

HIV Entry Inhibitors: Mechanism of Action

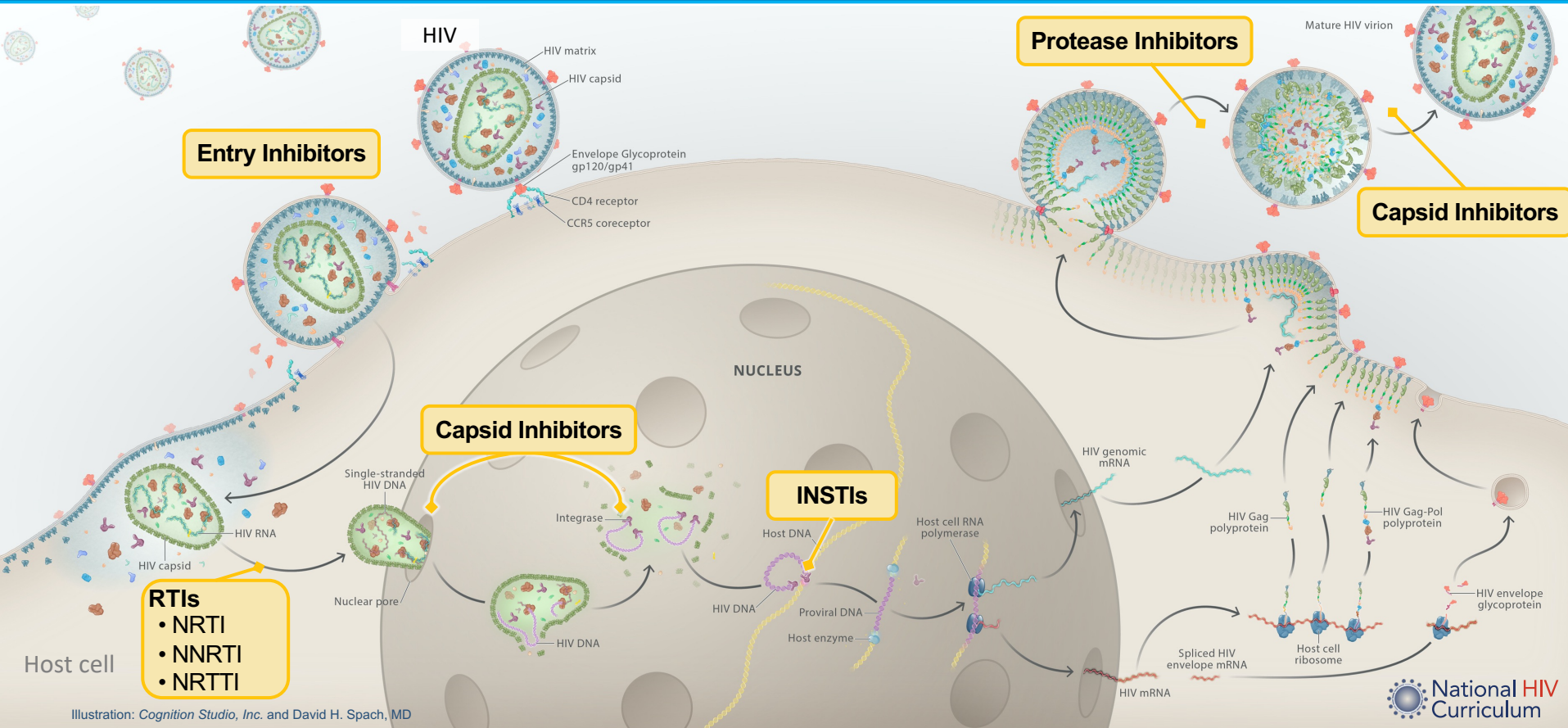
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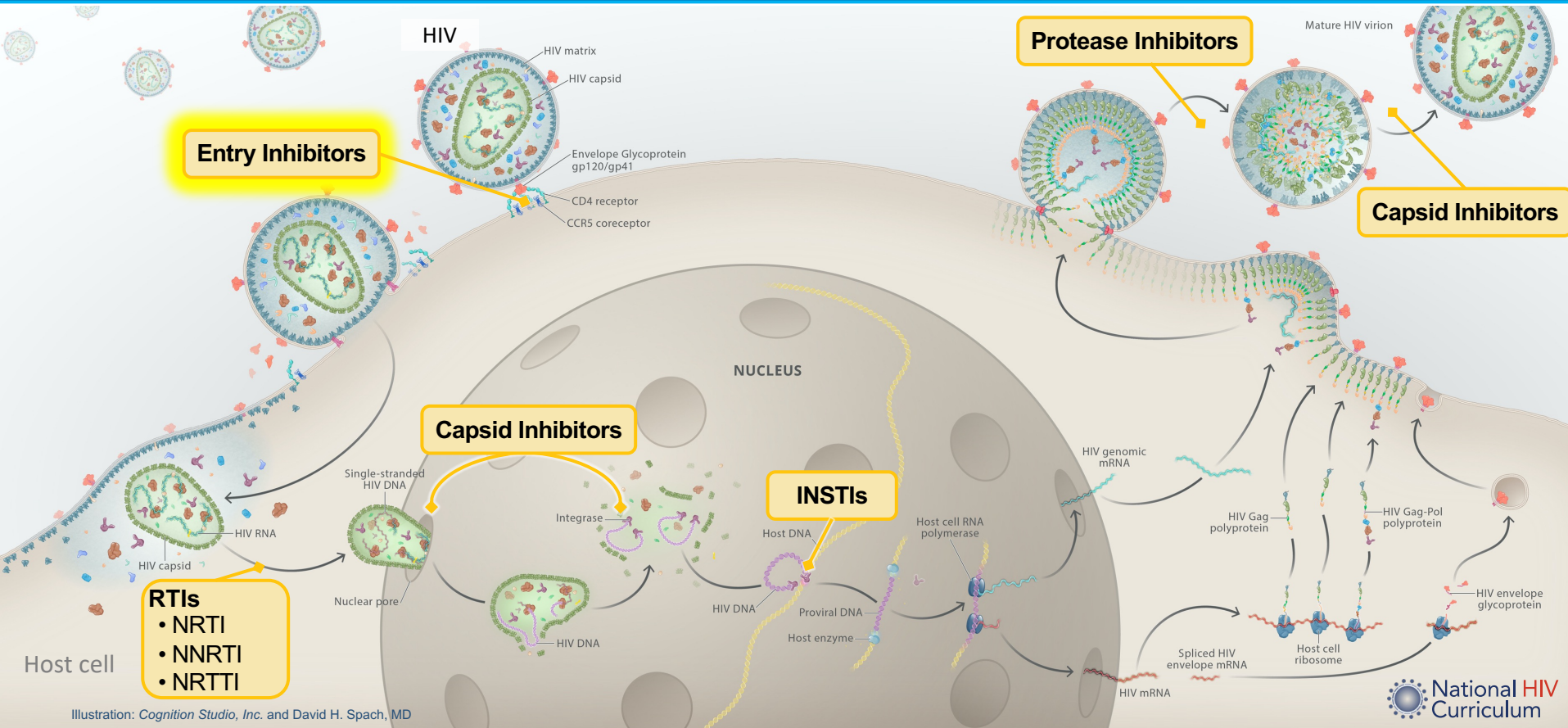
Disclosures

Dr. Spach does not have any disclosures.

HIV Antiretroviral Therapy



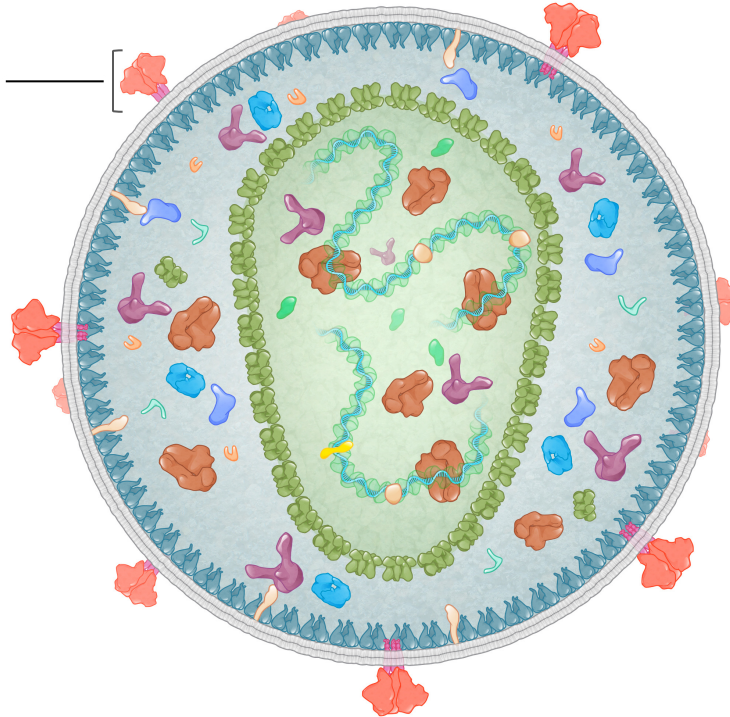
HIV Antiretroviral Therapy



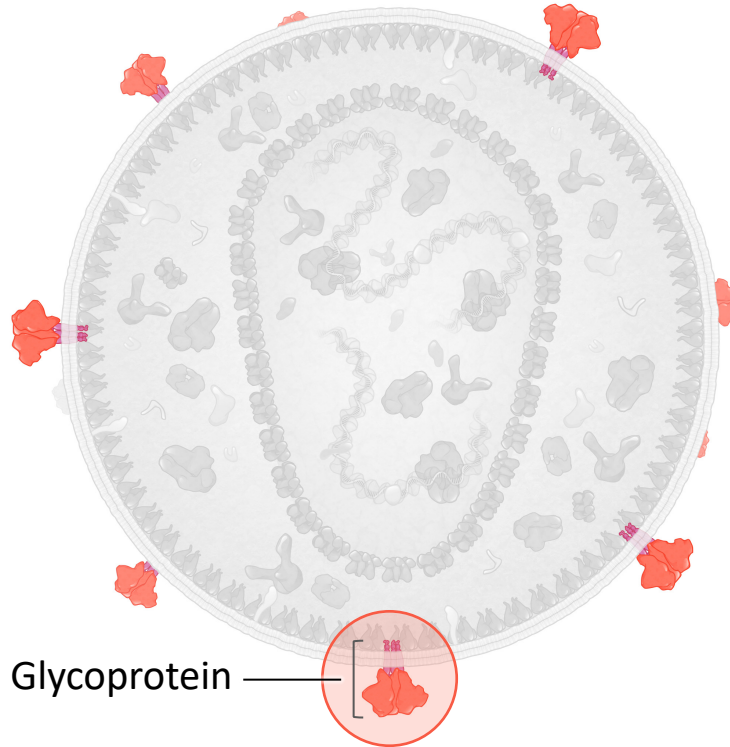
Targets for HIV Entry Inhibitors

HIV Envelope Glycoprotein

HIV Envelope Glycoprotein

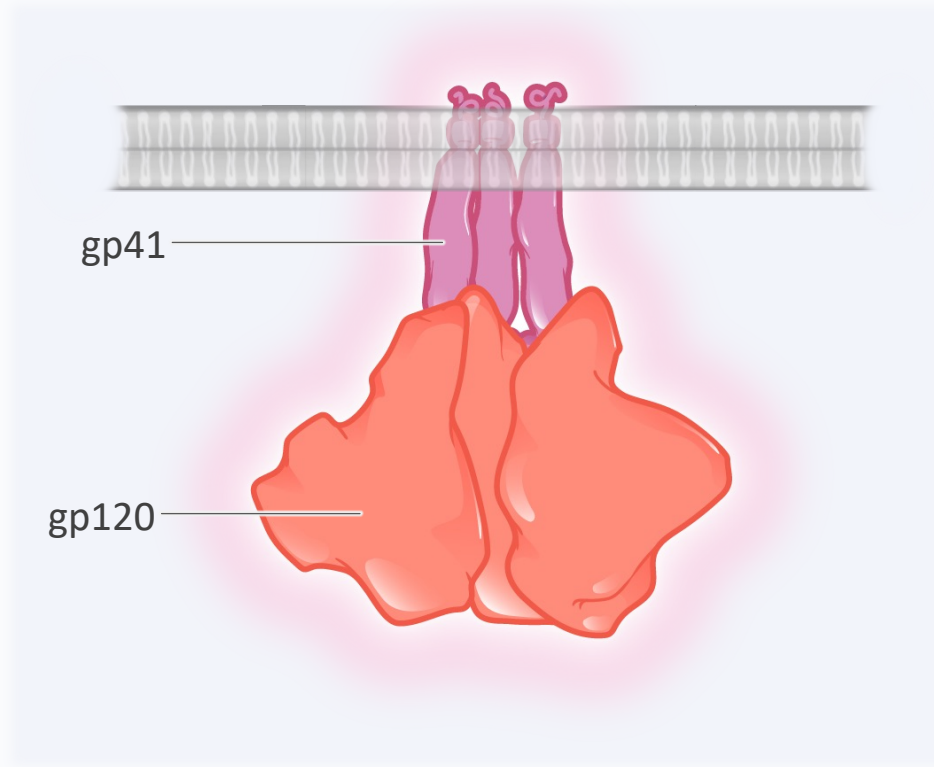


HIV Envelope Glycoprotein

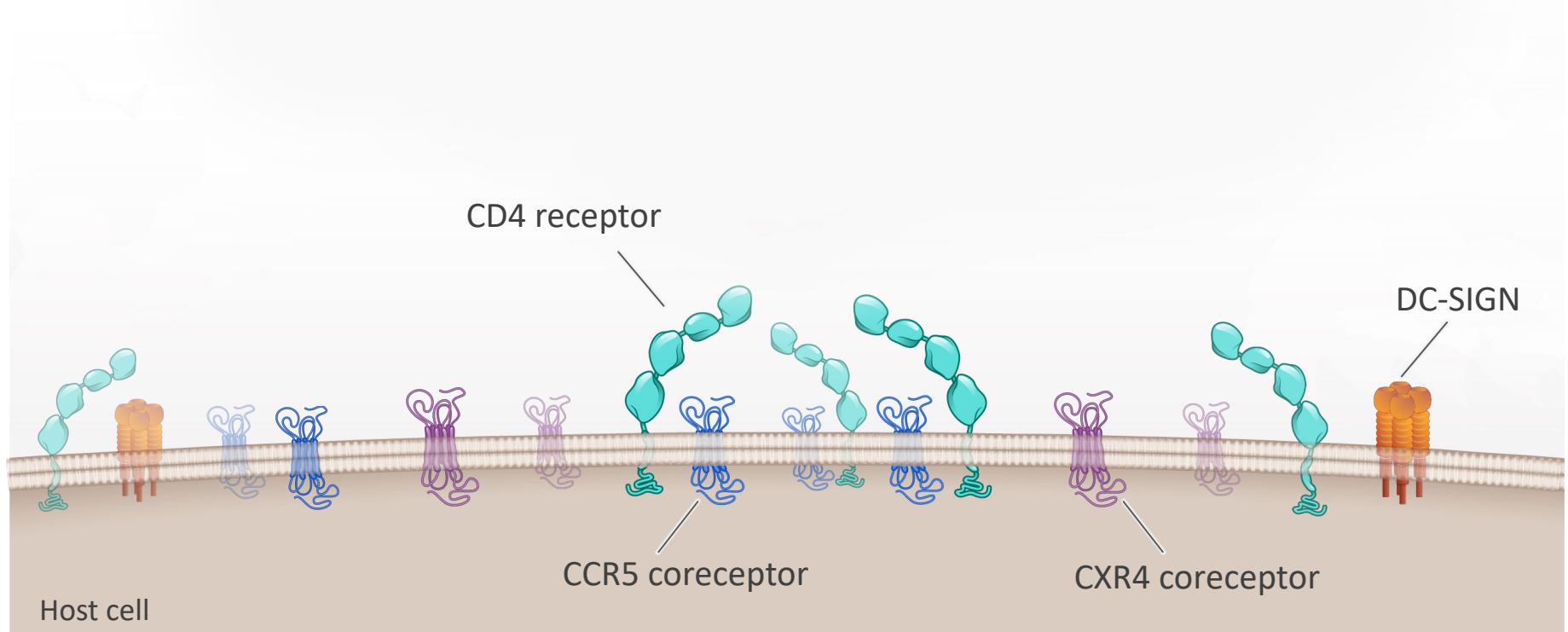


HIV Envelope Glycoprotein

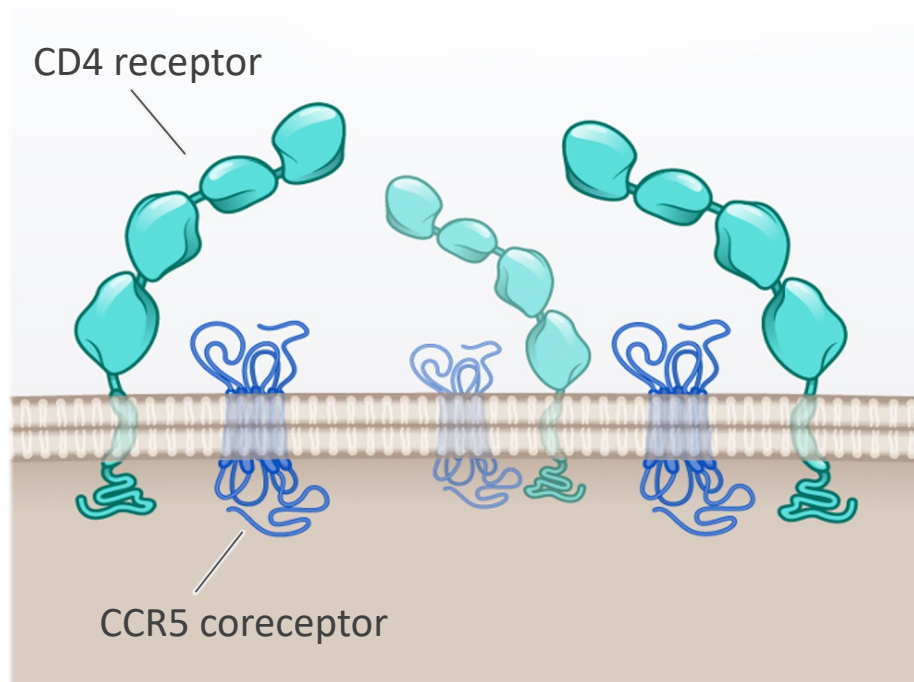
HIV Envelope



Host Cell Surface Receptors



Cell Surface Receptors Targeted by HIV Entry Inhibitors



Subclasses of HIV Entry Inhibitors

Key Steps for HIV Cell Entry

1

Attachment

2

Coreceptor Binding

3

Fusion

HIV Cell Entry and HIV Entry Inhibitors

Key Steps for HIV Entry

1

Attachment

2

Coreceptor Binding

3

Fusion

HIV Entry Inhibitor Subclasses

Attachment Inhibitors

CCR5 Antagonists

Fusion Inhibitors

HIV Cell Entry and HIV Entry Inhibitors

Key Steps for HIV Entry

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HIV Entry Inhibitor Subclasses

Attachment Inhibitors

Post-Attachment Inhibitors

CCR5 Antagonists

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HIV Cell Entry and HIV Entry Inhibitors

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Fusion Inhibitors

HIV Entry Inhibitor Medications

Fostemsavir

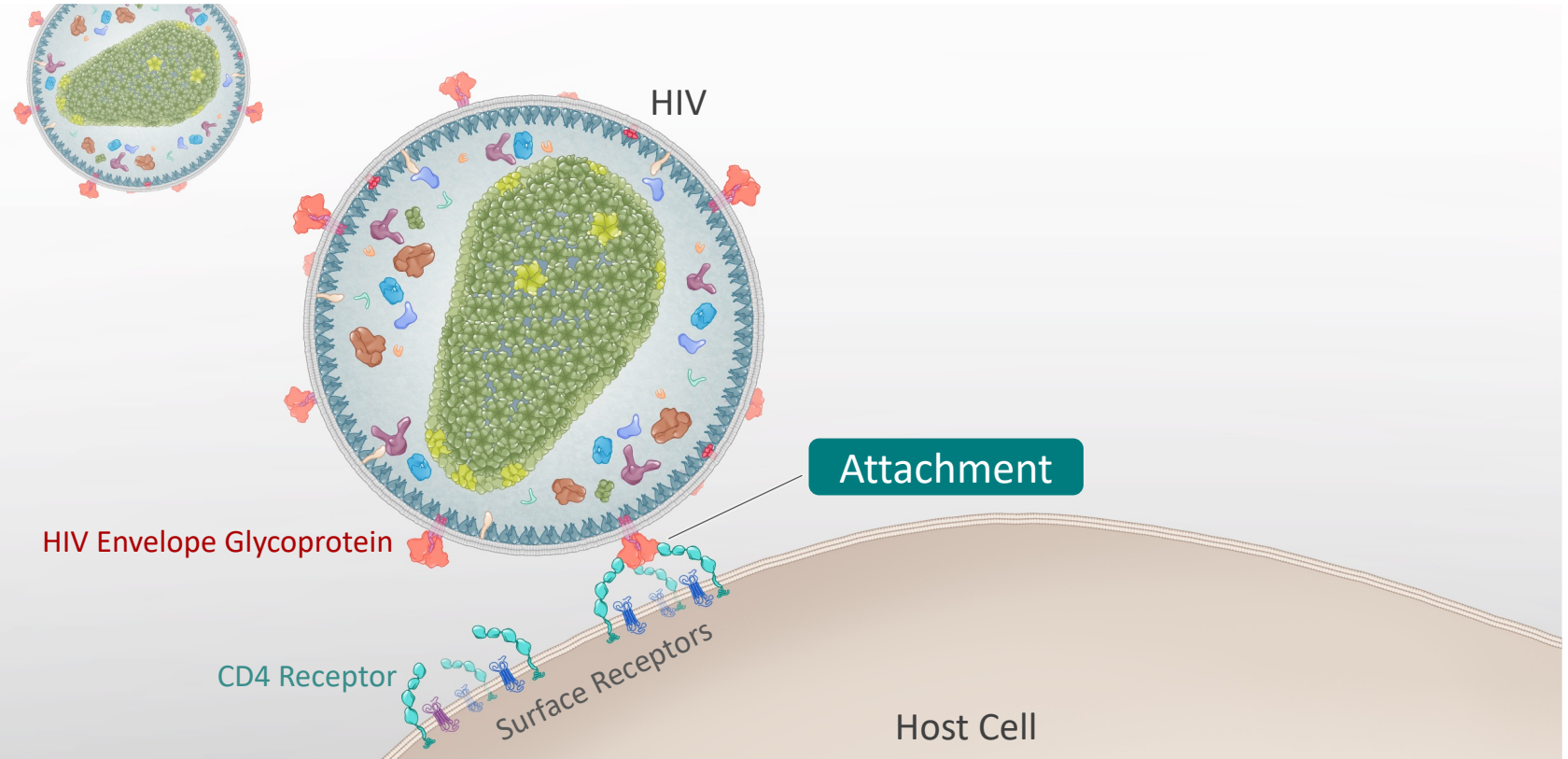
Ibalizumab

Maraviroc

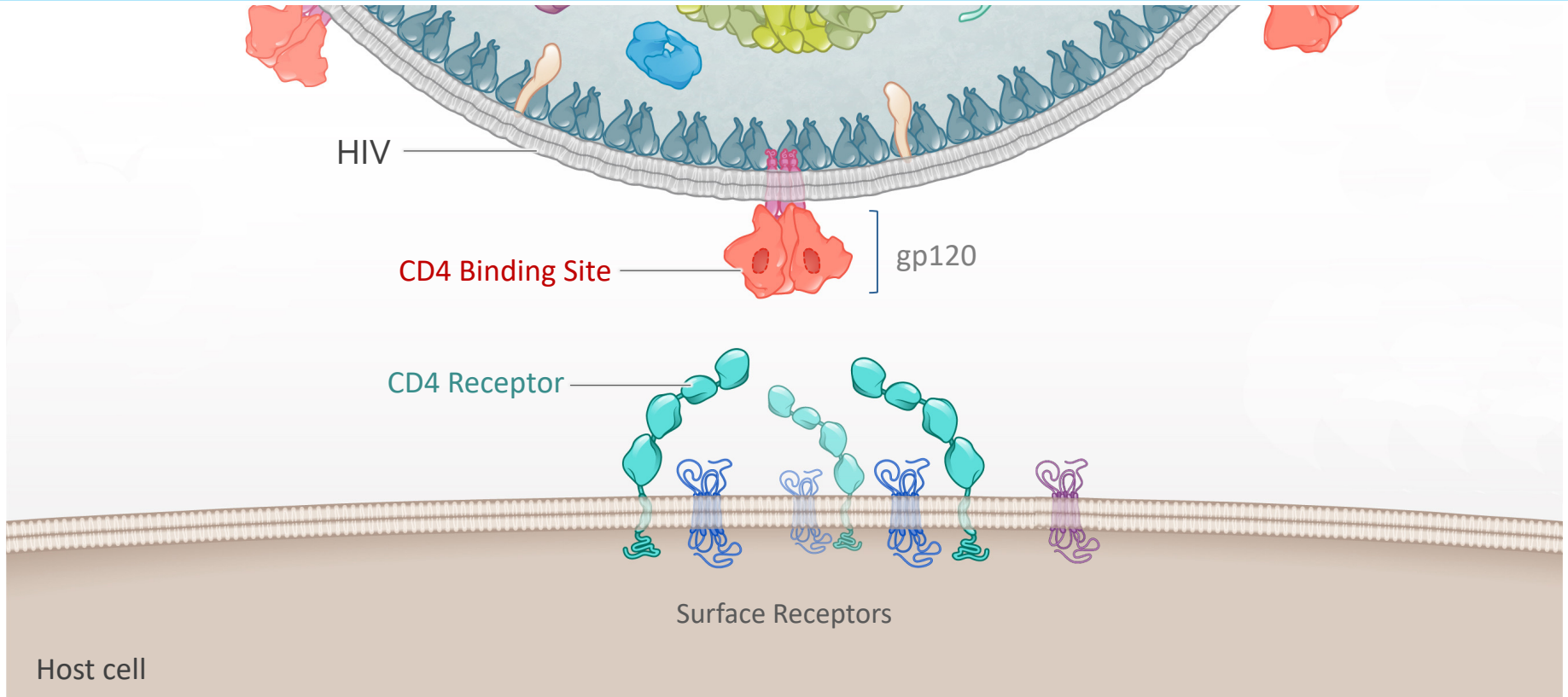
Enfuvirtide

Attachment Inhibitors

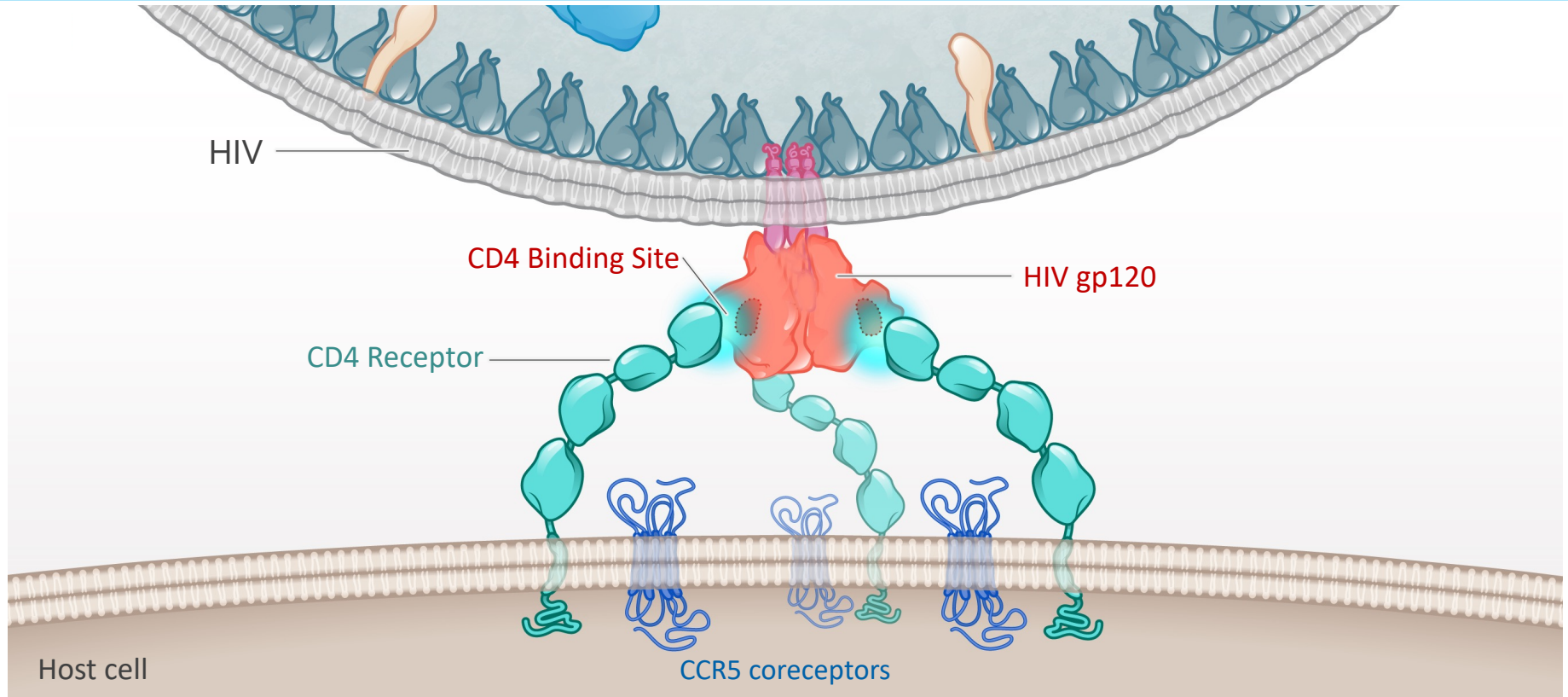
HIV Entry: Attachment



HIV Attachment: HIV CD4 Binding Site and Host CD4 Receptor



HIV Attachment: CD4 Receptor and CD4 Binding Site



Attachment Inhibitor

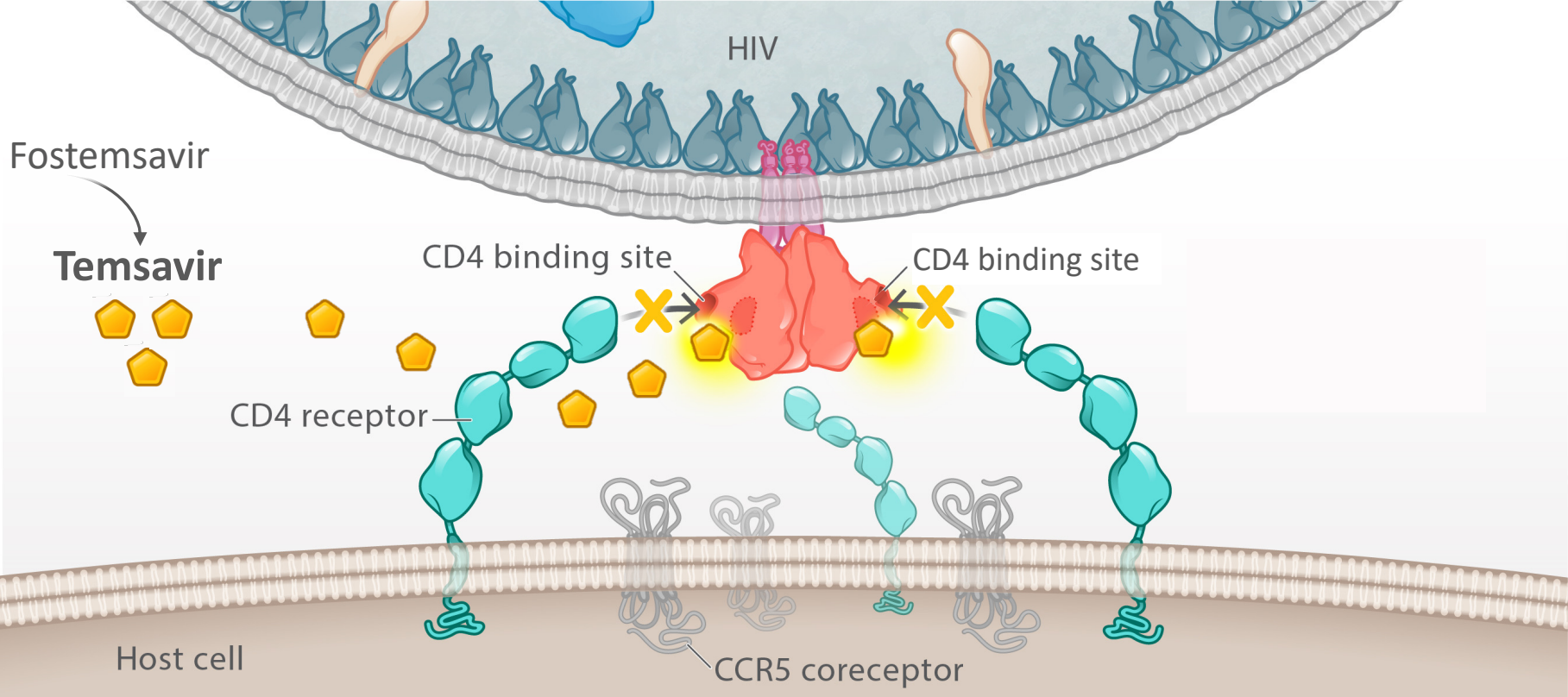
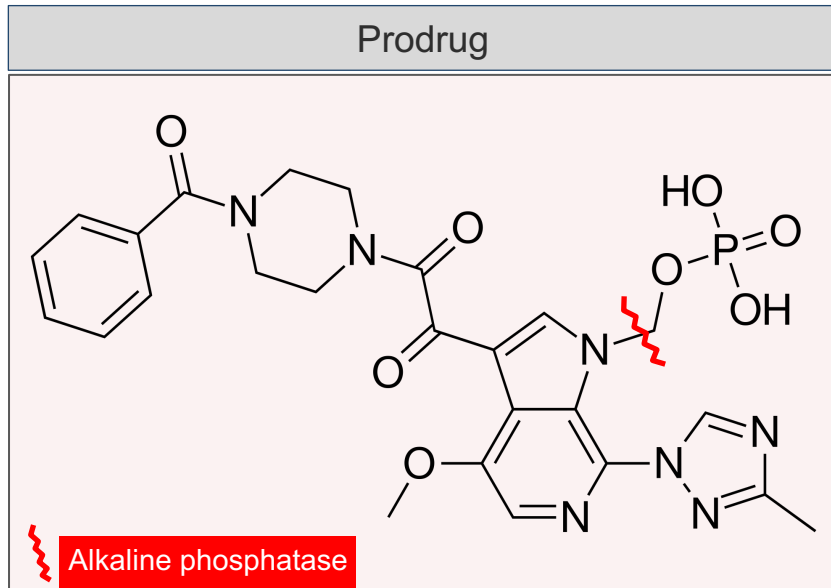


Illustration: Cognition Studio, Inc. and David H. Spach, MD

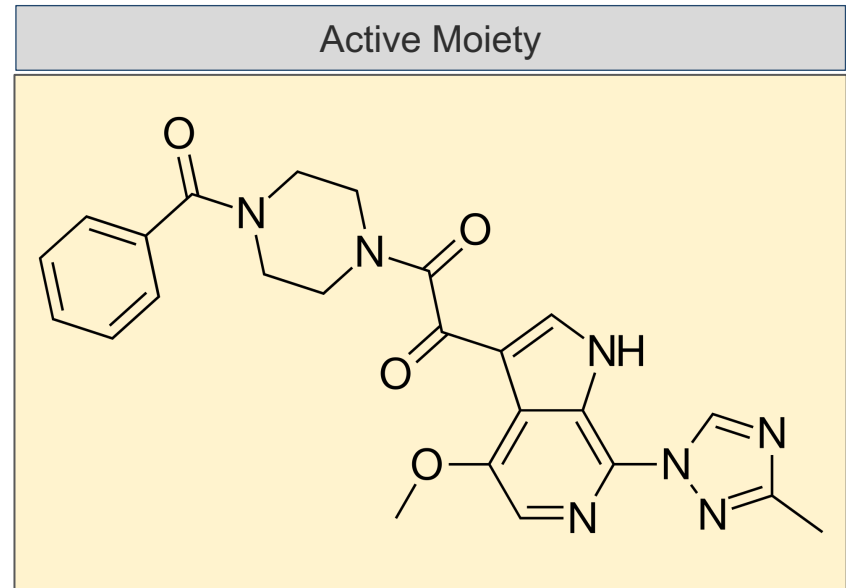
Fostemsavir (*Rukobia*)

Fostemsavir Dosing (Oral)

- 600 mg BID
- Take with or without food

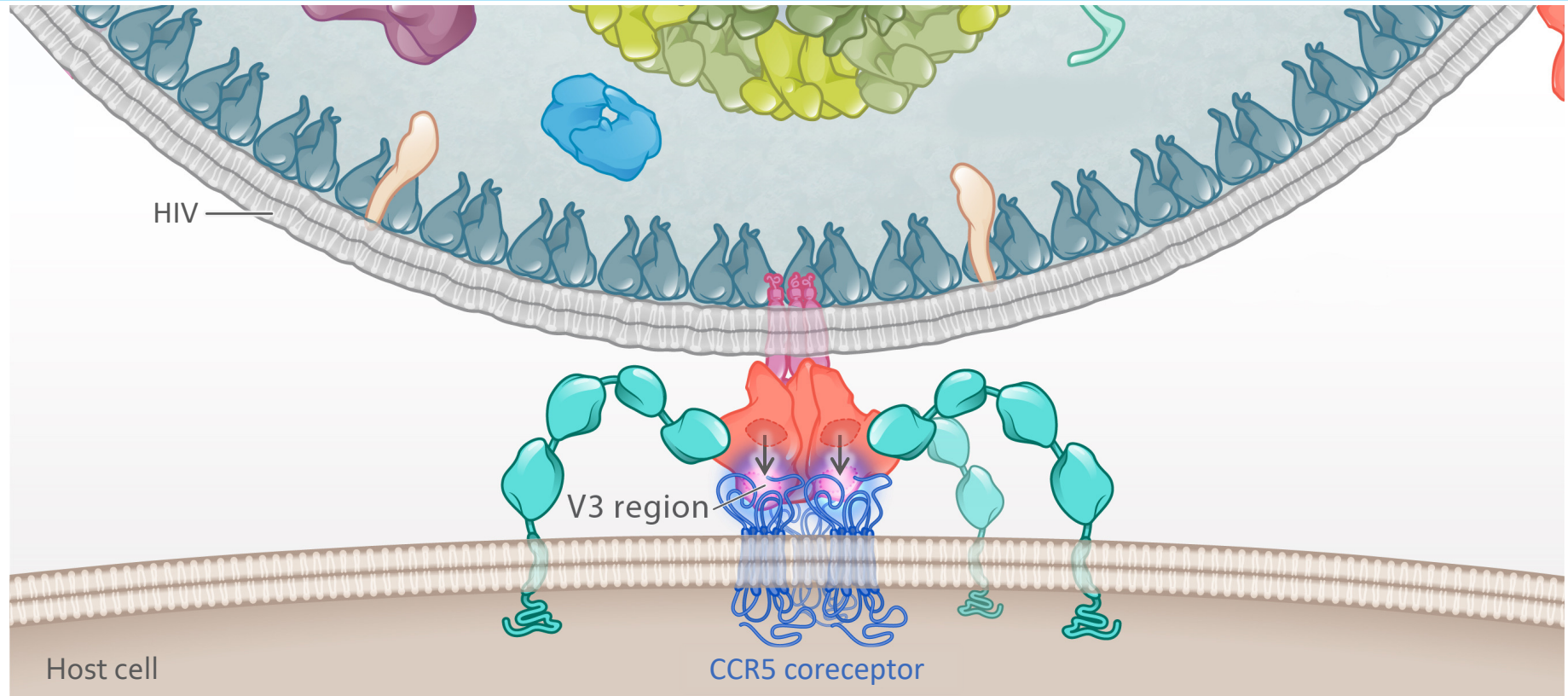


Tenofovir

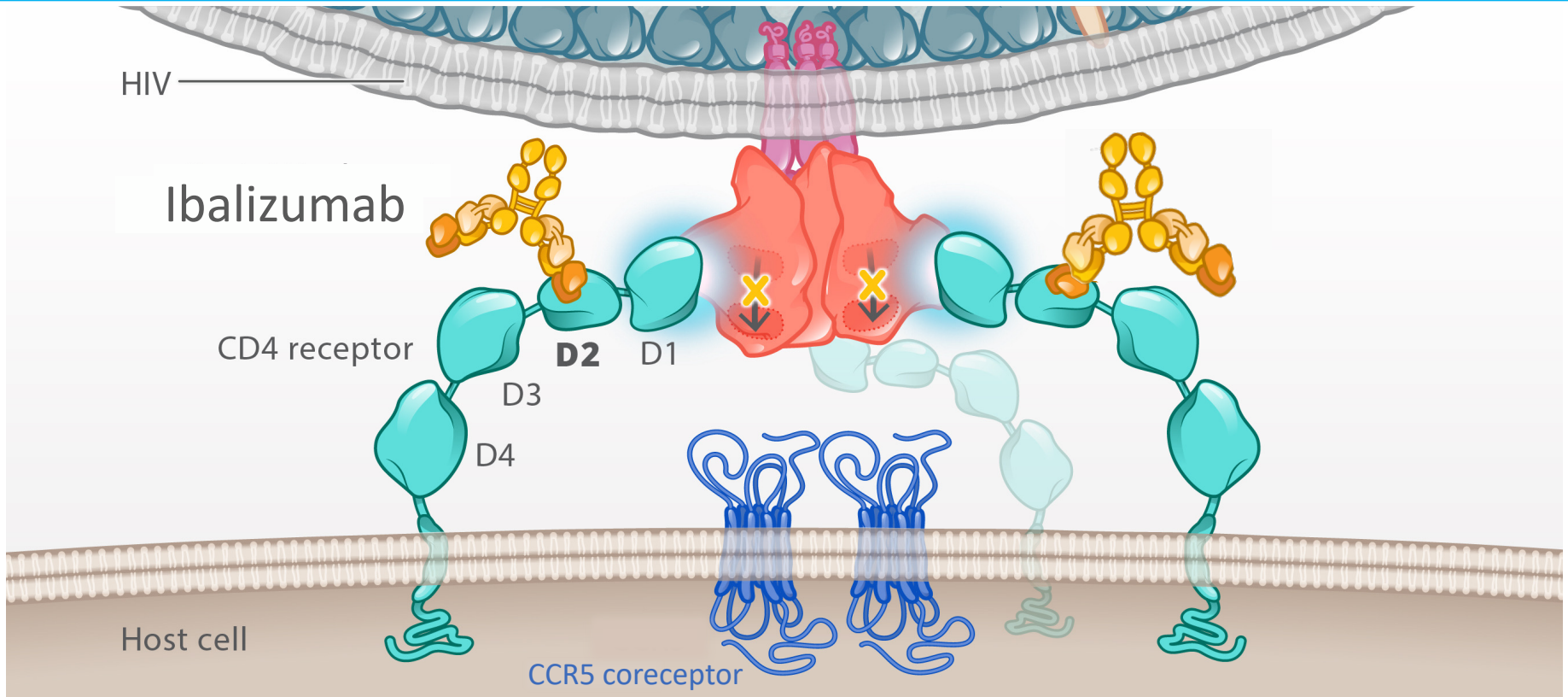


Post-Attachment Inhibitor

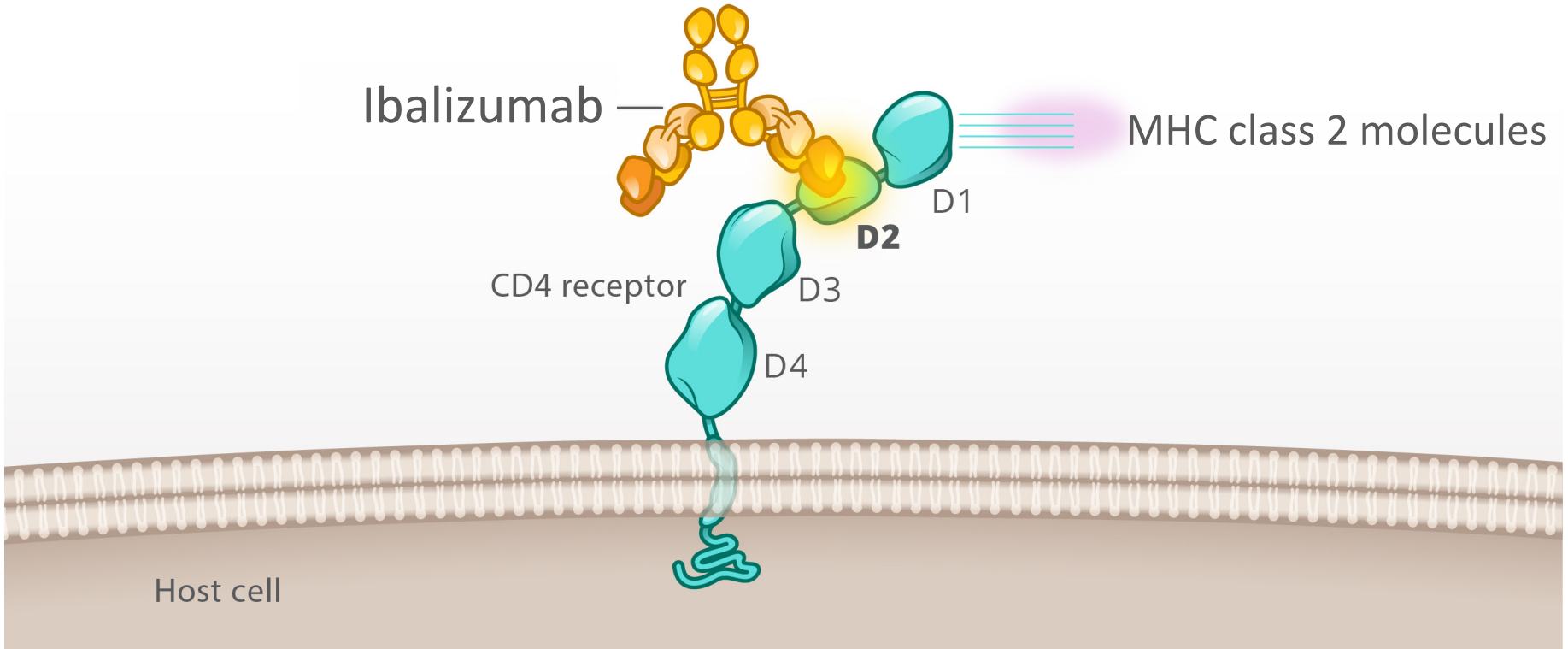
Post Attachment HIV Envelope Conformational Change



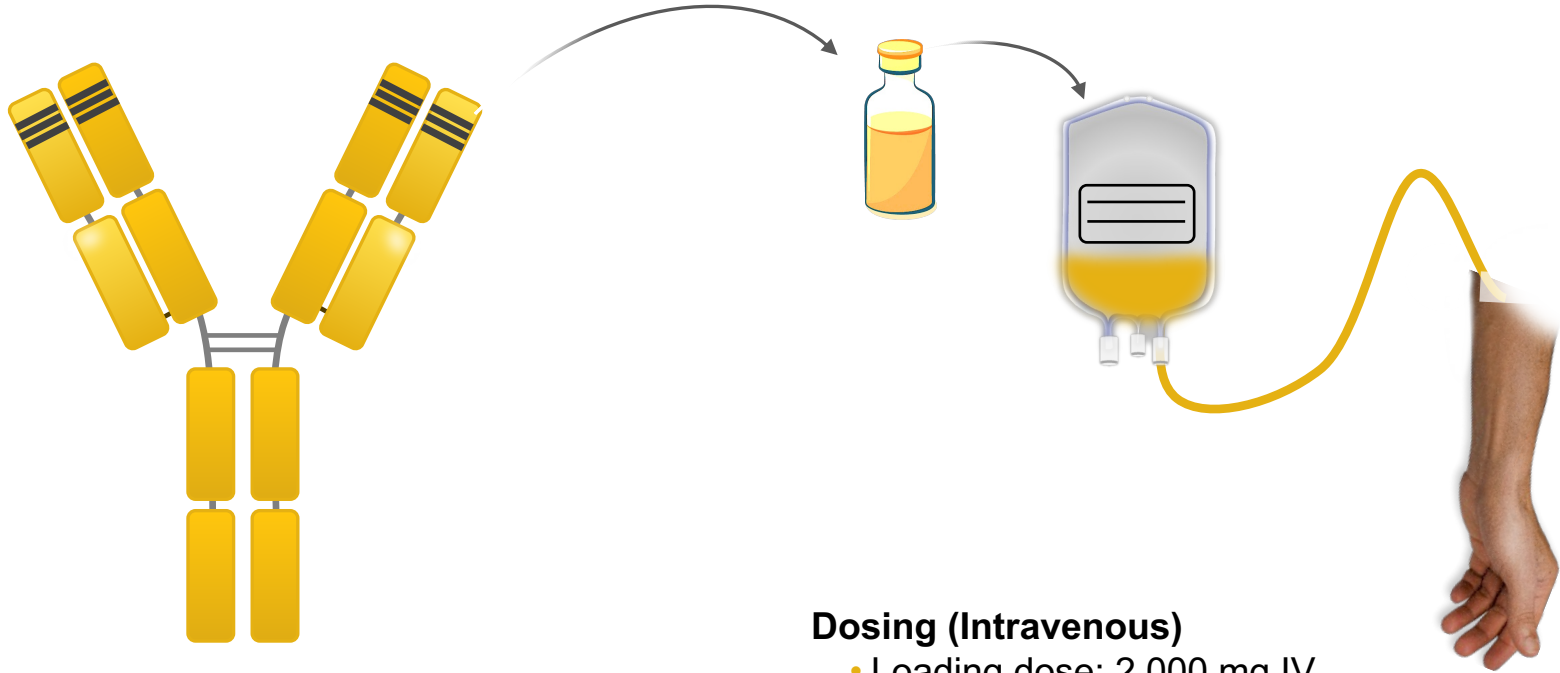
Post Attachment Inhibitor: Ibalizumab



Post Attachment Inhibitor: Ibalizumab



Ibalizumab (*Trogarzo*)



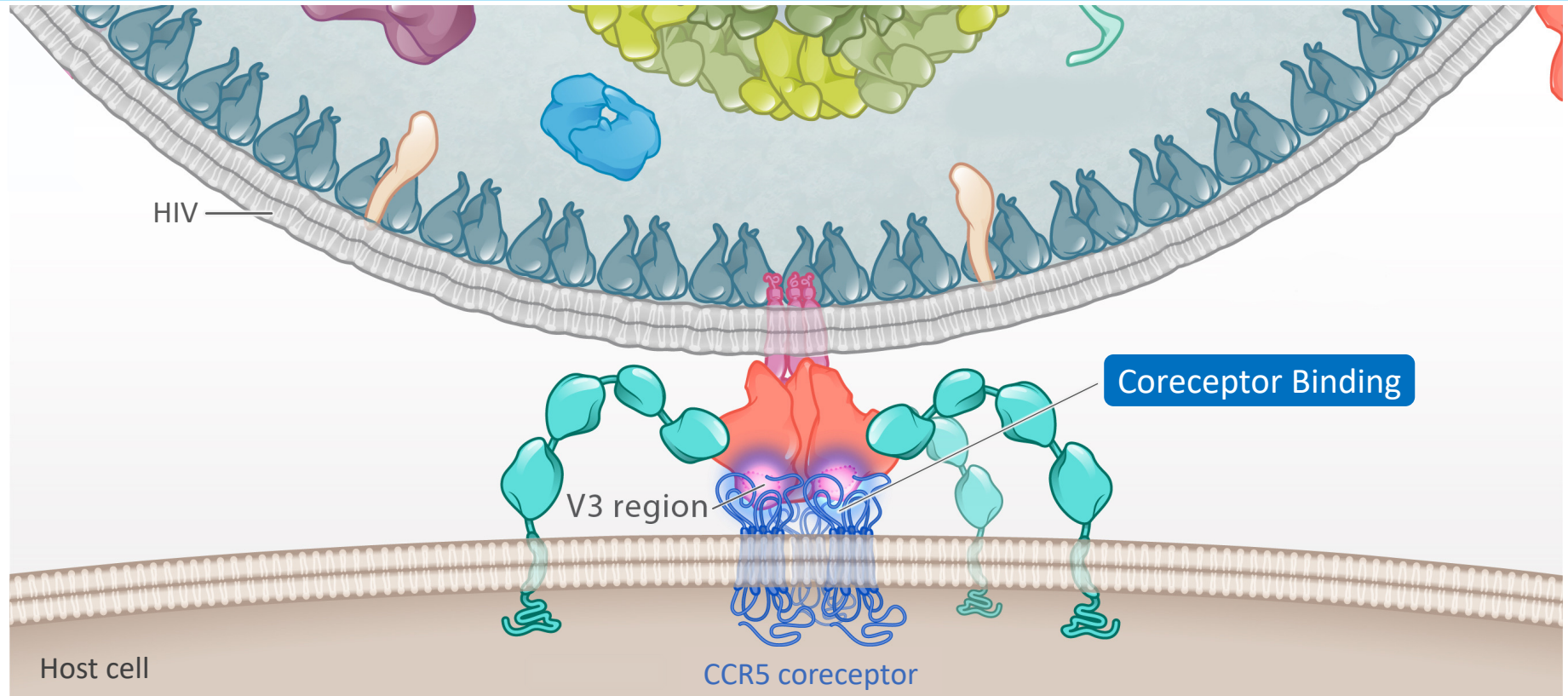
Humanized Monoclonal Antibody

Dosing (Intravenous)

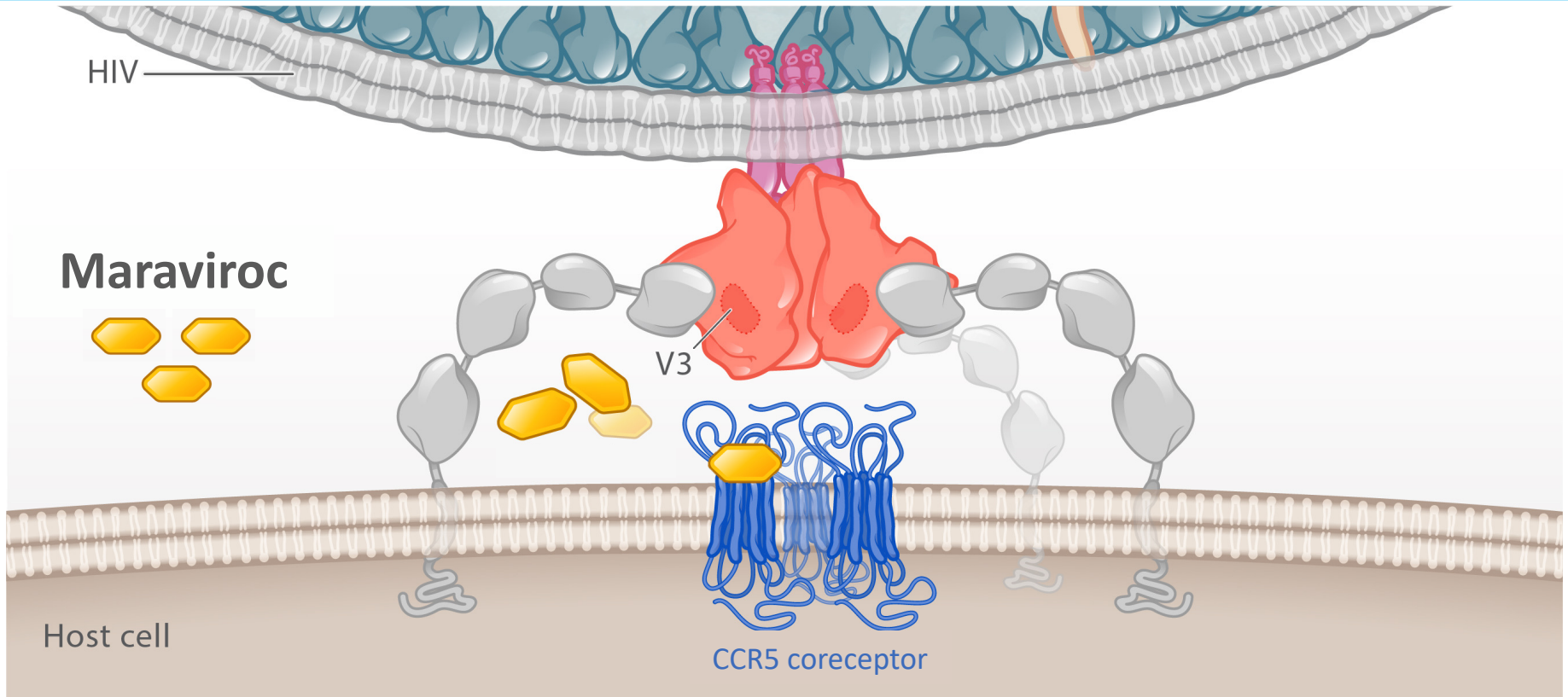
- Loading dose: 2,000 mg IV
- Maintenance dose: 800 mg IV every 2 weeks

Coreceptor Antagonist

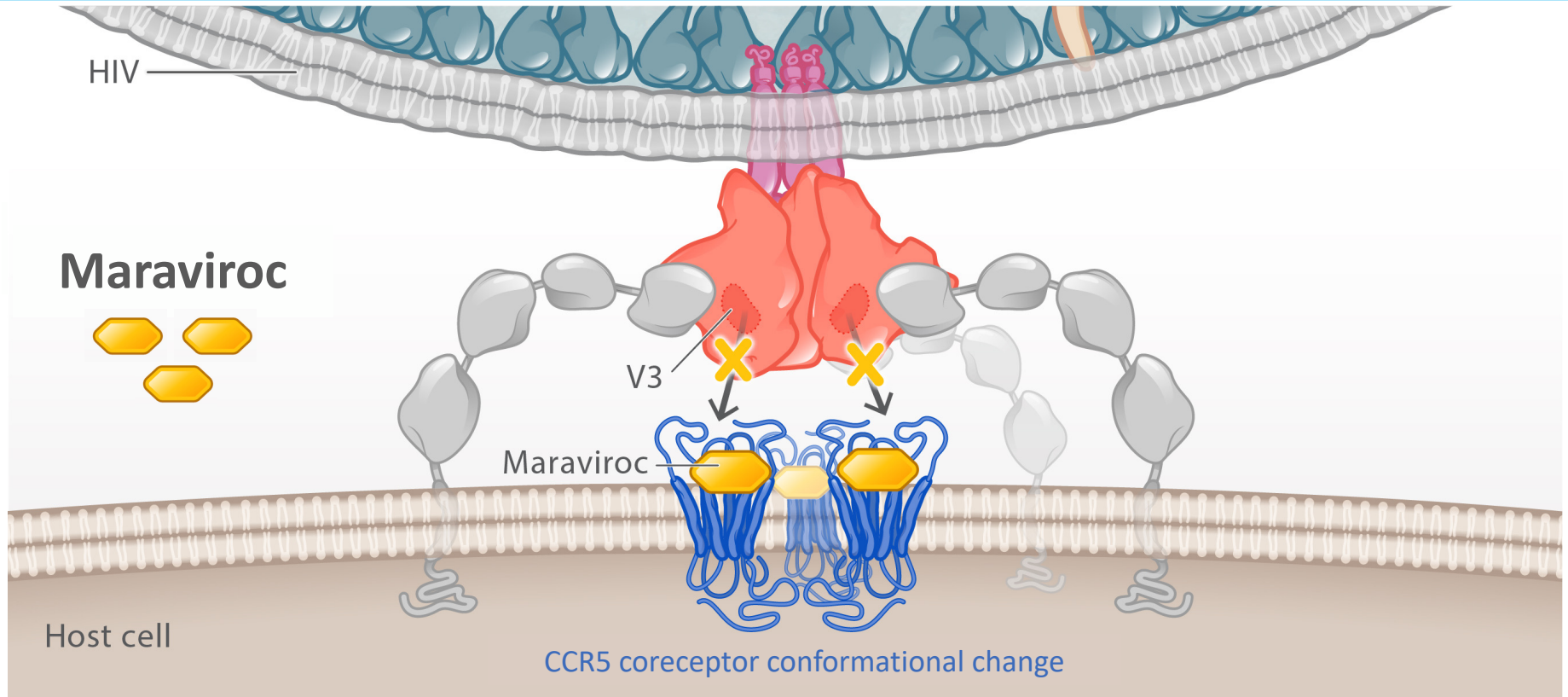
HIV gp120 and Coreceptor Binding



HIV Coreceptor Antagonist: Maraviroc



HIV Coreceptor Antagonist: Maraviroc



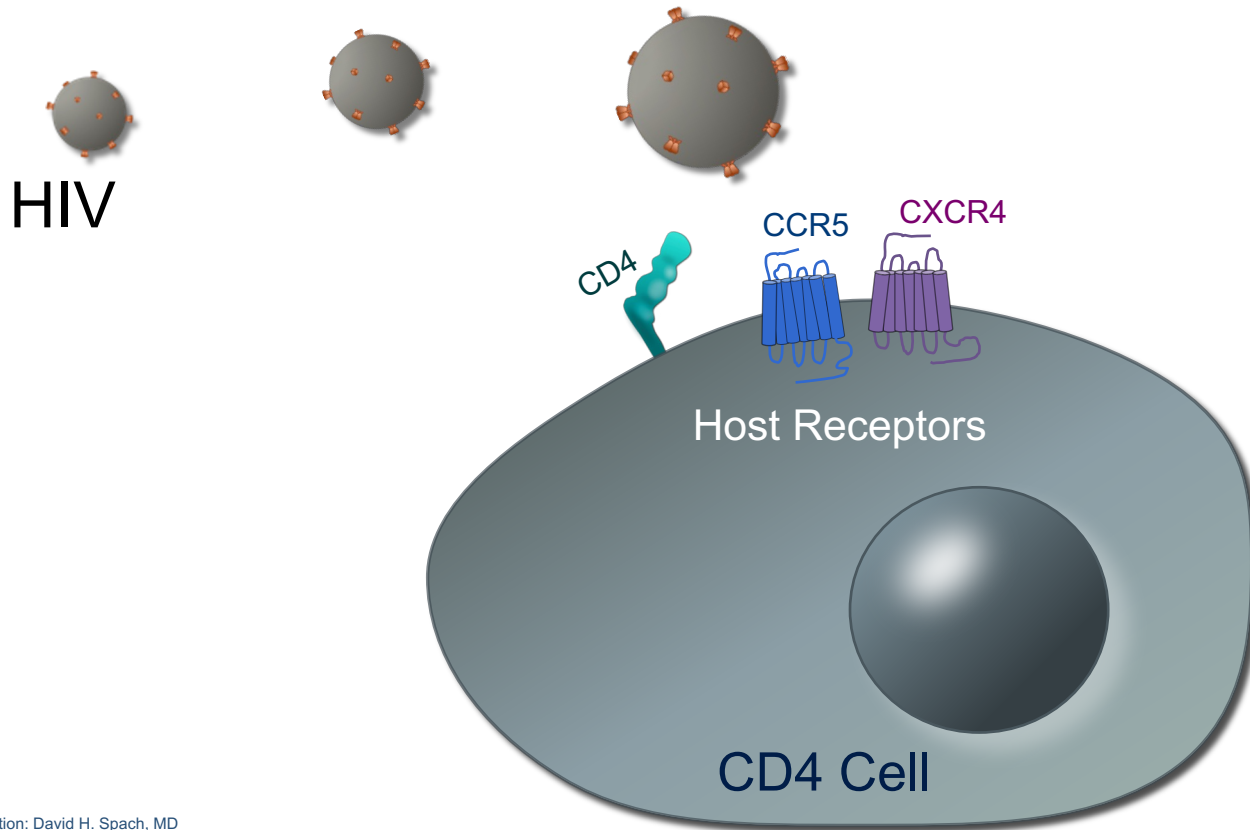
Maraviroc (*Selzentry*)

Maraviroc: Recommended Dosage in Adults*

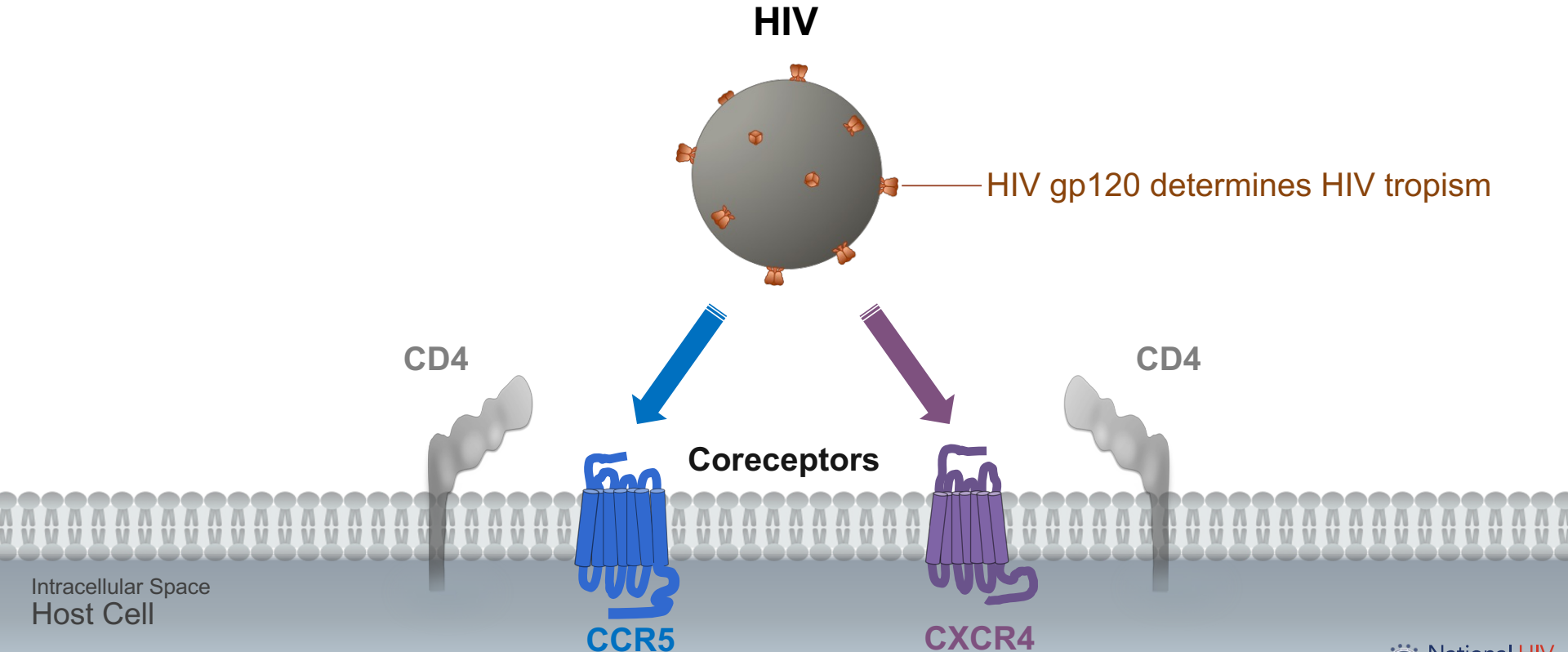
Concomitant Medications	Dose
Noninteracting concomitant medications	300 mg twice a day
Potent CYP3A inhibitors (+/- potent CYP3A inducer)	150 mg twice a day
Potent and moderate CYP3A inducers (without a potent CYP3A inhibitor)	600 mg twice a day

*Take with or without food

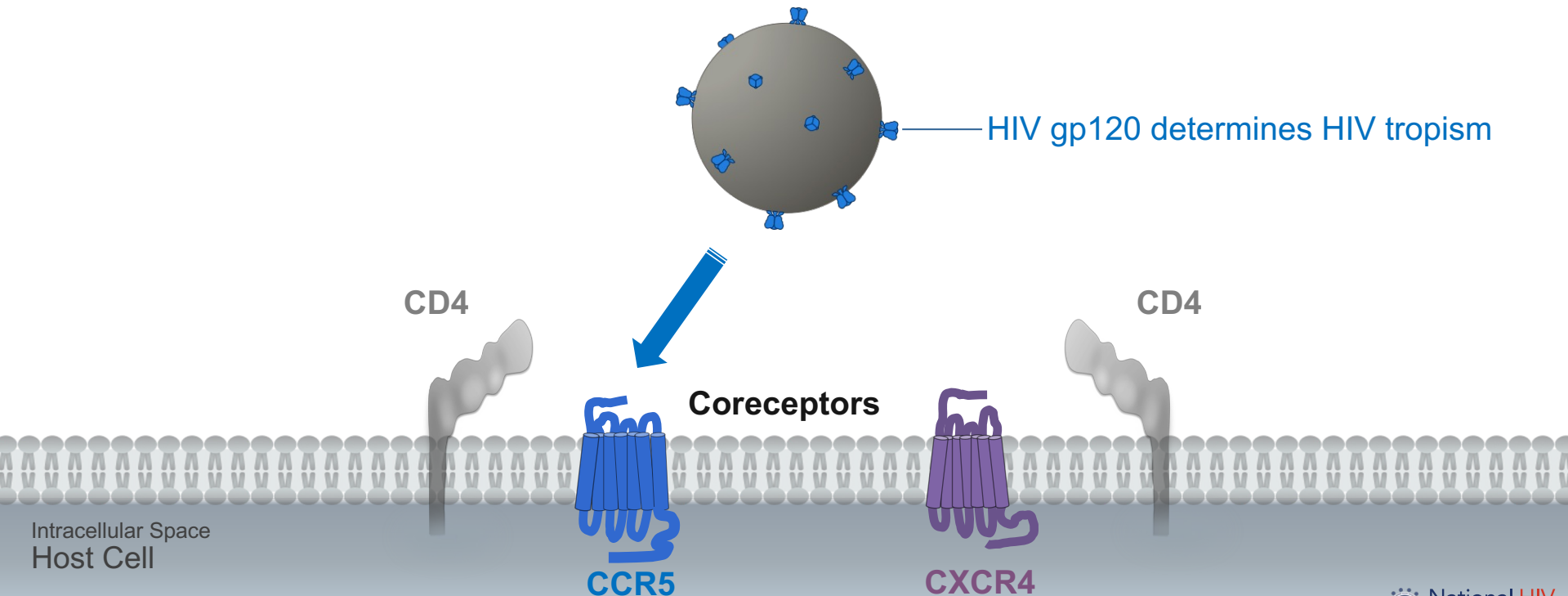
Host Receptors and HIV Entry



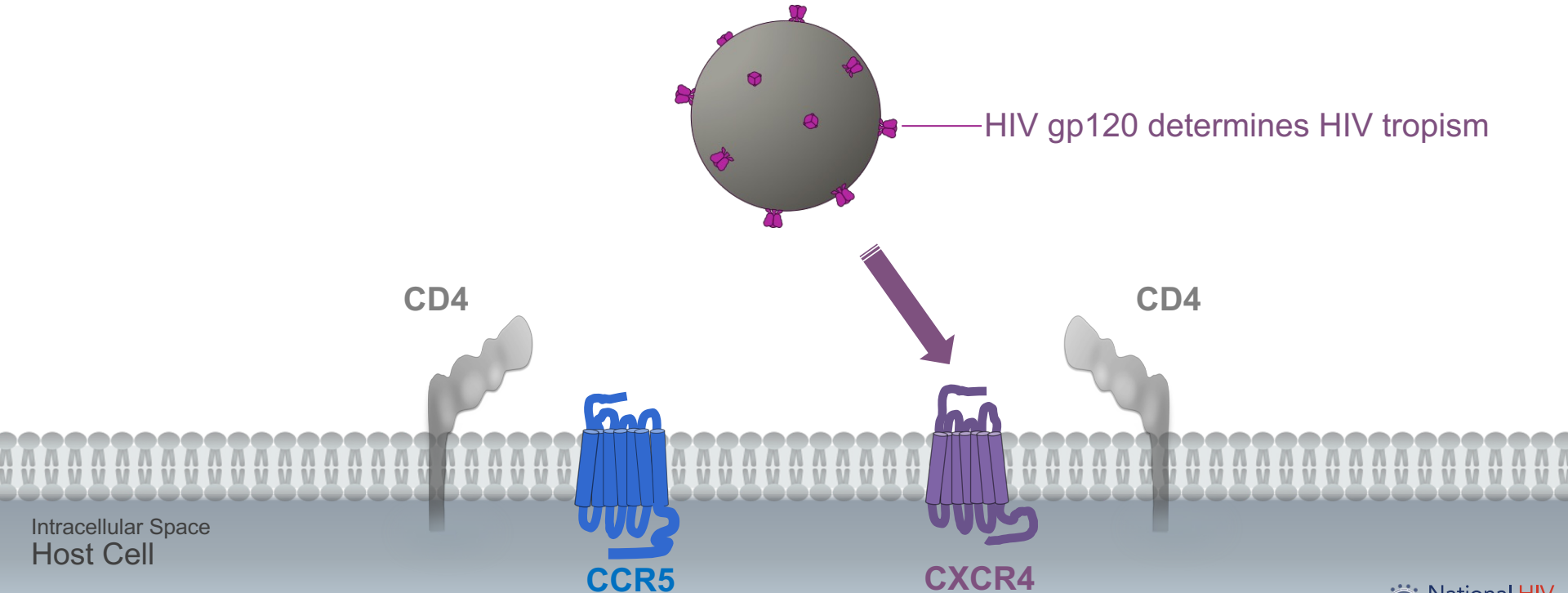
Host Cellular Co-Receptors Involved in HIV Entry



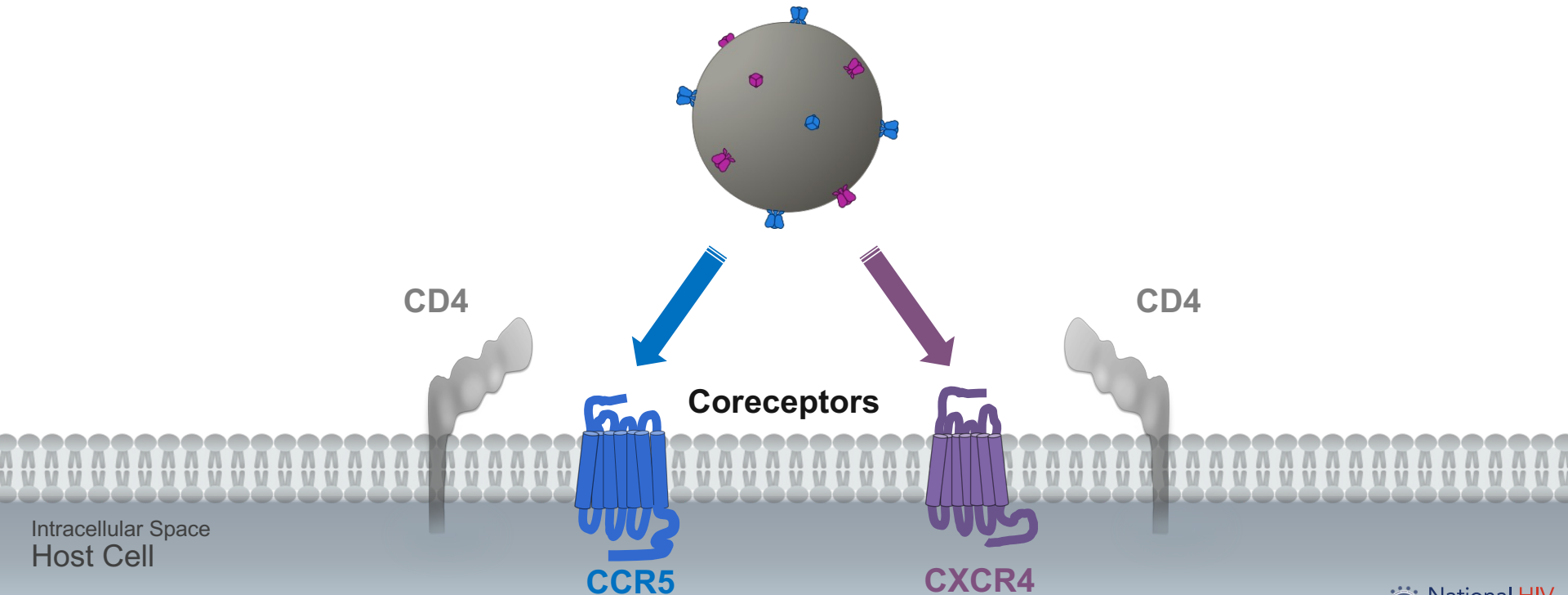
R5-Tropic HIV (R5 HIV)



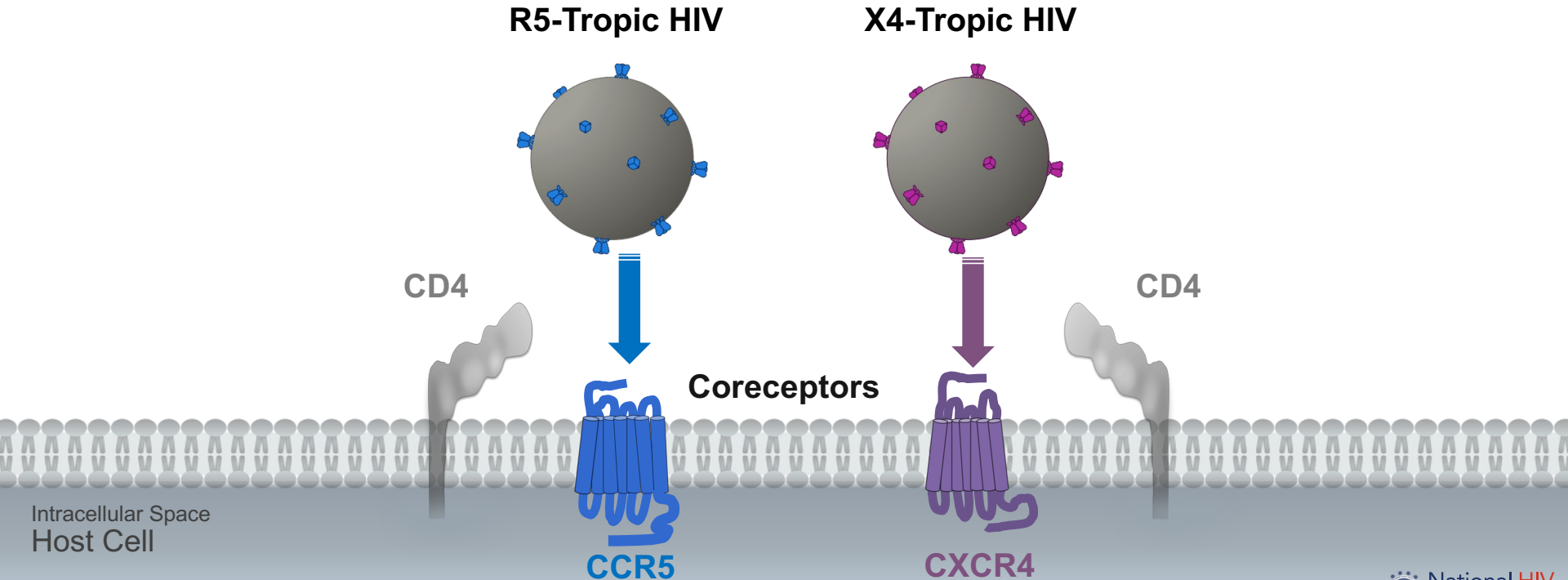
X4-Tropic HIV (X4 HIV)



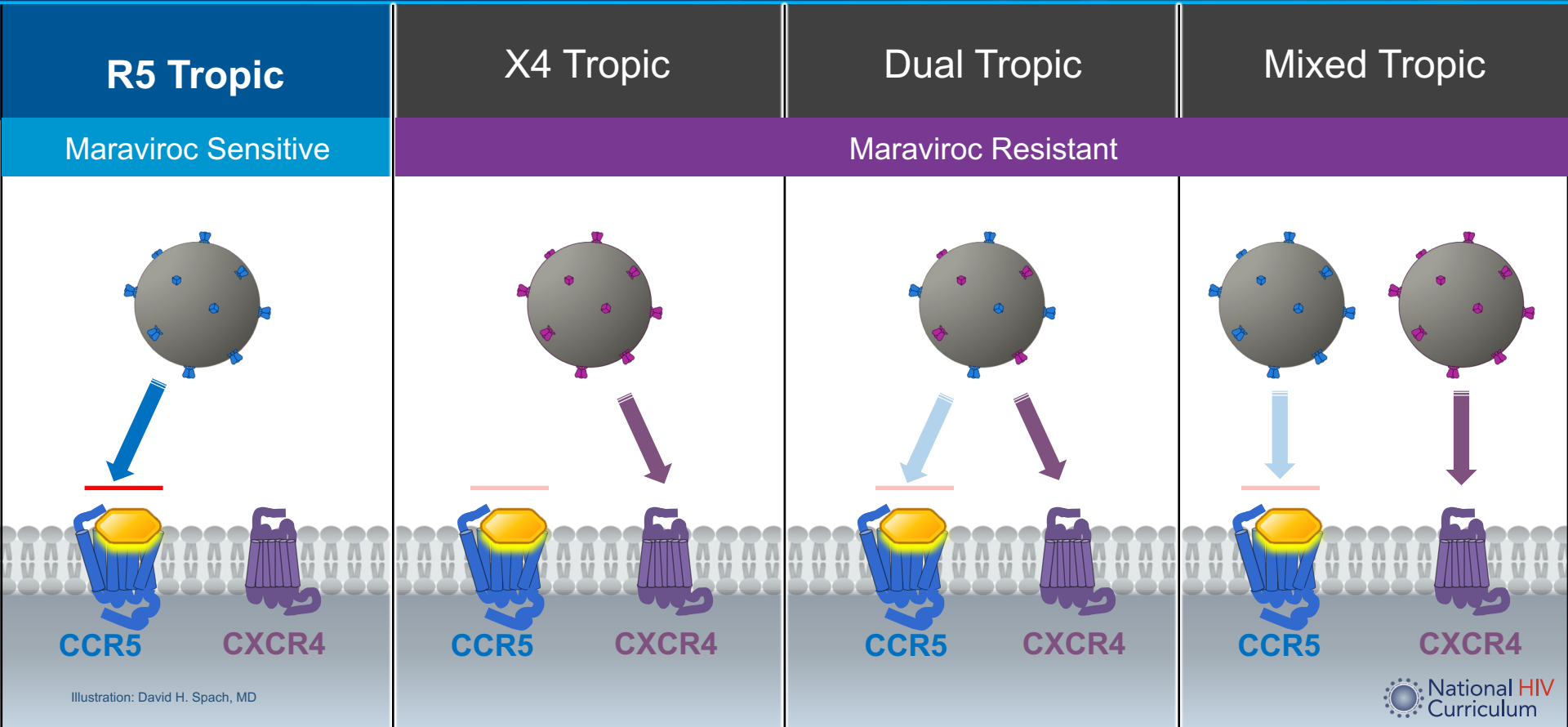
Dual-Tropic HIV



Mixed-Tropic HIV

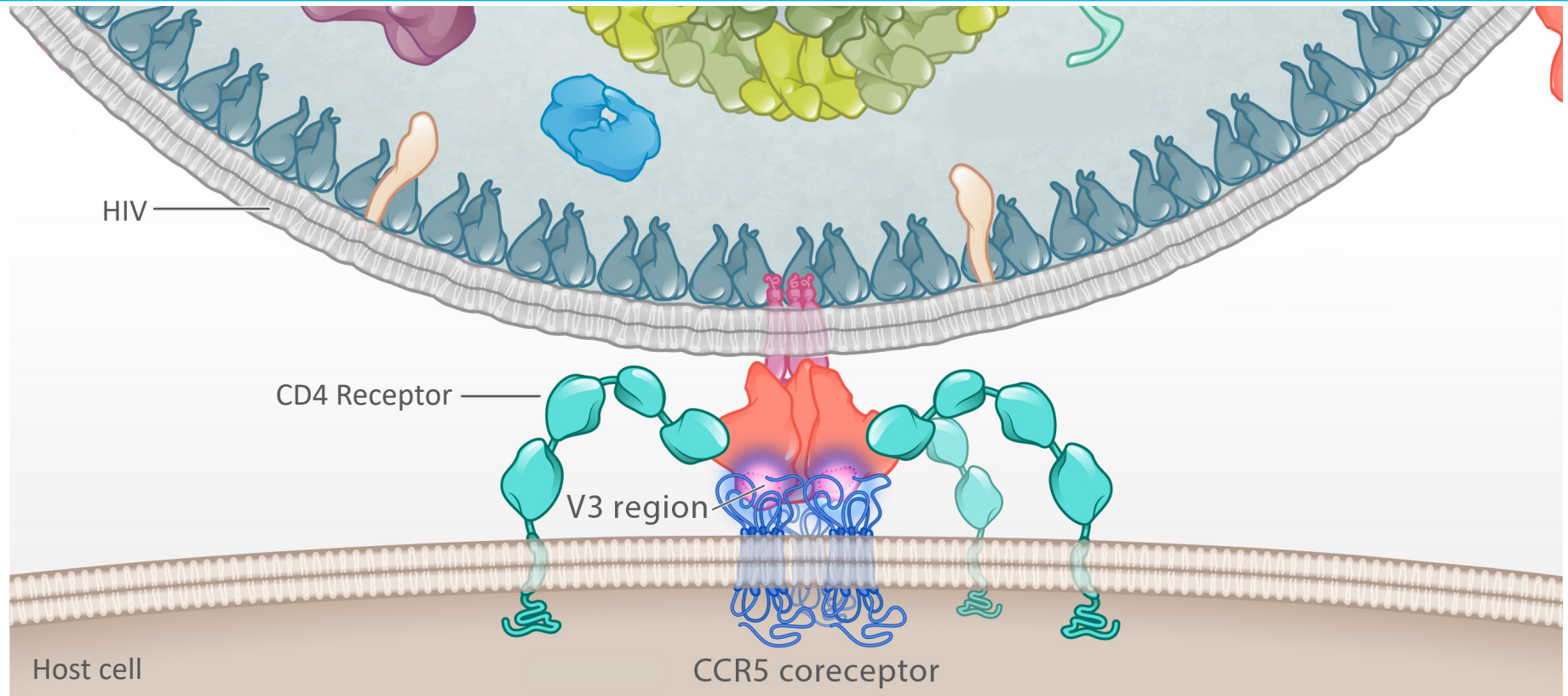


Maraviroc Activity Depends On HIV Tropism

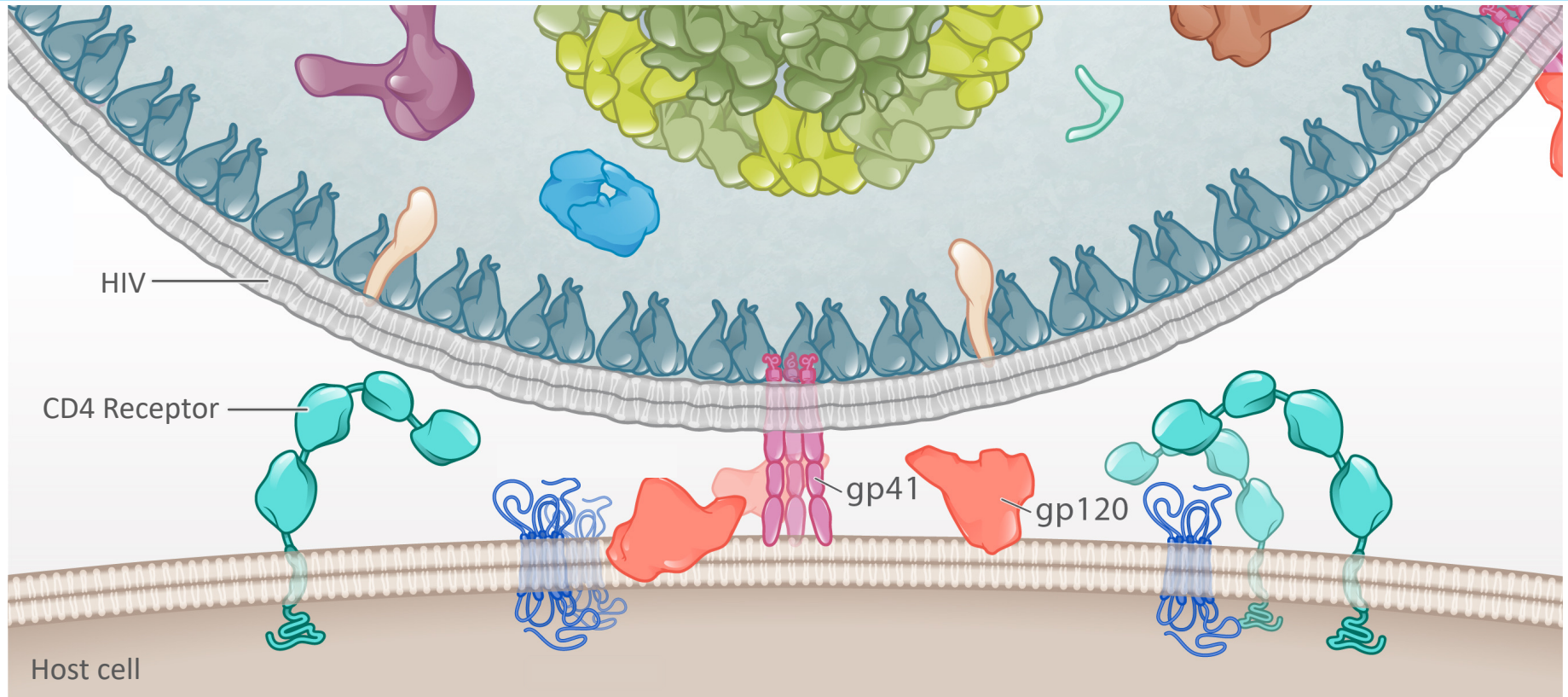


Fusion Inhibitor

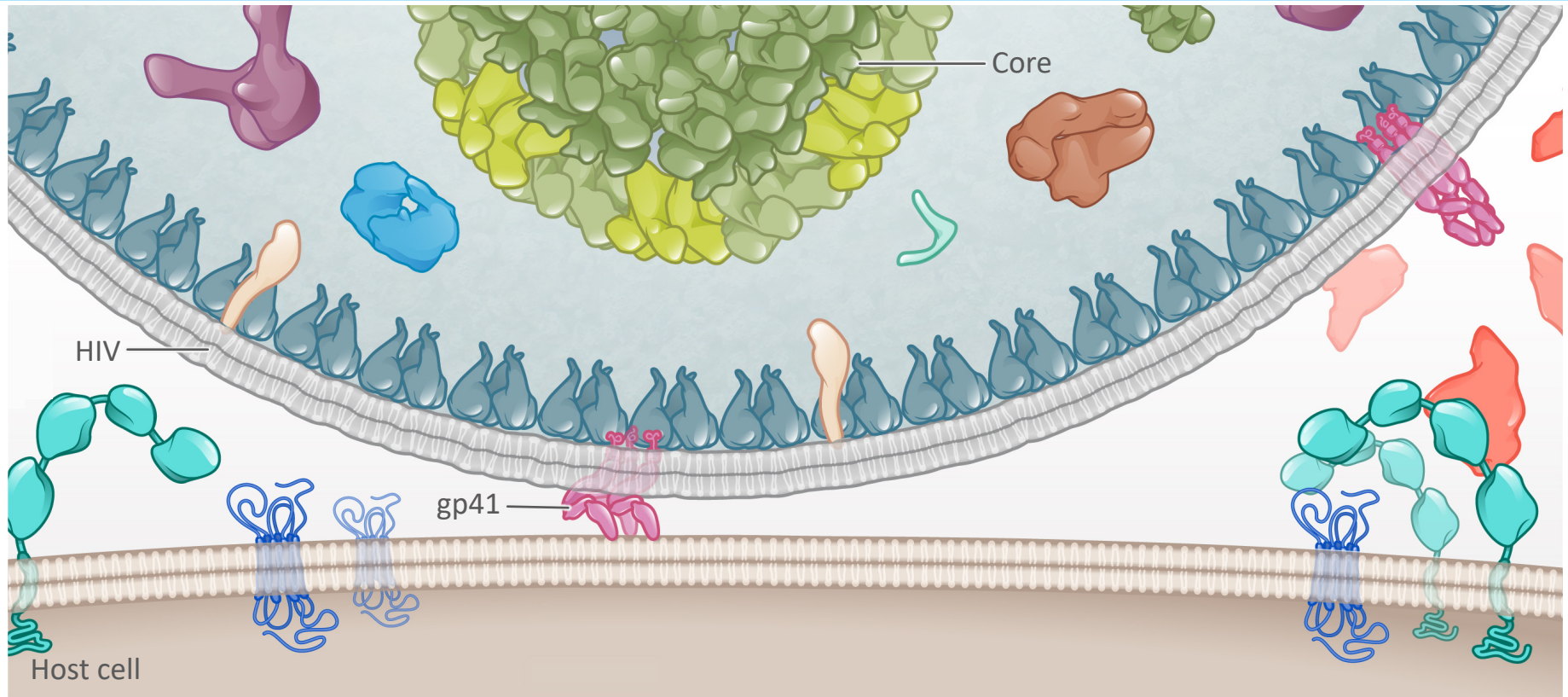
HIV Fusion



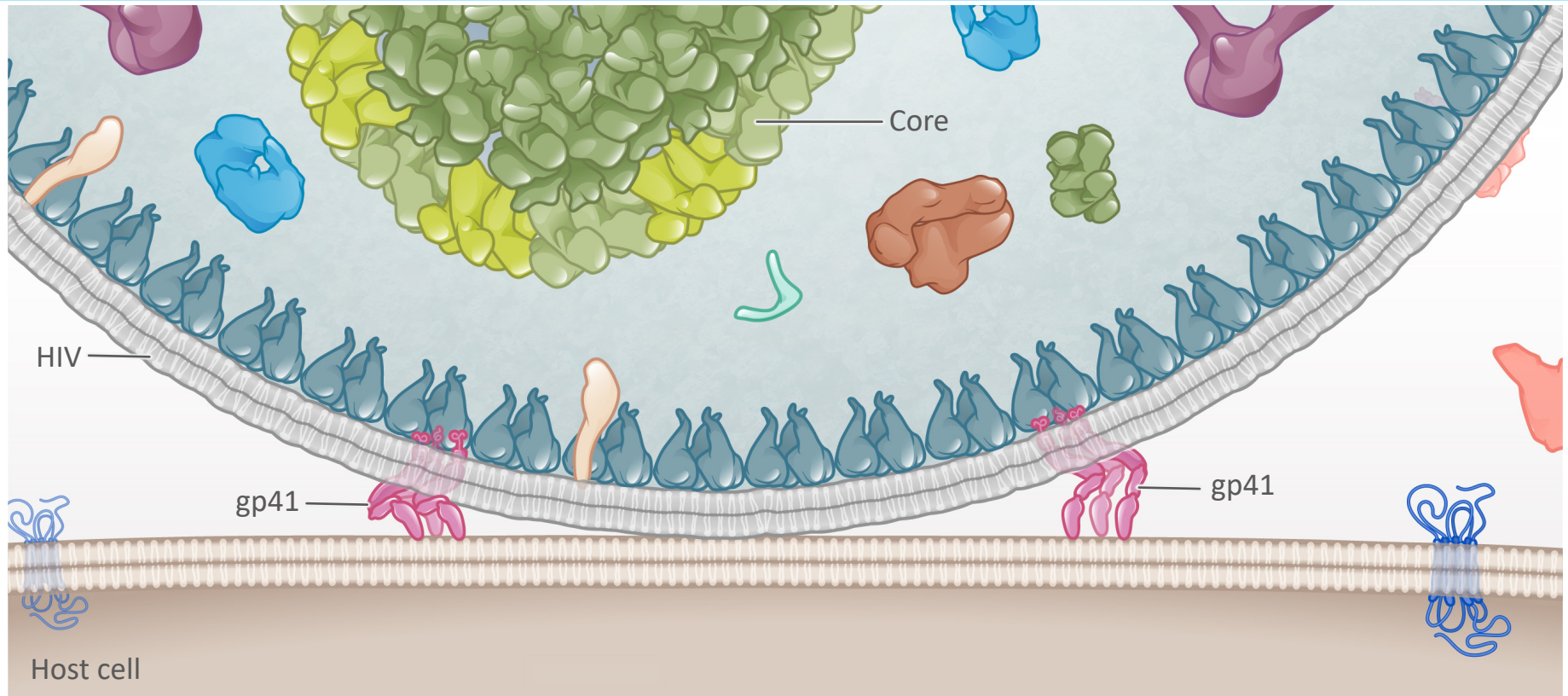
HIV Fusion



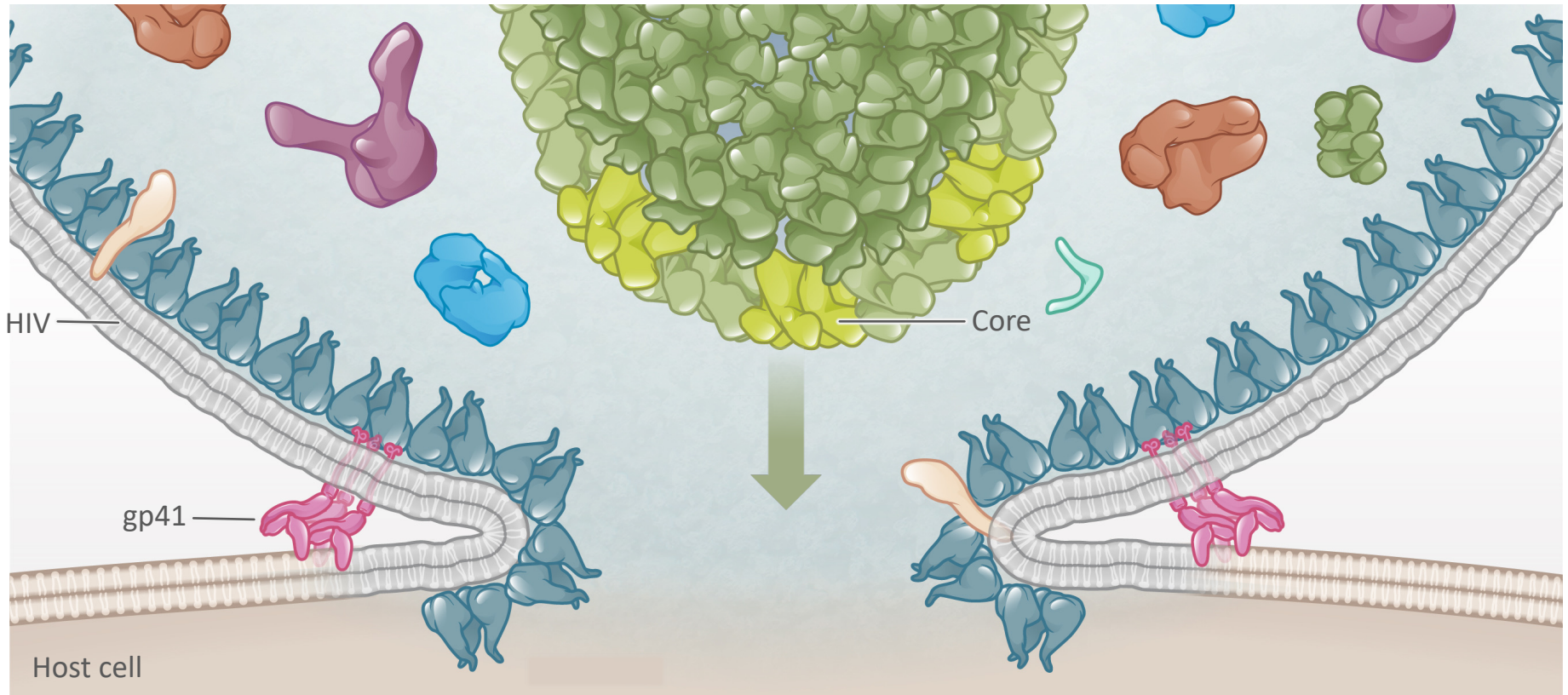
HIV Fusion: Early gp41 Folding



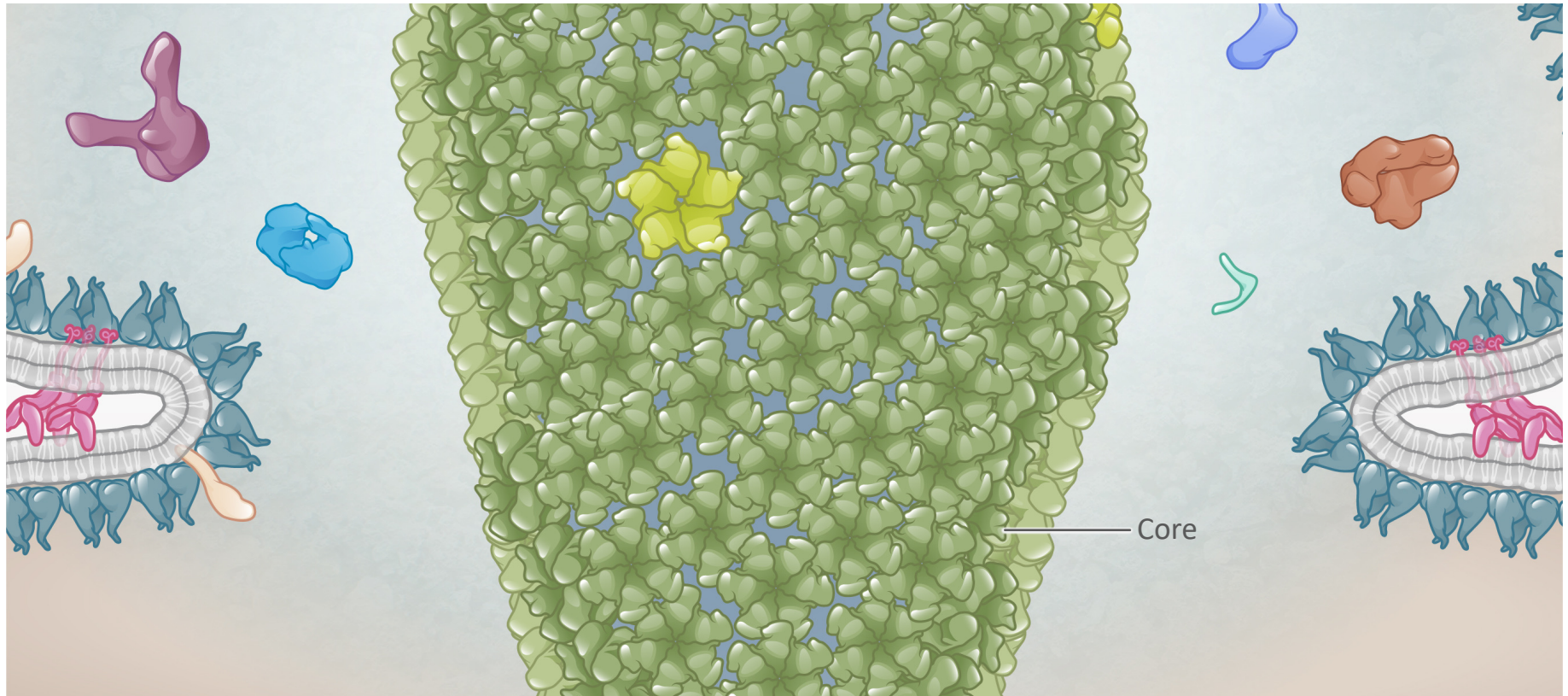
HIV Fusion: Late gp41 Folding



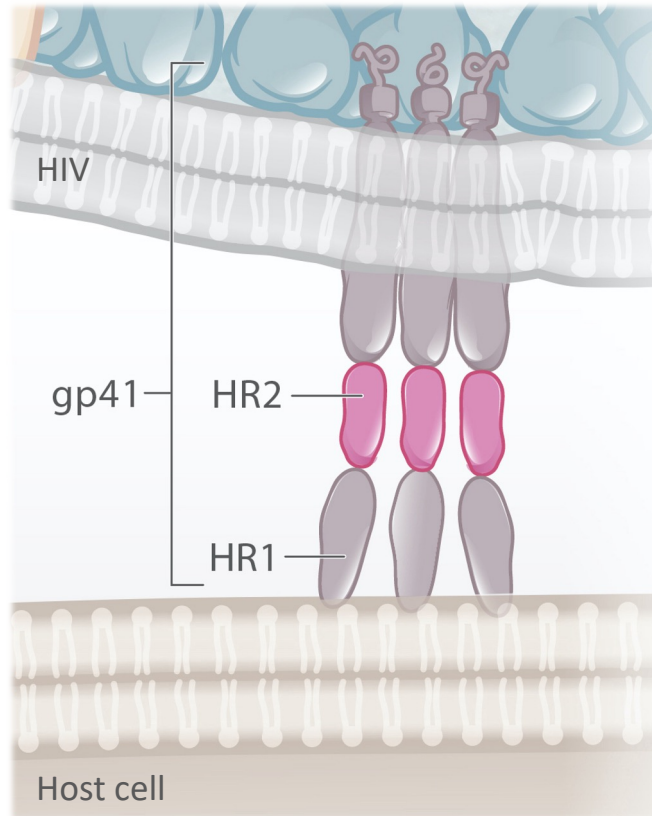
HIV Fusion: Merger of HIV and Host Cell Membranes



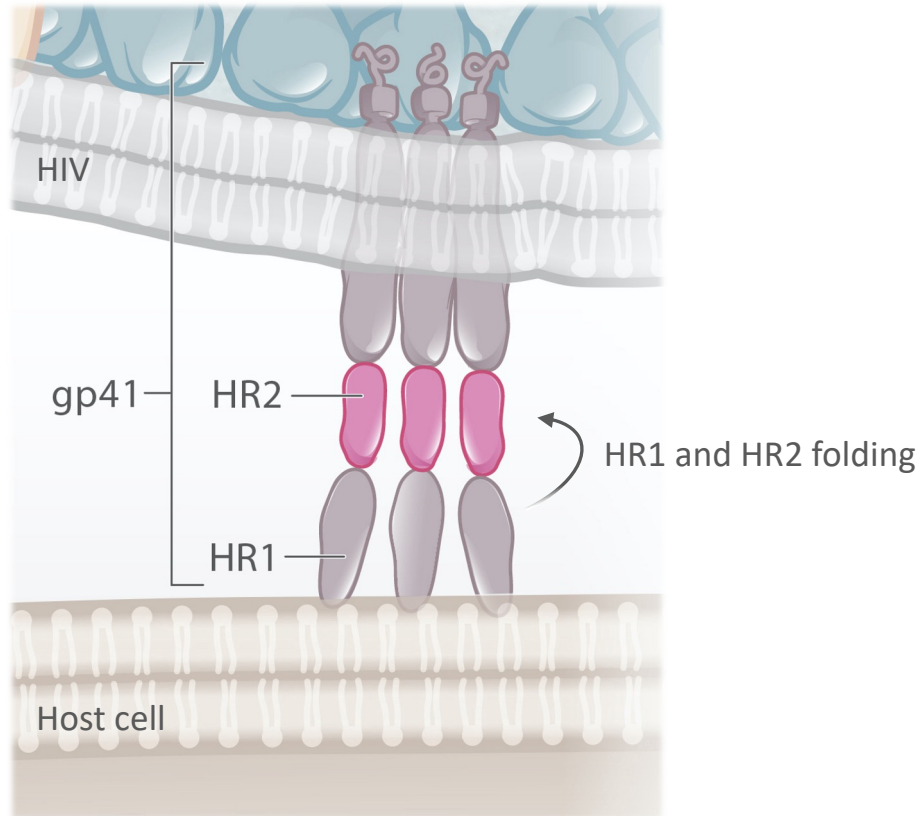
HIV Core Entering Host Cell



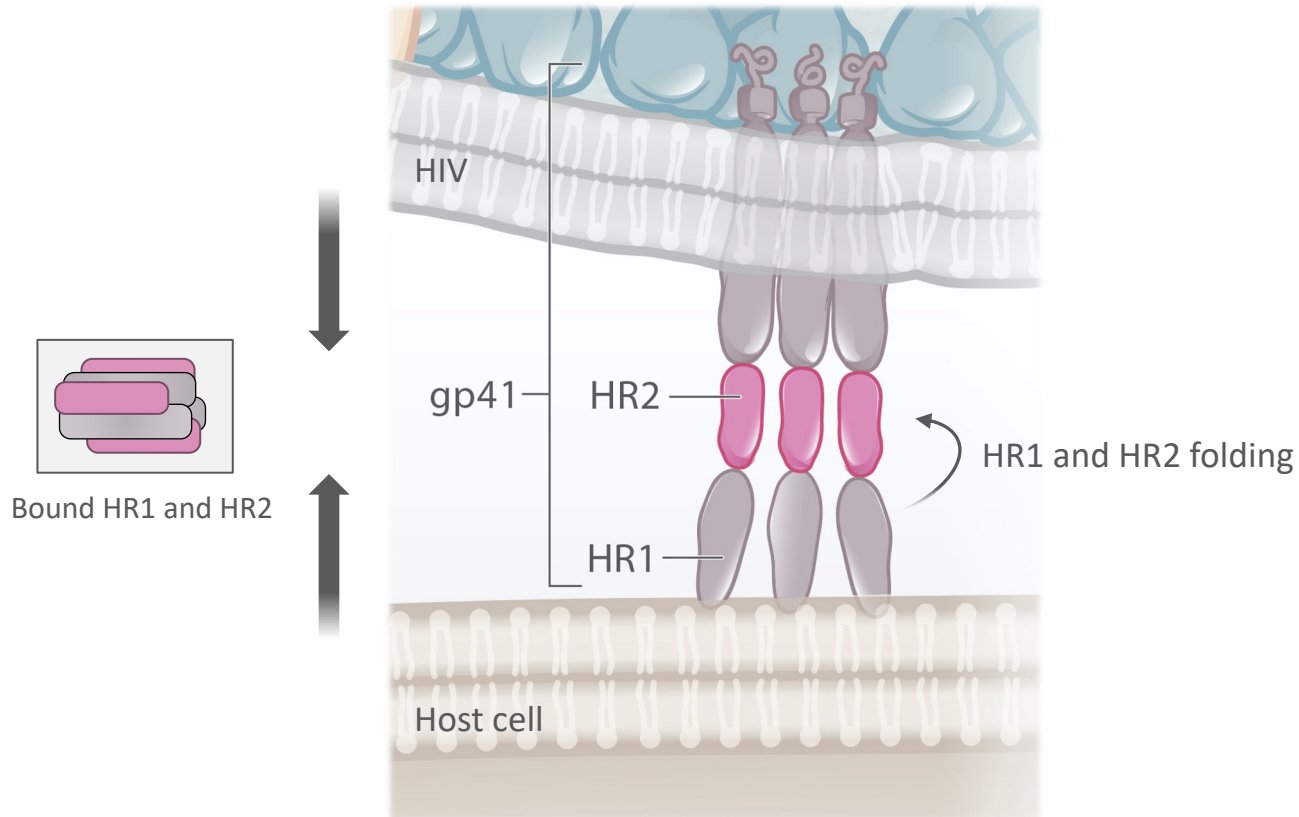
HIV Fusion and gp41 Folding



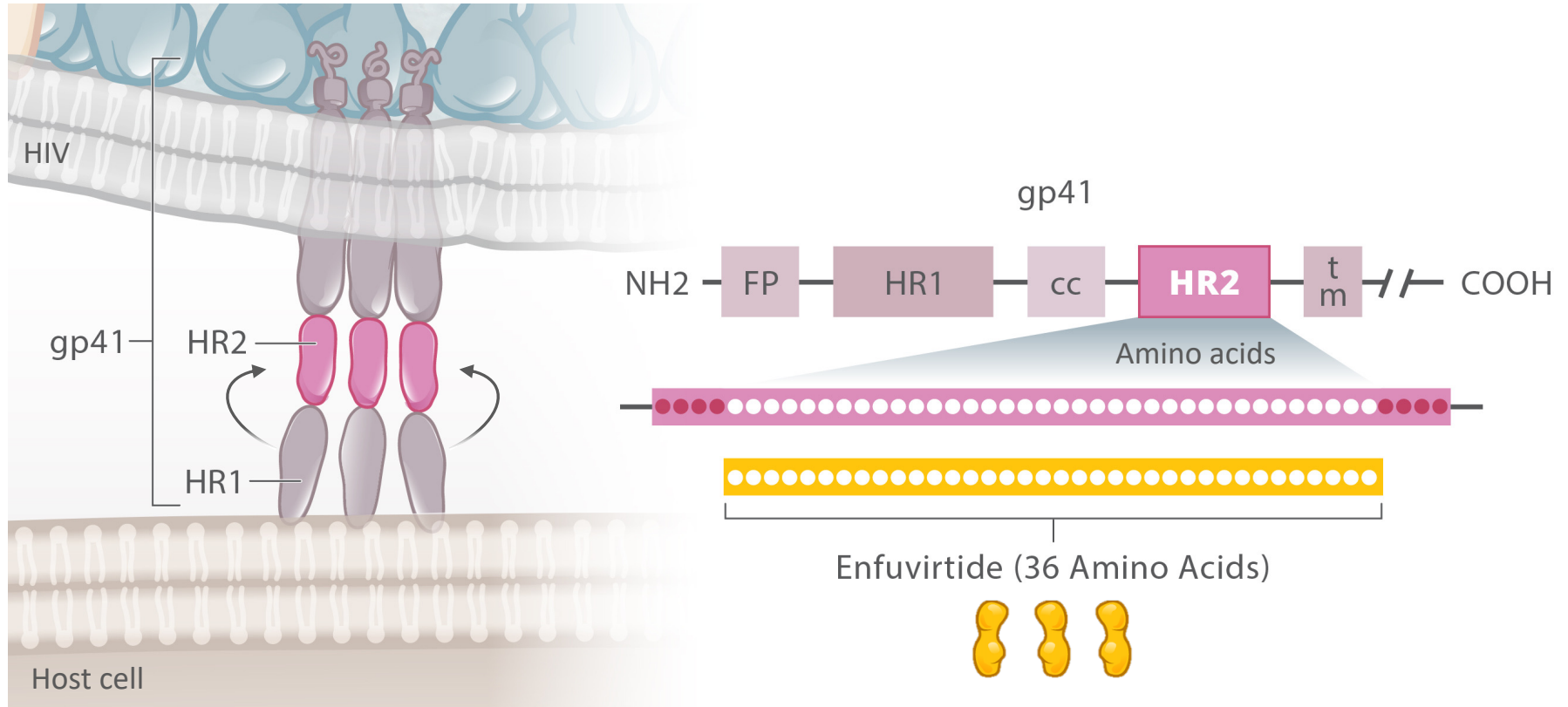
HIV Fusion and gp41 Folding



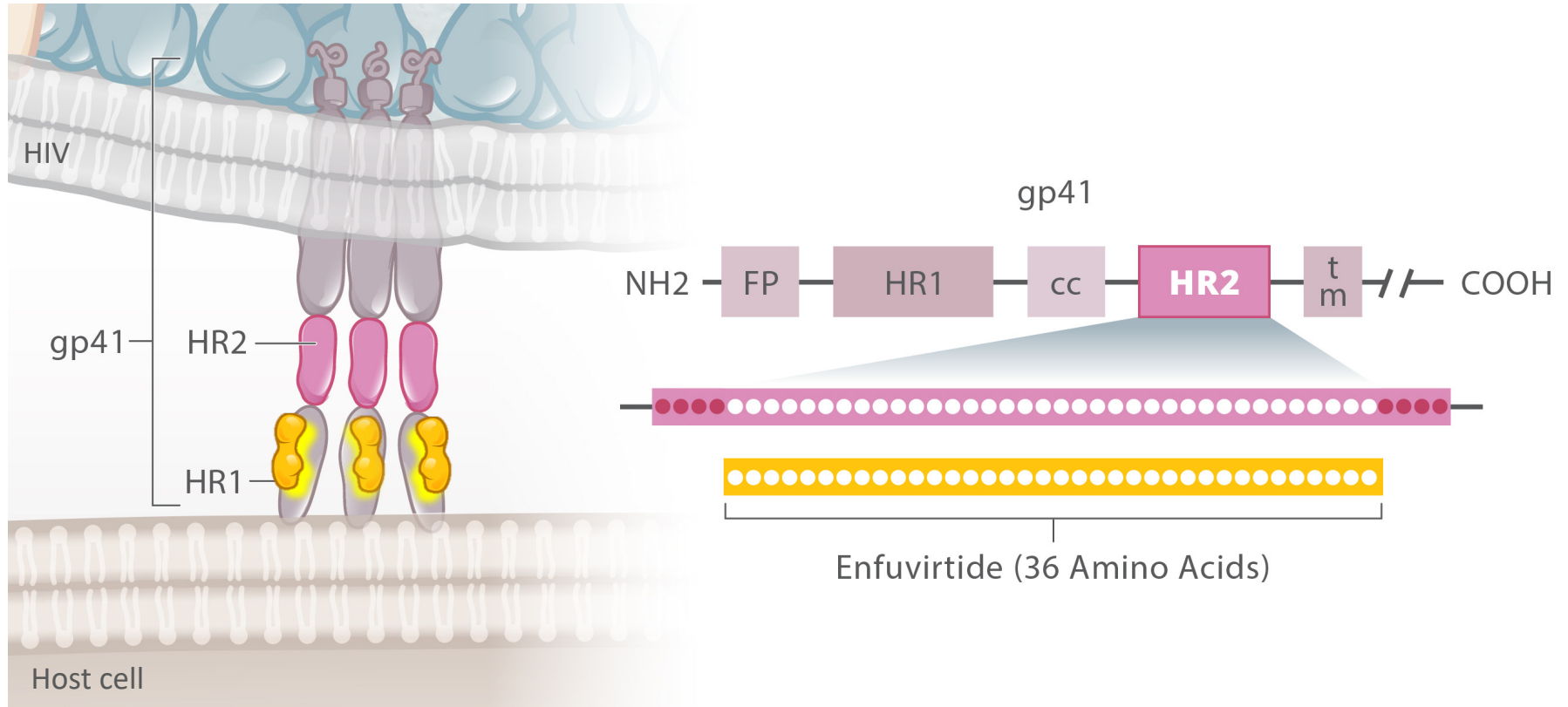
HIV Fusion and gp41 Folding



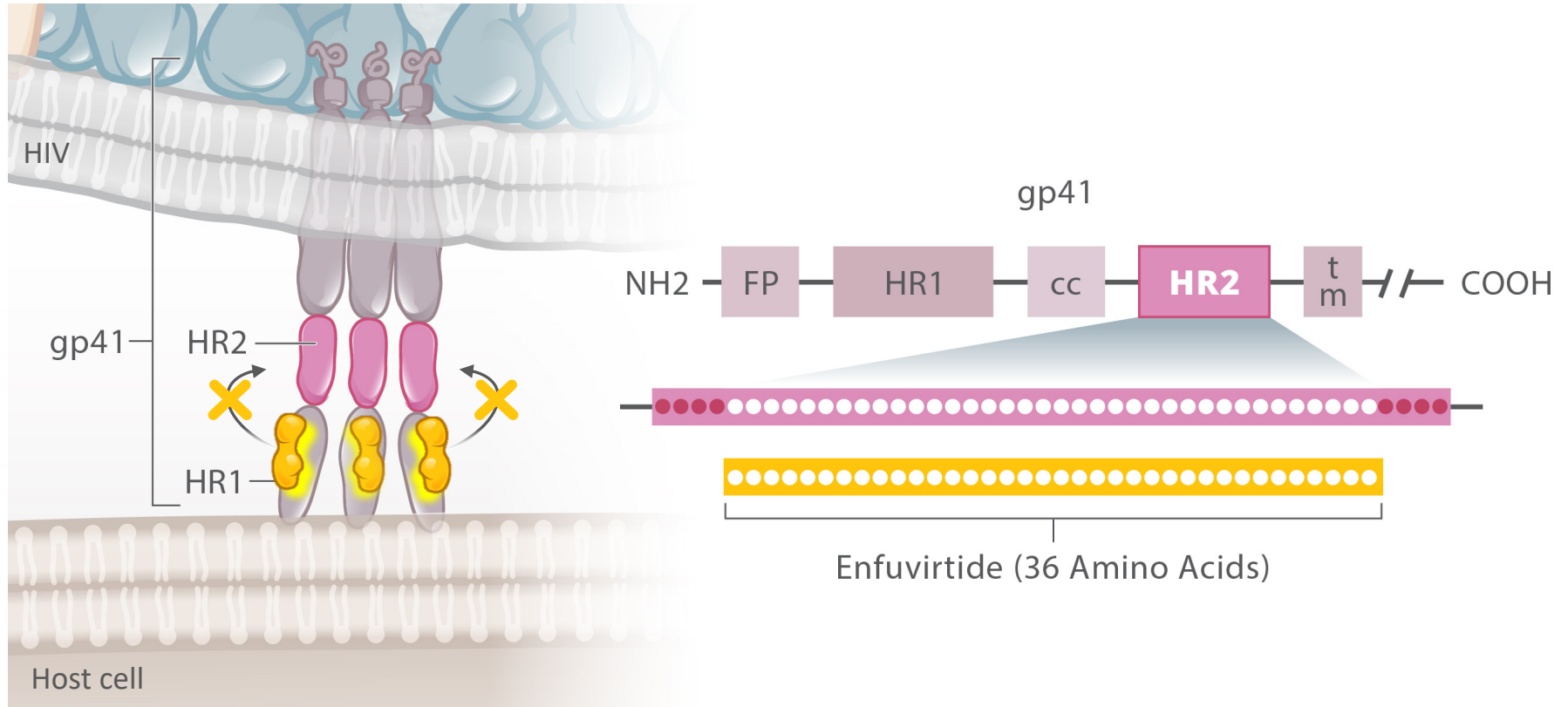
HIV Fusion Inhibitor



HIV Fusion Inhibitor



HIV Fusion Inhibitor

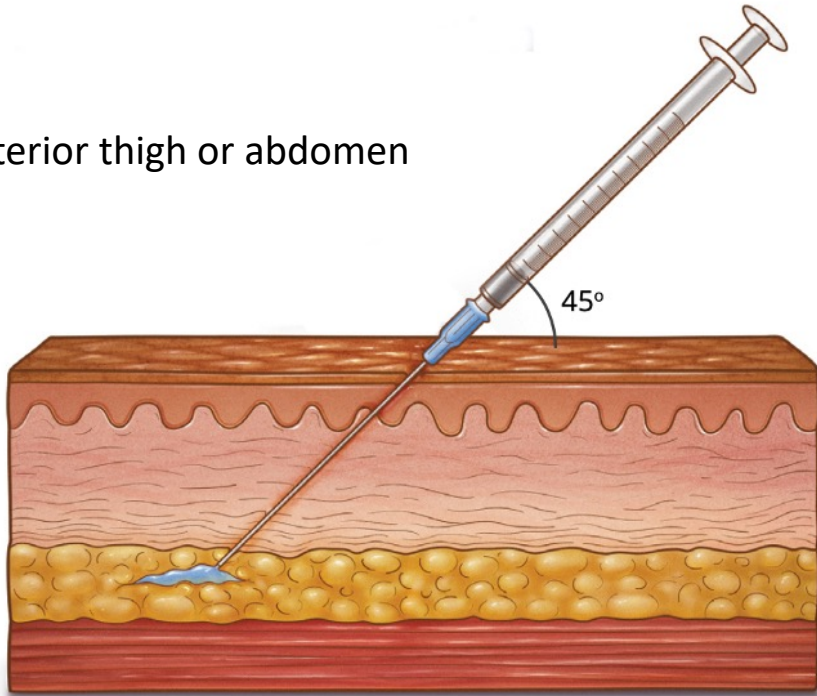


Enfuvirtide (*Fuzeon*)



Dosing (Subcutaneous)

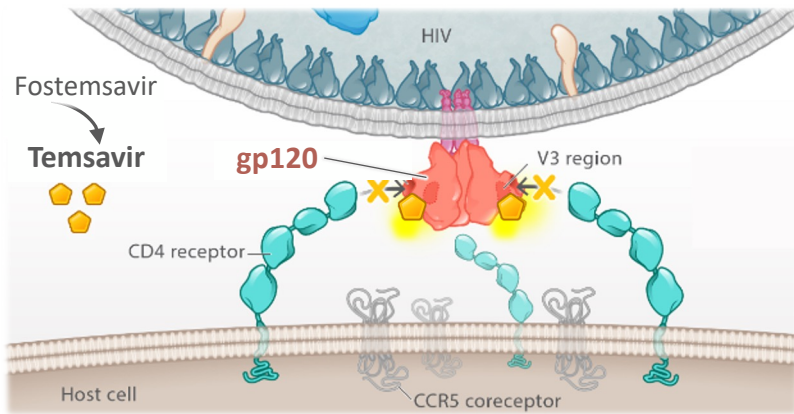
- 90 mg (1 mL) bid
- Inject into upper arm, anterior thigh or abdomen



Summary Concepts

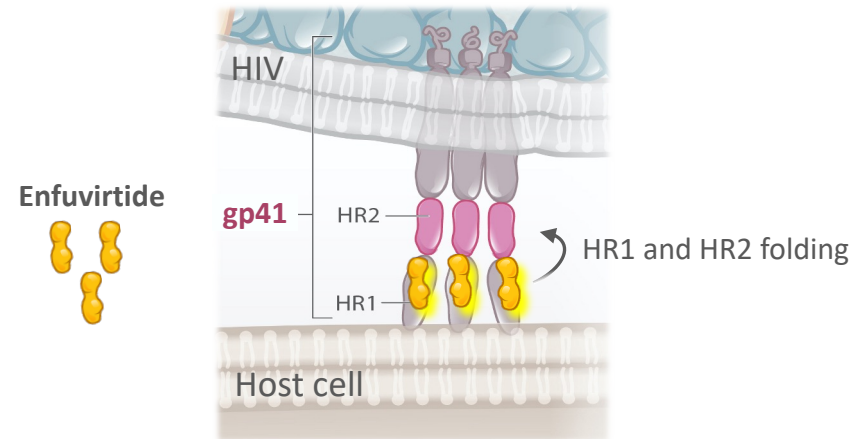
HIV Entry Inhibitors that Bind to HIV

Attachment Inhibitor (binds to HIV gp120)



Fostemsavir

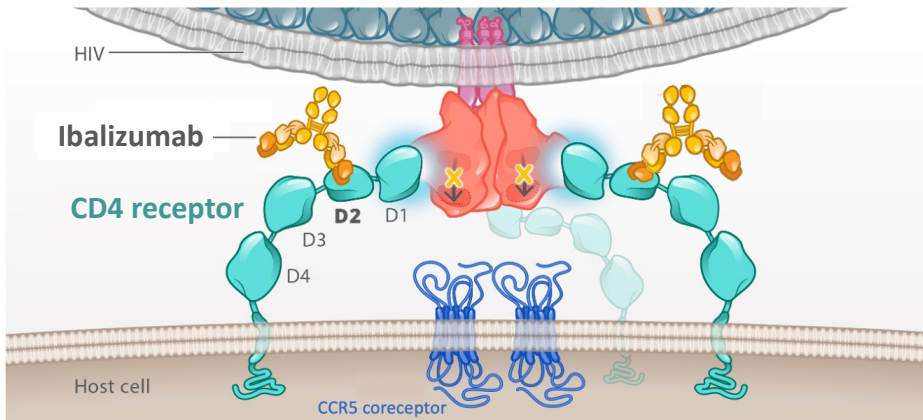
Fusion Inhibitor (binds to HIV gp41)



Enfuvirtide

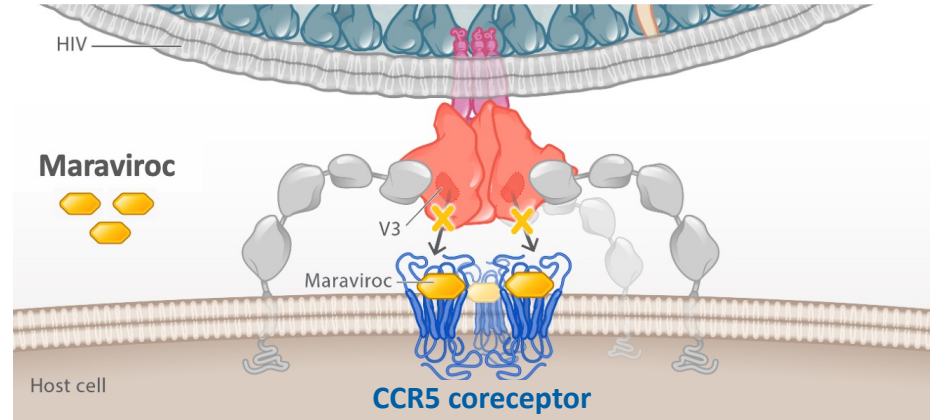
HIV Entry Inhibitors that Bind to Host Cell Receptors

Post-Attachment Inhibitor (binds to Host CD4 Receptor)



Ibalizumab

CCR5 Receptor Antagonist (binds to Host CCR5 Coreceptor)



Maraviroc

HIV Cell Entry and HIV Entry Inhibitors

Key Steps for HIV Entry

1

CD4 Attachment

2

Coreceptor Binding

3

Fusion

HIV Cell Entry and HIV Entry Inhibitors

Key Steps for HIV Entry

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Entry Inhibitor Subclasses

Attachment Inhibitors

Post-Attachment Inhibitors

CCR5 Antagonist

Fusion Inhibitors

HIV Cell Entry and HIV Entry Inhibitors

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Fusion Inhibitors

Entry Inhibitor Medications

Fostemsavir

Ibalizumab

Maraviroc

Enfuvirtide

Acknowledgment

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