

HIV Capsid Inhibitors: Mechanism of Action

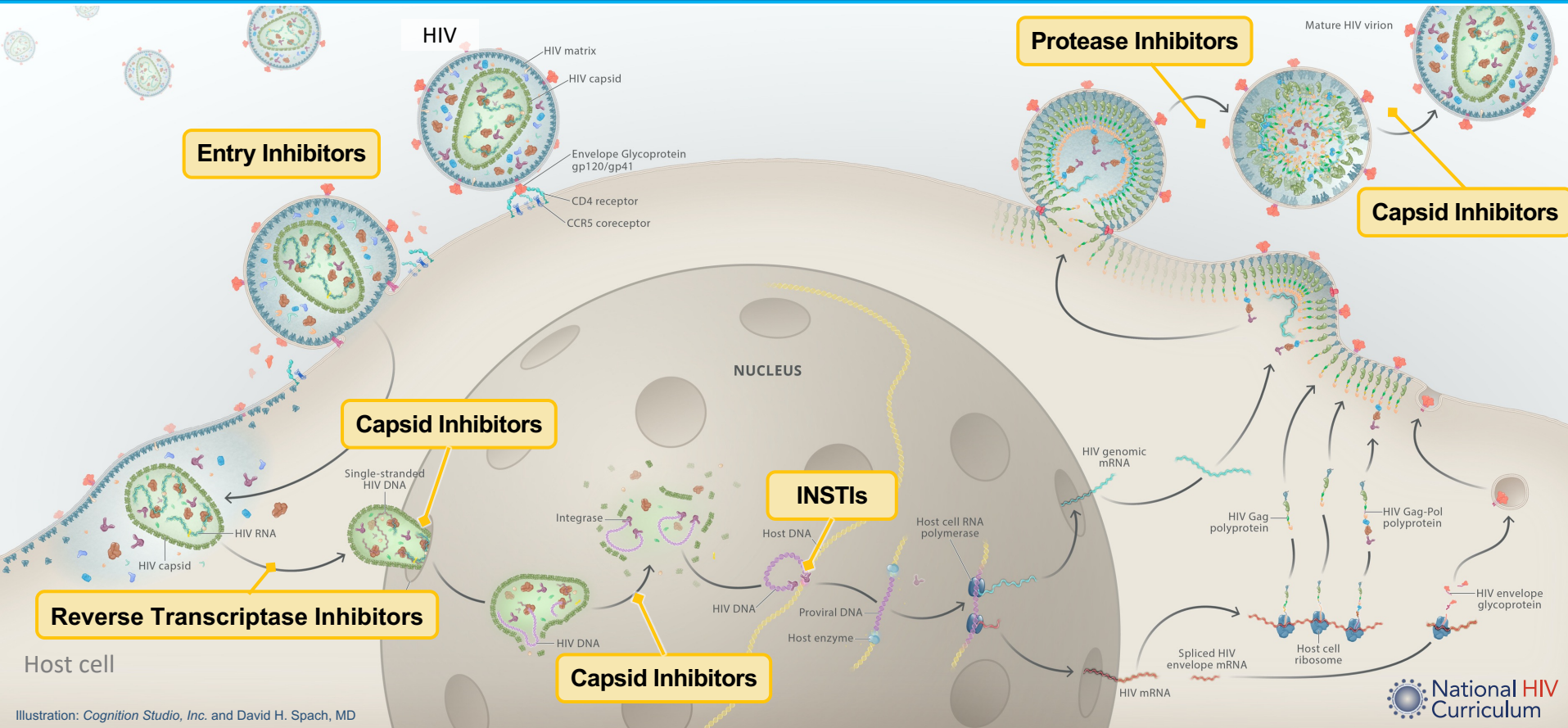
David H. Spach, MD
Editor-in-Chief, National HIV Curriculum
Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

July 9, 2024

Disclosures

Dr. Spach does not have any disclosures.

HIV Antiretroviral Therapy



Entry Inhibitors

HIV

Protease Inhibitors

Mature HIV virion

Capsid Inhibitors

Capsid Inhibitors

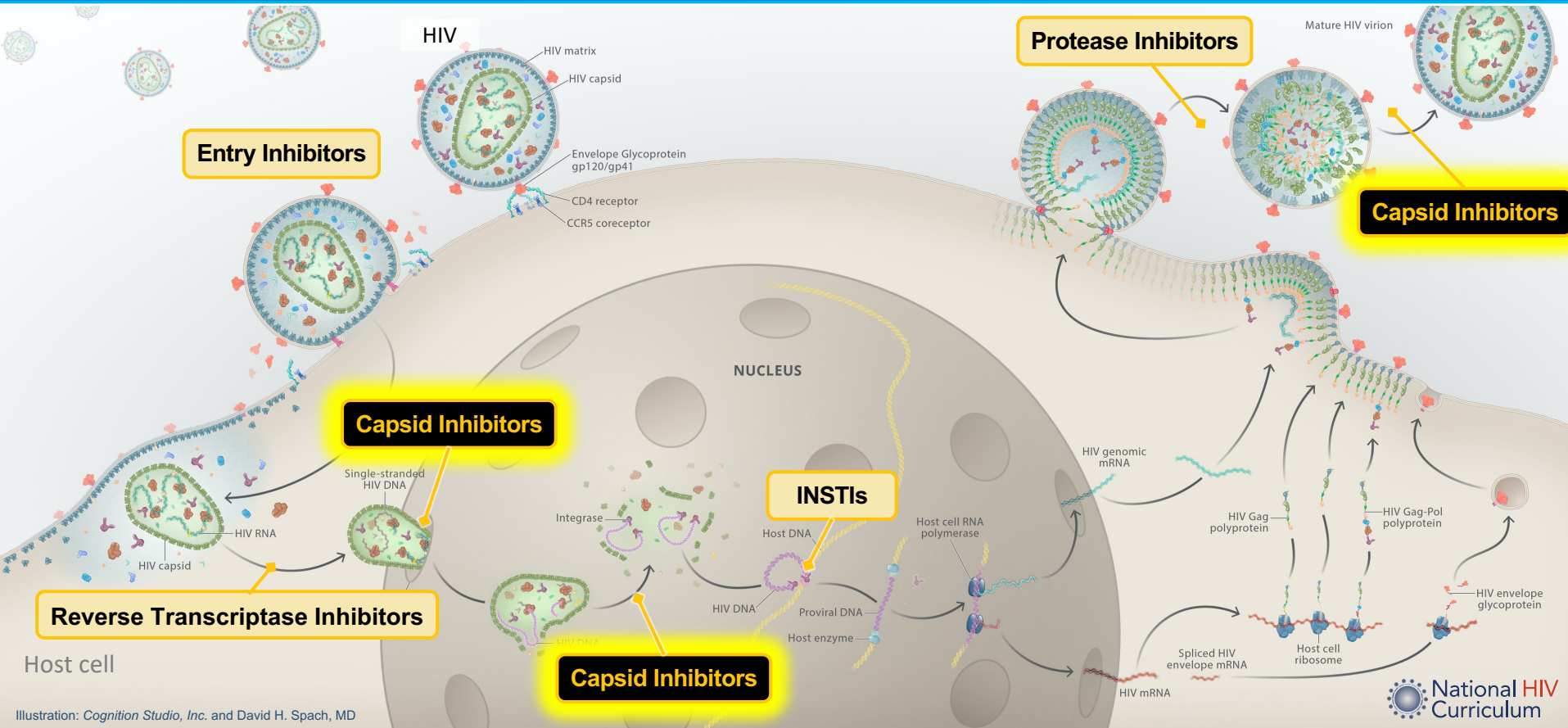
INSTIs

Reverse Transcriptase Inhibitors

Capsid Inhibitors

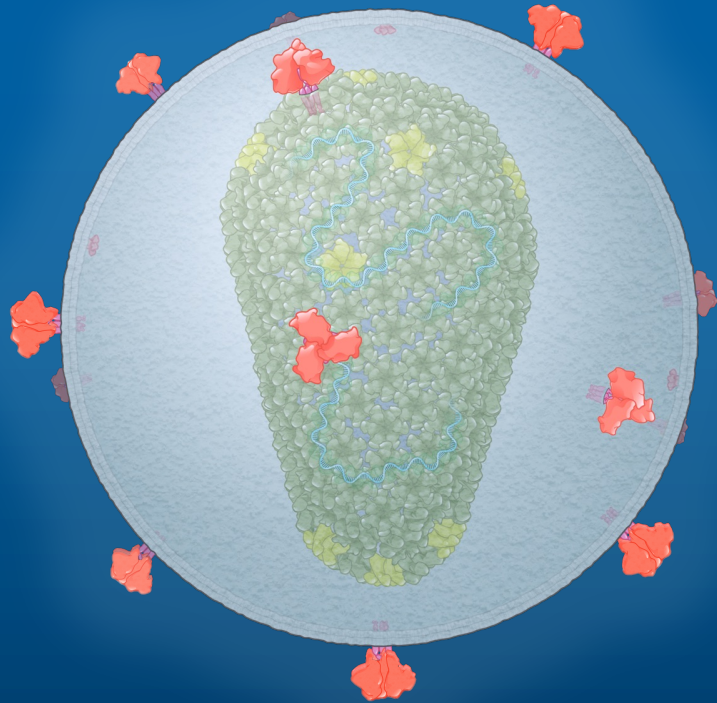
Host cell

HIV Antiretroviral Therapy: Capsid Inhibitors

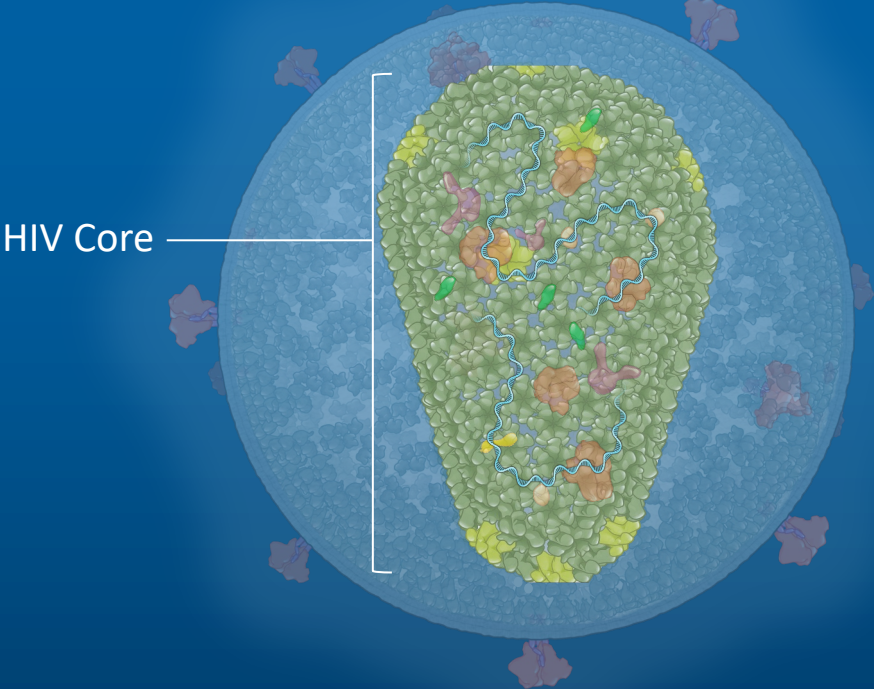


HIV Capsid Structure and Function

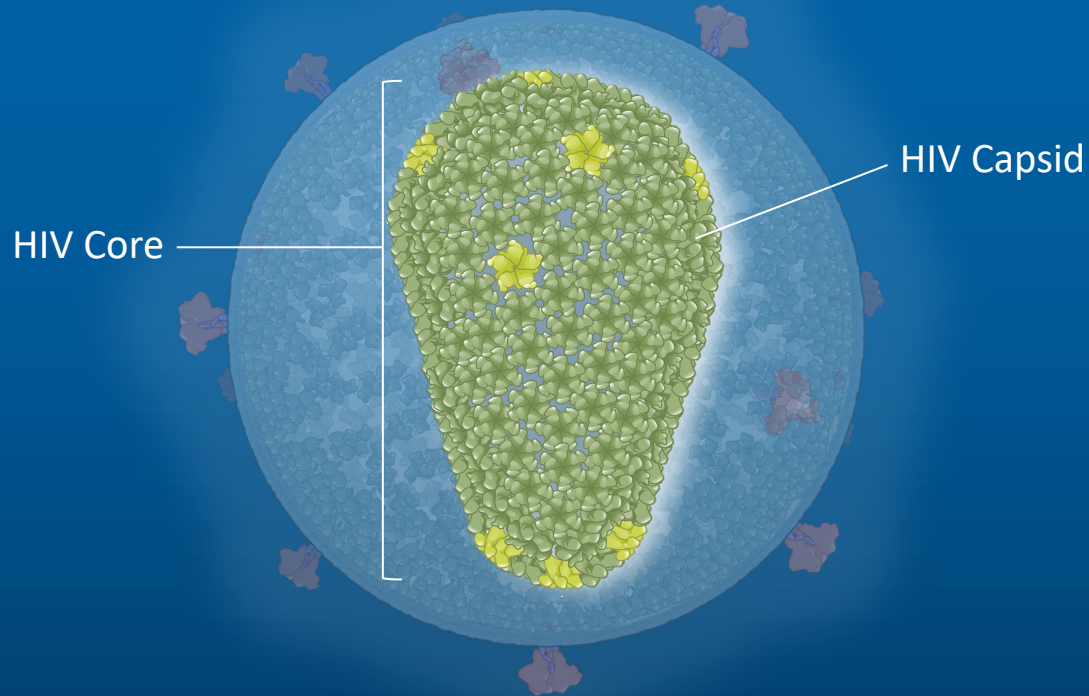
HIV



HIV Core

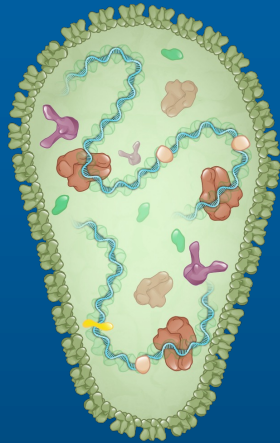


HIV Core and HIV Capsid

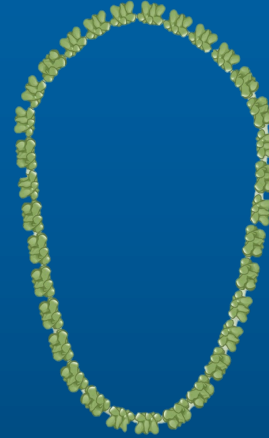


HIV Core and HIV Capsid

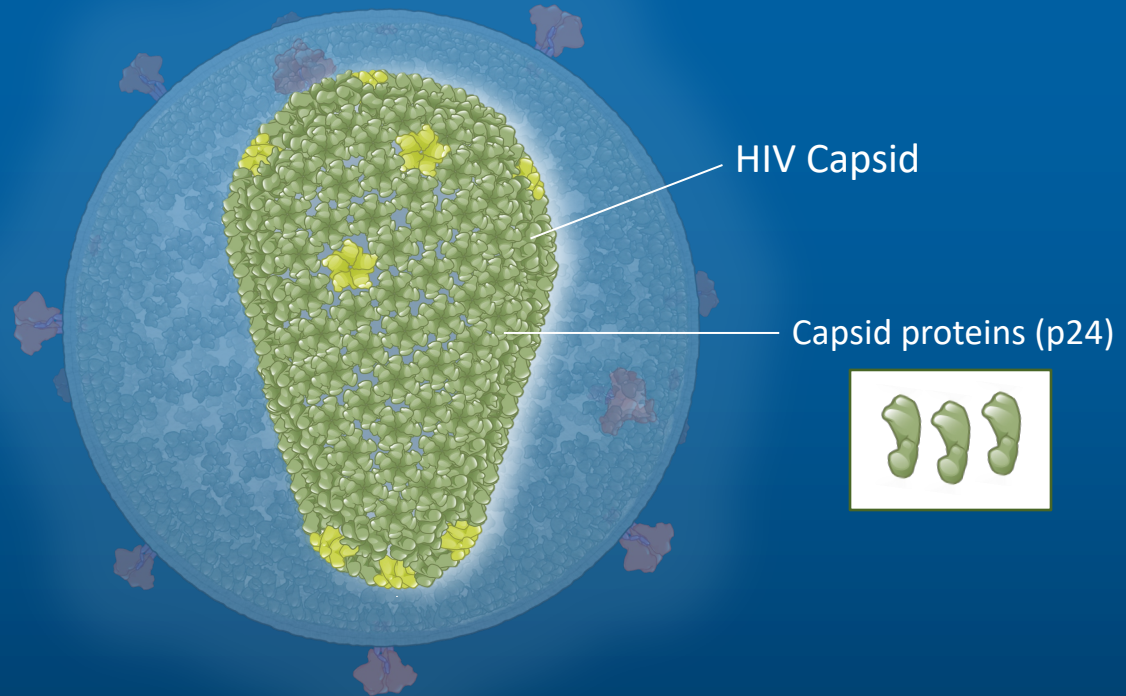
HIV Core



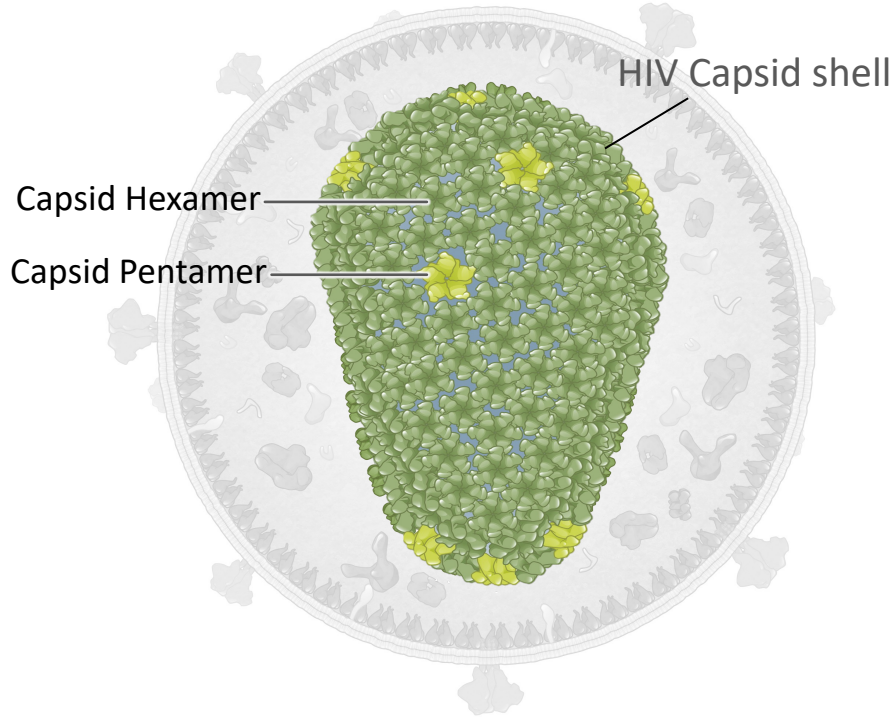
HIV Capsid



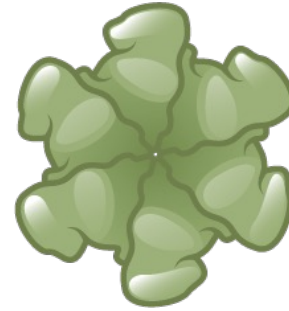
HIV Capsid Shell and Capsid Proteins



HIV Capsid Hexamers and Pentamers and HIV Capsid Shell



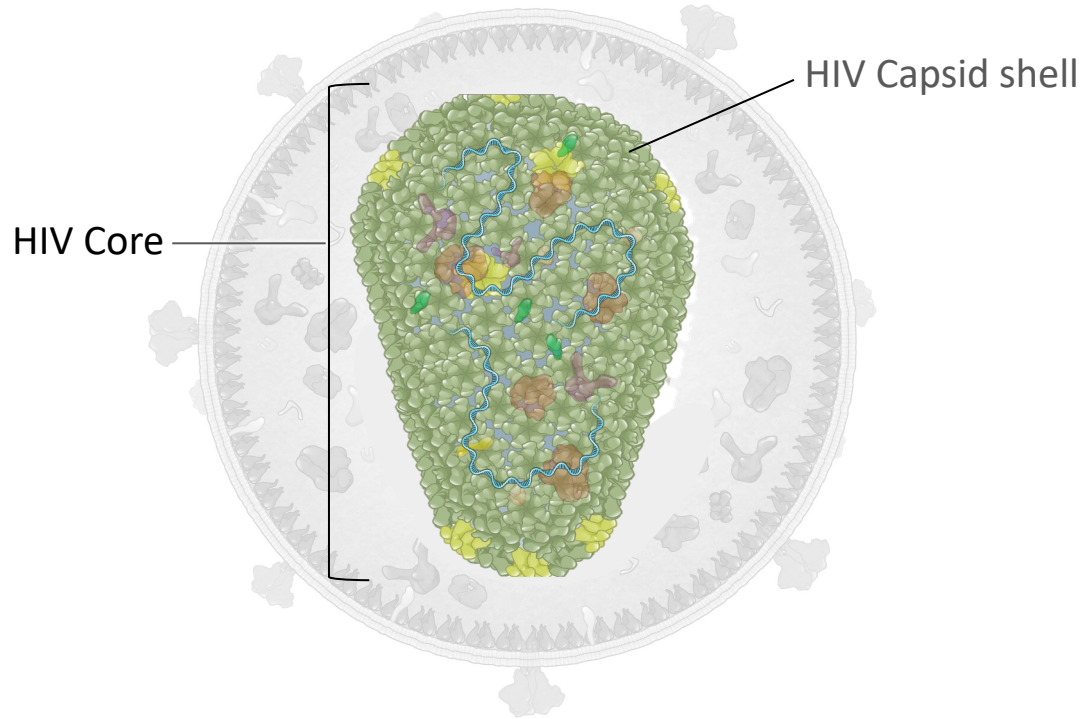
Capsid Hexamer



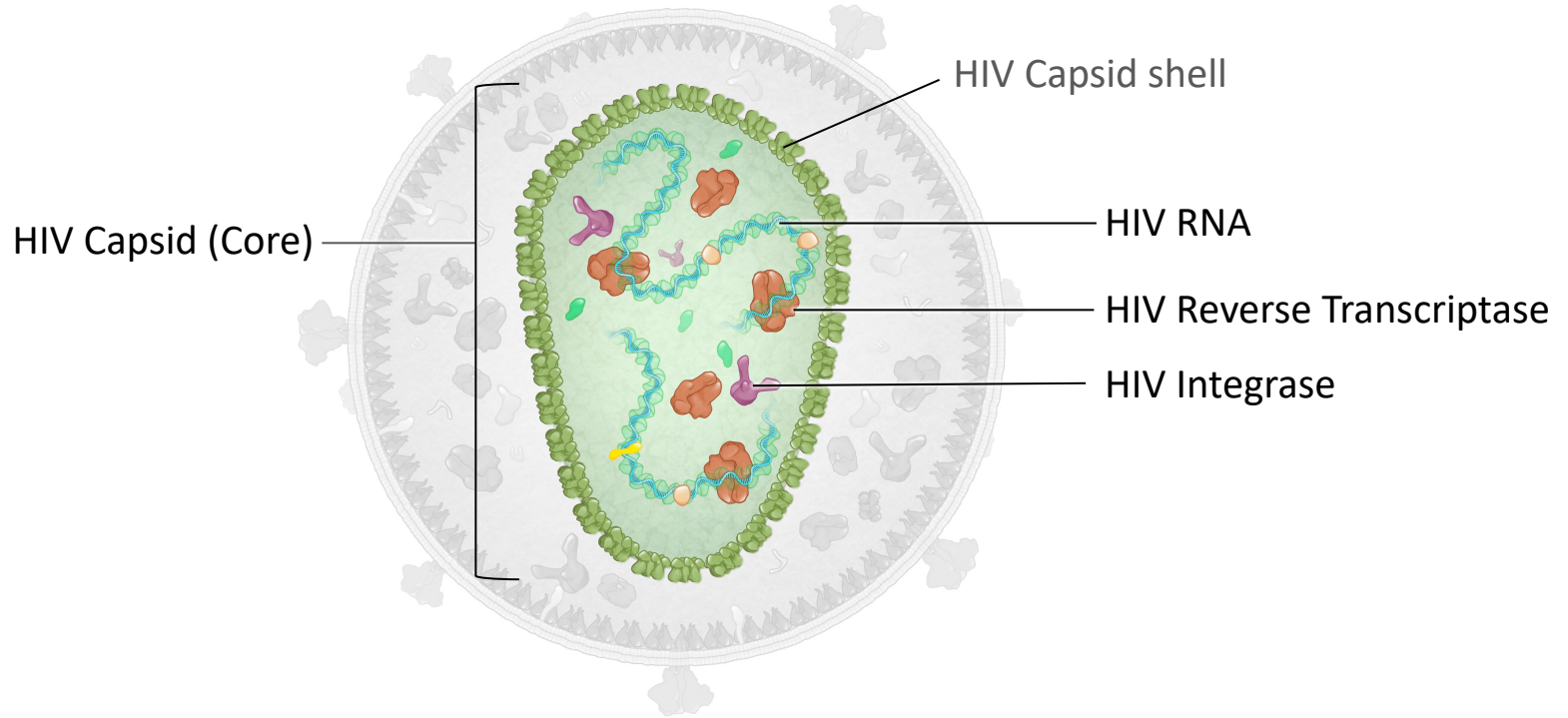
Capsid Pentamer



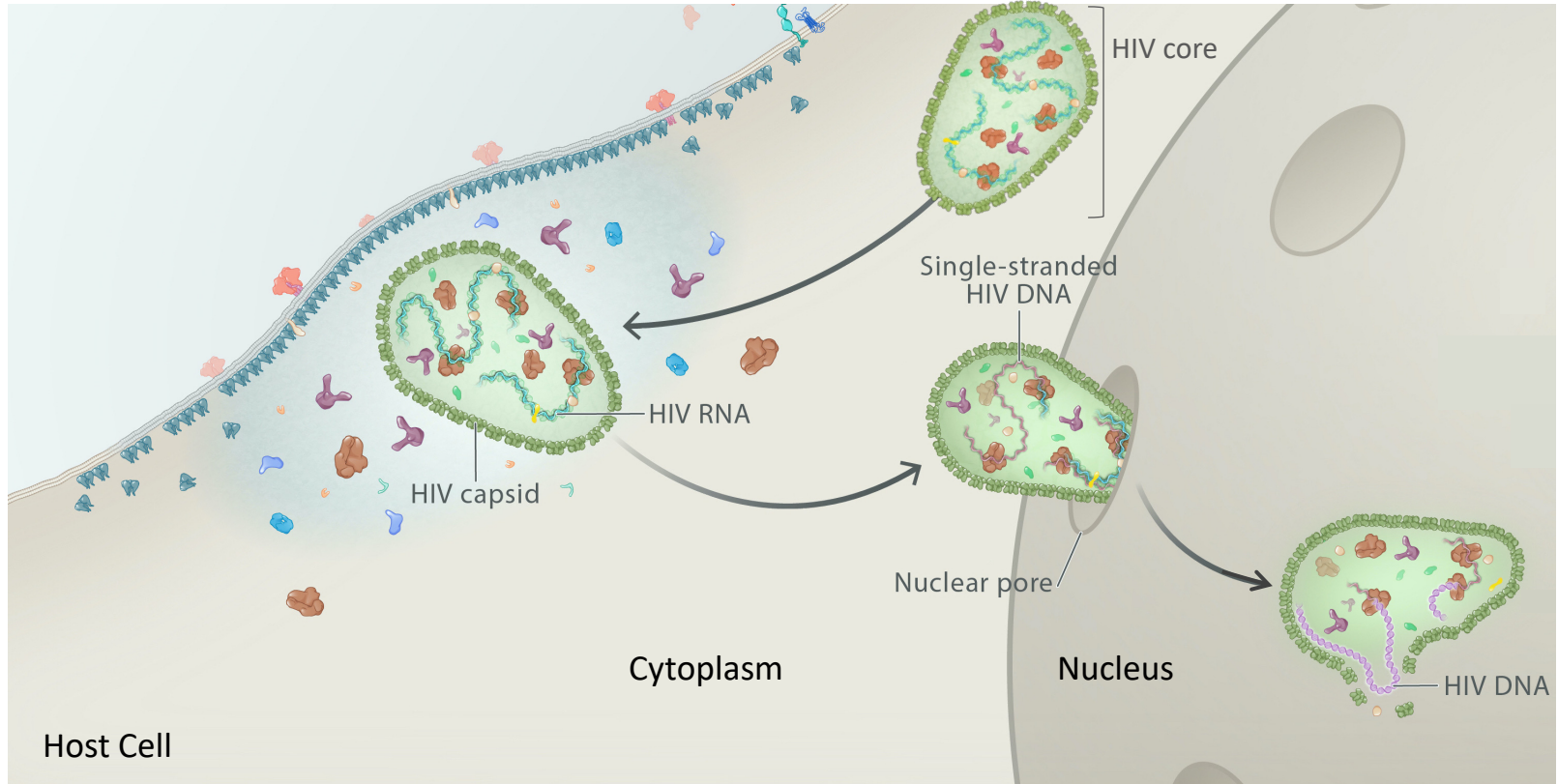
Function of HIV Core and HIV Capsid



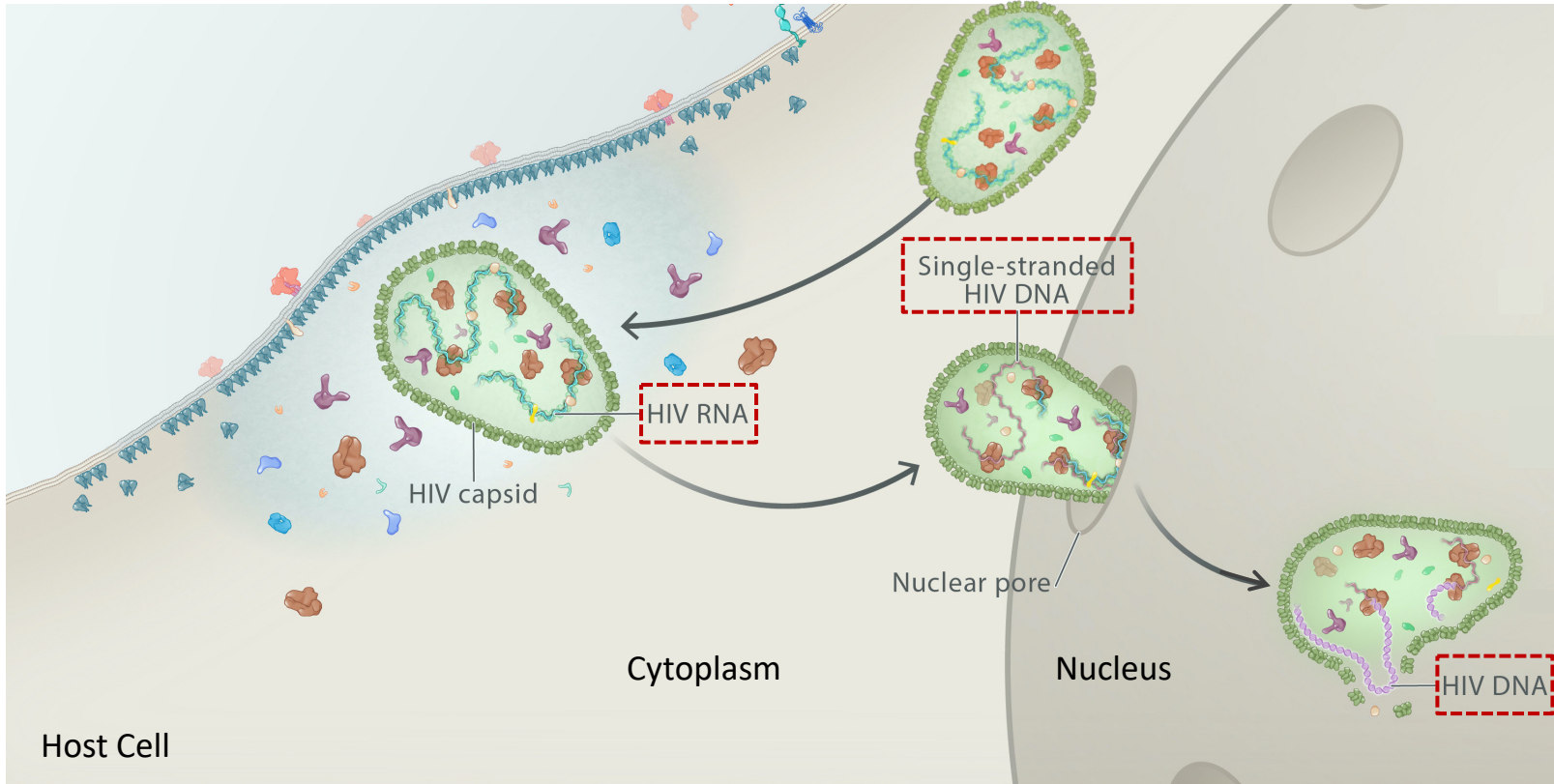
Function of HIV Core and HIV Capsid



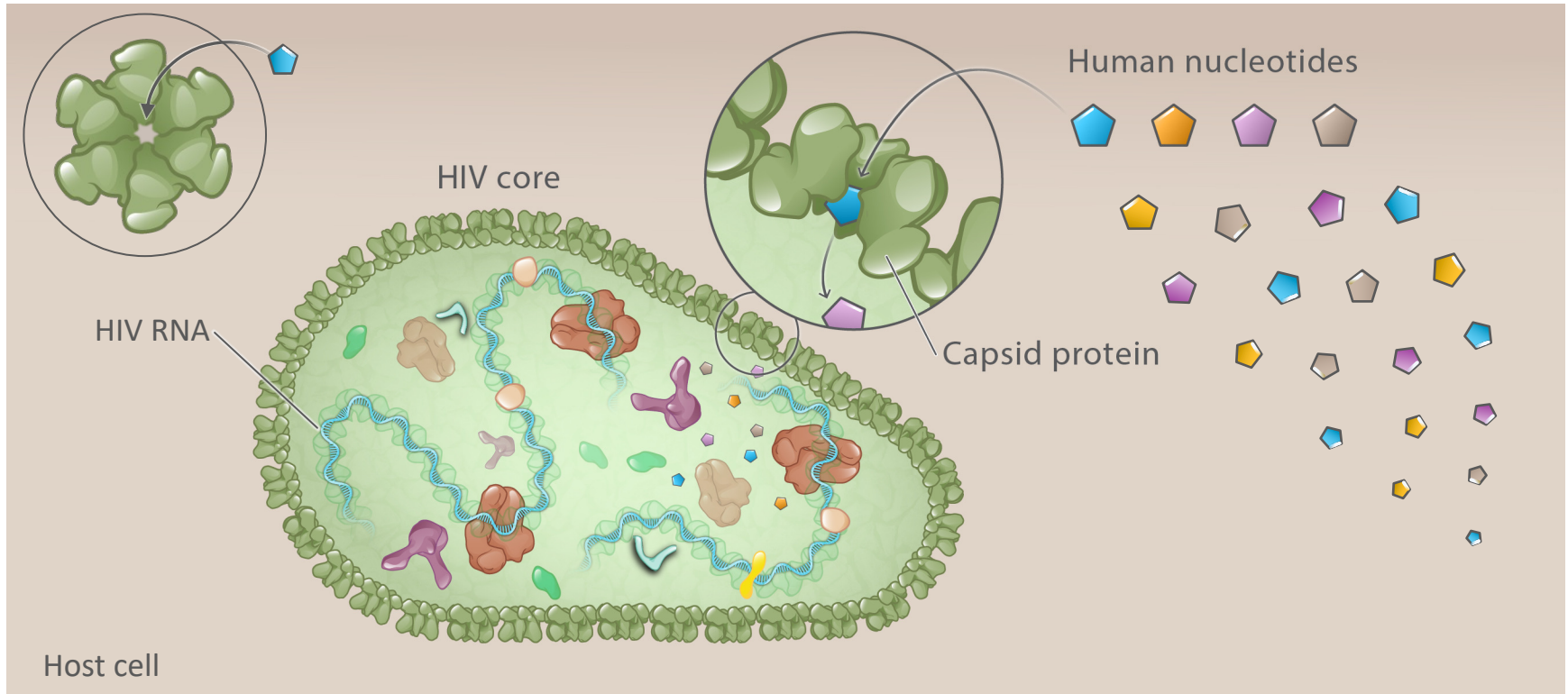
HIV Core Transport Inside Host Cell



HIV Core Transport Inside Host Cell

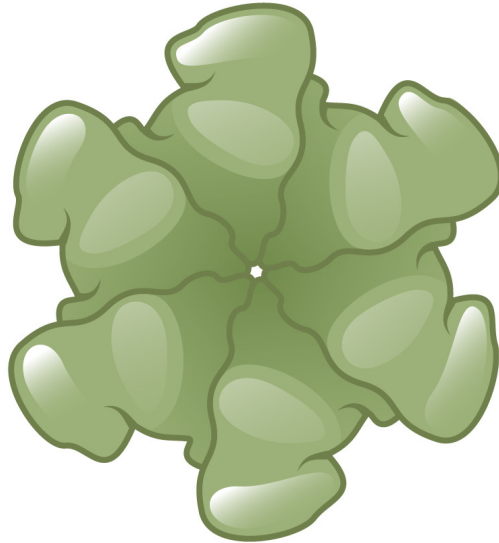


HIV Reverse Transcription



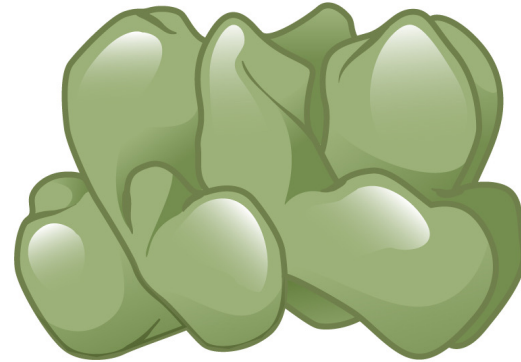
Lenacapavir and Capsid Binding

HIV Capsid Hexamer



Top view

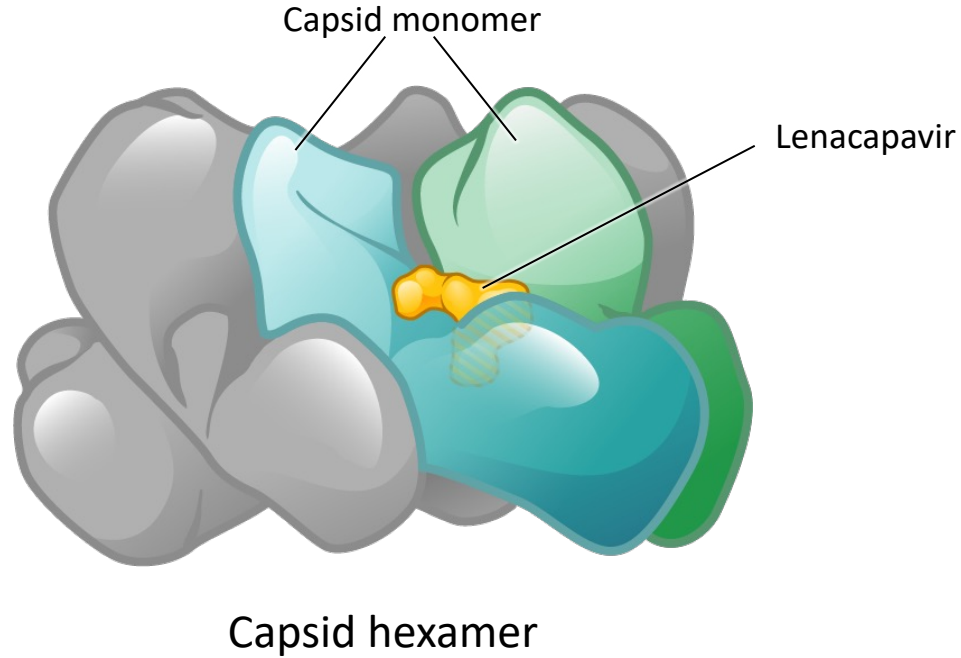
↻ 90°



Side view

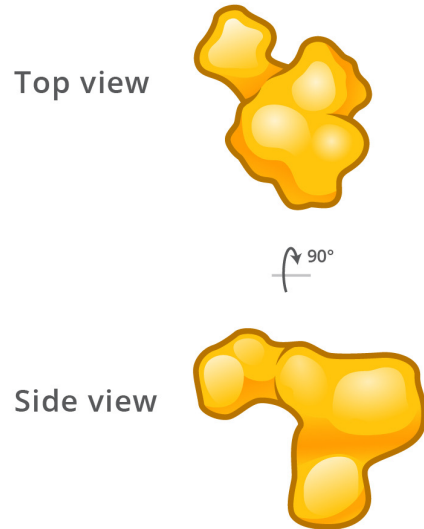
Lenacapavir Capsid Binding Pocket

Lenacapavir

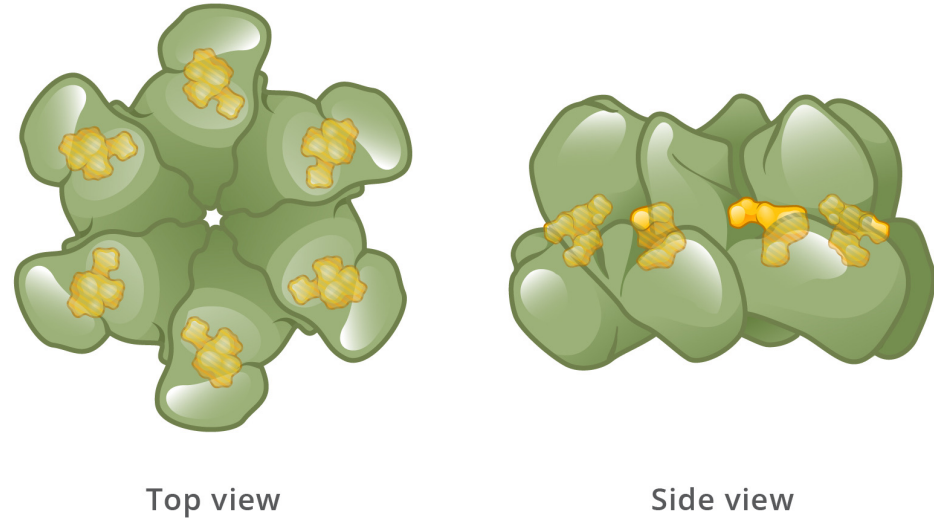


Lenacapavir Binding to Capsid Hexamer

Lenacapavir



Lenacapavir and Intra-Hexamer Binding

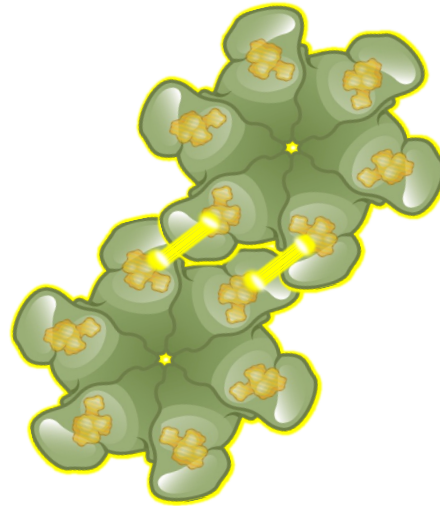


Lenacapavir Capsid Protein Binding Pocket

Lenacapavir

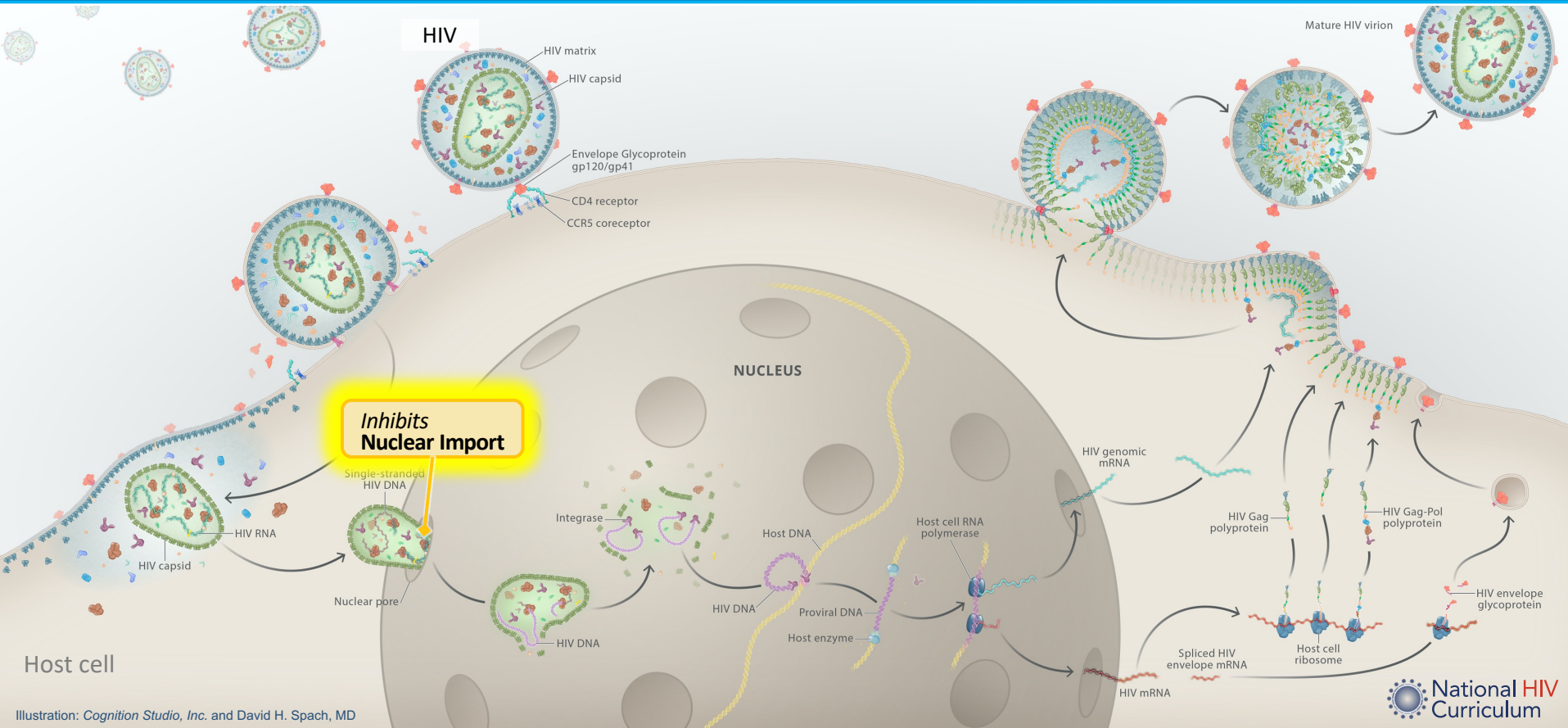


Lenacapavir and Inter-Hexamer Binding

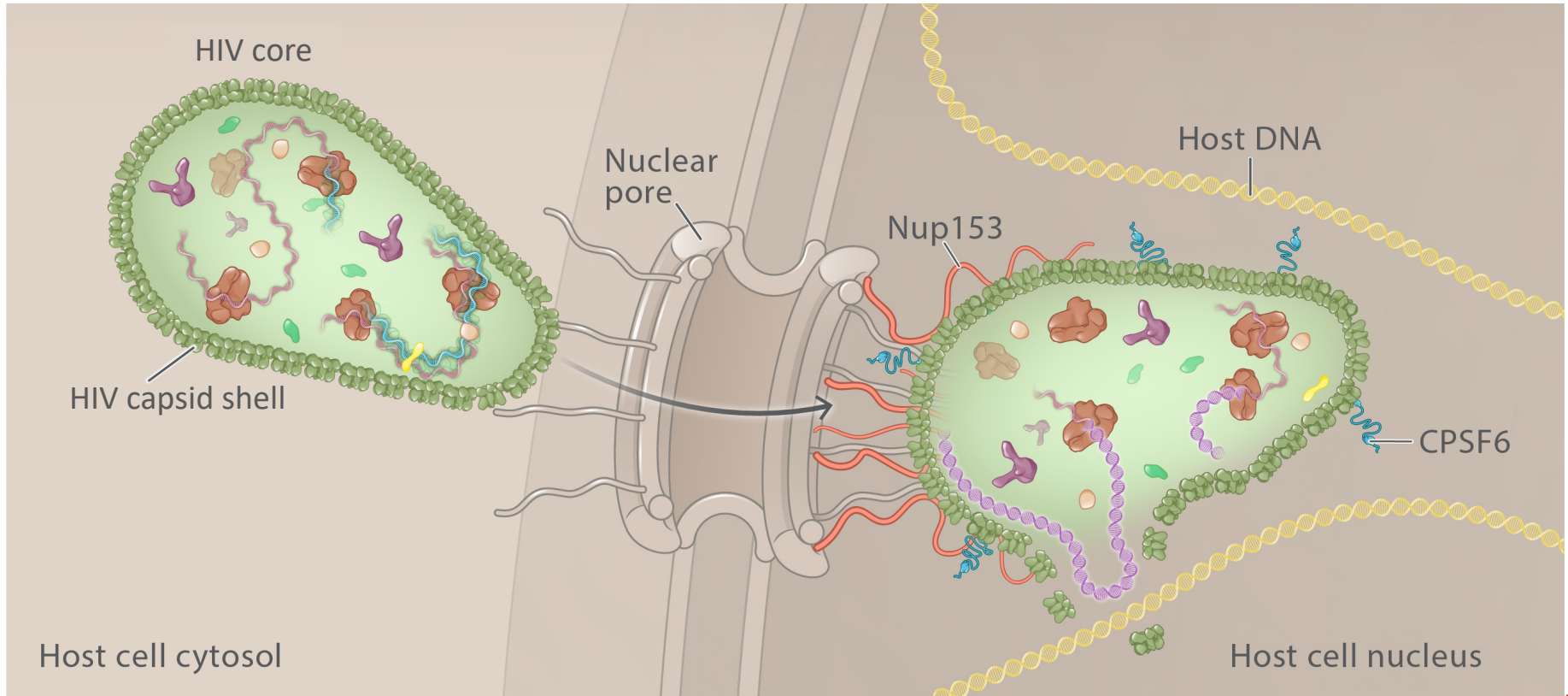


Mechanism of Action of HIV Capsid Inhibitors

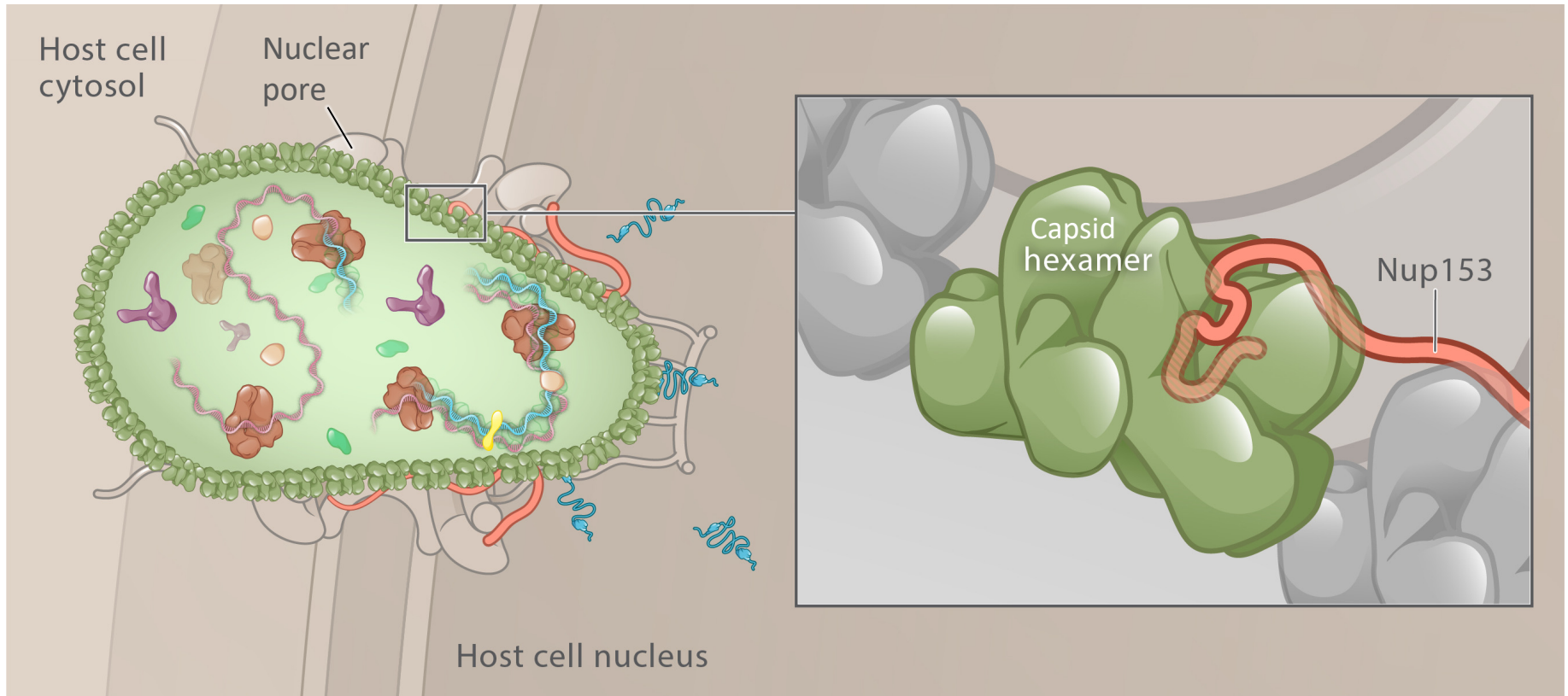
Capsid Inhibitors: Inhibition of Nuclear Import



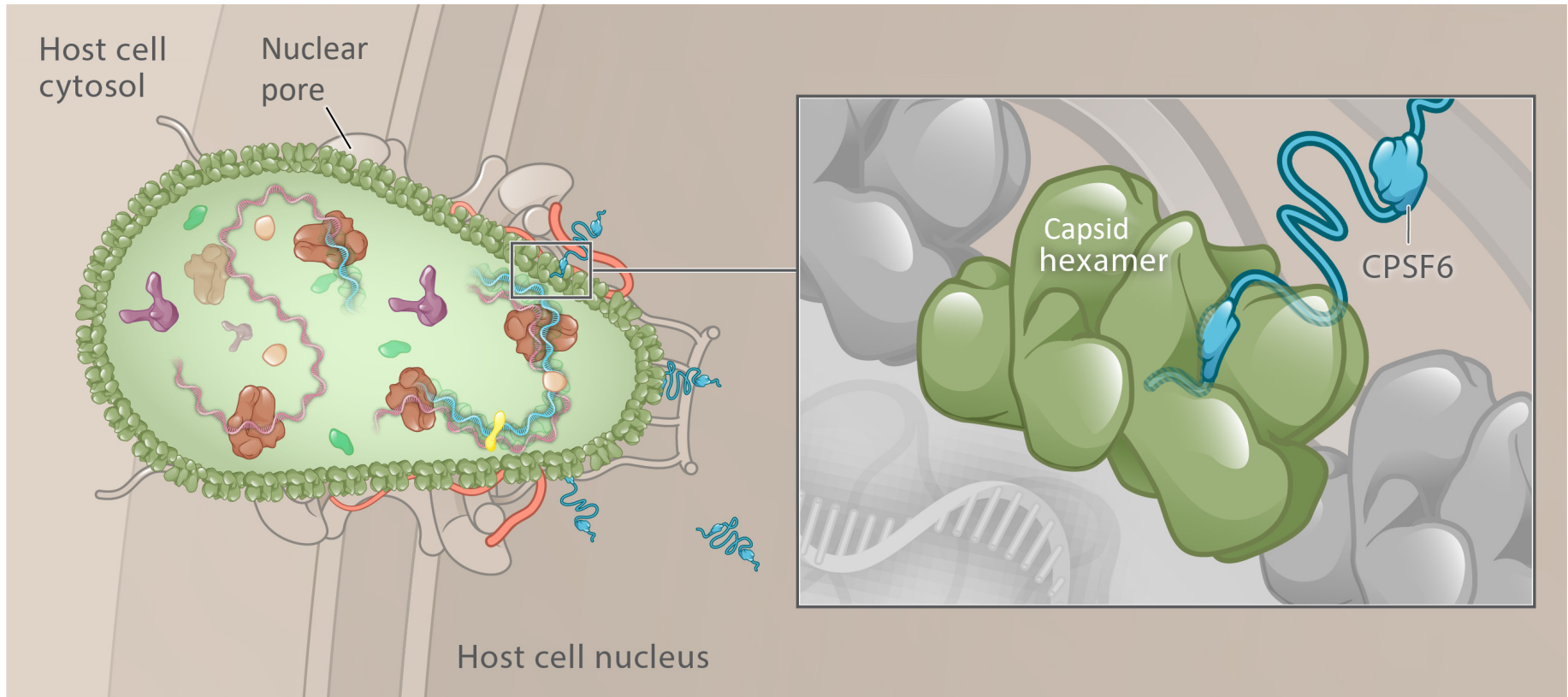
Nuclear Import and Host Proteins



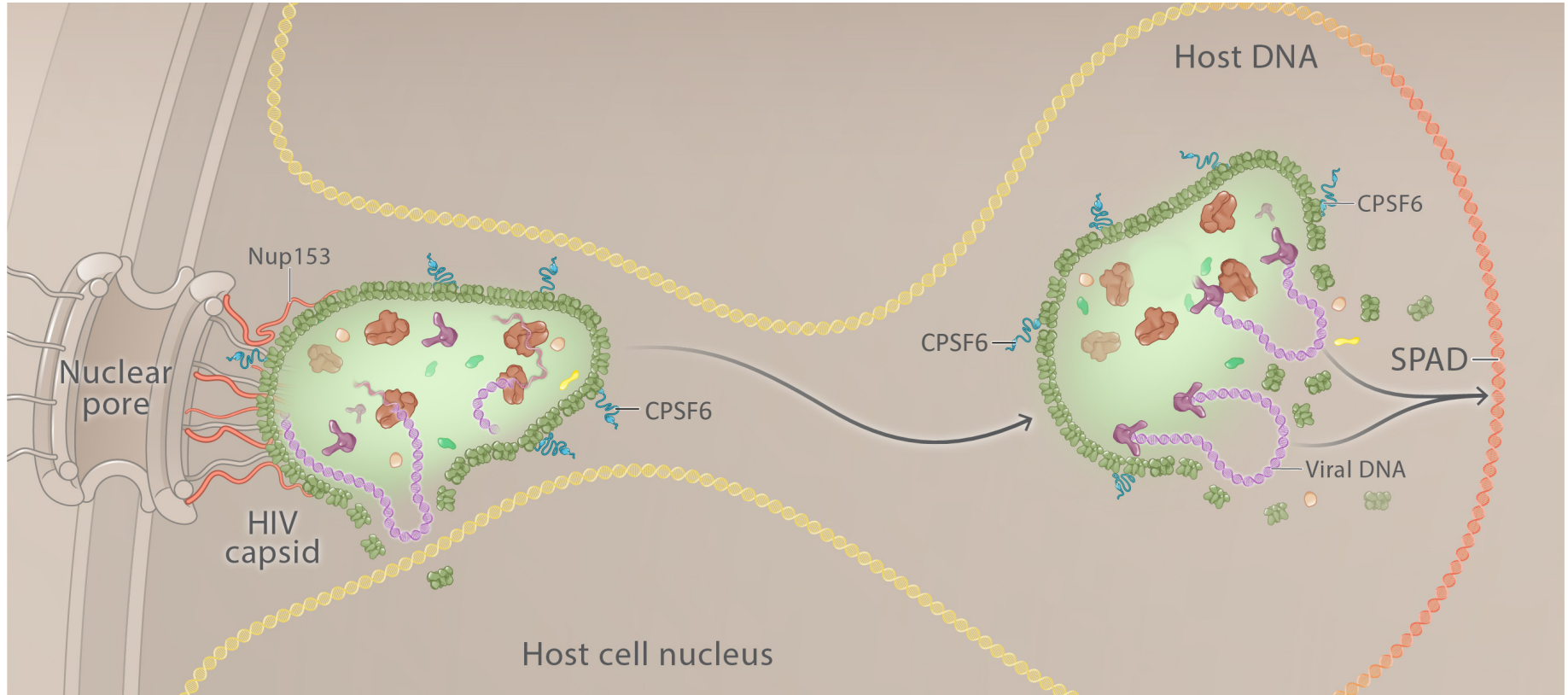
Nup 153 and Capsid Binding



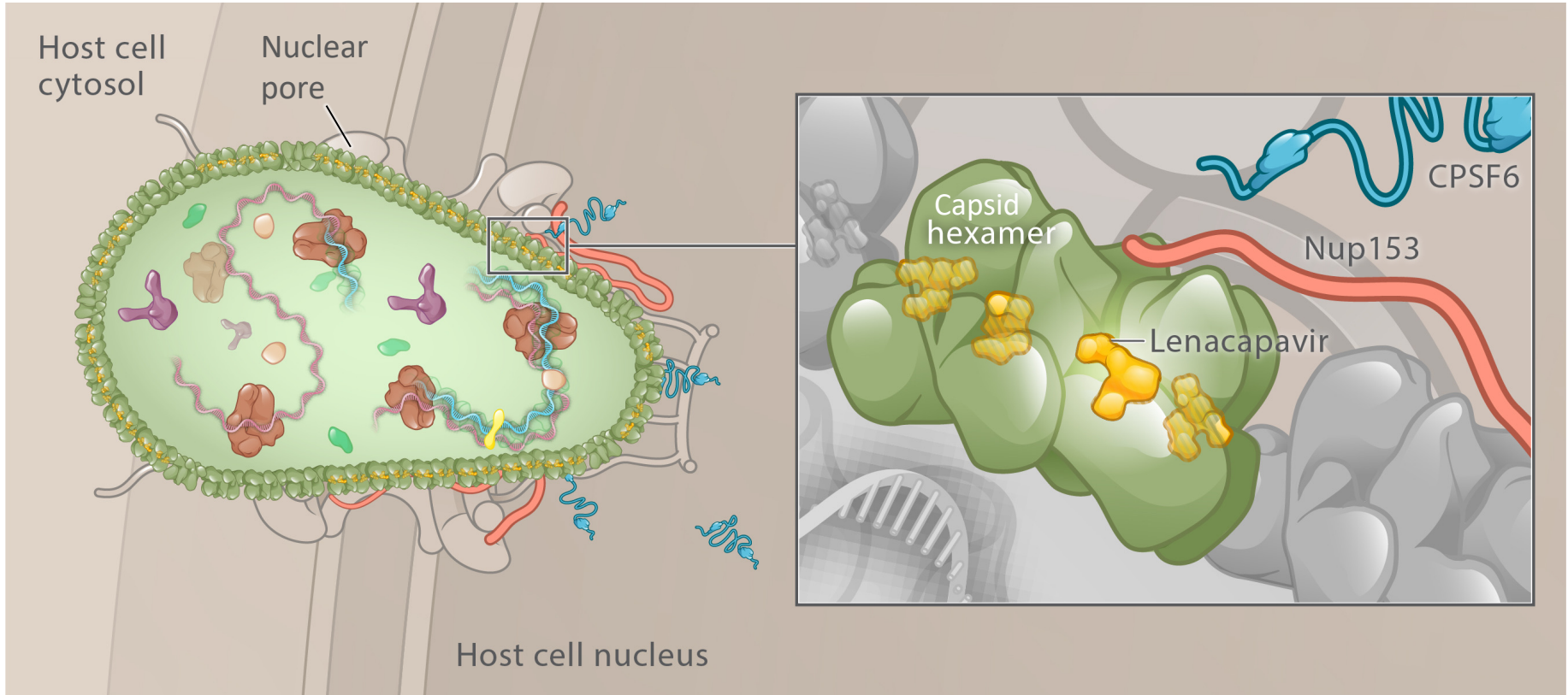
CPSF6 and Capsid Binding



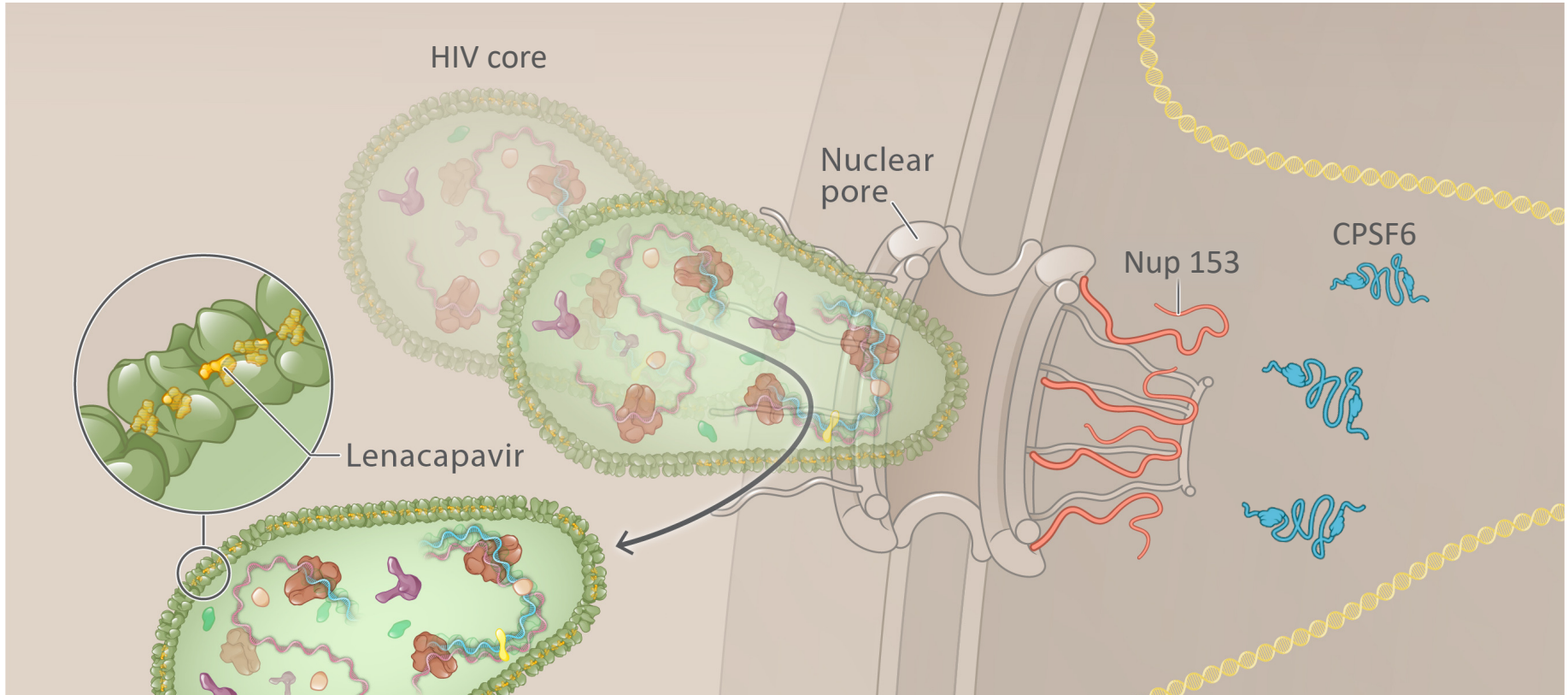
CPSF6 Augmented Capsid Migration to Host DNA SPAD Region



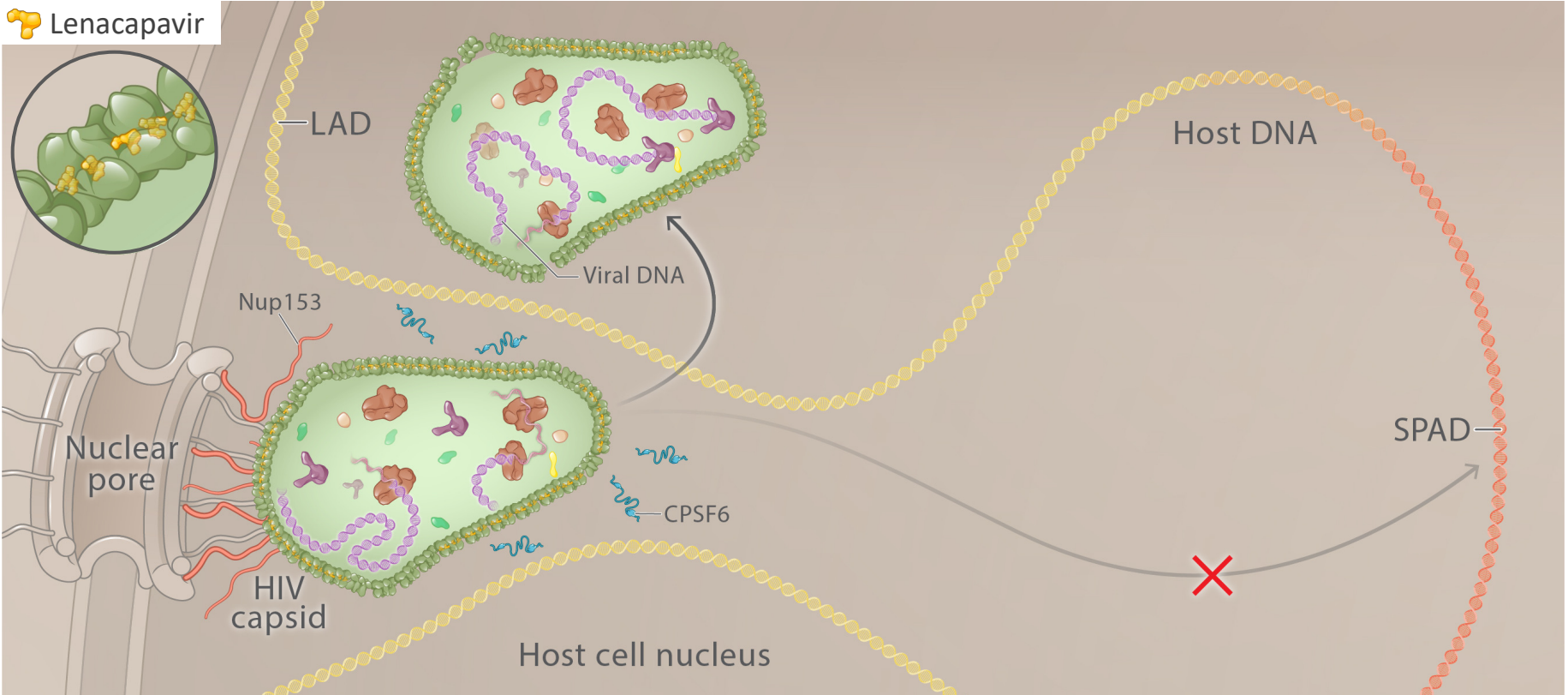
Lenacapavir Inhibition of Nup 153 and CPSF6 Capsid Binding



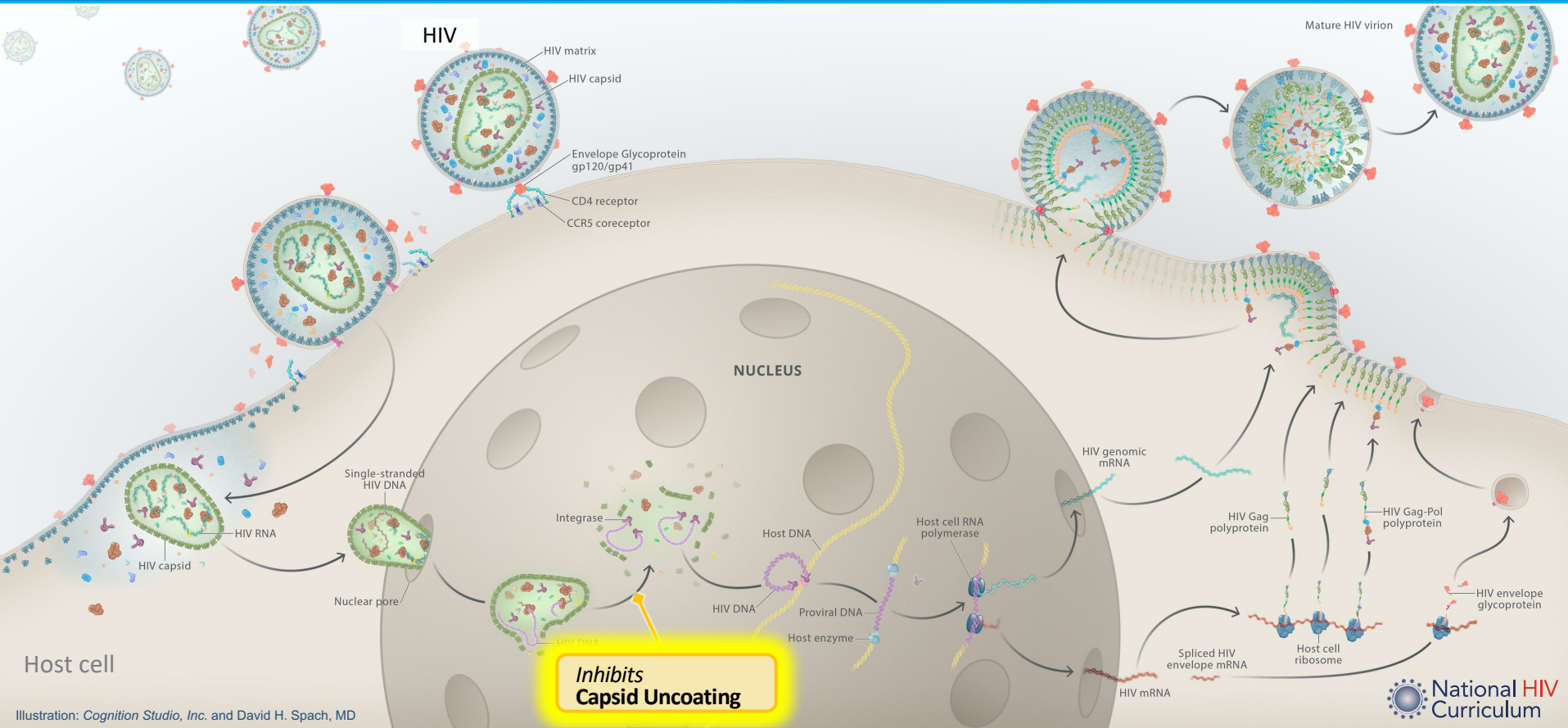
Lenacapavir and Inhibition of Nuclear Pore Transport



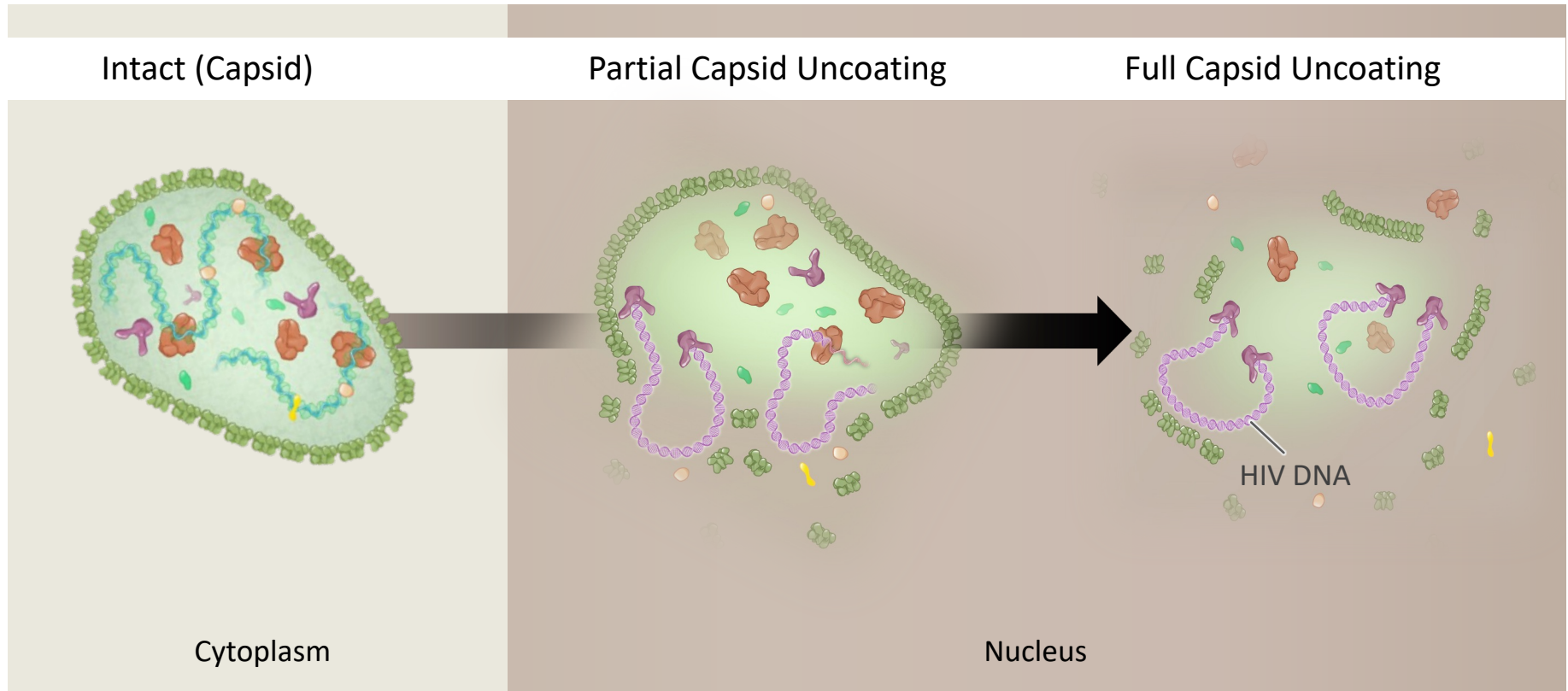
Lenacapavir and Inhibition of Capsid Migration to Host DNA



Capsid Inhibitors: Inhibition of Capsid Uncoating

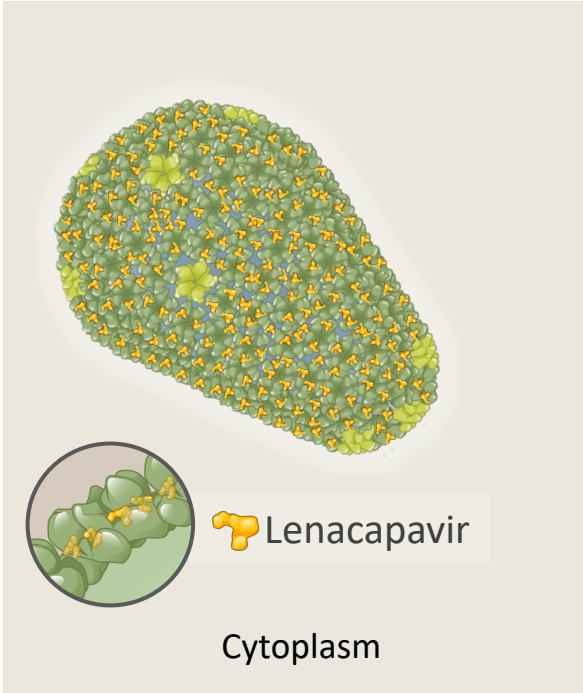


Capsid Uncoating



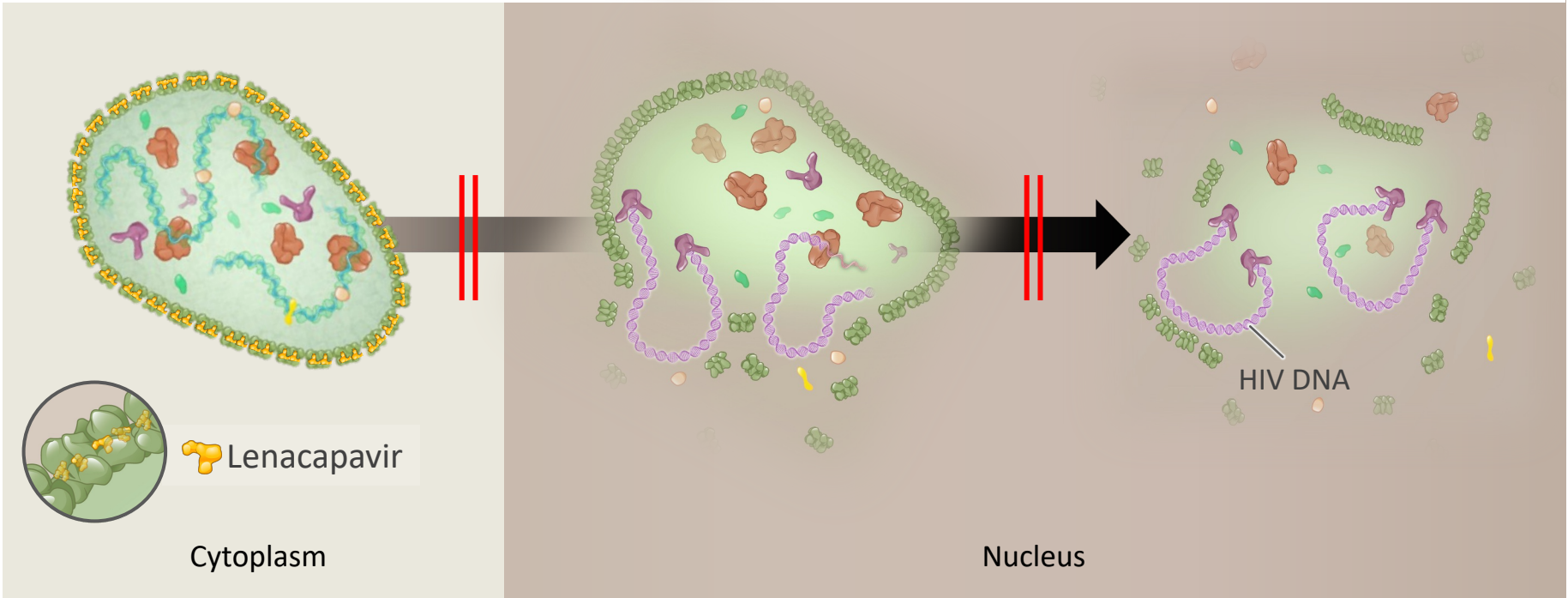
Lenacapavir and Inhibition of Capsid Uncoating

Lenacapavir Stabilized Capsid



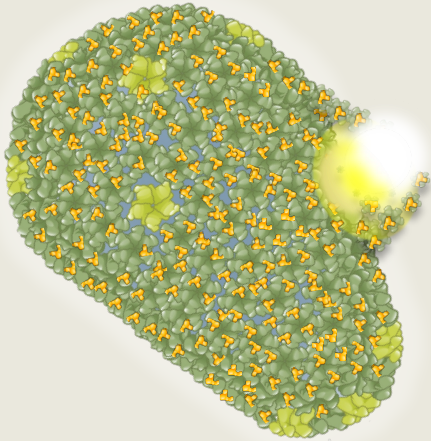
Lenacapavir and Inhibition of Capsid Uncoating


Lenacapavir Stabilized Capsid



Premature Capsid Disassembly

Lenacapavir Stabilized Capsid

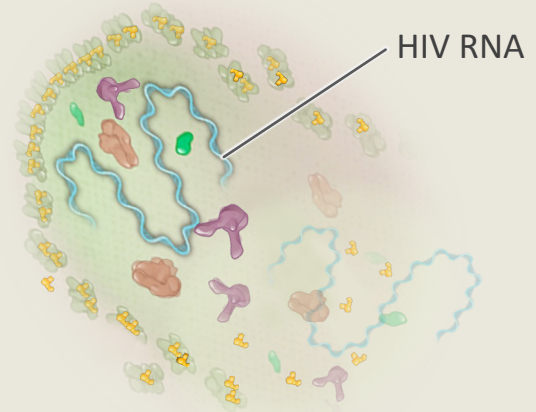


 Lenacapavir

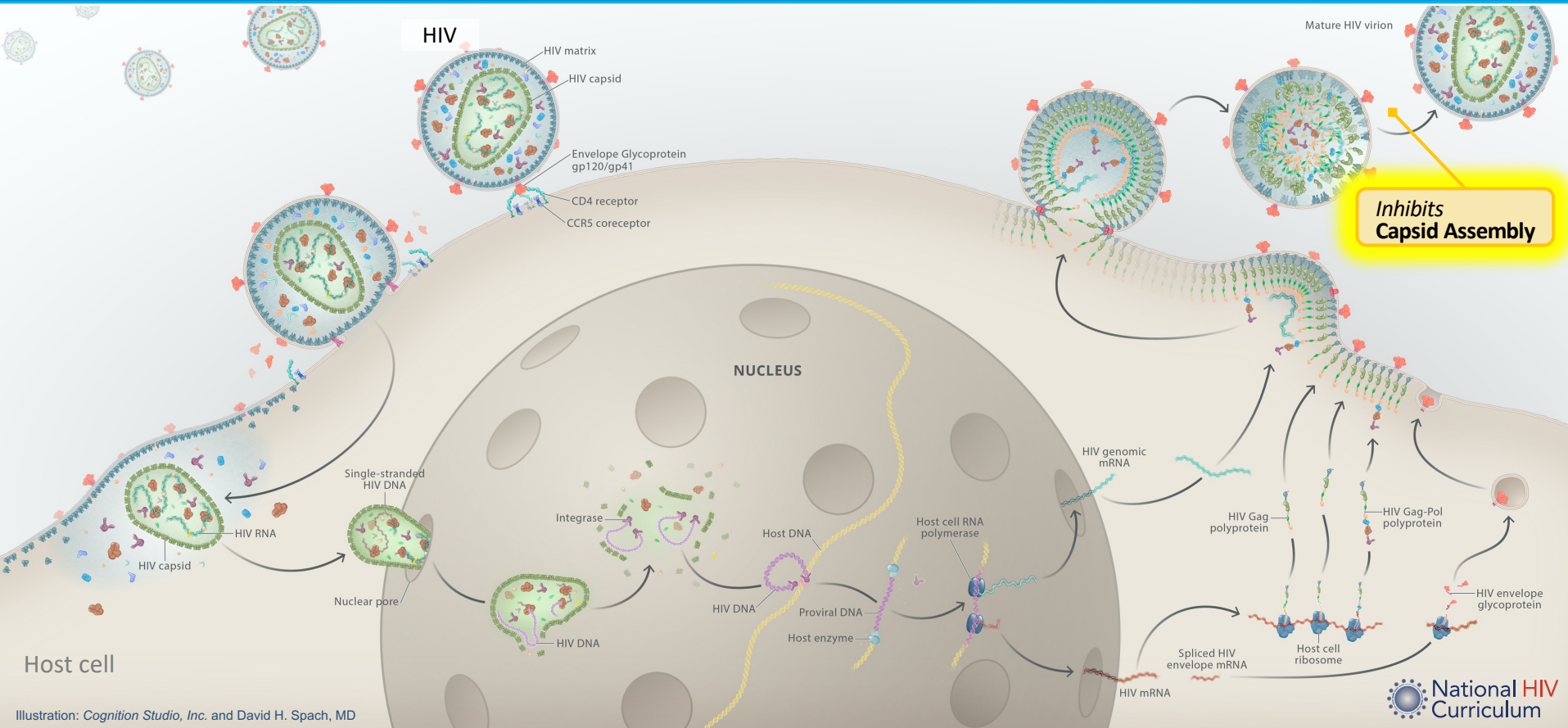
Premature Capsid Rupture



Failure to Convert HIV RNA to HIV DNA

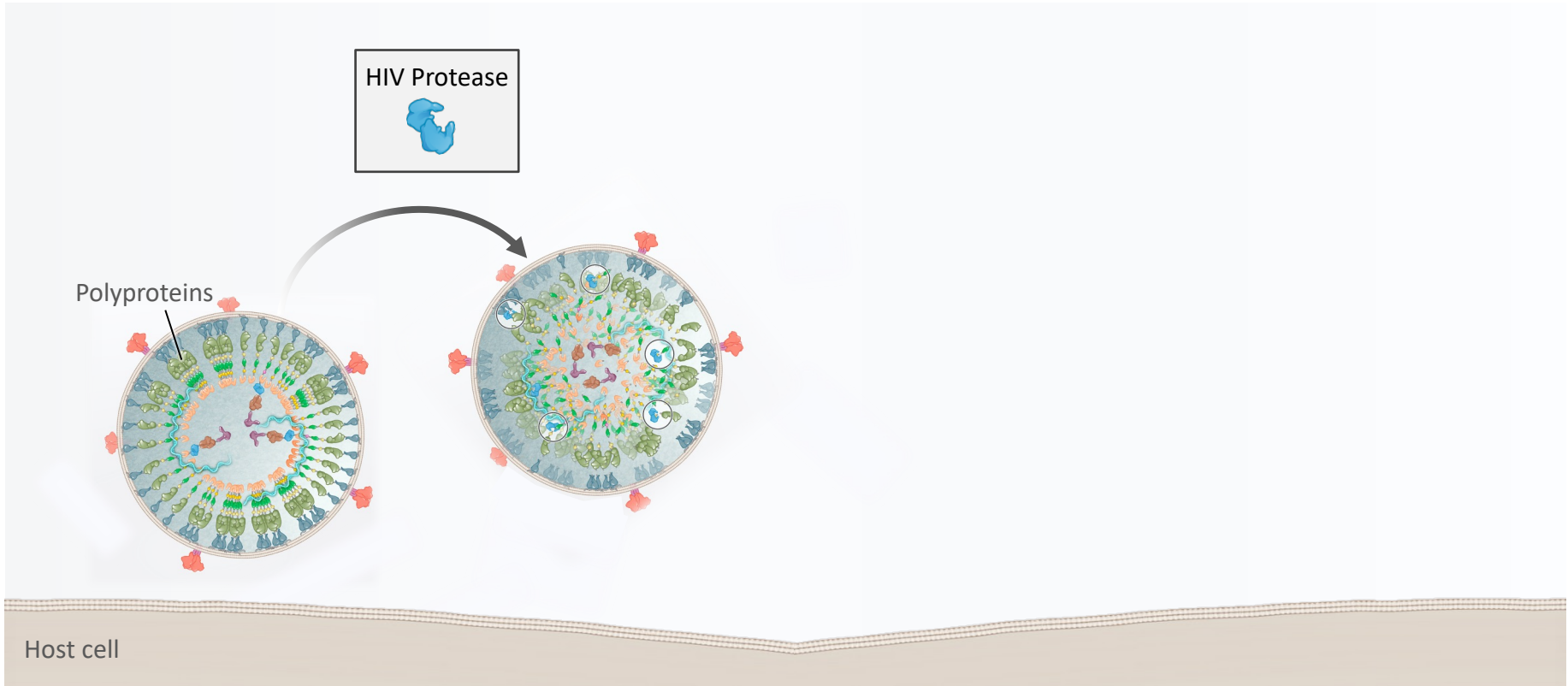


Capsid Inhibitors: Inhibition of Capsid Assembly

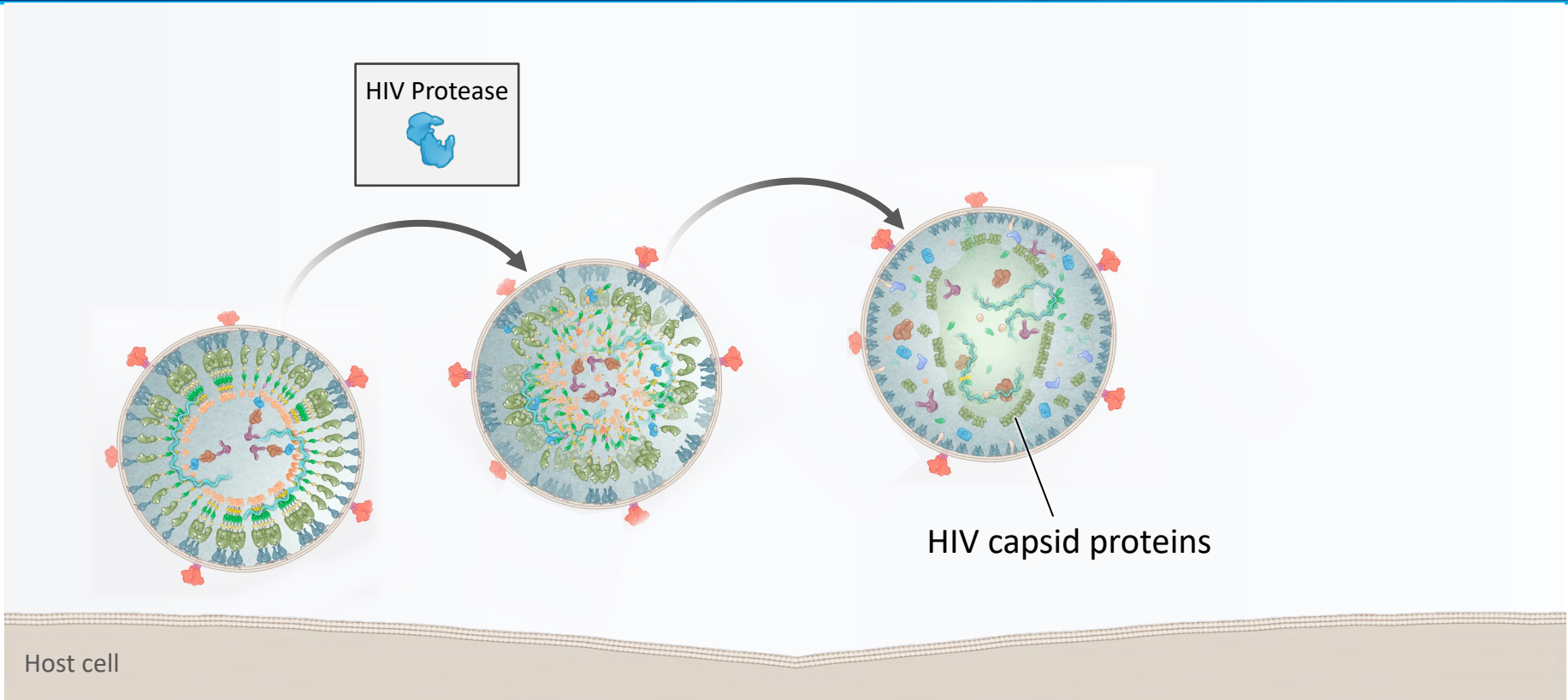


Host cell

HIV Maturation



HIV Capsid (Core) Formation

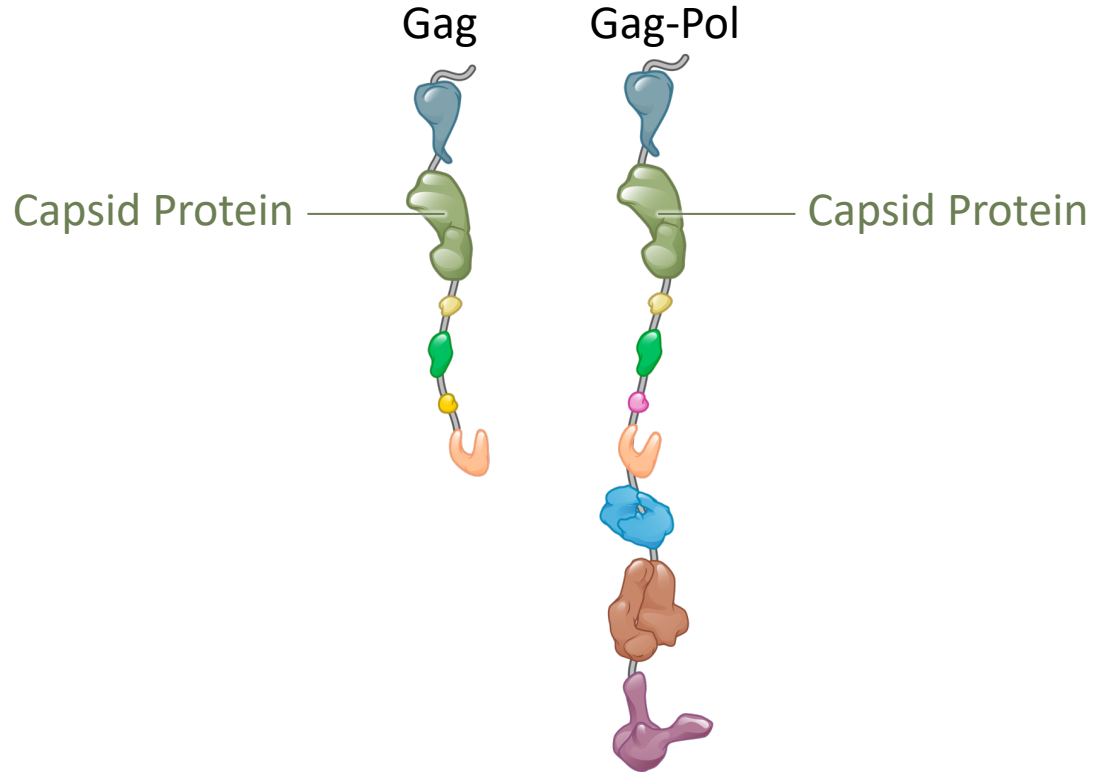


HIV Capsid (Core) Formation

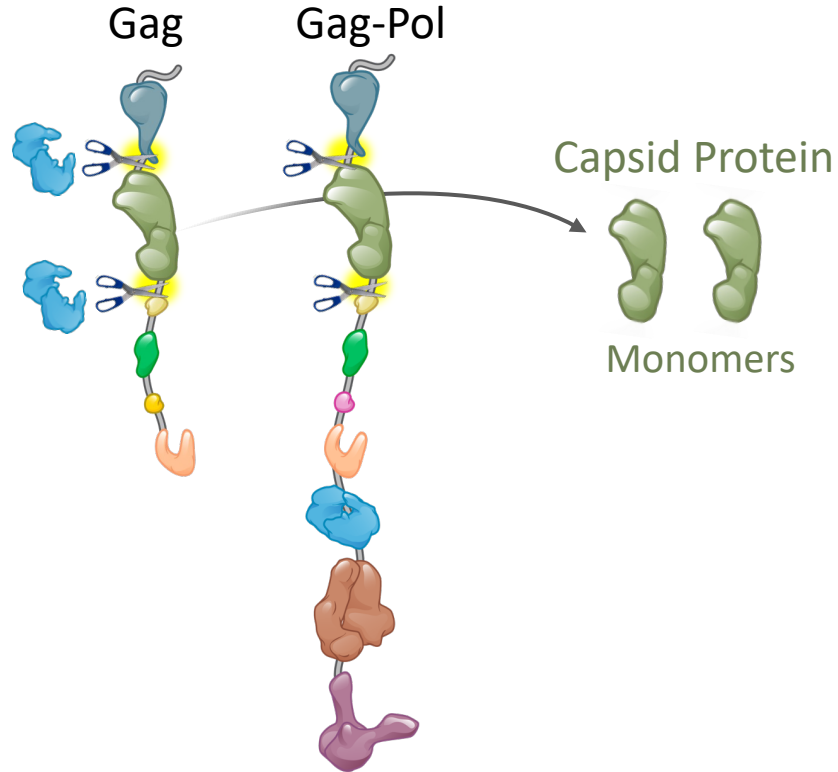


Host cell

HIV Polyproteins



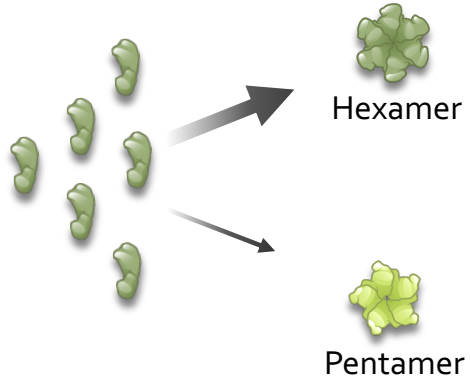
Polyprotein Cleavage



HIV Capsid Formation

Monomers

Polymers

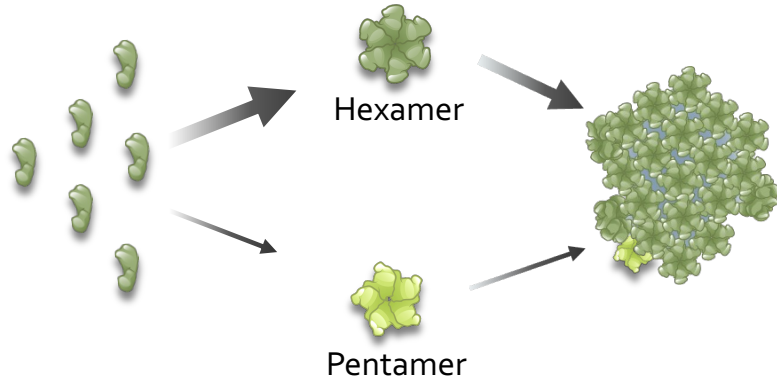


HIV Capsid Formation

Monomers

Polymers

Clusters



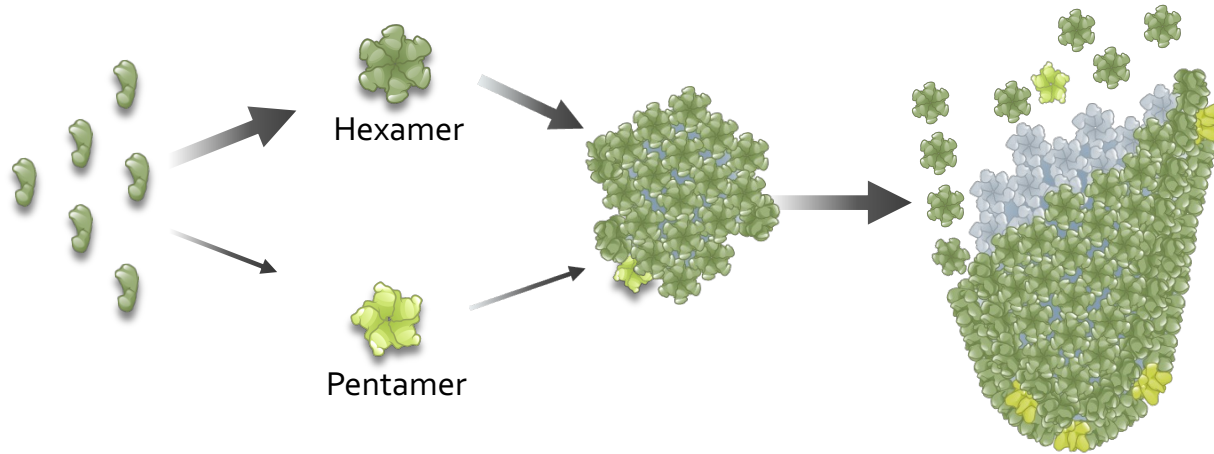
HIV Capsid Formation

Monomers

Polymers

Clusters

Early Capsid Assembly



HIV Capsid Formation

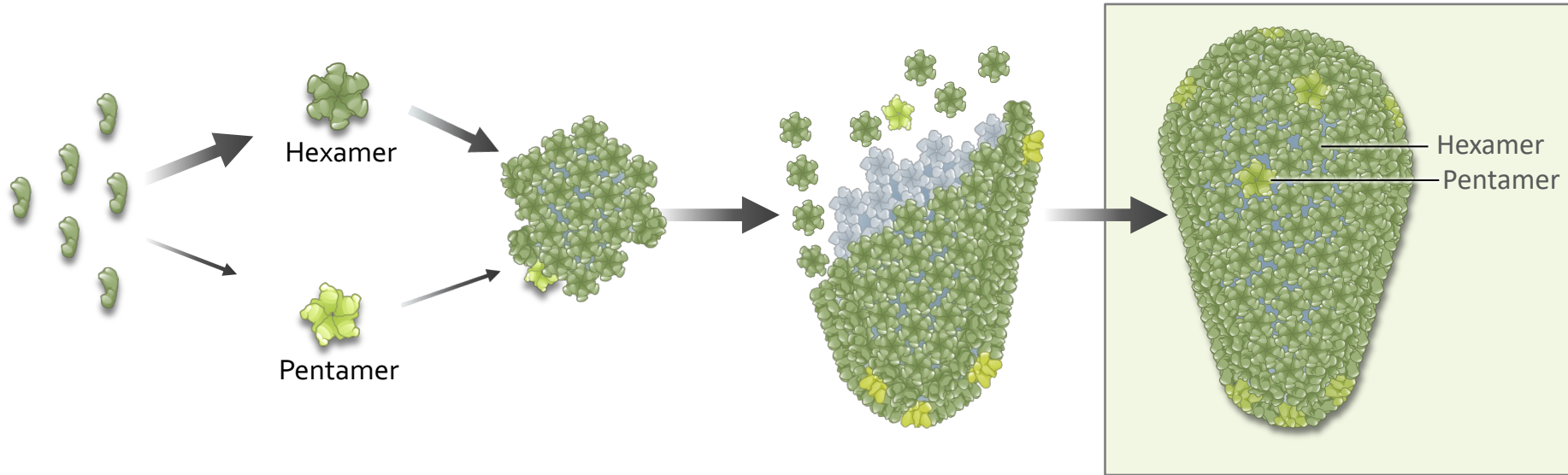
Monomers

Polymers

Clusters

Early Capsid Assembly

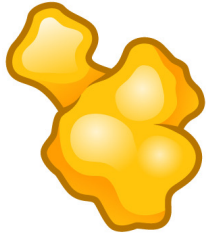
HIV Capsid



Lenacapavir Bound to Capsid (p24) Hexamer

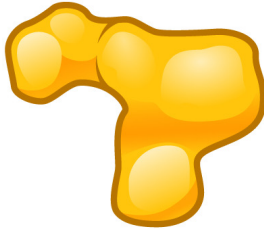
Lenacapavir

Top view

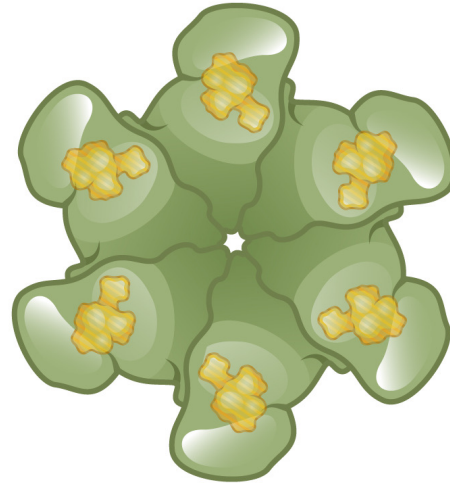


↻ 90°

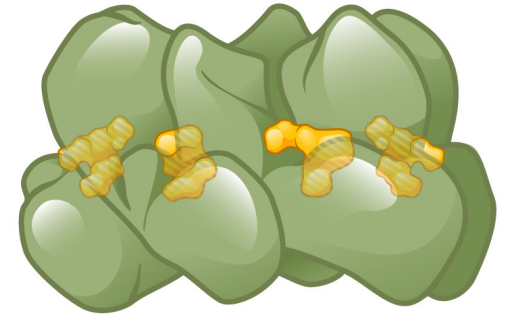
Side view



Lenacapavir within p24 hexamer



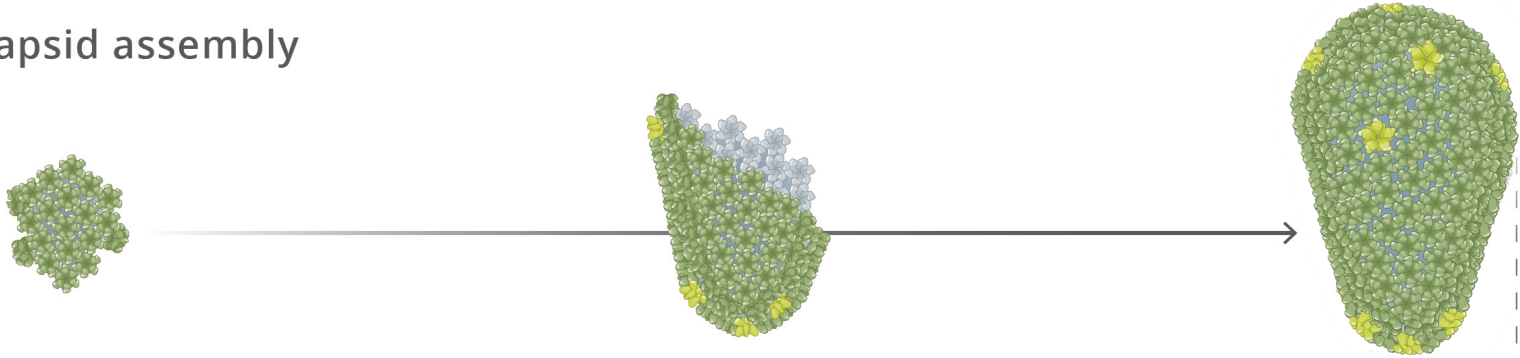
Top view



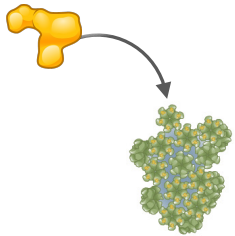
Side view

HIV Capsid Assembly: Impact of Lenacapavir

HIV capsid assembly



Lenacapavir-bound capsid assembly

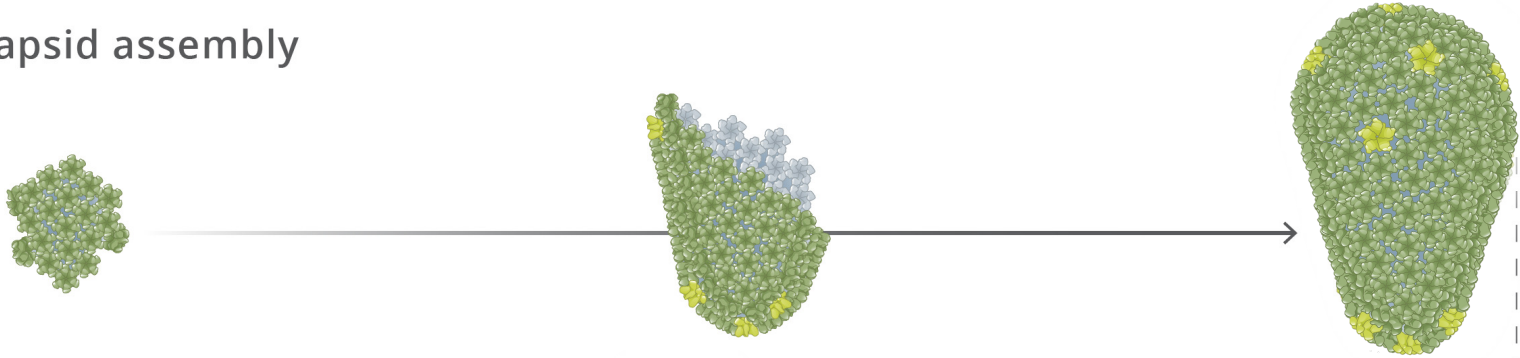


TIME

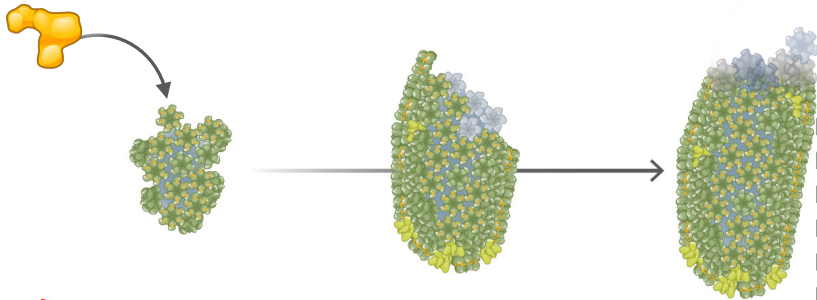


HIV Capsid Assembly: Impact of Lenacapavir

HIV capsid assembly



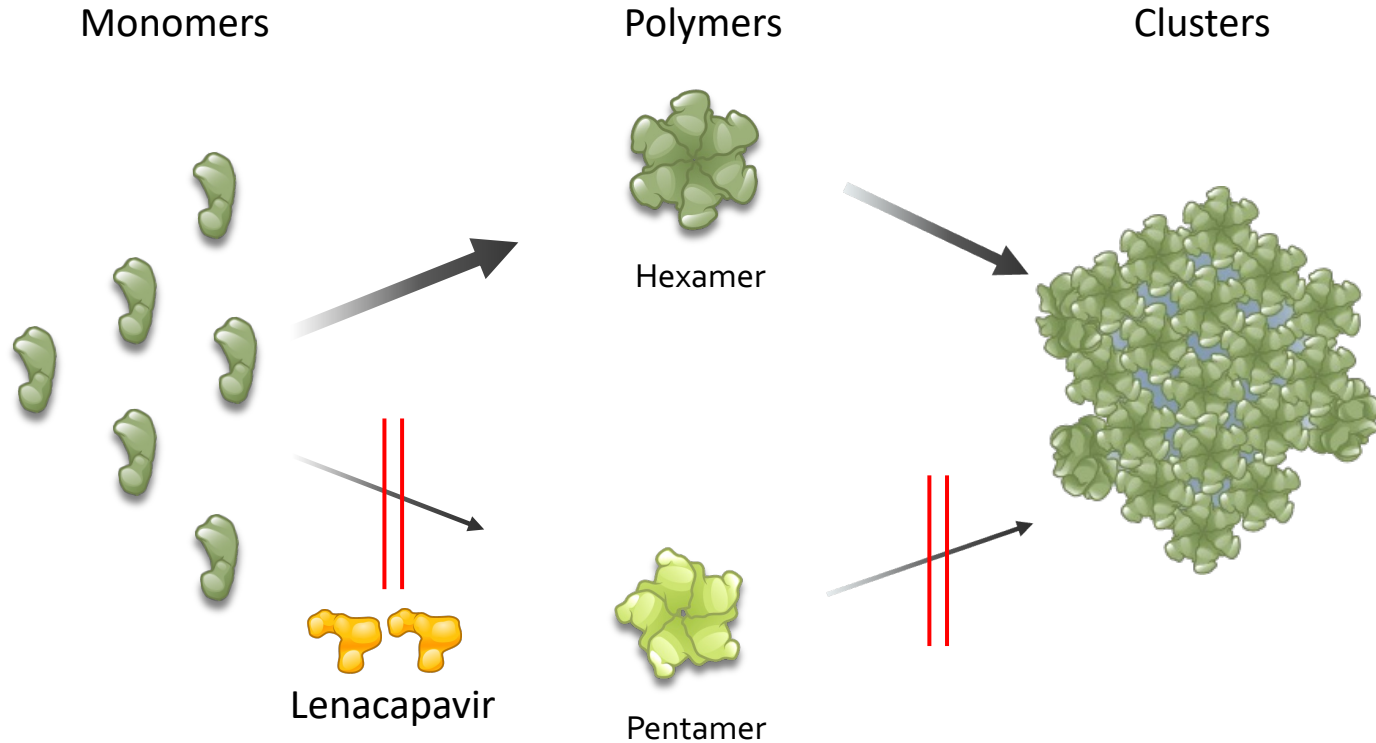
Lenacapavir-bound capsid assembly



TIME



HIV Capsid Assembly: Impact of Lenacapavir



Lenacapavir

Lenacapavir (*Sunlenca*)

Oral Lenacapavir



300 mg tablets

Take with or without food

Subcutaneous Lenacapavir



1.5 mL vial = 463.5 mg

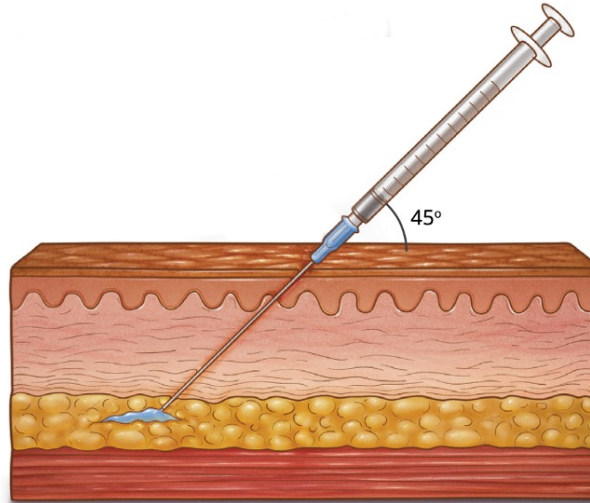
Administer as Subcutaneous Injection

Lenacapavir (*Sunlenca*)



Dosing (Subcutaneous Injection)

- 2 x 1.5 mL single dose vials
- Inject 2 x 1.5 mL (927 mg total) every 6 months (26 weeks +/- 2 weeks)



Lenacapavir Dosing for HIV Treatment: Initiation Option 1

Initiation Option 1

Day 1



600 mg

Day 2



600 mg



927 mg



Oral lenacapavir 300 mg



Subcutaneous lenacapavir 463.5 mg

Lenacapavir Dosing for HIV Treatment: Initiation Option 1

Initiation Option 1

Day 1



600 mg

Day 2



600 mg



927 mg

6 months

Month 6



927 mg

6 months

Month 12



927 mg

6 months

Month 18



927 mg

Maintenance



Oral lenacapavir 300 mg



Subcutaneous lenacapavir 463.5 mg

Lenacapavir Dosing for HIV Treatment: Initiation Option 2

Initiation Option 2

Day 1



600 mg

Day 2



600 mg

Day 8



300 mg

Day 15



927 mg



Oral lenacapavir 300 mg



Subcutaneous lenacapavir 463.5 mg

Lenacapavir Dosing for HIV Treatment: Initiation Option 2

Initiation Option 2

Day 1



600 mg

Day 2



600 mg

Day 8



300 mg

Day 15



927 mg

6 months



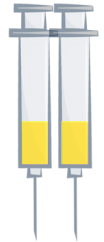
927 mg

6 months



927 mg

6 months



927 mg

Maintenance



Oral lenacapavir 300 mg



Subcutaneous lenacapavir 463.5 mg

Lenacapavir Dosing for HIV PrEP

Initiation

Day 1

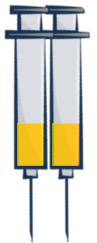


600 mg

Day 2



600 mg



927 mg

6 months

Maintenance

Month 6



927 mg

6 months

Month 12




927 mg

6 months

Month 18



927 mg

 Oral lenacapavir 300 mg


 Subcutaneous lenacapavir 463.5 mg

Illustration: David H. Spach, MD

Summary

Capsid Inhibitors and Multistage Mechanism of Action

1

Inhibits Capsid Nuclear Import

2

Inhibits Capsid Uncoating

3

Inhibits Capsid Assembly

Acknowledgment

The production of this **National HIV Curriculum** Mini-Lecture was supported by Grant U1OHA32104 from the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS). Its contents are solely the responsibility of University of Washington IDEA Program and do not necessarily represent the official views of HRSA or HHS.

