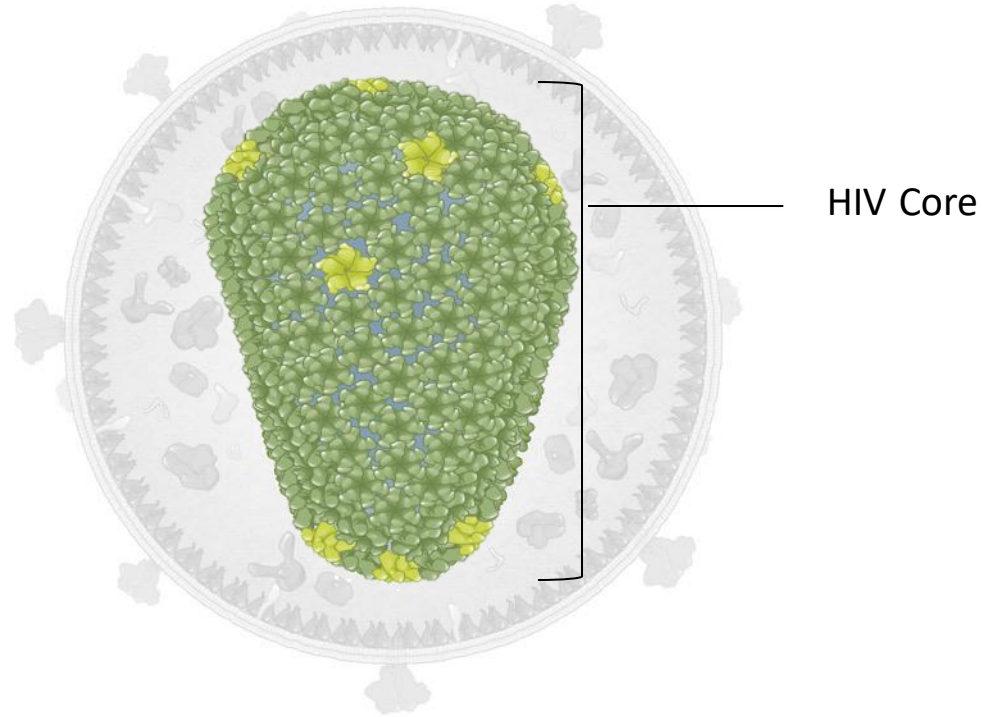
HIV Core



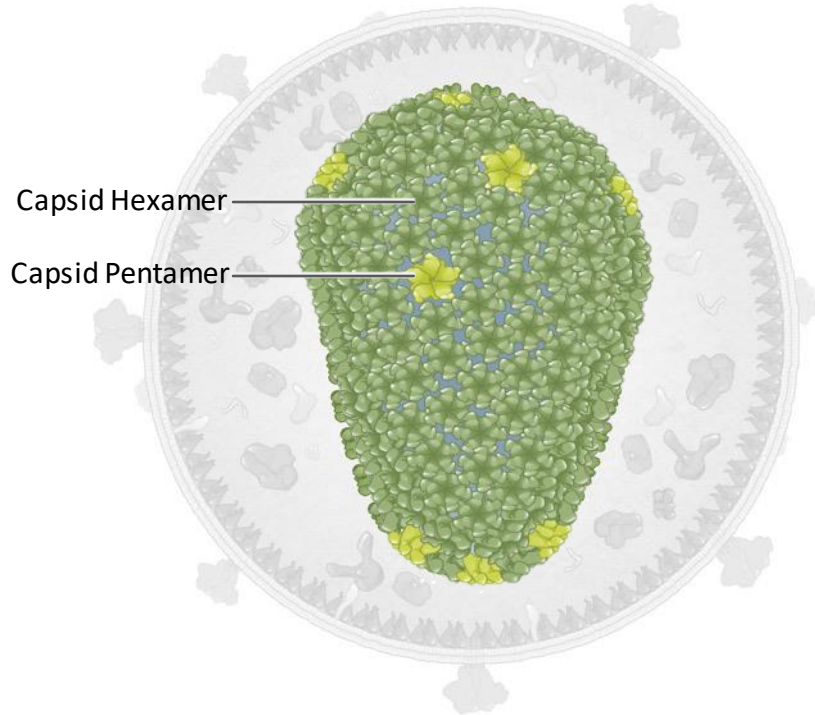
HIV Capsid and HIV Core



HIV Core and Fullerene Cone Structure



HIV Capsid Hexamers and Pentamers and HIV Core



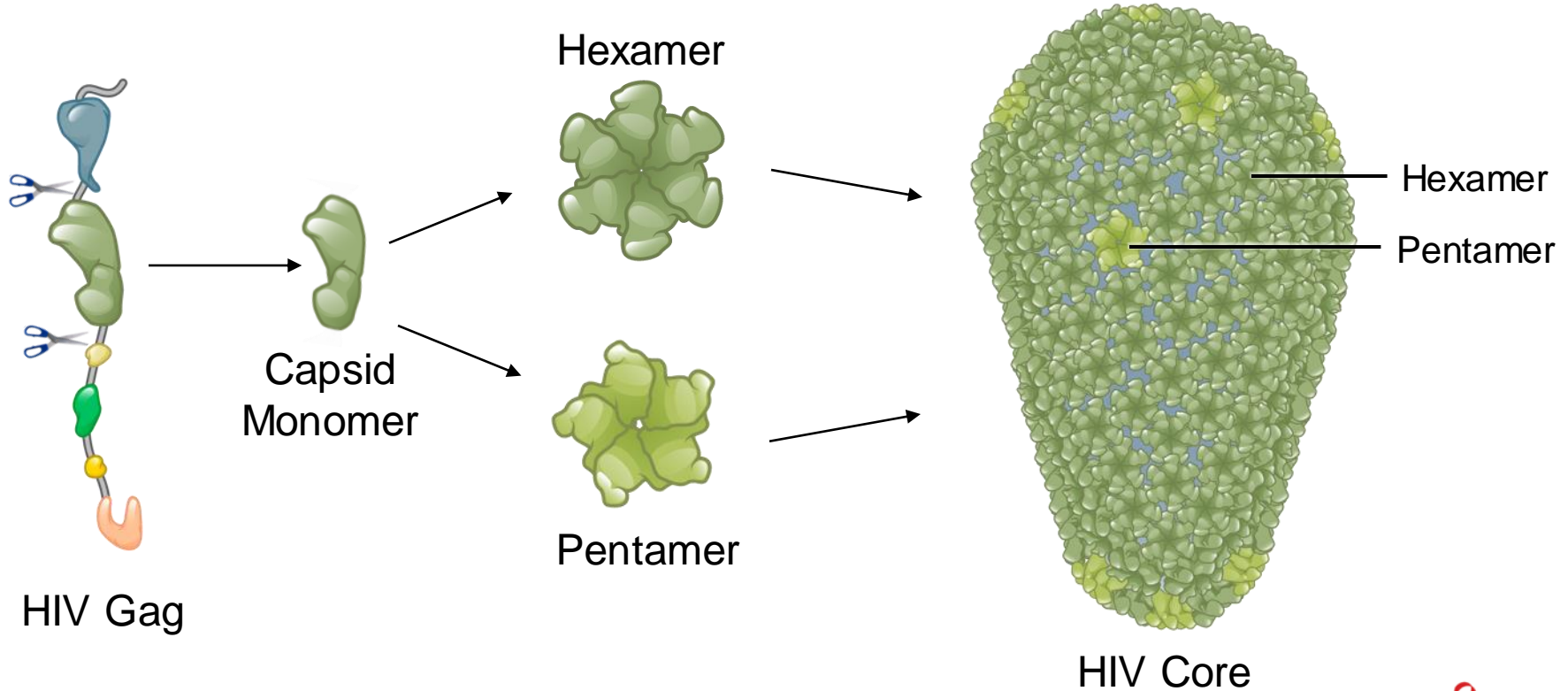
Capsid Hexamer



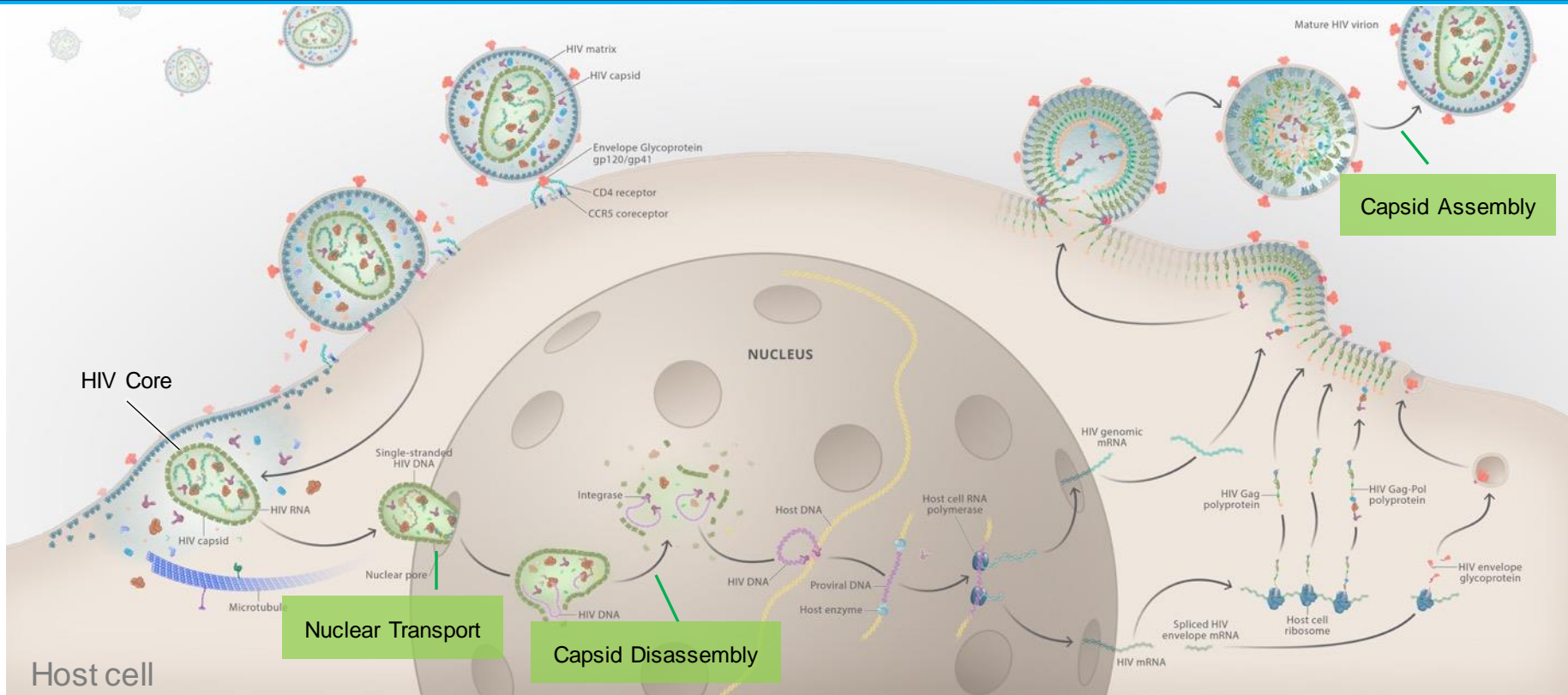
Capsid Pentamer



HIV Capsid and Core Formation



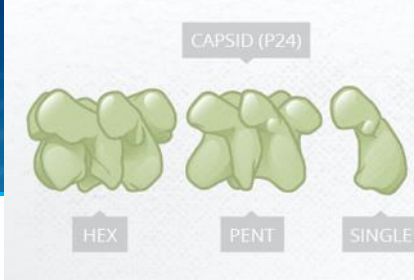
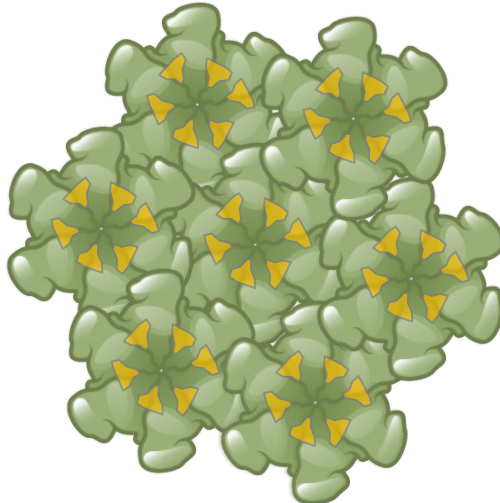
HIV Capsid: Transport, Disassembly, Assembly



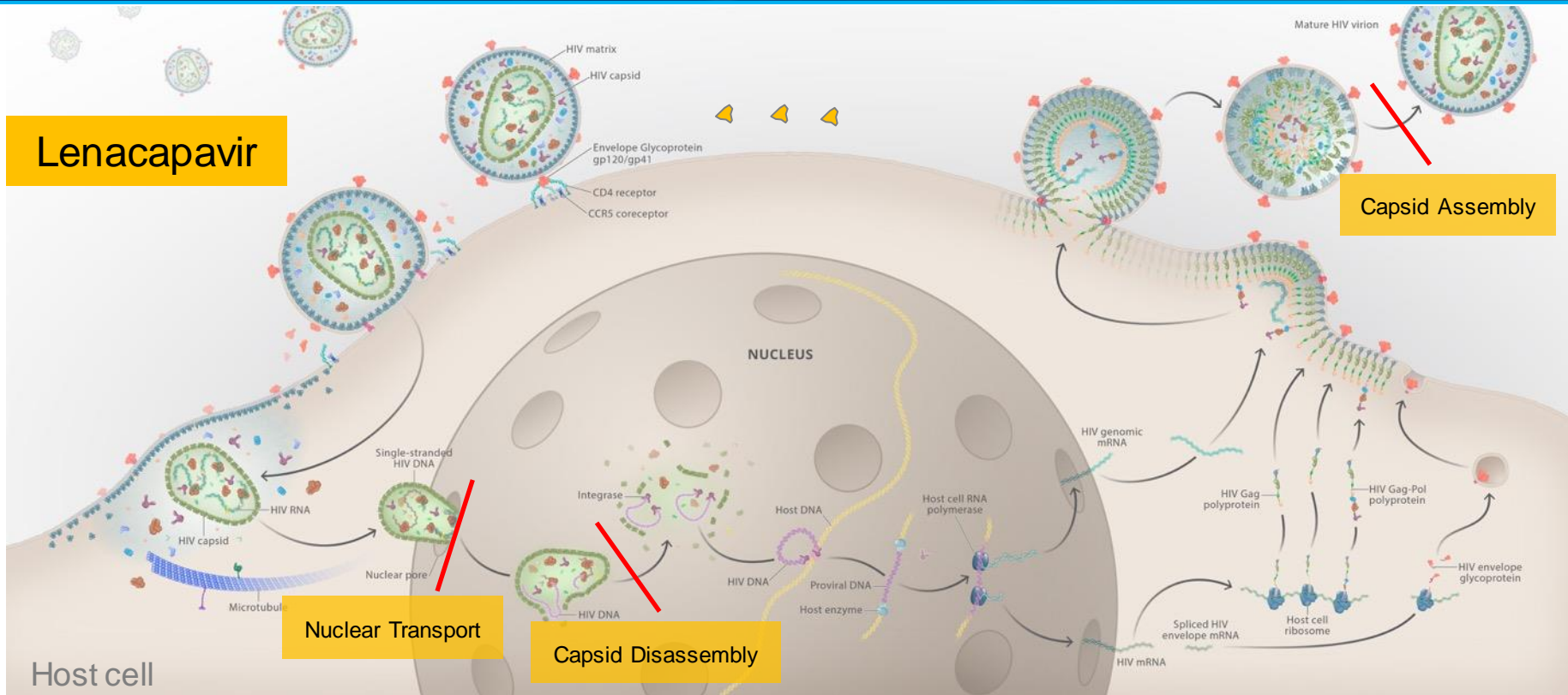
Lenacapavir



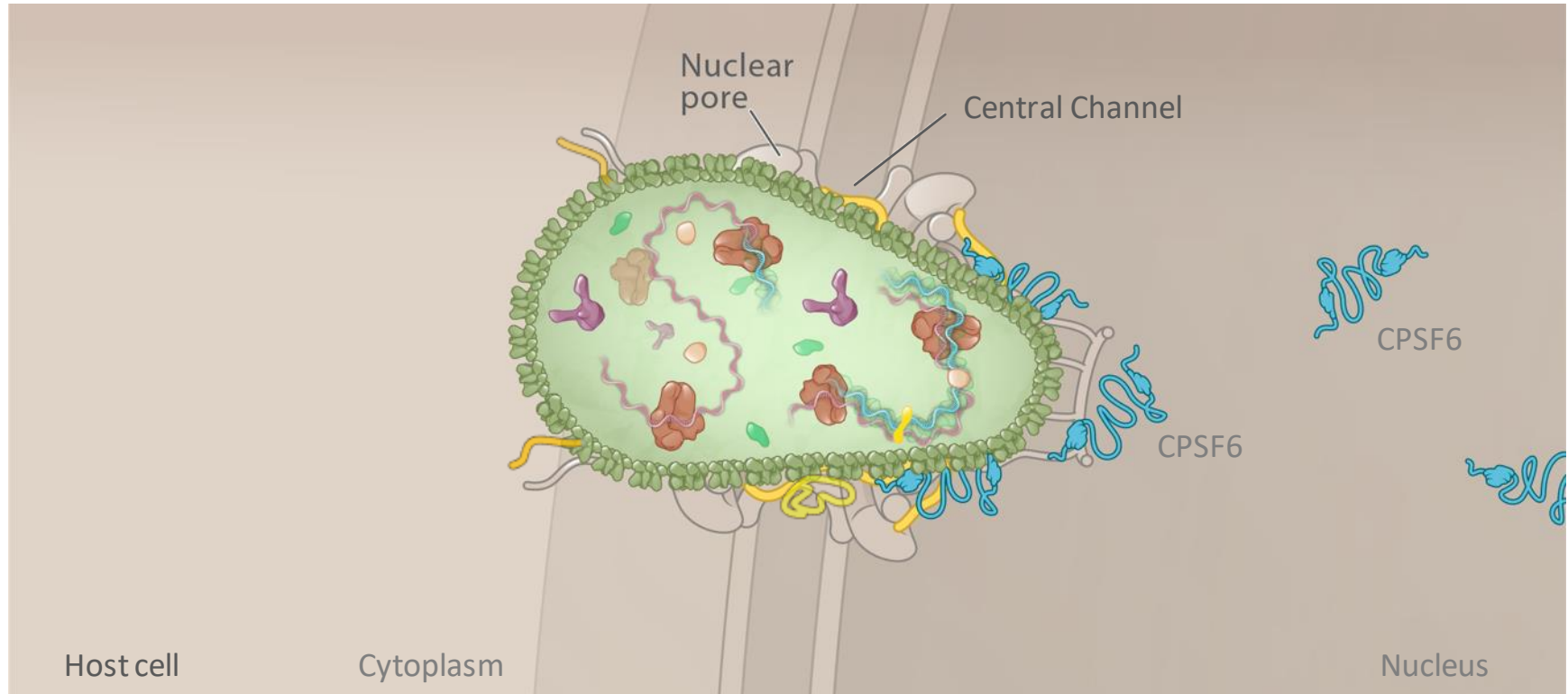
Lenacapavir



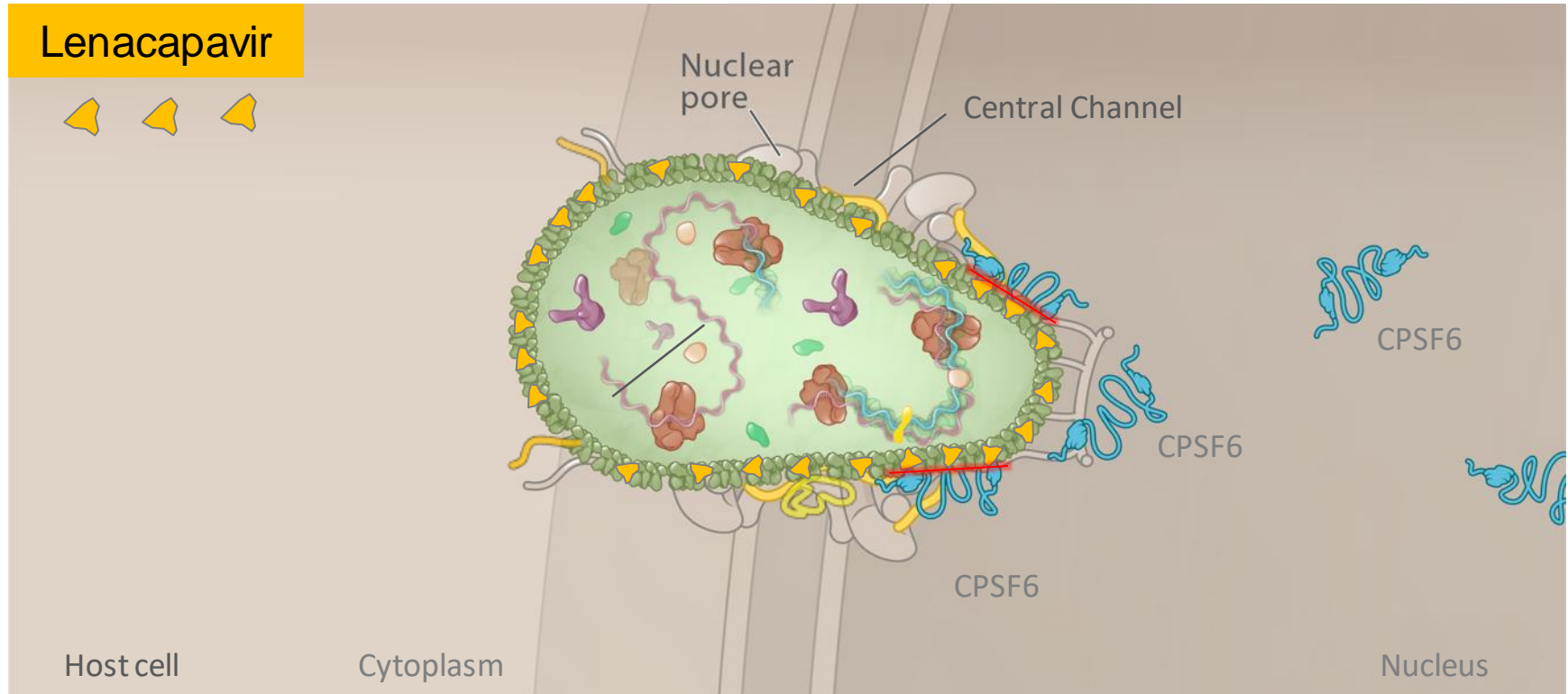
Lenacapavir: Multi-Step Mechanism of Action



Nuclear Import of HIV Core



Lenacapavir and Inhibition of Nuclear Import



Capsid Disassembly

Lenacapavir 

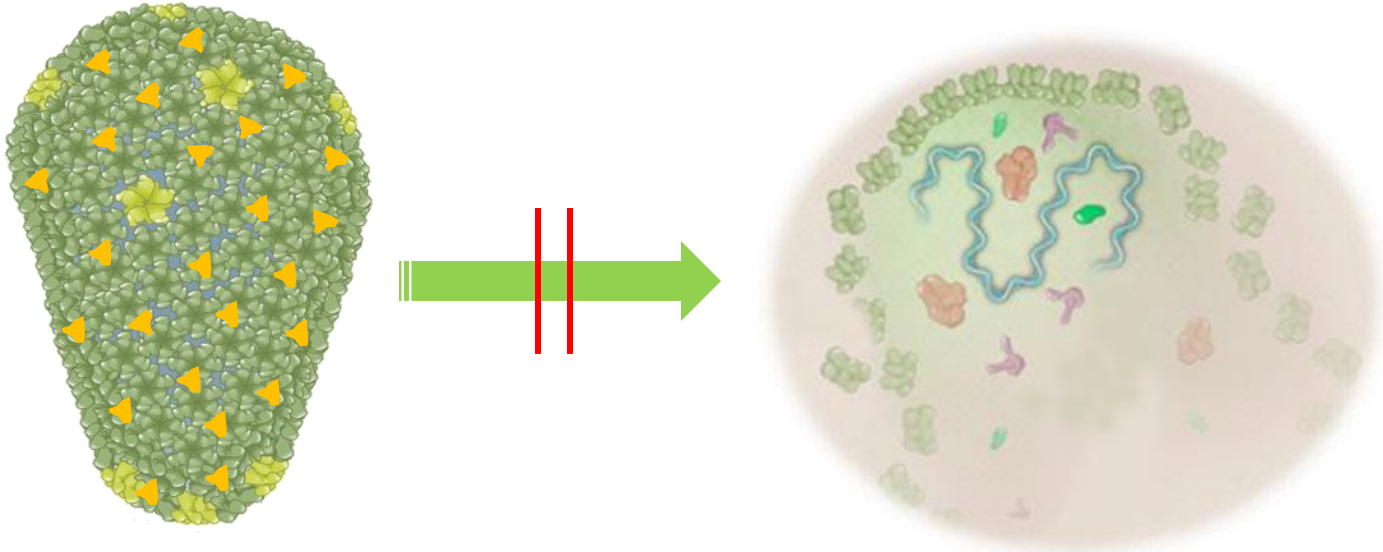
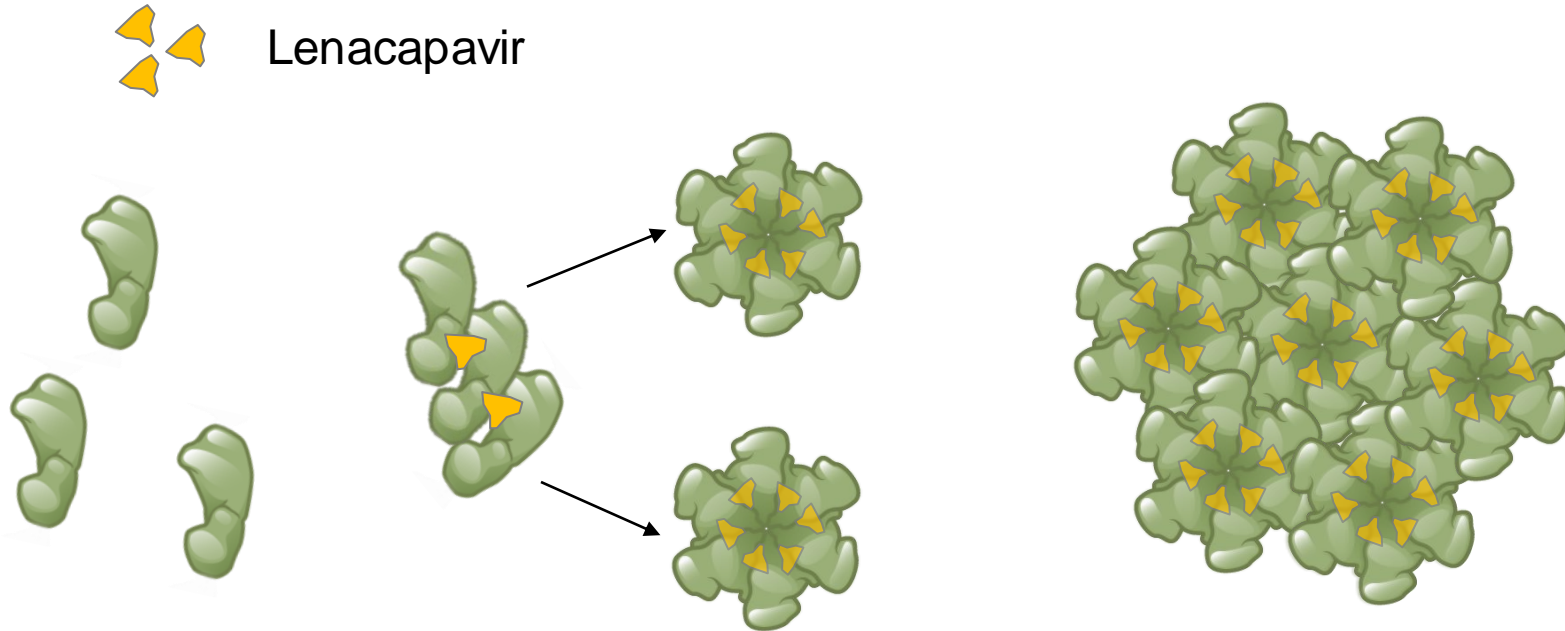


Illustration: Jared Travnicek (Cognition Studio) and David Spach, MD

Lenacapavir and Accelerated Capsid Assembly



Lenacapavir in Multidrug-Resistant HIV

Lenacapavir in Multidrug-Resistant HIV
CAPELLA

Lenacapavir in Multidrug Resistant HIV

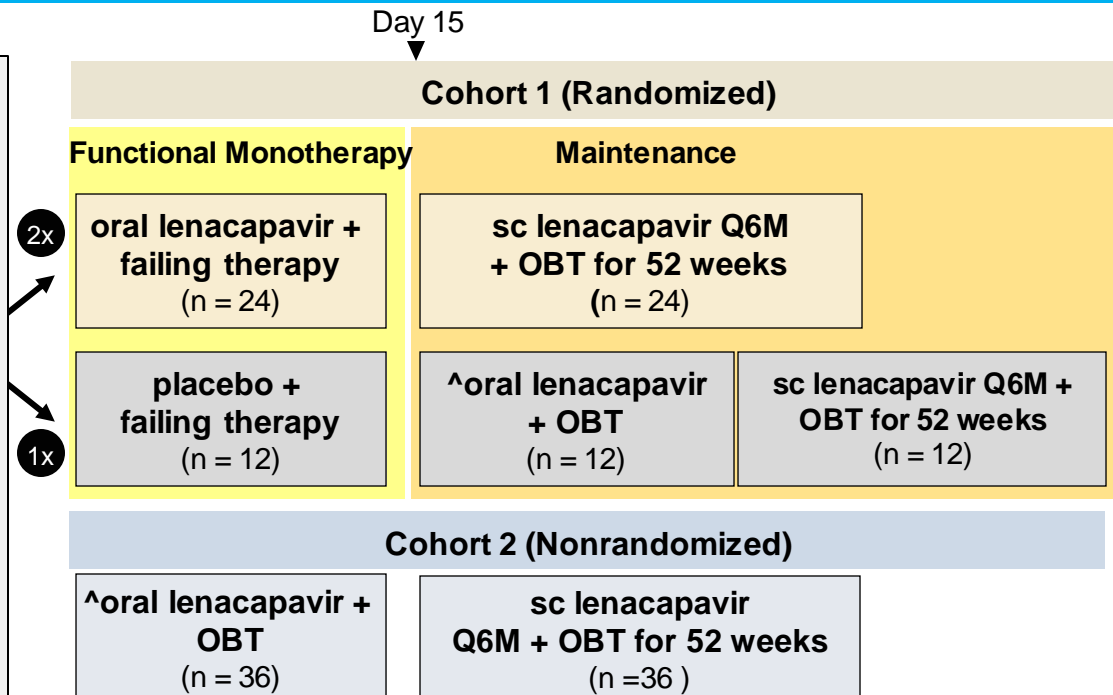
CAPELLA Study: Background

- Background**

- Phase 3, randomized trial with oral and subcutaneous lenacapavir versus optimized background therapy (OBT)

- Enrollment Criteria:**

- Age ≥ 12 years
- Virologic failure on current ART
- HIV RNA >400 copies/mL ≥ 8 wks
- Multiclass ART resistance
- At least one fully active agent



*OBT = optimized background regimen

*oral lenacapavir = 600 mg days 1 and 2, 300 mg day 8

^oral lenacapavir = 600 mg days 15 and 16, 300 mg day 22

sc lenacapavir = 927 mg every 6 months

Lenacapavir in Multidrug Resistant HIV

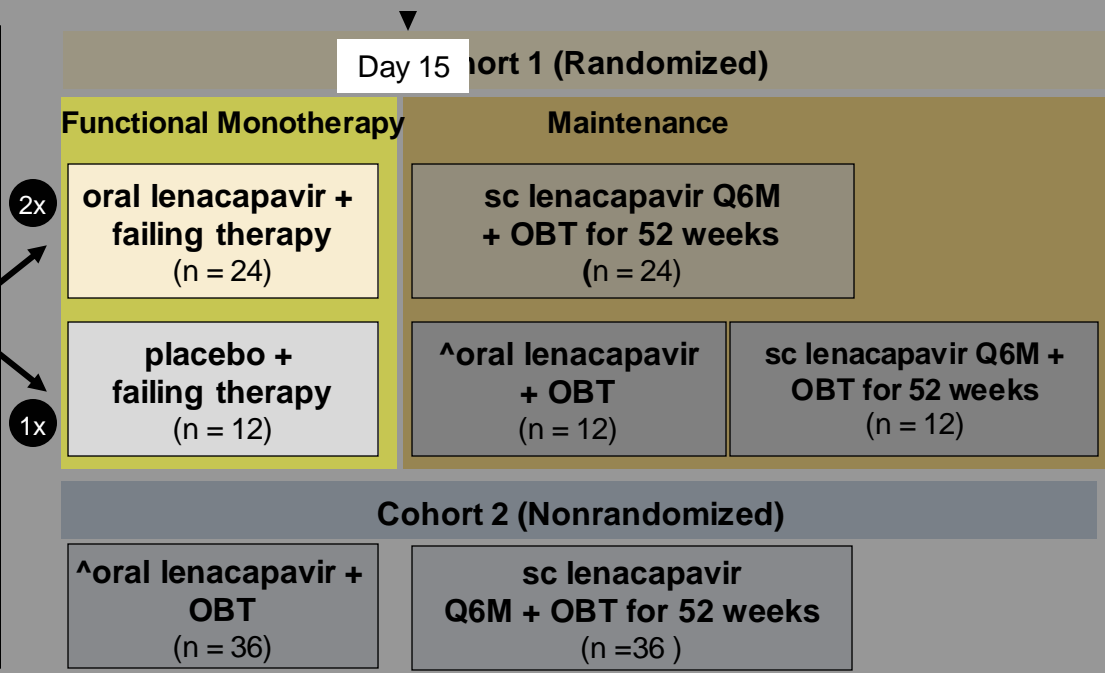
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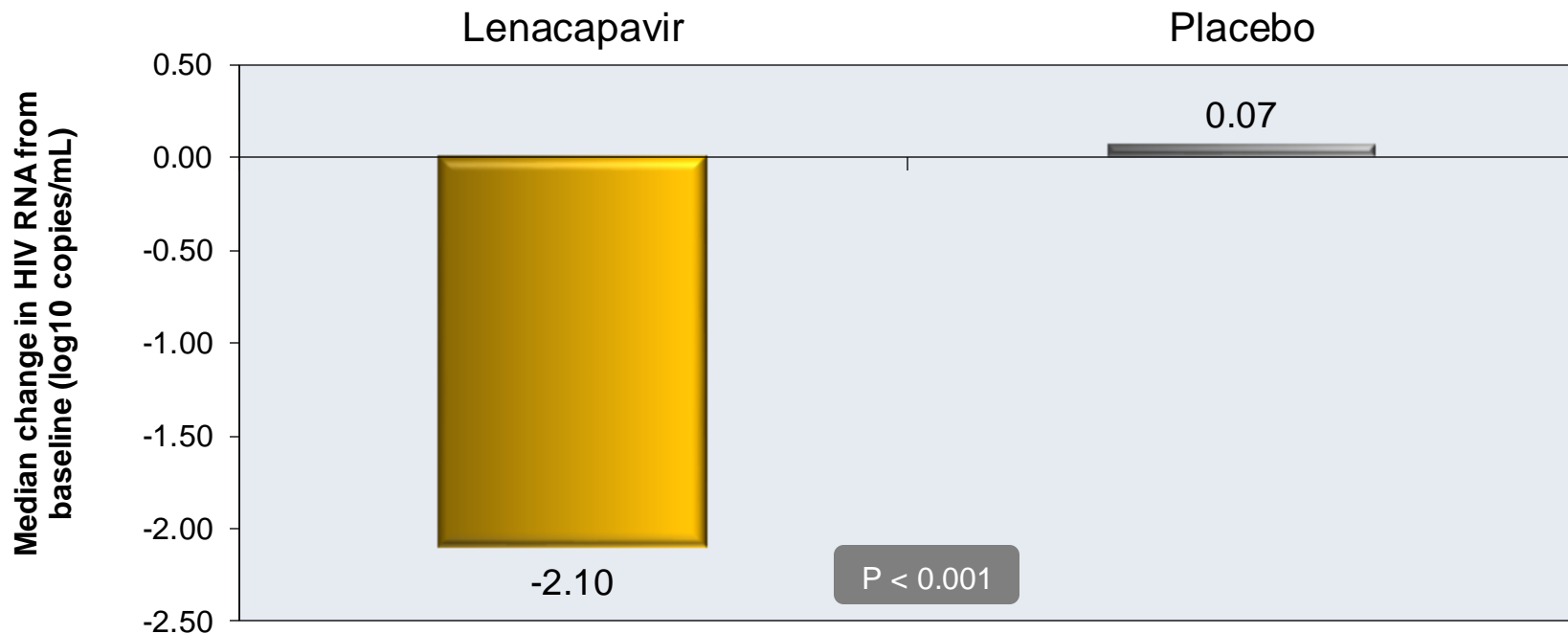
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Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Results

Baseline to Day 15 Change in HIV RNA Level



Lenacapavir in Multidrug Resistant HIV

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2x

oral lenacapavir +
failing therapy
(n = 24)

1x

placebo +
failing therapy
(n = 12)

Day 15 Cohort 1 (Randomized)

Functional Monotherapy

Maintenance

sc lenacapavir Q6M
+ OBT for 52 weeks
(n = 24)

[^]oral lenacapavir
+ OBT
(n = 12)

sc lenacapavir Q6M
+ OBT for 52 weeks
(n = 12)

Cohort 2 (Nonrandomized)

[^]oral lenacapavir
+ OBT
(n = 36)

sc lenacapavir Q6M
+ OBT for 52 weeks
(n = 36)

*OBT = optimized background regimen

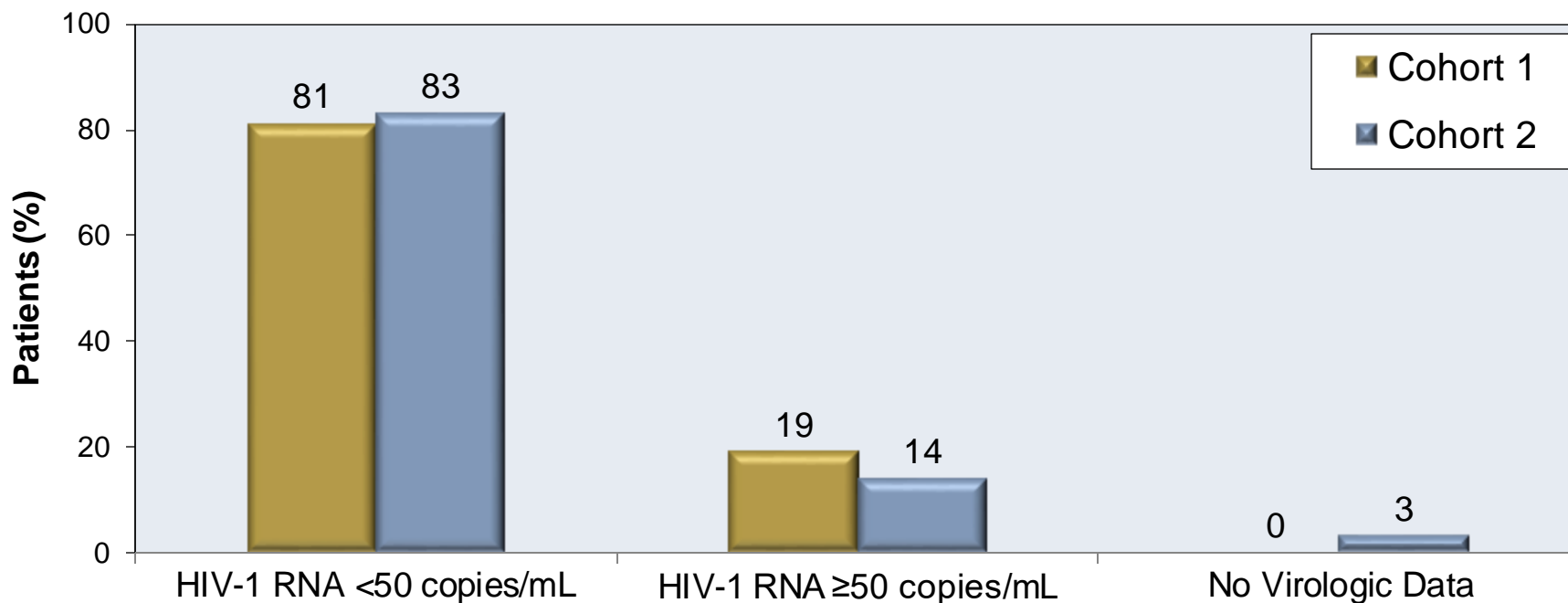
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Lenacapavir in Multidrug Resistant HIV CAPELLA Study: Results

HIV RNA at 26 Weeks



Lenacapavir and Resistance

Lenacapavir: Resistance

7 mutations arising at 6 amino acid positions in capsid protein (CA)

- L56I
- **M66I**
- **Q67H**
- K70N
- **N74D/S**
- T107N

Lenacapavir: Studies

- **Treatment**

- Initial therapy (LEN (PO/SQ) + TAF-FTC (CALLIBRATE))
- Oral Daily Initial
- Subcutaneous Injections: every 6 months

- **PrEP**

- SubQ Injections every 6 months (PURPOSE-1, PURPOSE-2)

Acknowledgment

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