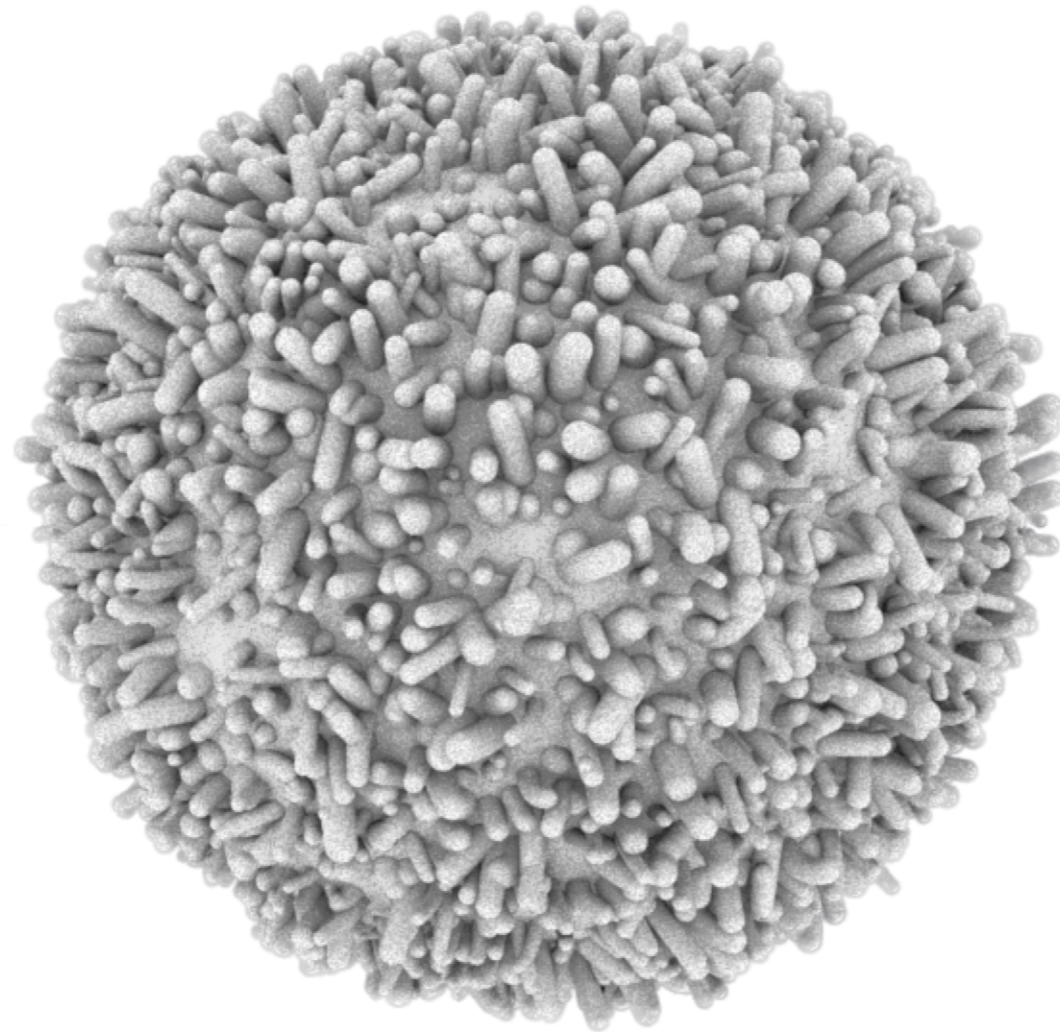
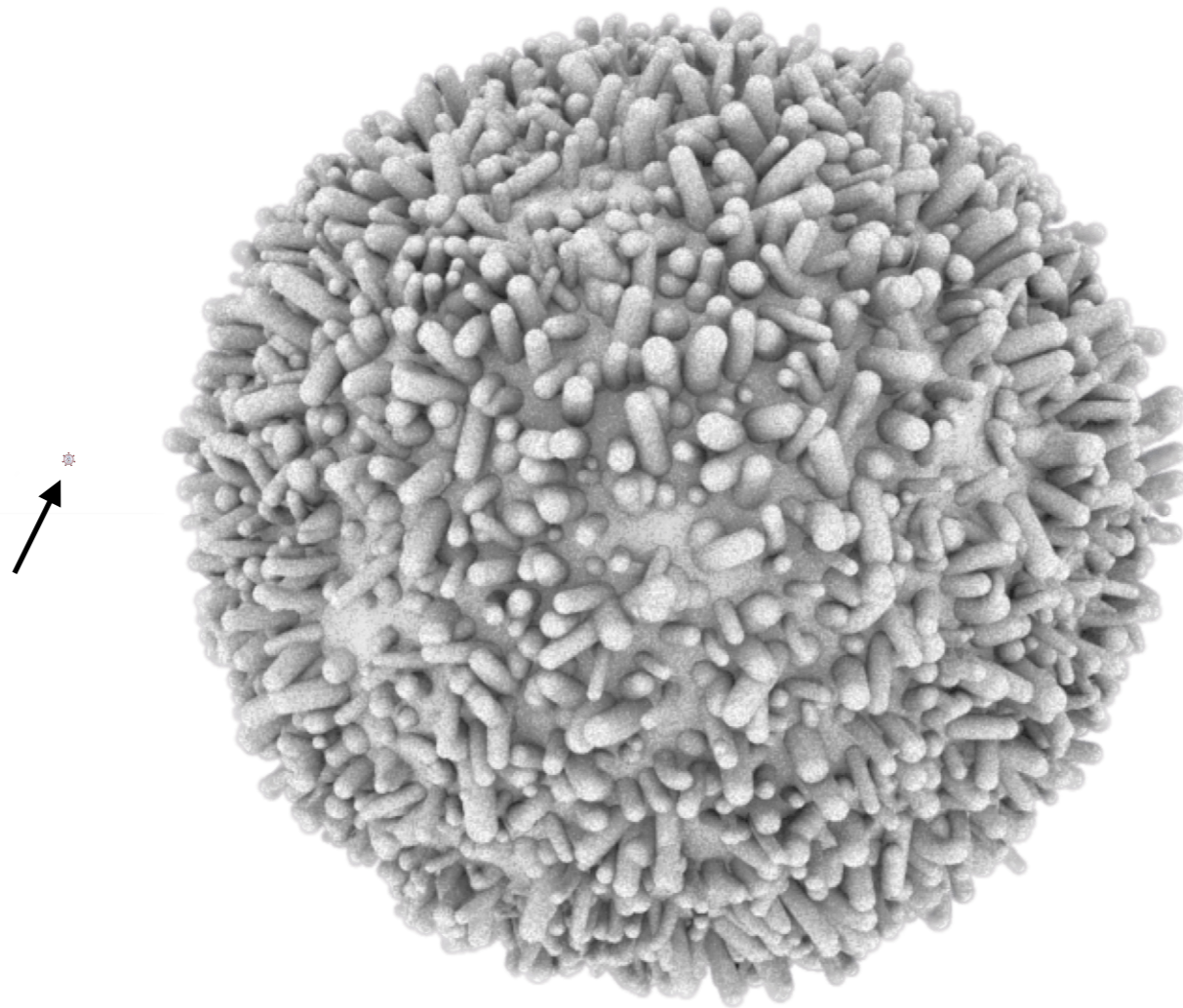


# *HIV/AIDS*



Alice Long  
**Literature Talk**  
May 30th, 2023

# *HIV/AIDS*

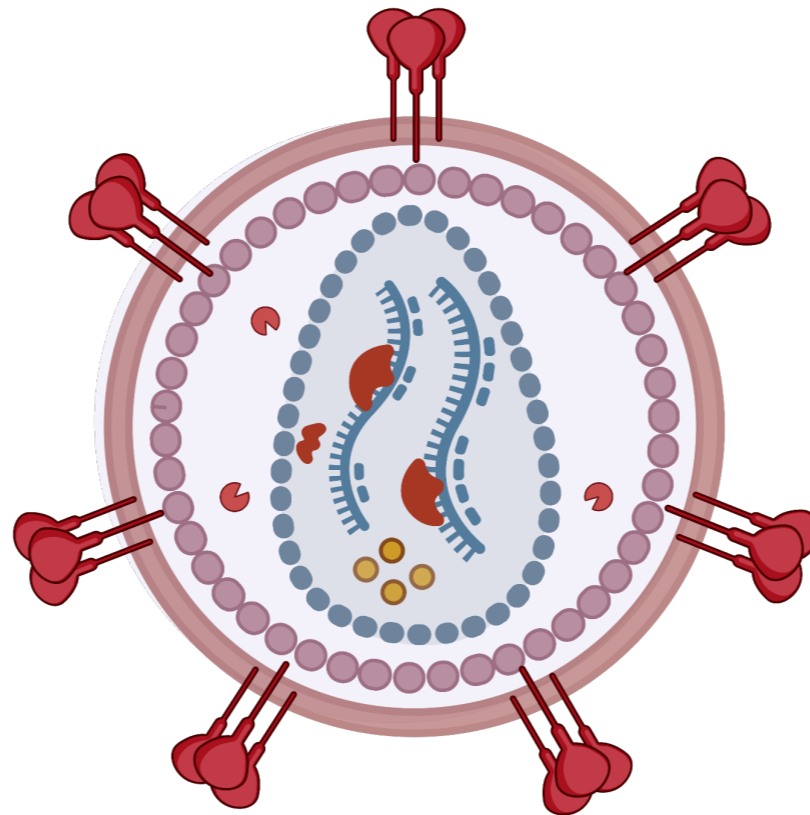


Alice Long  
**Literature Talk**  
May 30th, 2023

## What is HIV/AIDS?

HIV = **human immunodeficiency virus**, which is the virus that causes HIV infection.

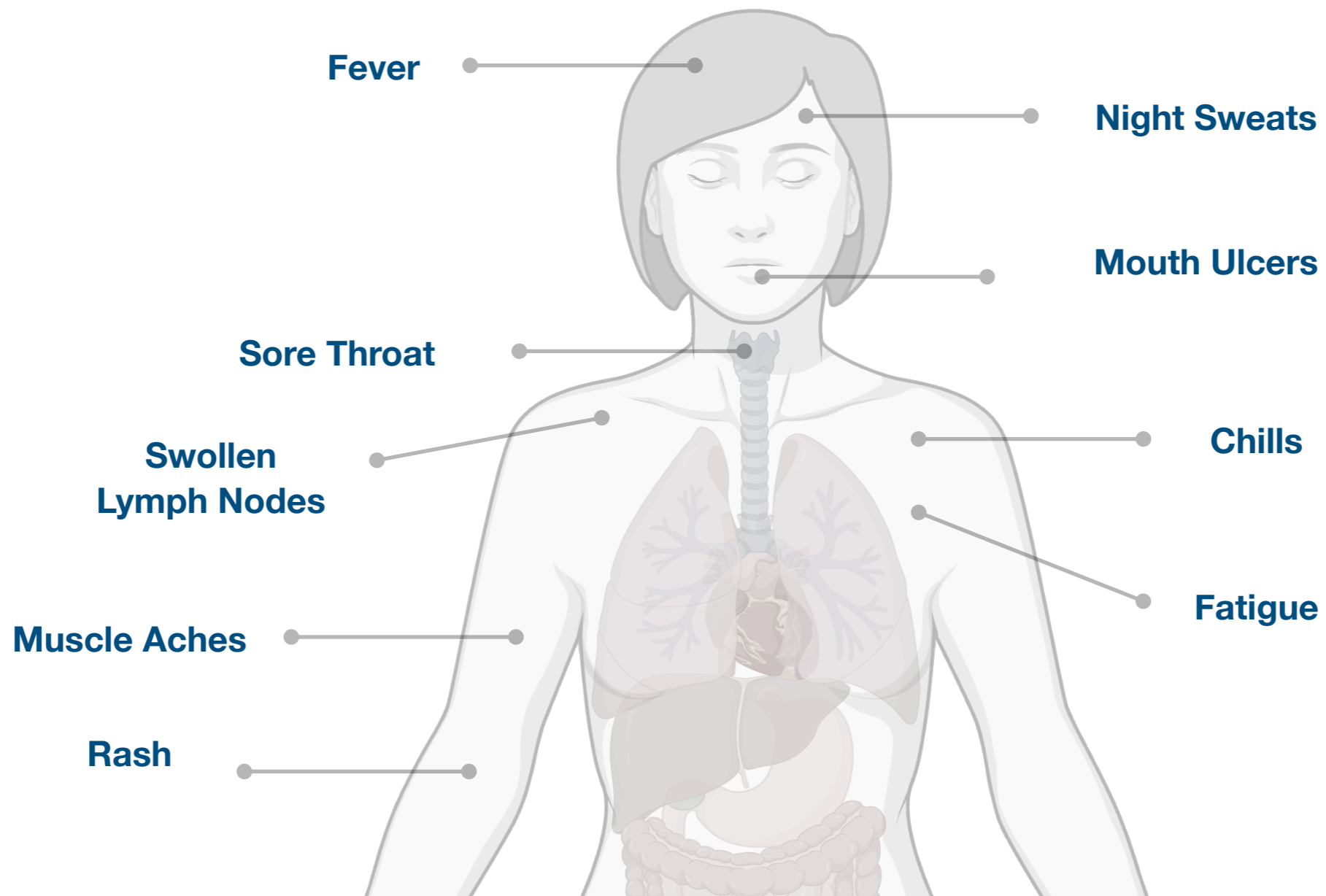
AIDS = **acquired immunodeficiency syndrome**. AIDS is the most advanced stage of HIV infection.



# What is HIV/AIDS?

## Actue HIV Infection

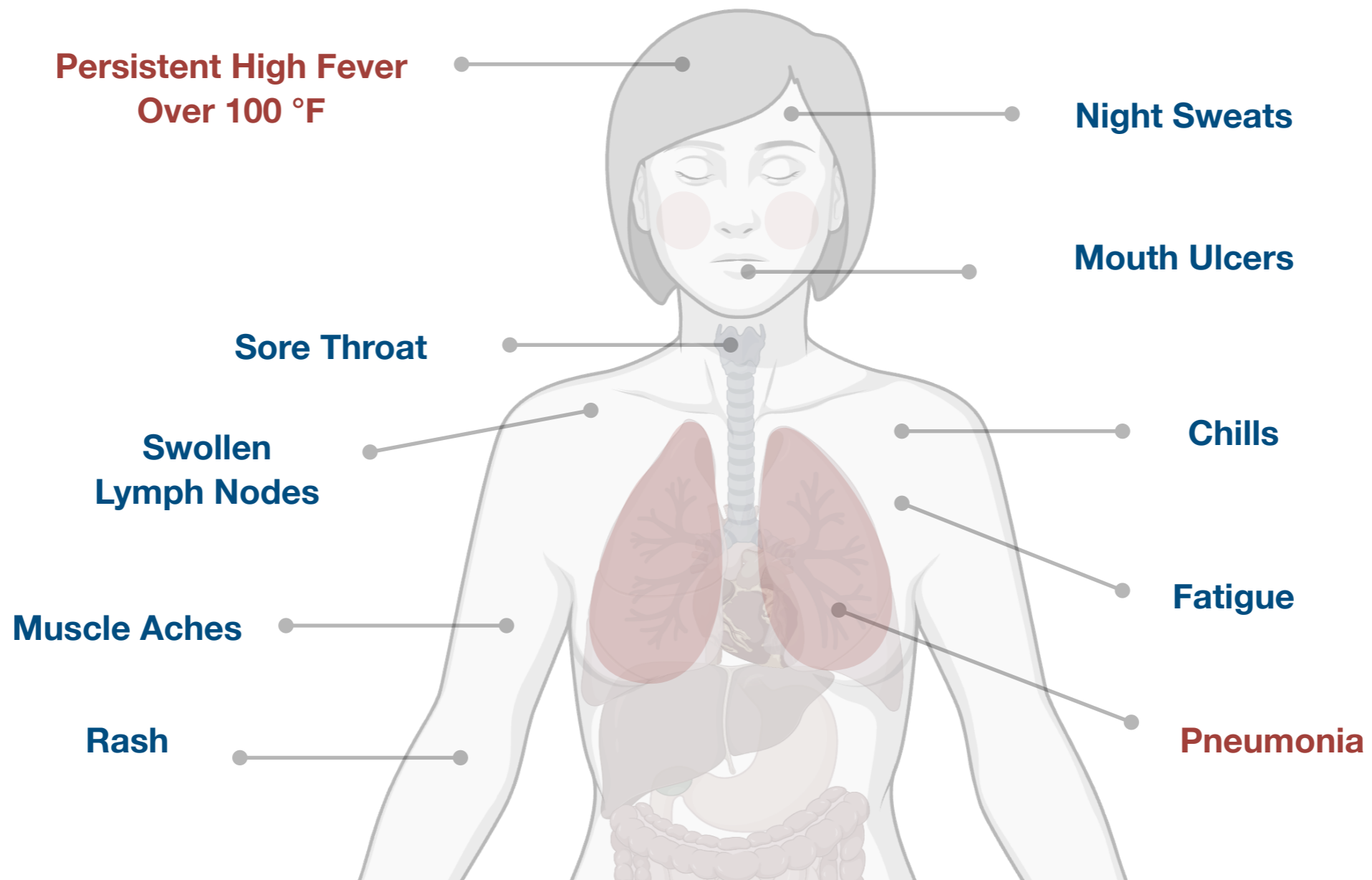
early symptoms 2-4 weeks after first exposure



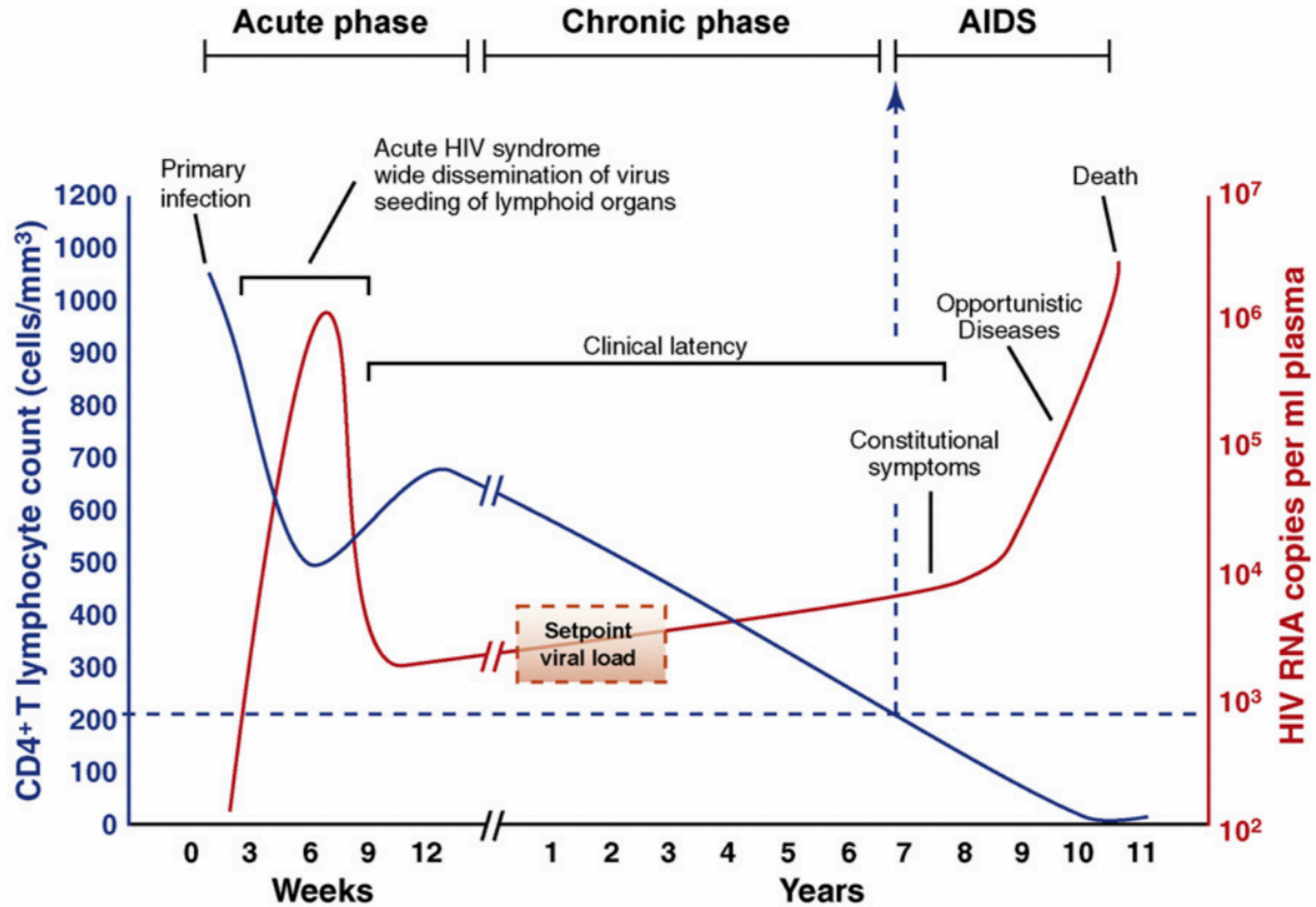
# What is HIV/AIDS?

## AIDS

CD4 levels decrease below 200 cells per cubic millimeter of blood

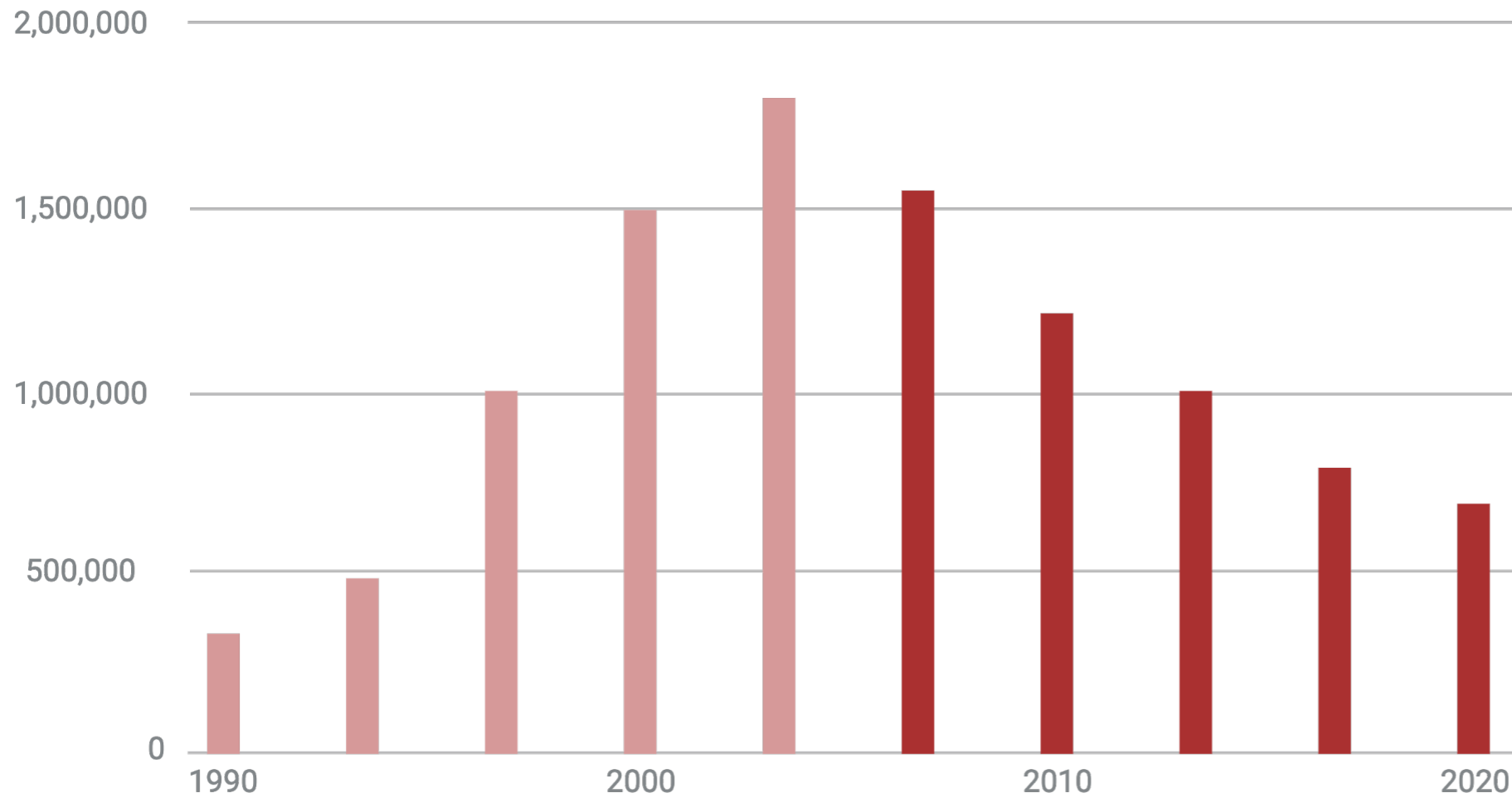


# HIV vs AIDS



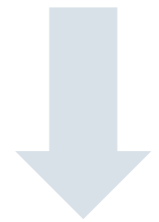
# What is HIV/AIDS?

## Estimated Number of AIDS-related deaths worldwide



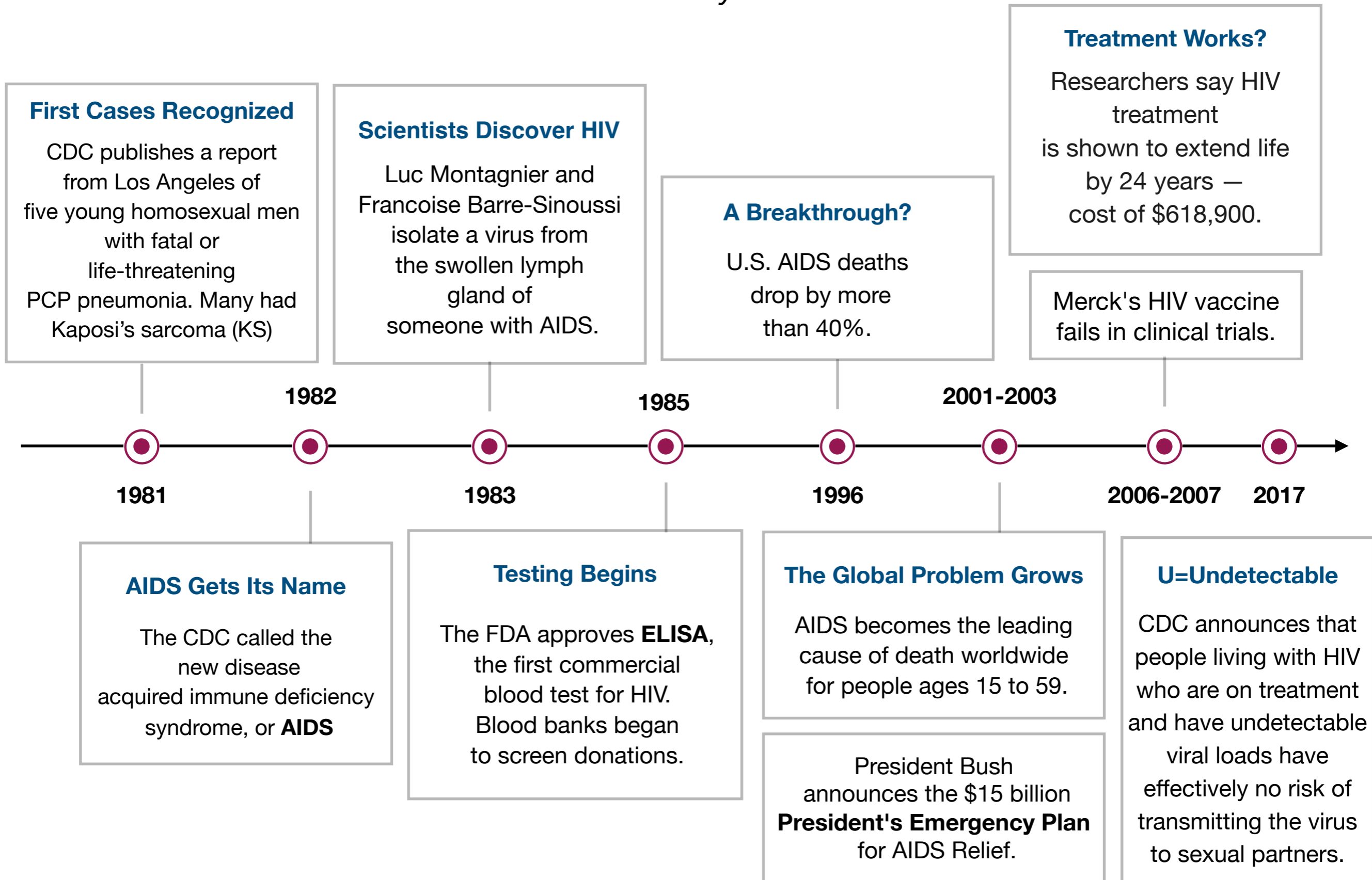
**HIV in 1980s**  
Lifespan upon exposure: **10-13 years**

**HIV in 2023**  
Lifespan upon exposure with proper treatment: **normal lifespan**



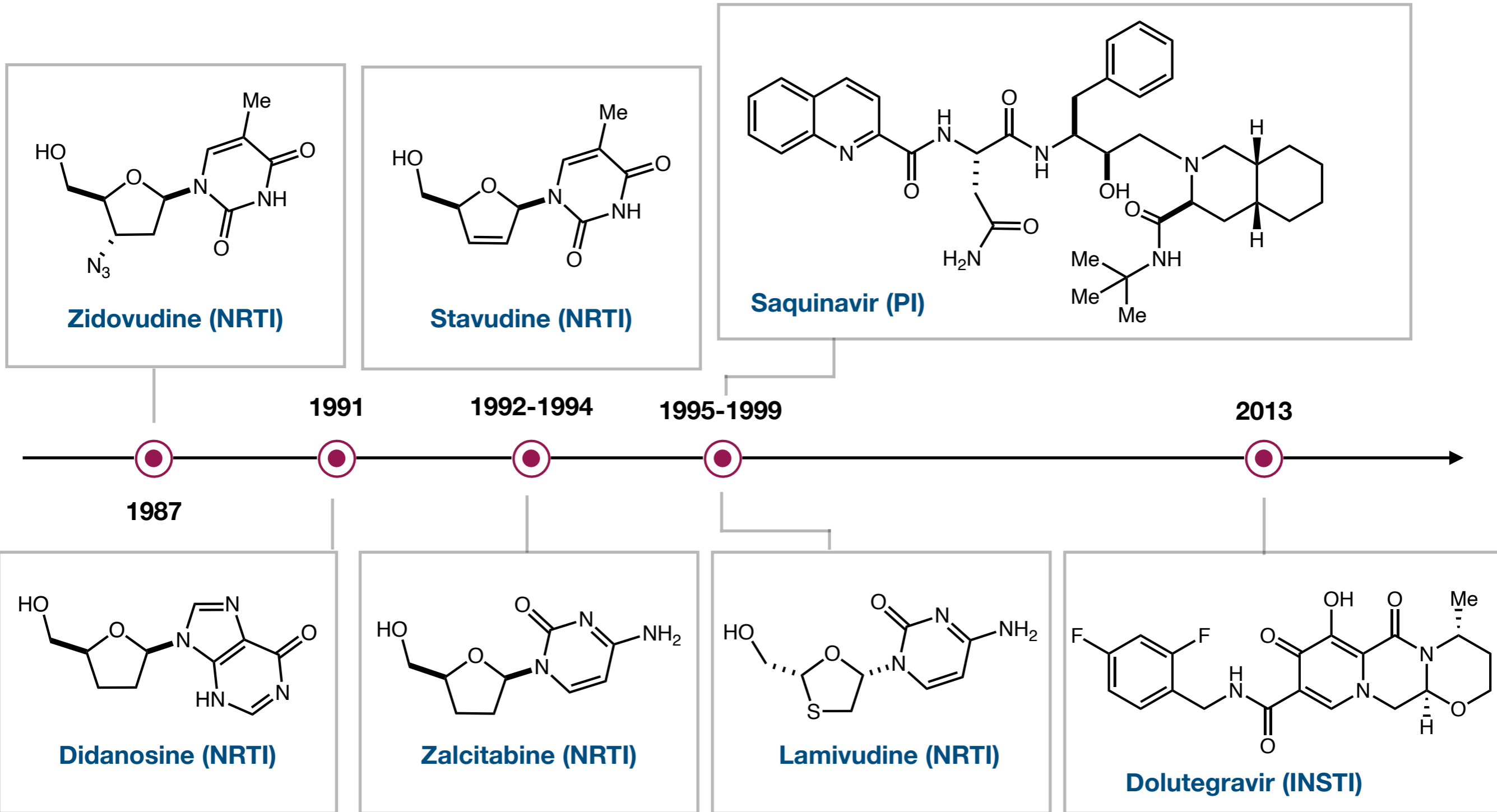
**How did we get to this point?**

# History



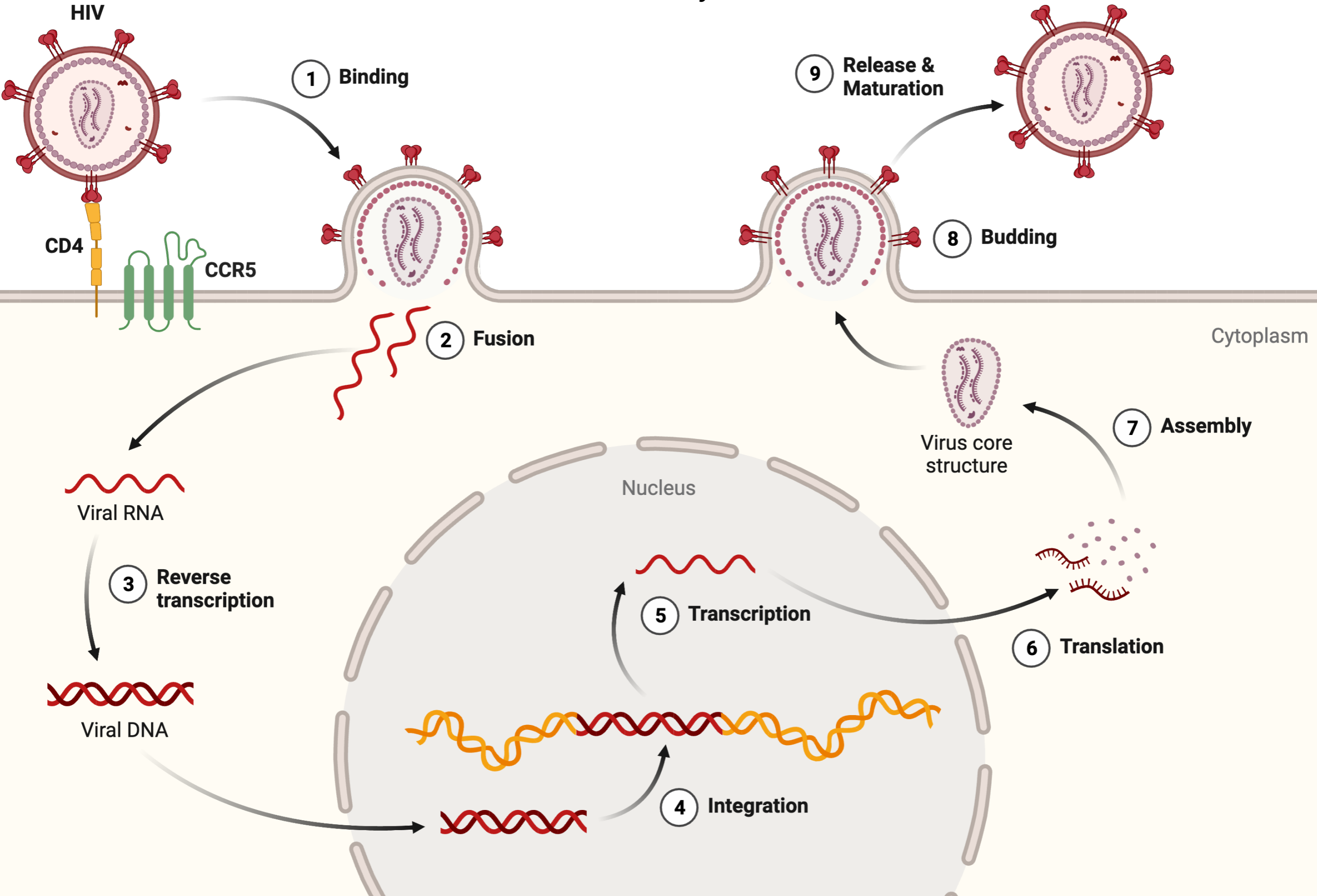


# History of HIV Drug Development

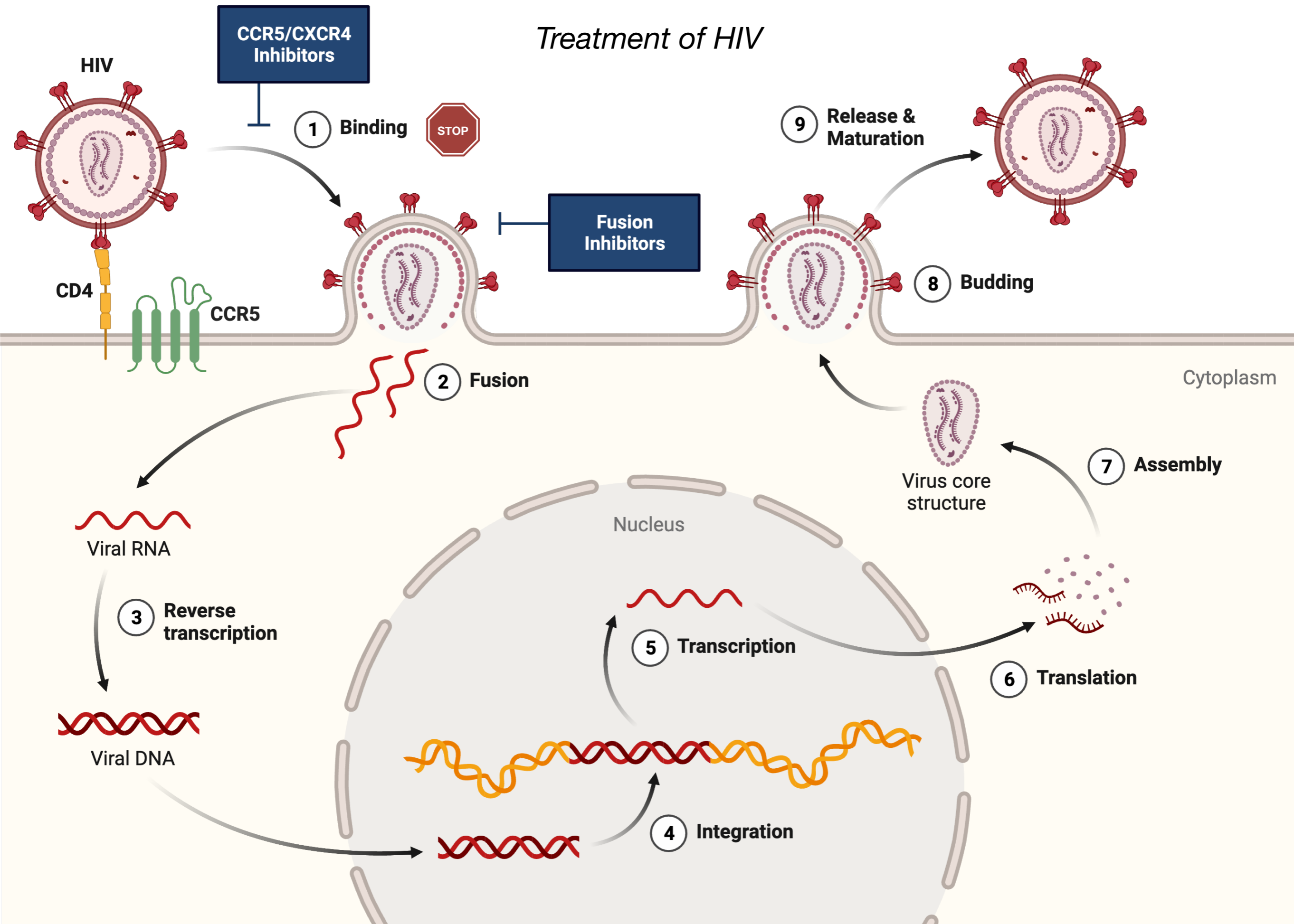


7 HIV drug classes → 58 types of HIV medication

# HIV Life Cycle

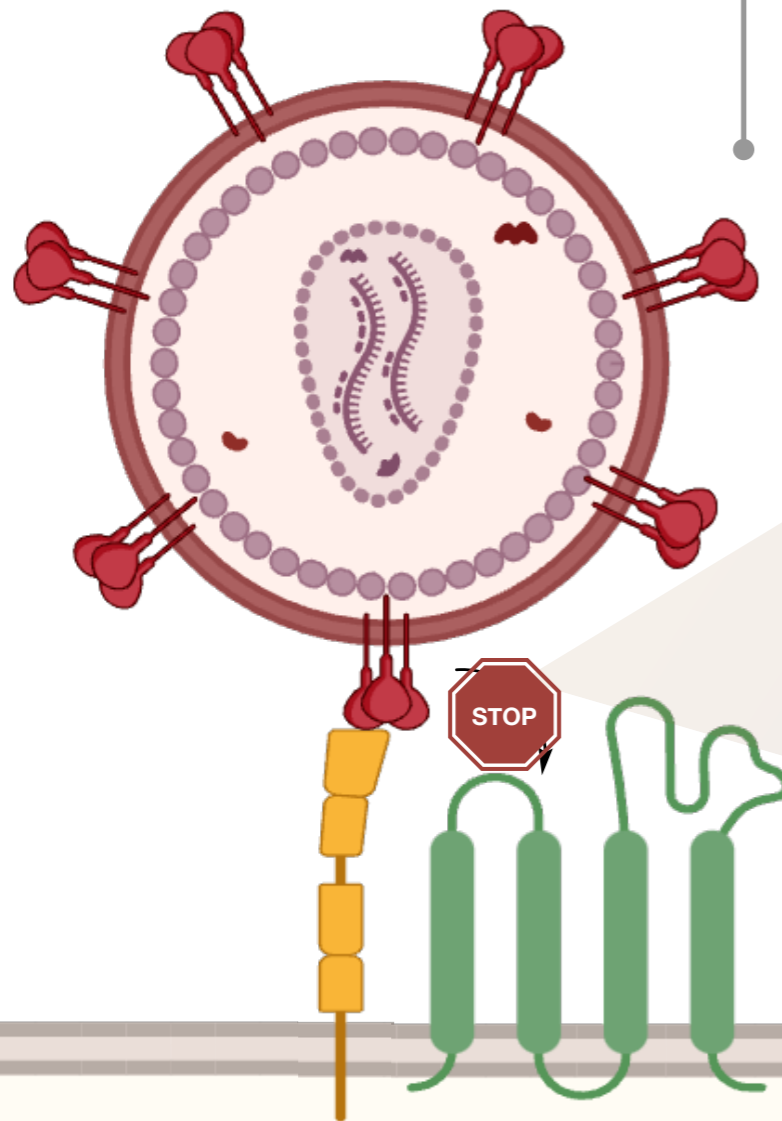


# Treatment of HIV

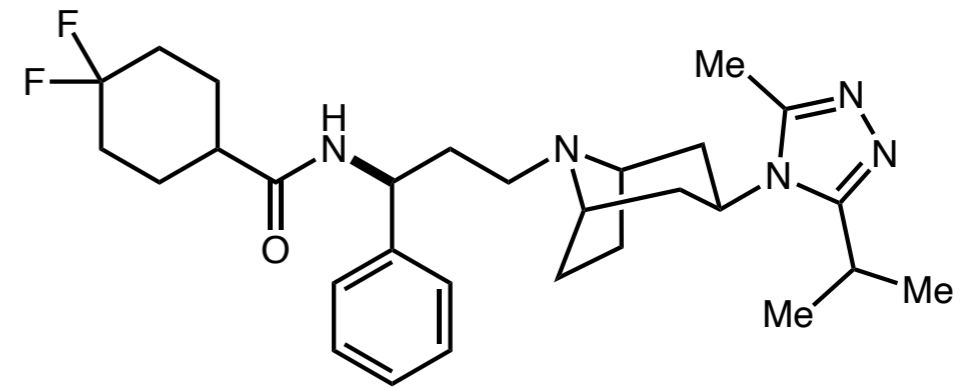


## Mechanism of Action - Entry Inhibitors

### Attachment



- 1** The binding of HIV surface protein gp120 to the CD4 receptor
- 2** A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41
- 3** The binding of gp120 to a co-receptor CCR5

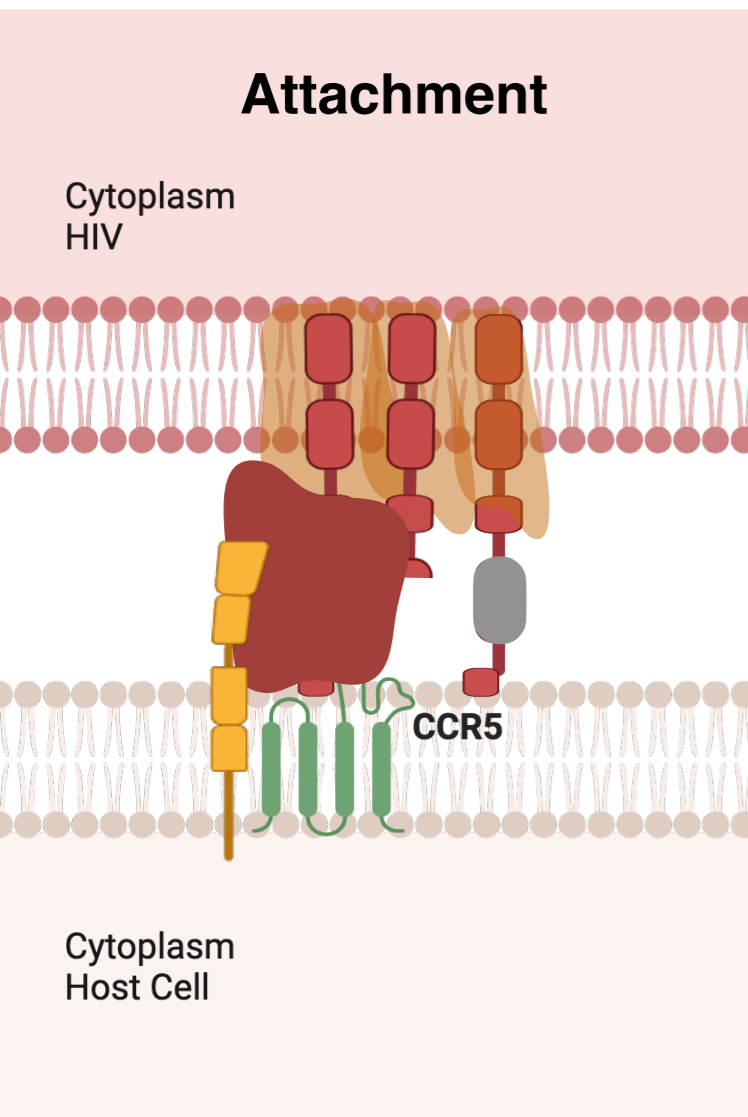


**Maraviroc**  
**CCR5 antagonist**  
**(post attachment inhibitor)**

## Mechanism of Action - Entry Inhibitors

### Attachment

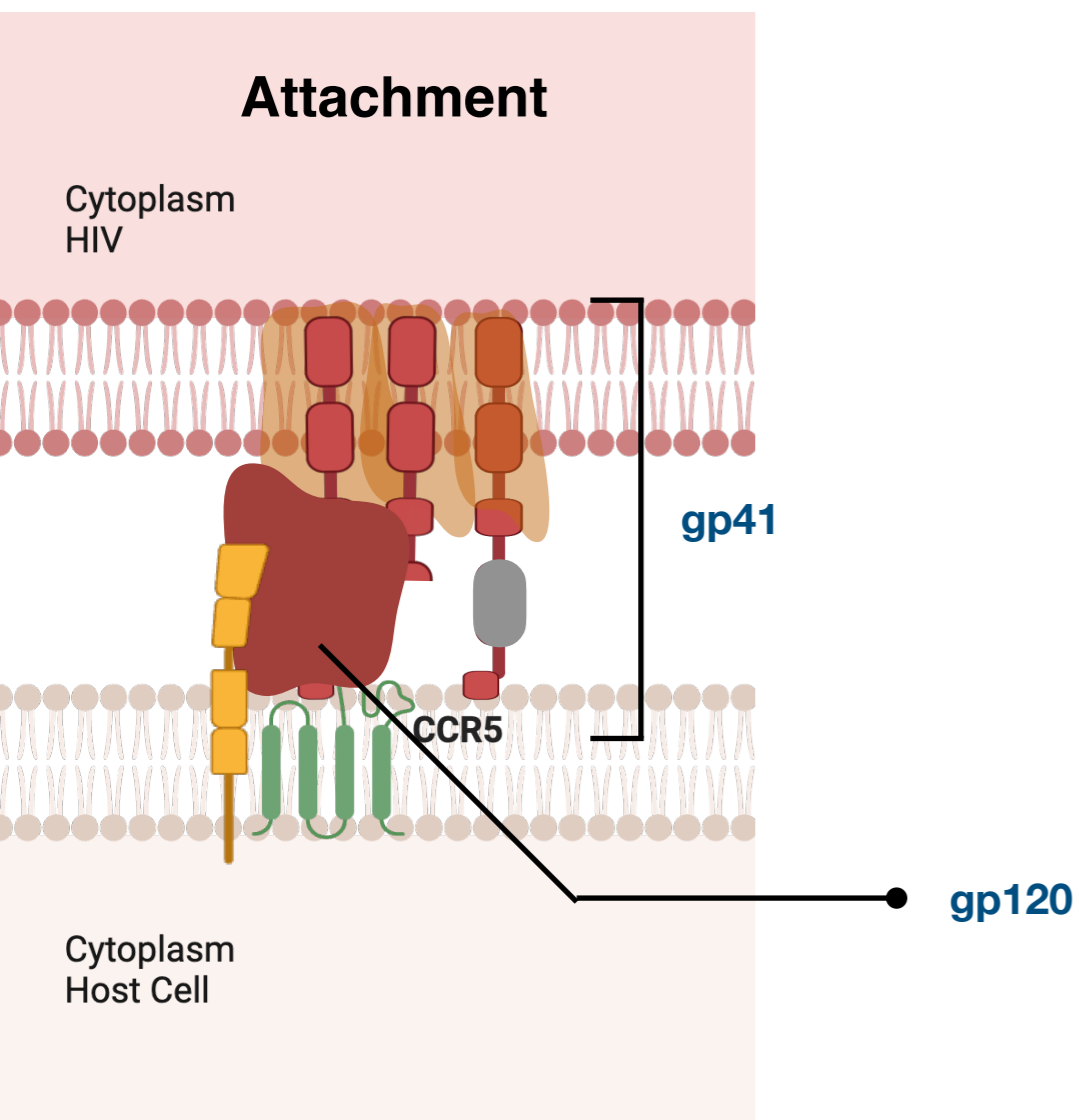
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## Mechanism of Action - Entry Inhibitors

### Attachment

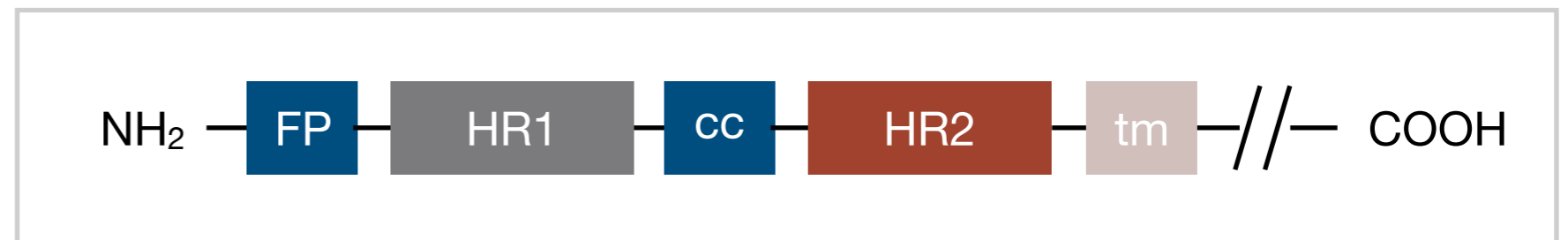
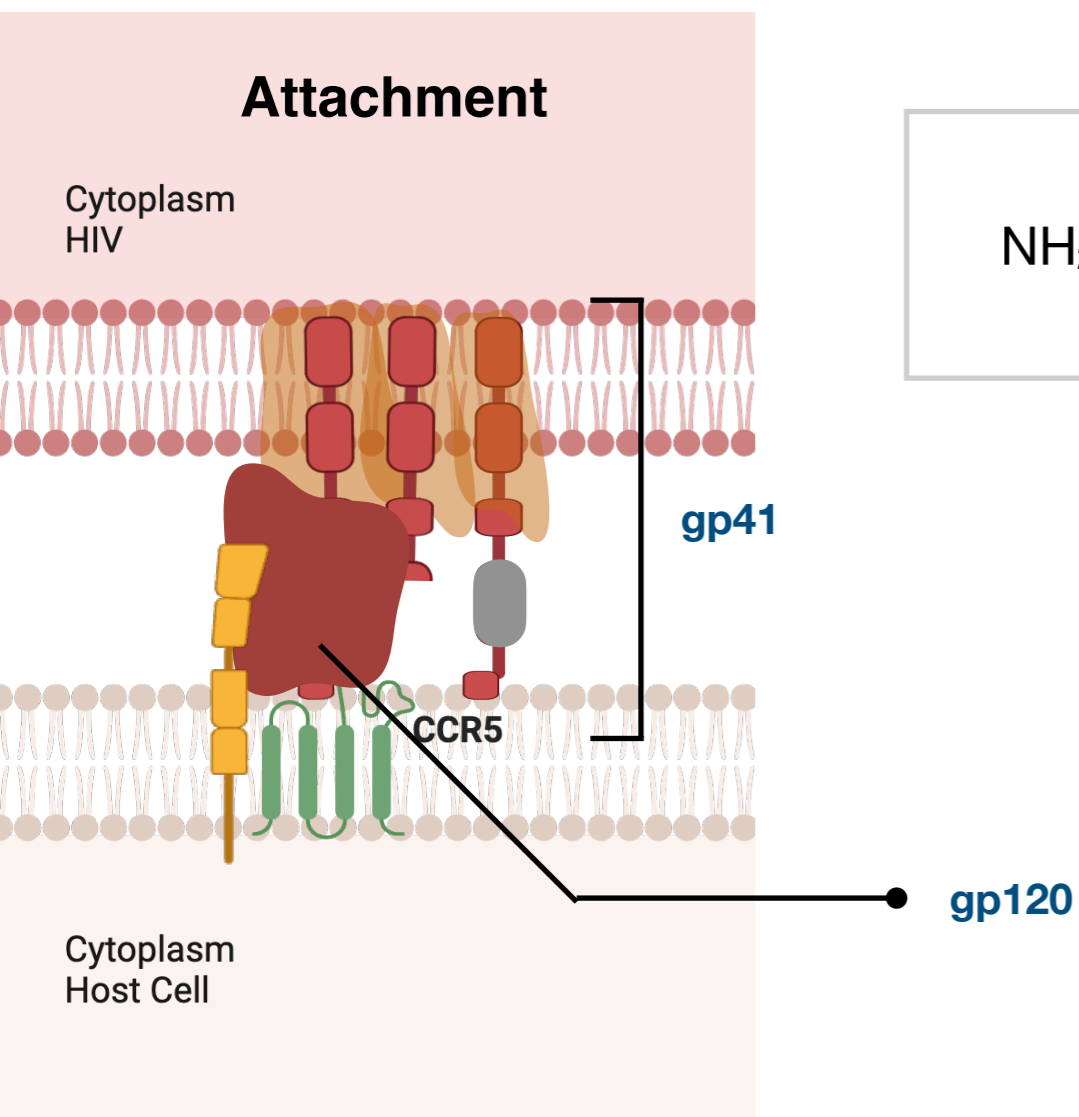
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## Mechanism of Action - Entry Inhibitors

### Attachment

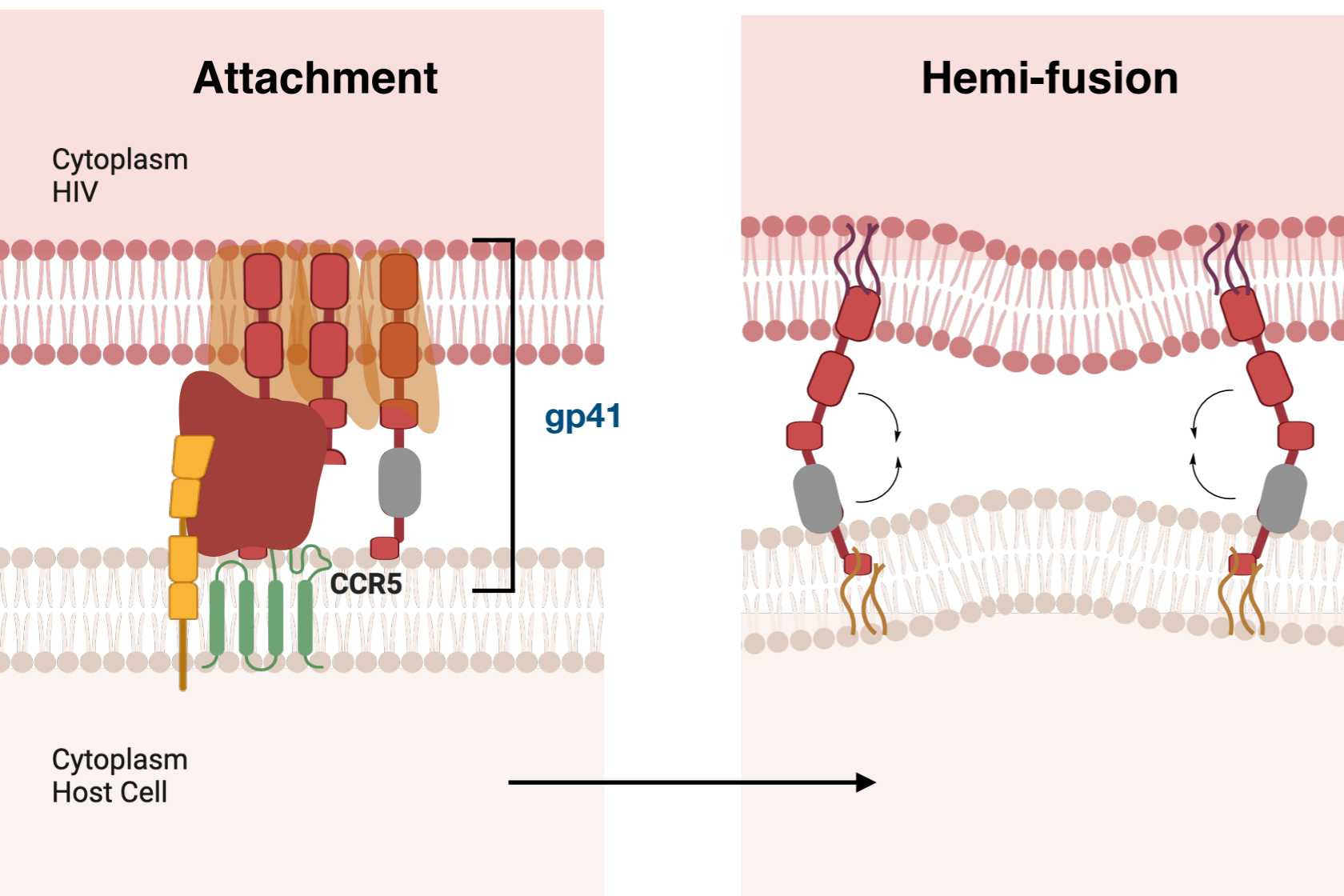
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## Mechanism of Action - Entry Inhibitors

### Attachment

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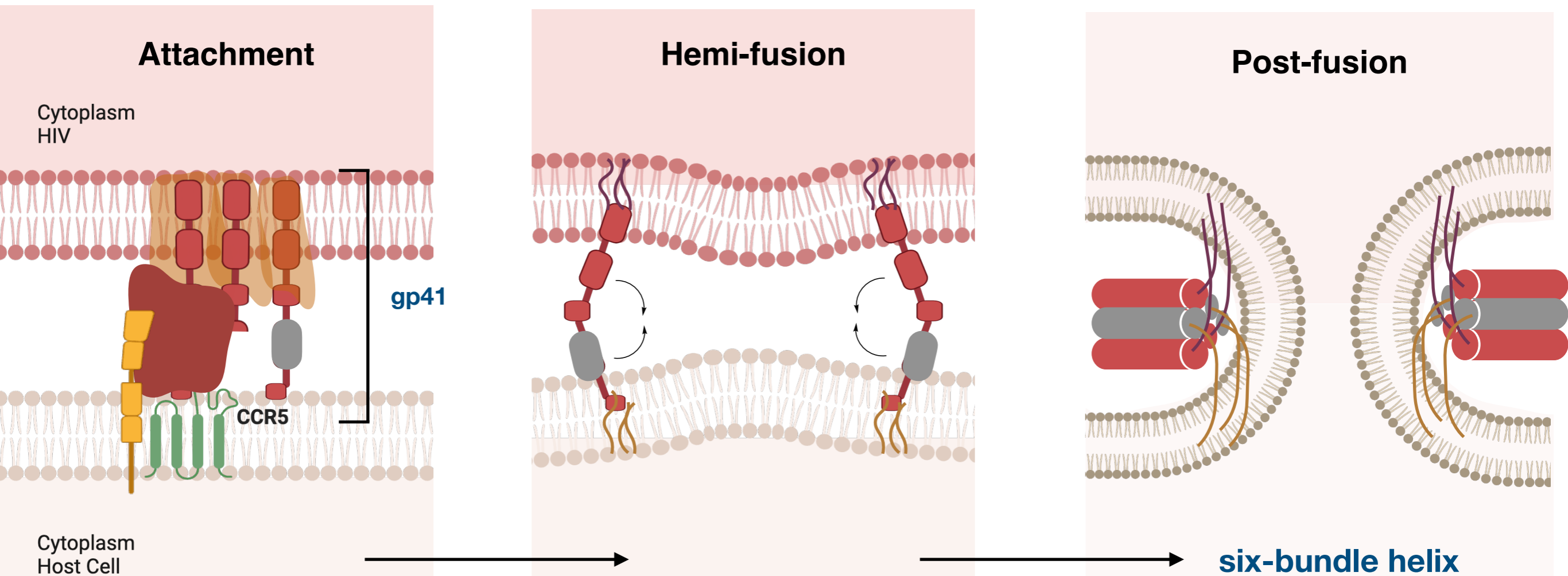




# Mechanism of Action - Entry Inhibitors

## Attachment

- 1 The binding of HIV surface protein gp120 to the CD4 receptor
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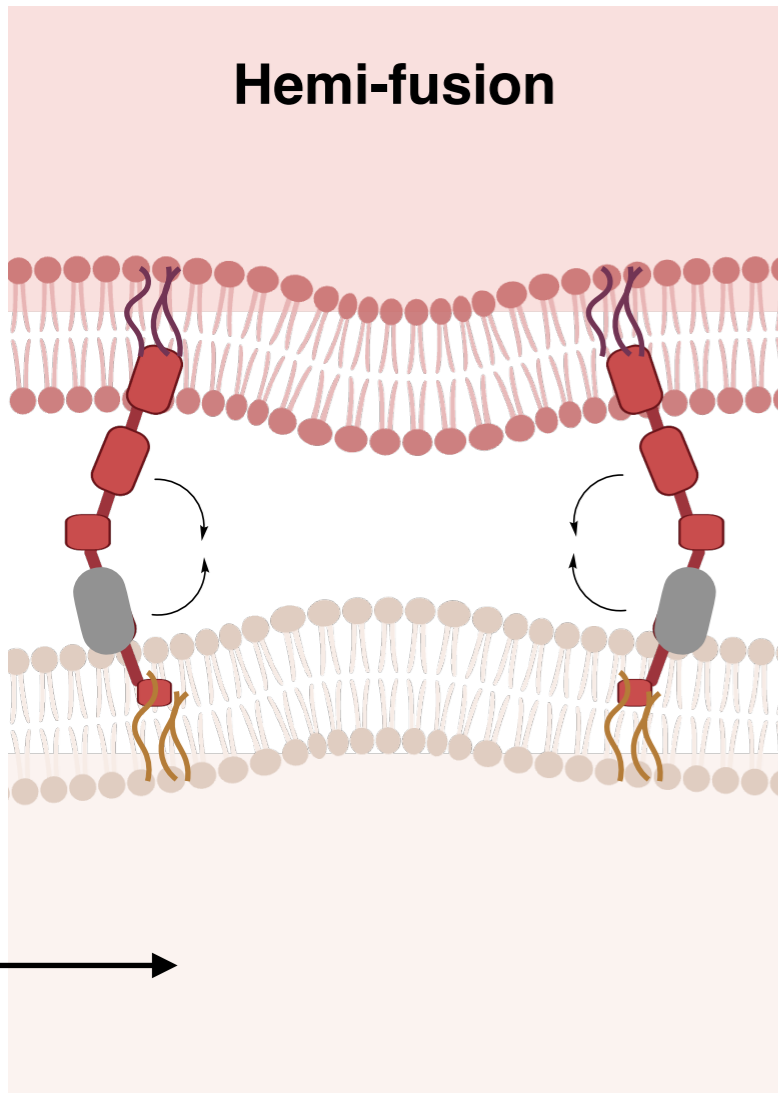


## Mechanism of Action - Entry Inhibitors

### Attachment

- 1 The binding of HIV surface protein gp120 to the CD4 receptor
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### Hemi-fusion



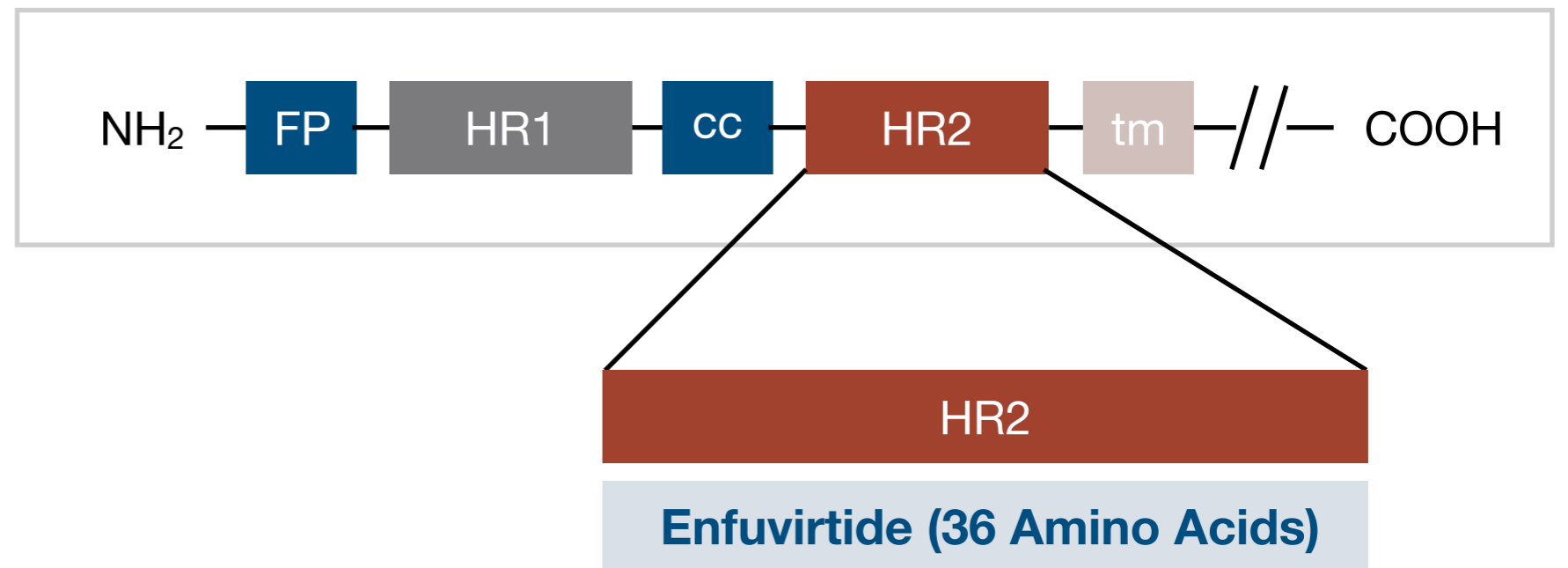
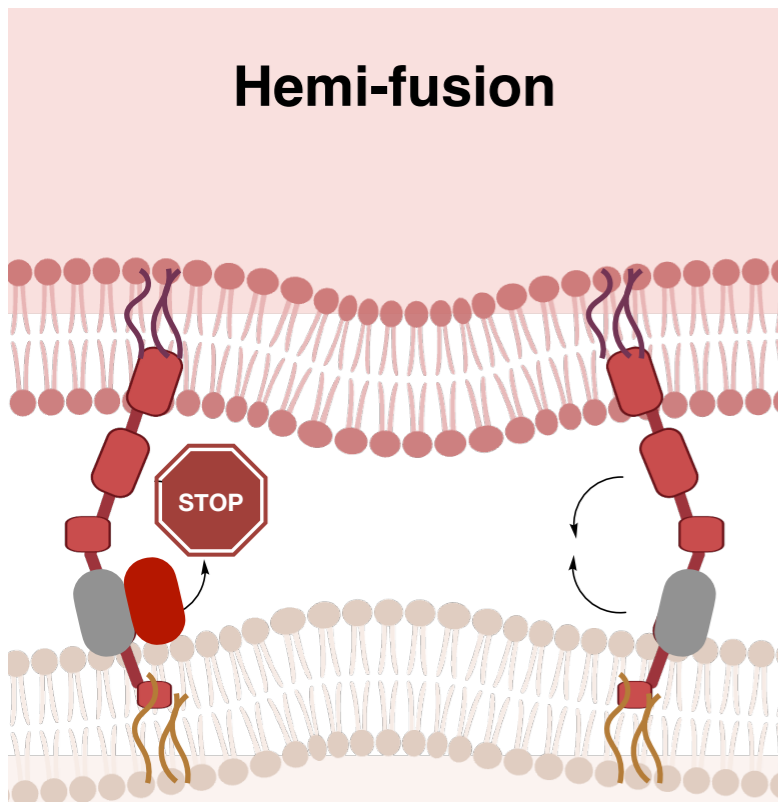
**What drug would you develop to halt this process?**

## Mechanism of Action - Entry Inhibitors

### Attachment

- 1 The binding of HIV surface protein gp120 to the CD4 receptor
- 2 A conformational change in gp120, which both increases its affinity for a co-receptor and exposes gp41
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### Hemi-fusion

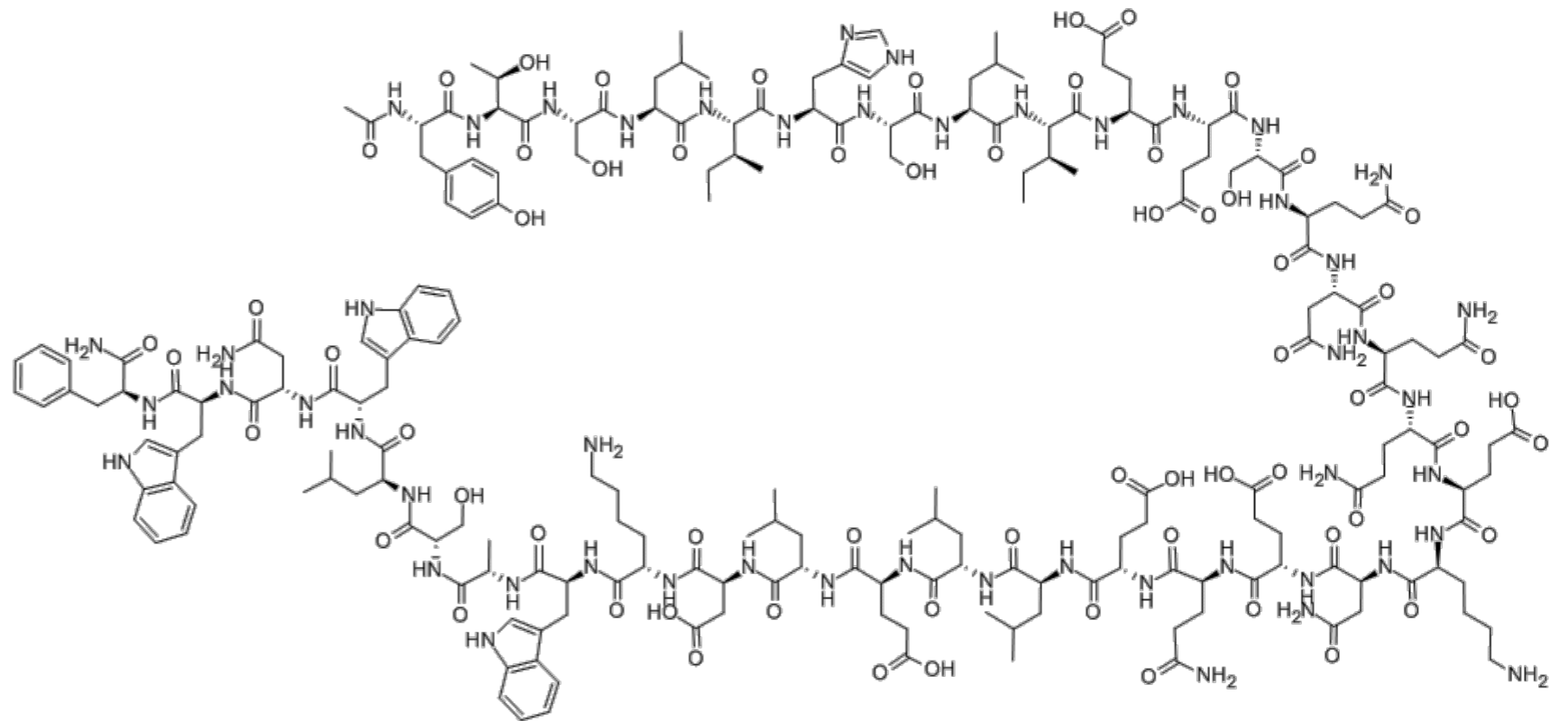
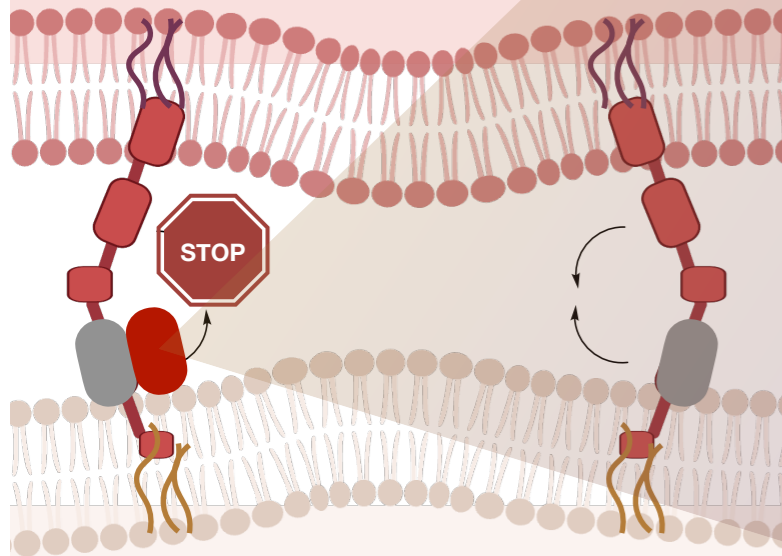


# Mechanism of Action - Entry Inhibitors

## Attachment

- 1 The binding of HIV surface protein gp120 to the CD4 receptor
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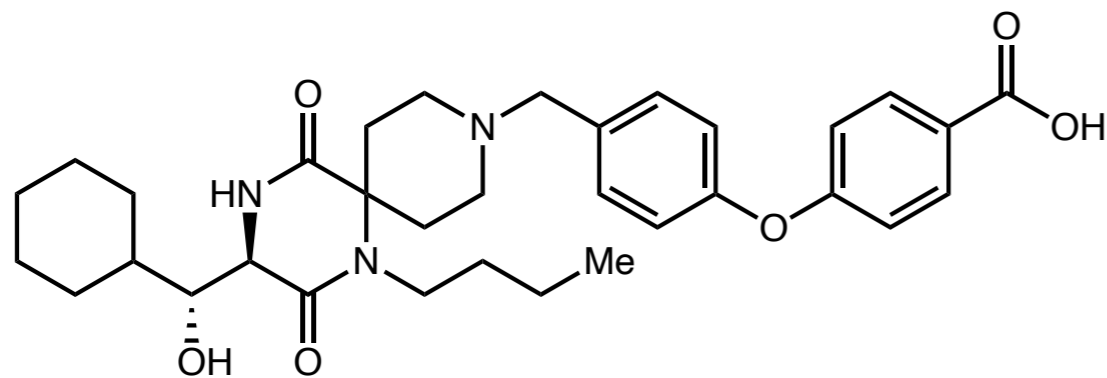
## Hemi-fusion



**Enfuvirtide (36 Amino Acids)**

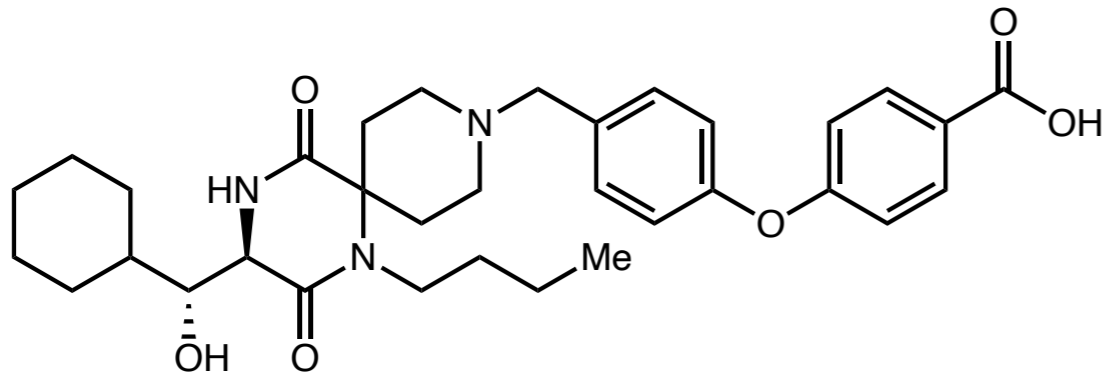
**MW: 4492 g/mol**

*Entry Inhibitors - Drugs on the Market*

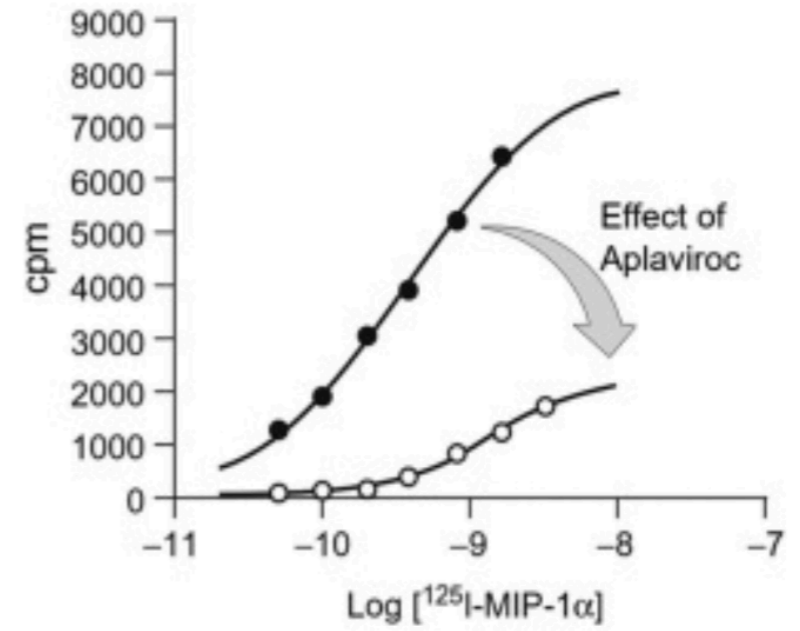


**Aplaviroc (GlaxoSmithKline)**  
**Allosteric Modulator,  $t_{1/2} = 100$  h**

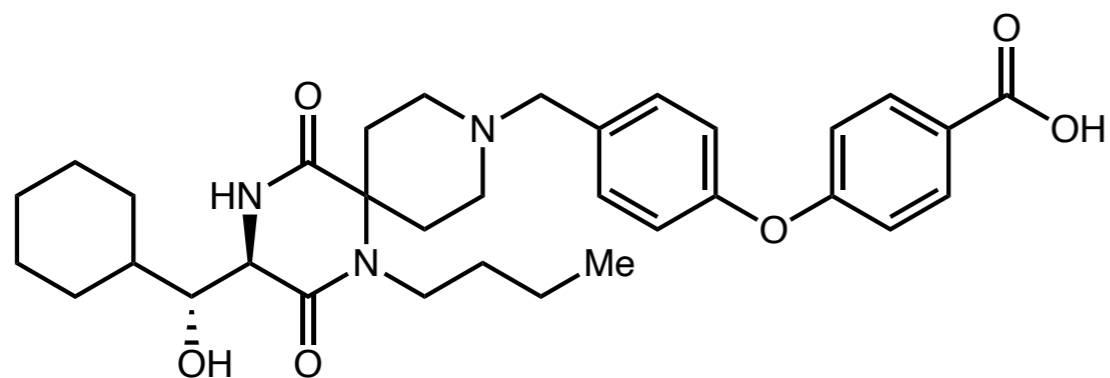
## Entry Inhibitors - Drugs on the Market



**Aplaviroc (GlaxoSmithKline)**  
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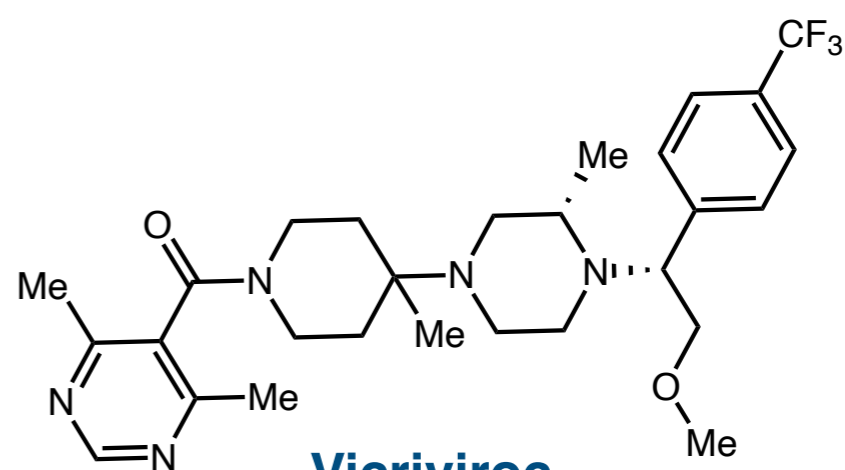


## Entry Inhibitors - Drugs on the Market



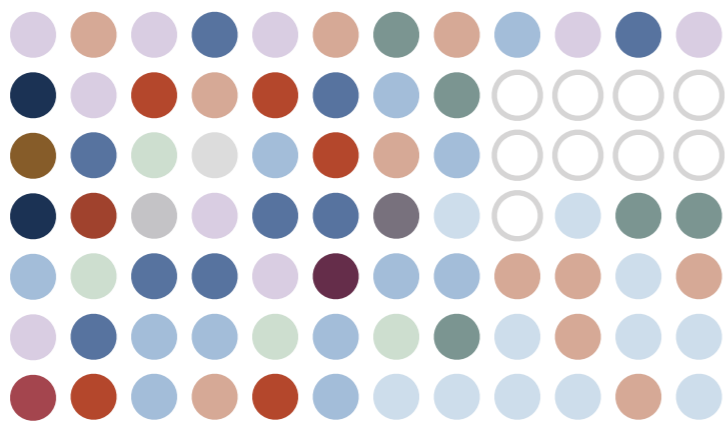
**Aplaviroc (GlaxoSmithKline)**  
Allosteric Modulator,  $t_{1/2} = 100$  h

↓  
**Failed early clinical trials**  
(Severe liver toxicity)

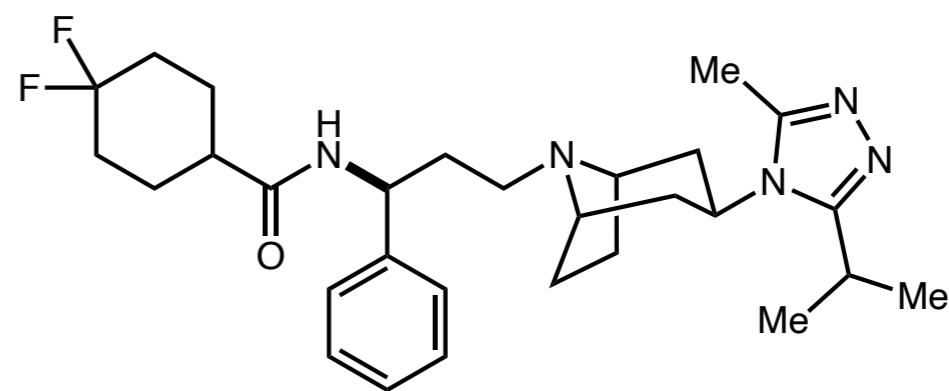


**Vicriviroc**  
(Schering-Plough)

↓  
**Failed Phase II clinical trials**

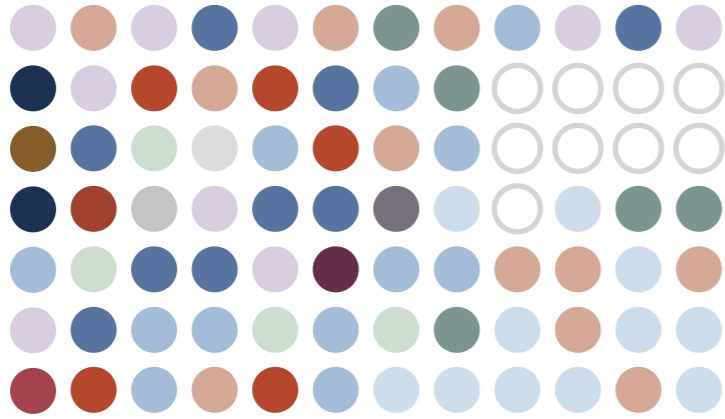


Evaluated over **500,000** compounds  
Assayed on the inhibition of MIP-1B  
binding to CCR5 receptor

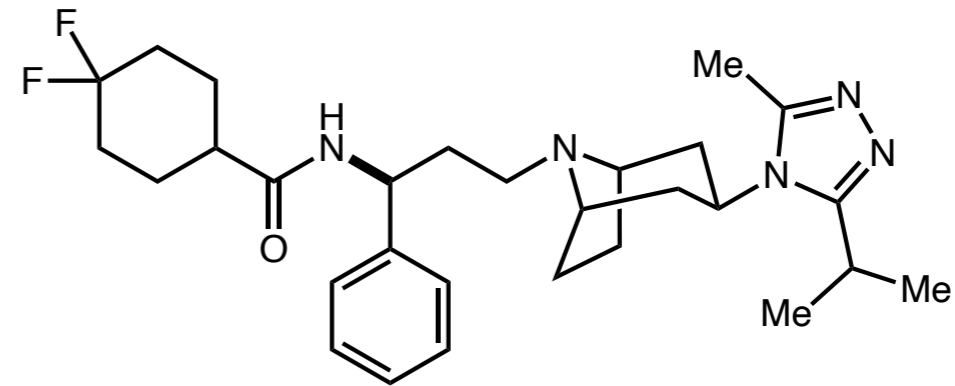


**Maraviroc (Pfizer)**  
 $IC_{50} = 0.2$  nM  
Antiviral  $IC_{90} = 2$  nM

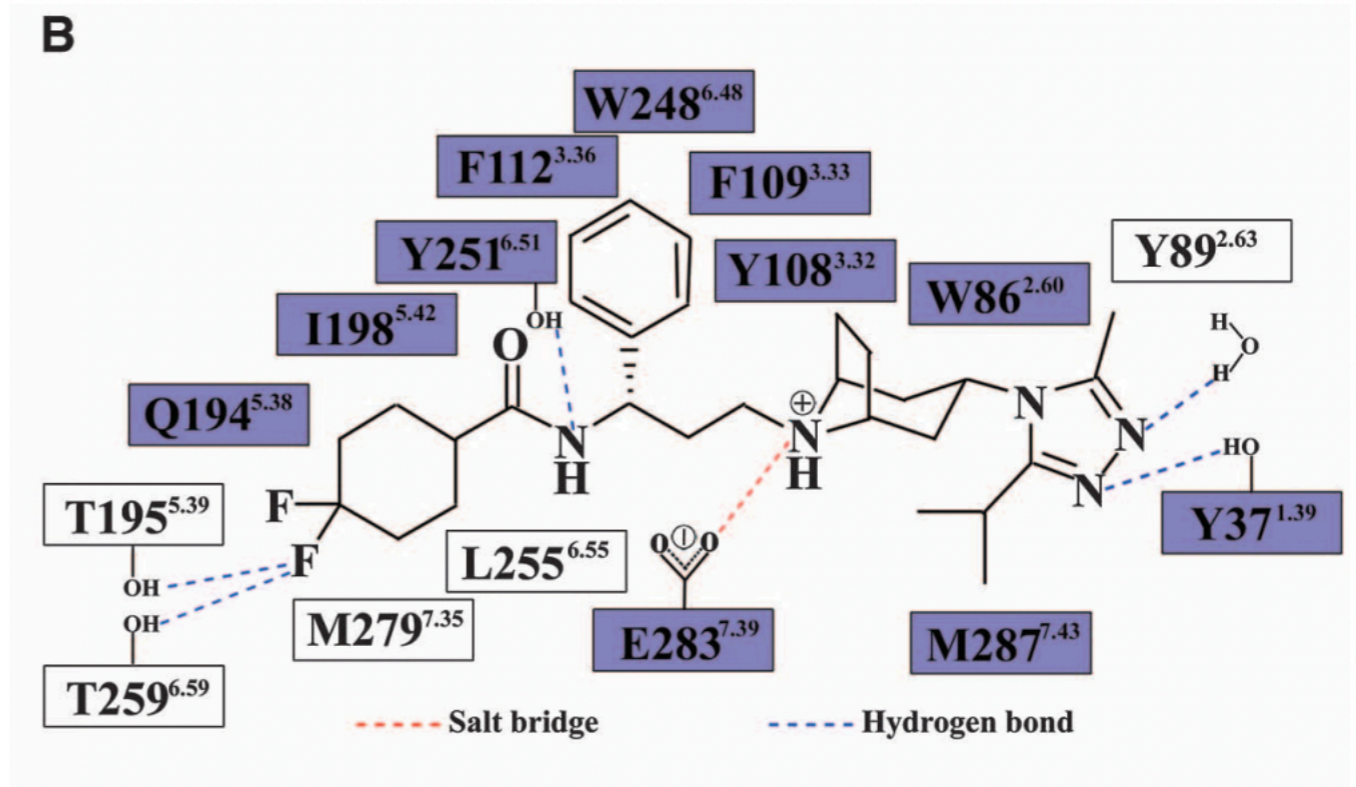
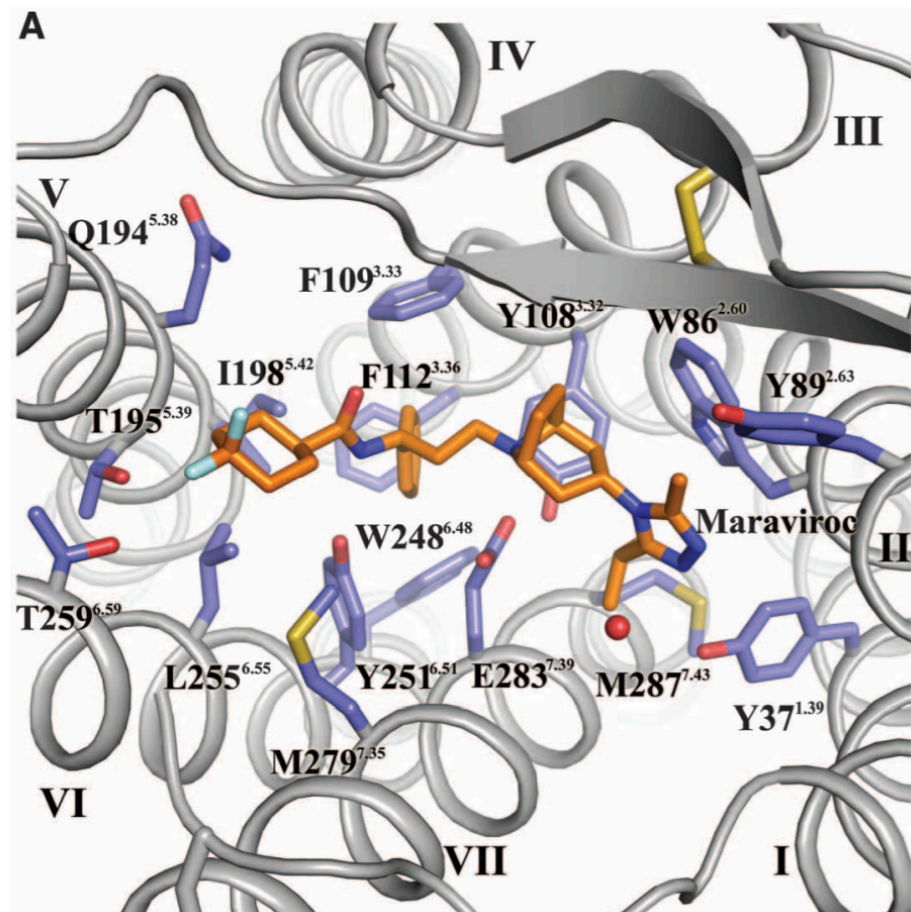
## Entry Inhibitors - Drugs on the Market



Evaluated over **500,000** compounds  
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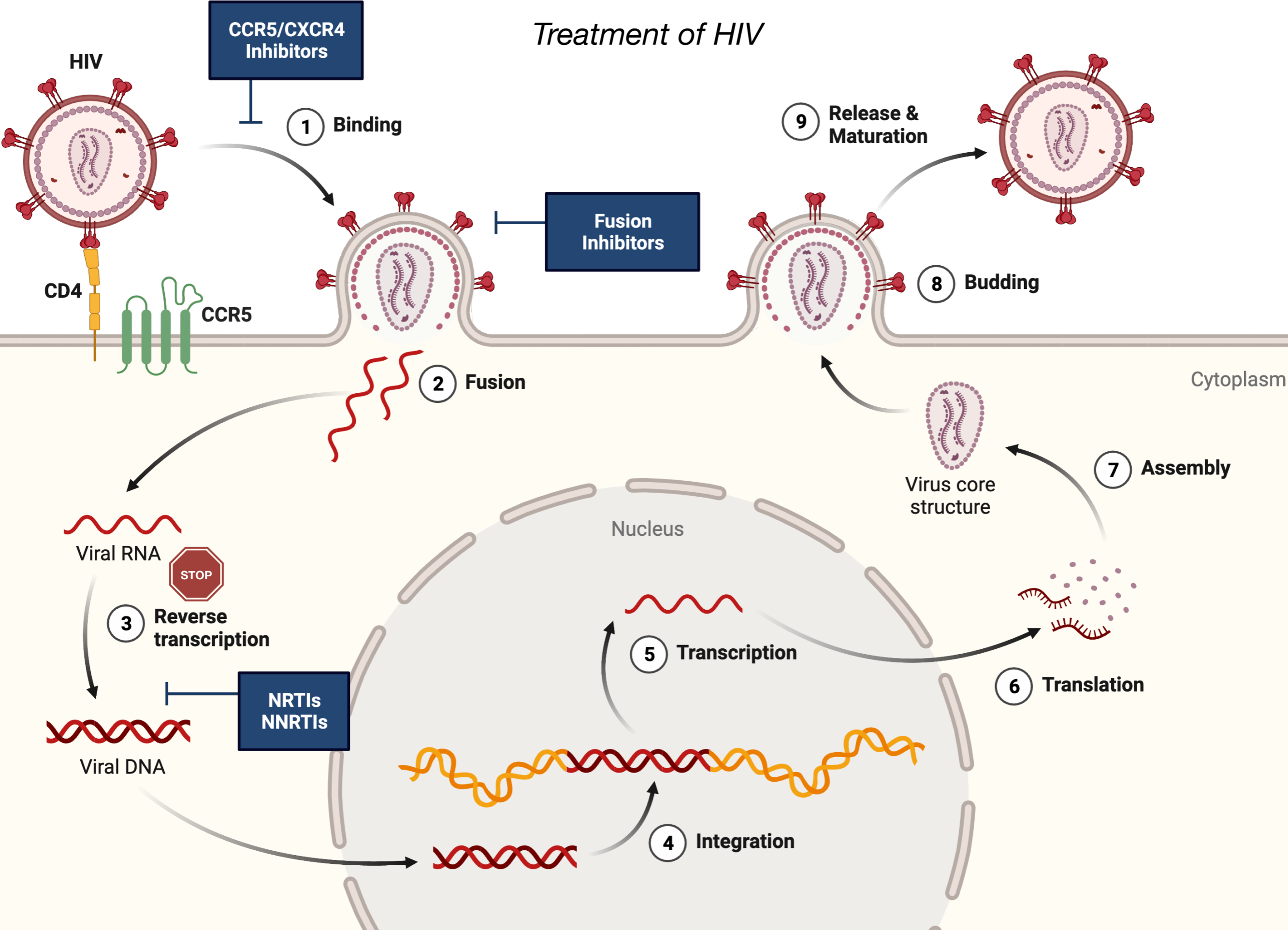


**Maraviroc (Pfizer)**  
 $IC_{50} = 0.2 \text{ nM}$ ,  $t_{1/2} = 14-18 \text{ h}$   
Antiviral  $IC_{90} = 2 \text{ nM}$





# Treatment of HIV



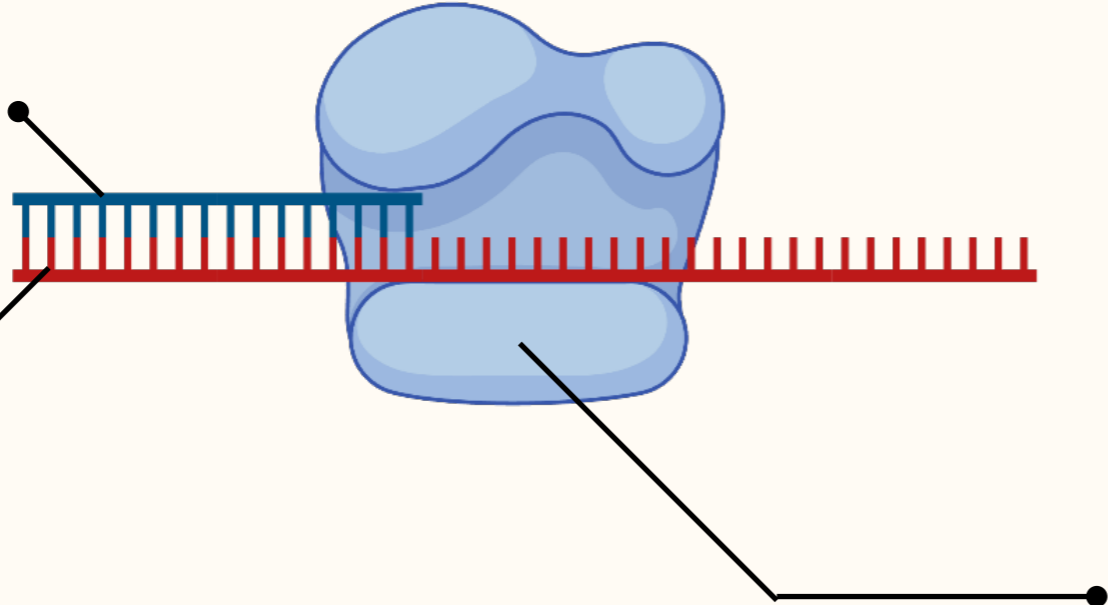
*Mechanism of Action - NRTIs*



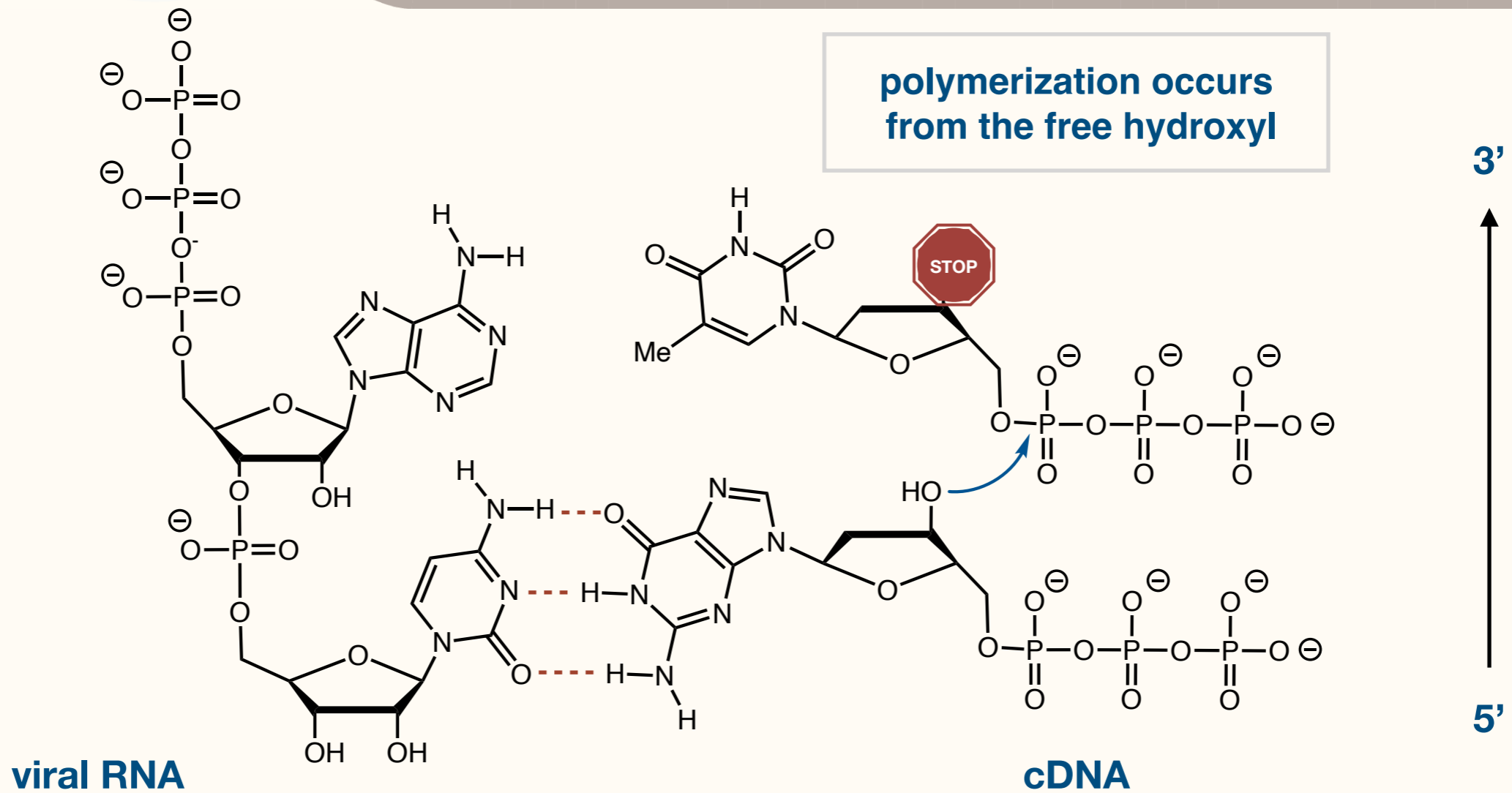
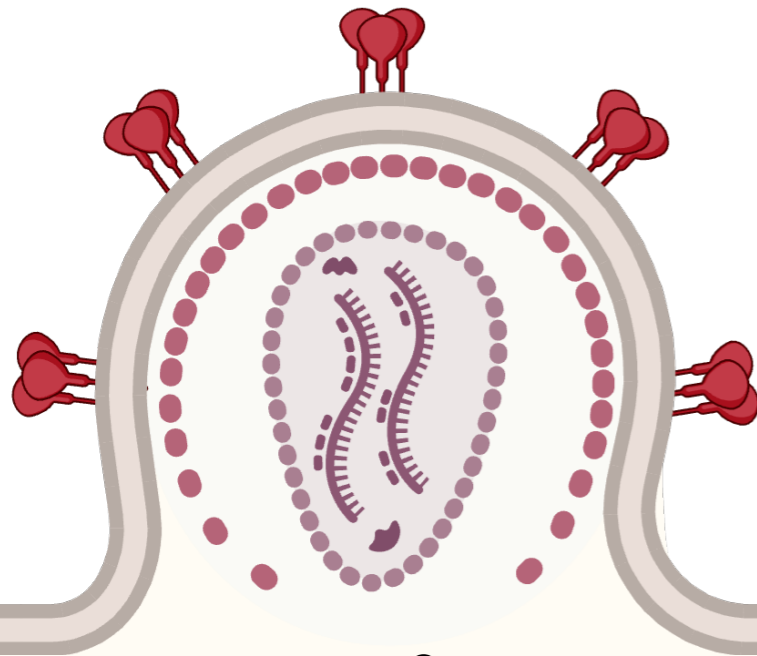
**proviral DNA**

**viral RNA**

**viral reverse transcriptase**



# Mechanism of Action - NRTIs

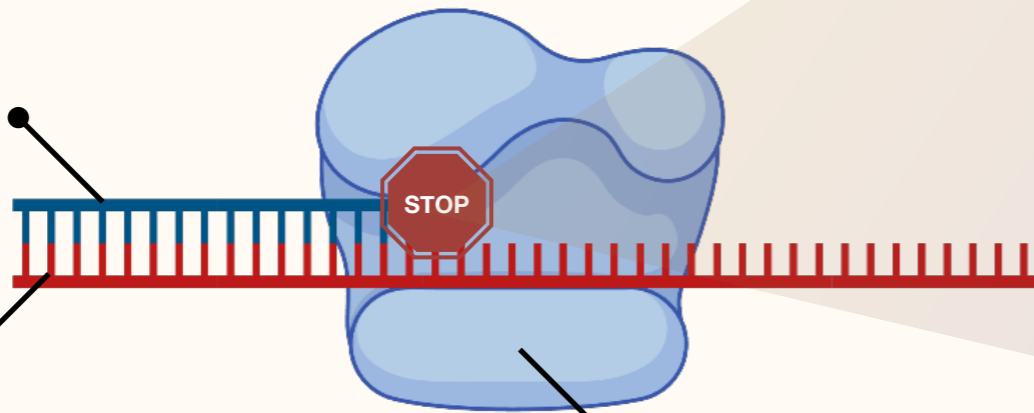


# Mechanism of Action - NRTIs

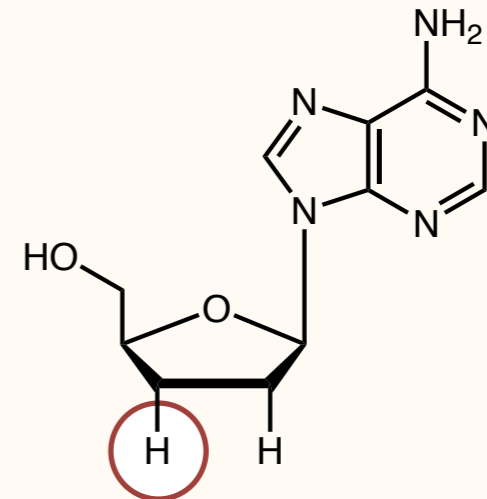


proviral DNA

viral RNA

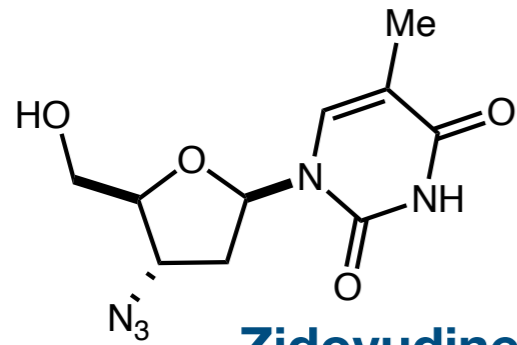


*'aspirational'*



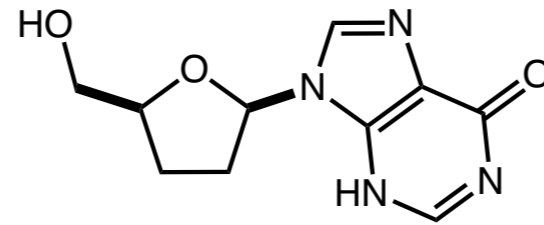
viral reverse transcriptase

## Mechanism of Action - NRTIs



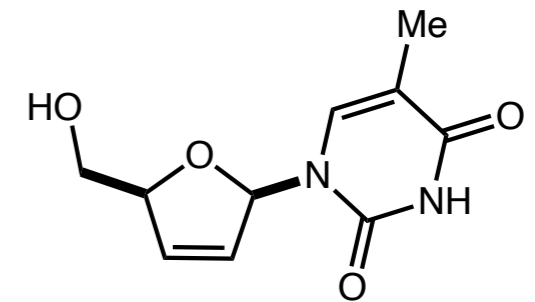
**Zidovudine**

**1987 FDA Approved**



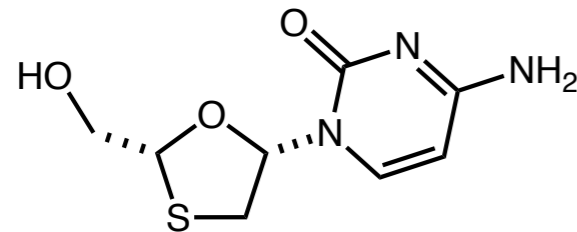
**Didanosine**

**1991 FDA Approved**



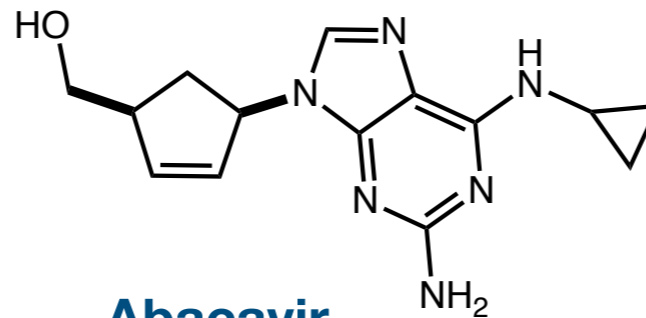
**Stavudine**

**1994 FDA Approved**



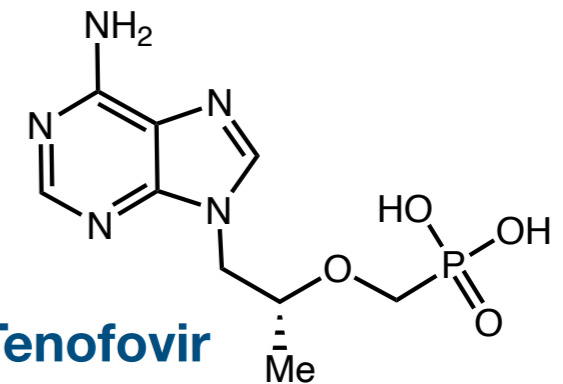
**Lamivudine**

**1995 FDA Approved**



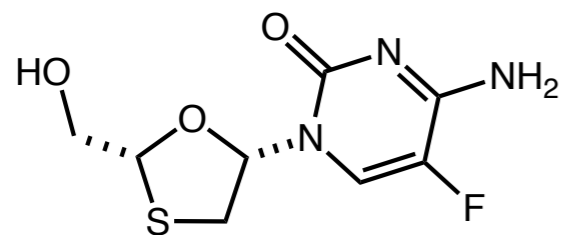
**Abacavir**

**1998 FDA Approved**



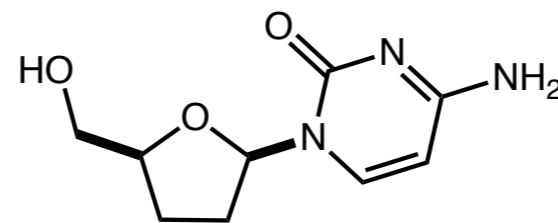
**Tenofovir**

**2001 FDA Approved**



**Emtricitabine**

**2006 FDA Approved**



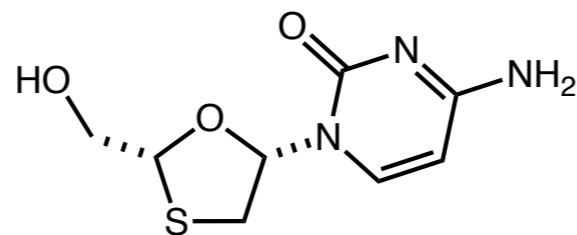
**Zalcitabine**

**Discontinued in 2006**

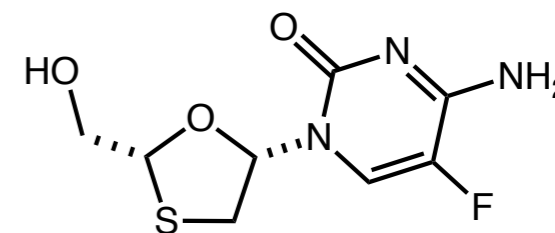
## Mechanism of Action - NRTIs



**Prof. Dennis C. Liotta**  
**Emory University**



**Lamivudine**  
**1995 FDA Approved**

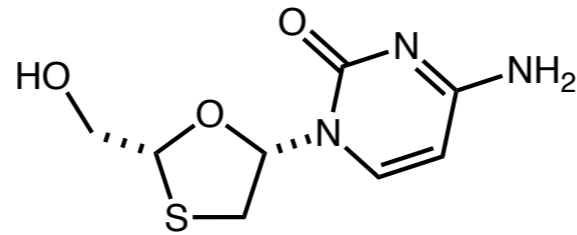


**Emtricitabine**  
**2006 FDA Approved**

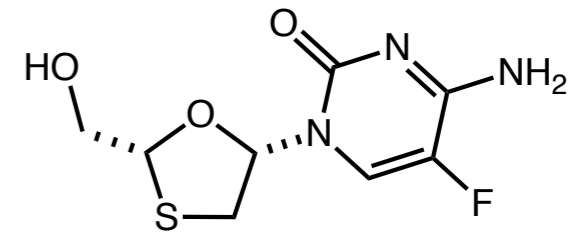
## Mechanism of Action - NRTIs



**Prof. Dennis C. Liotta**  
**Emory University**



**Lamivudine**  
**1995 FDA Approved**



**Emtricitabine**  
**2006 FDA Approved**



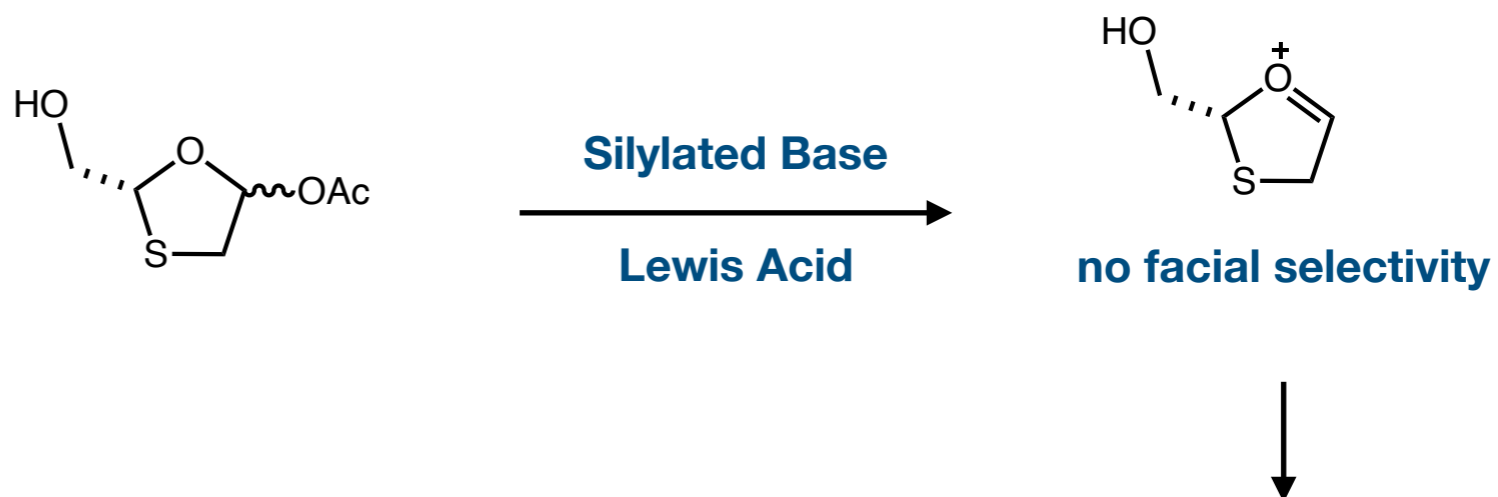
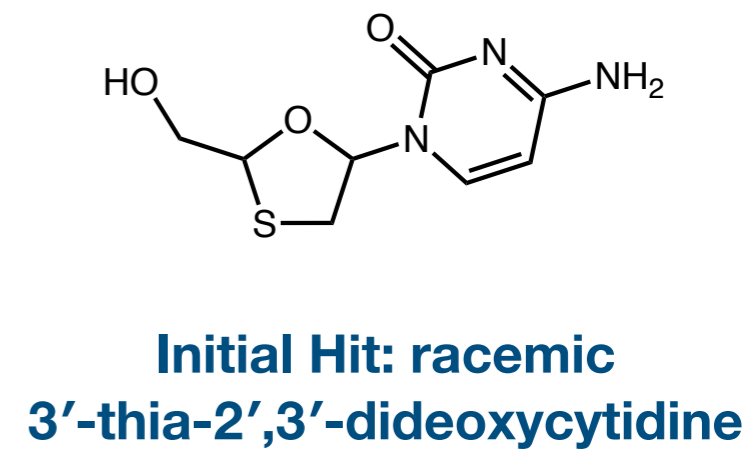
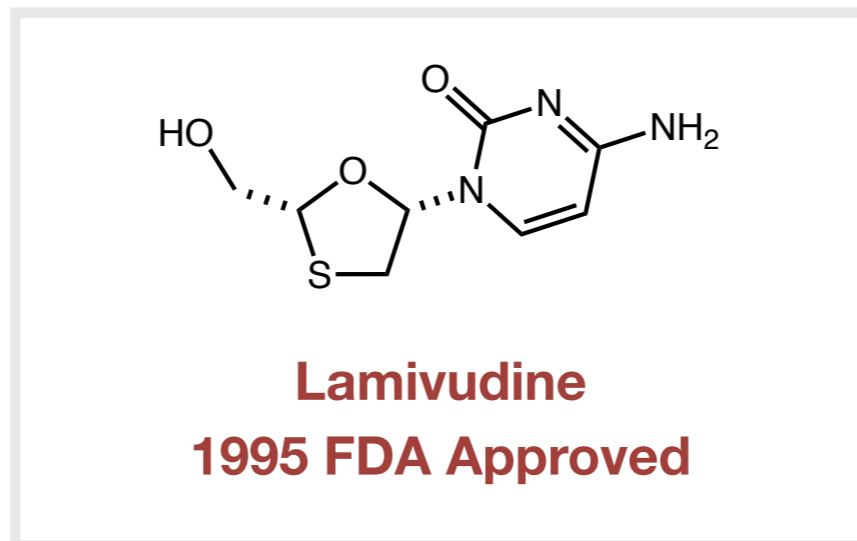
**18 life-saving FDA-approved drugs**

**How did this invention come to life?**

## Mechanism of Action - NRTIs



**Prof. Dennis C. Liotta**  
**Emory University**

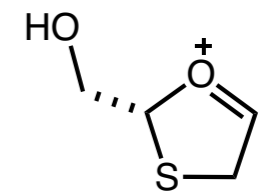
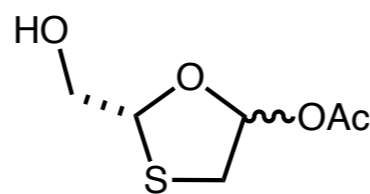
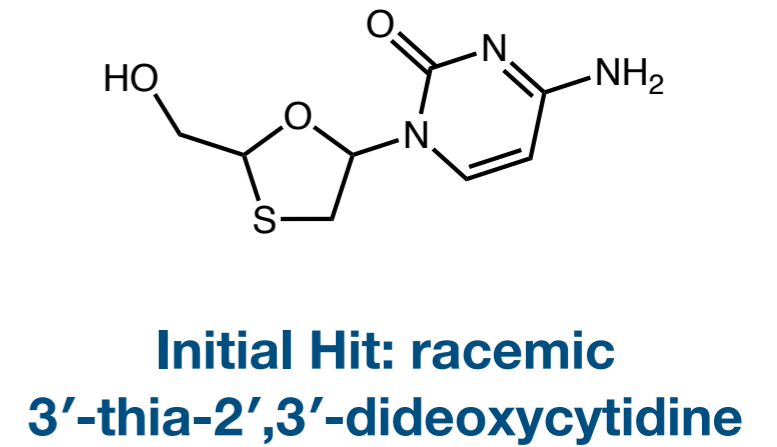
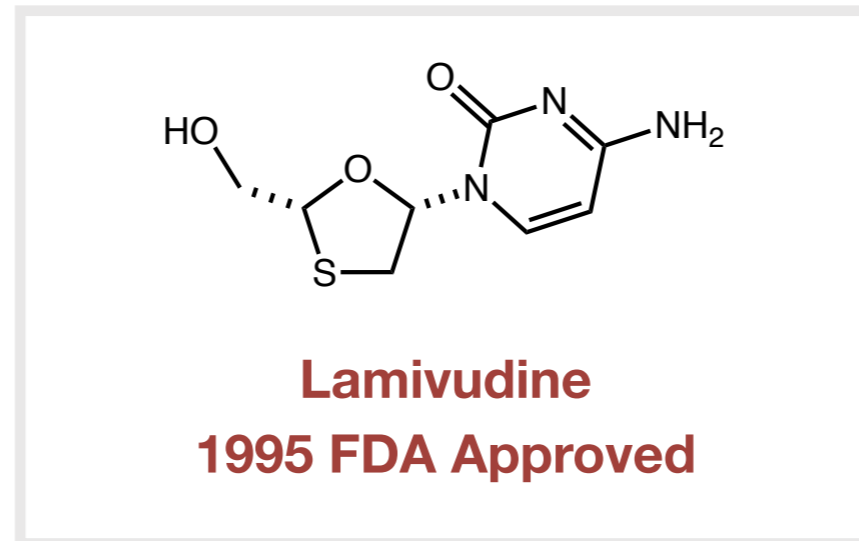




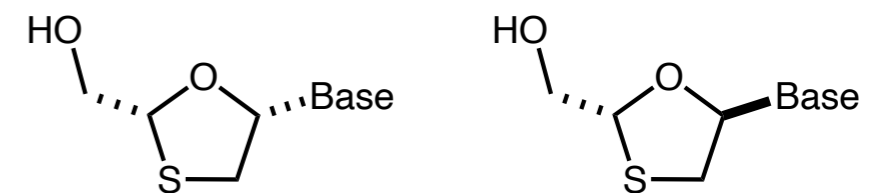
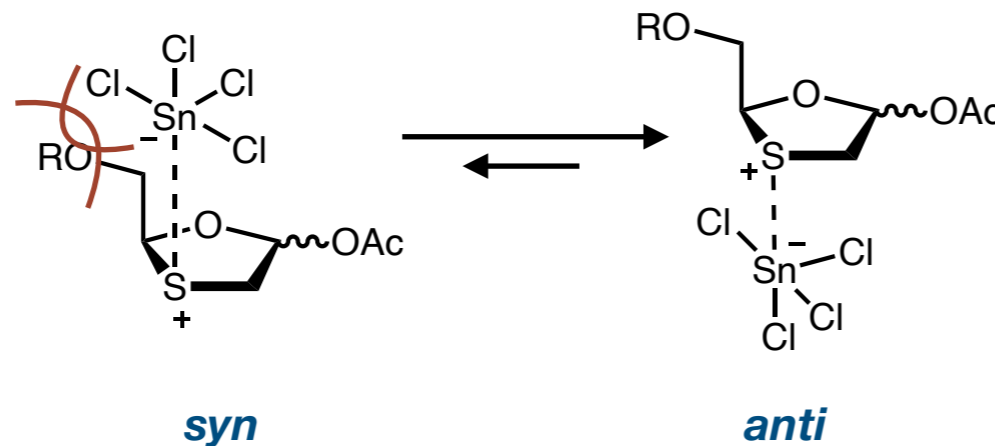
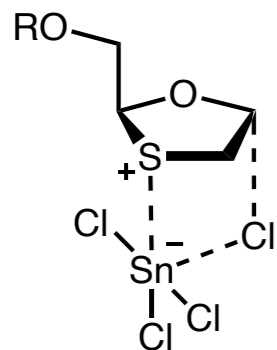
# Mechanism of Action - NRTIs



**Prof. Dennis C. Liotta**  
Emory University



no facial selectivity

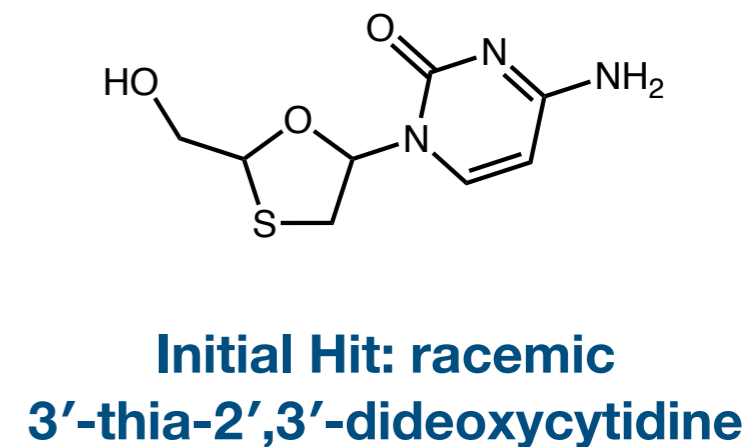
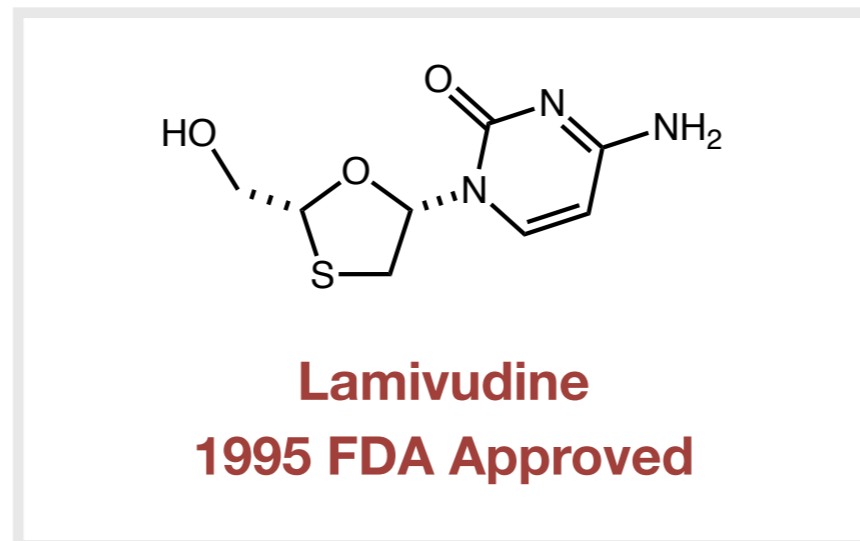


1:1 mixture of diastereomers

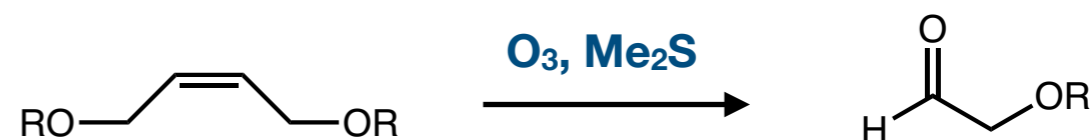
## Mechanism of Action - NRTIs



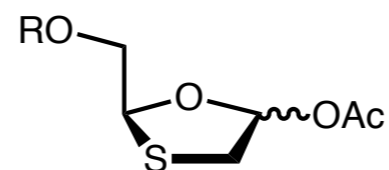
**Prof. Dennis C. Liotta**  
Emory University



Synthetic Route :



$\text{HSCH}_2\text{CO}_2\text{H}$

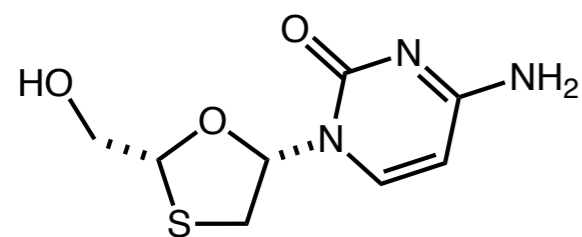


1) DIBAL-H

2)  $\text{Ac}_2\text{O}$

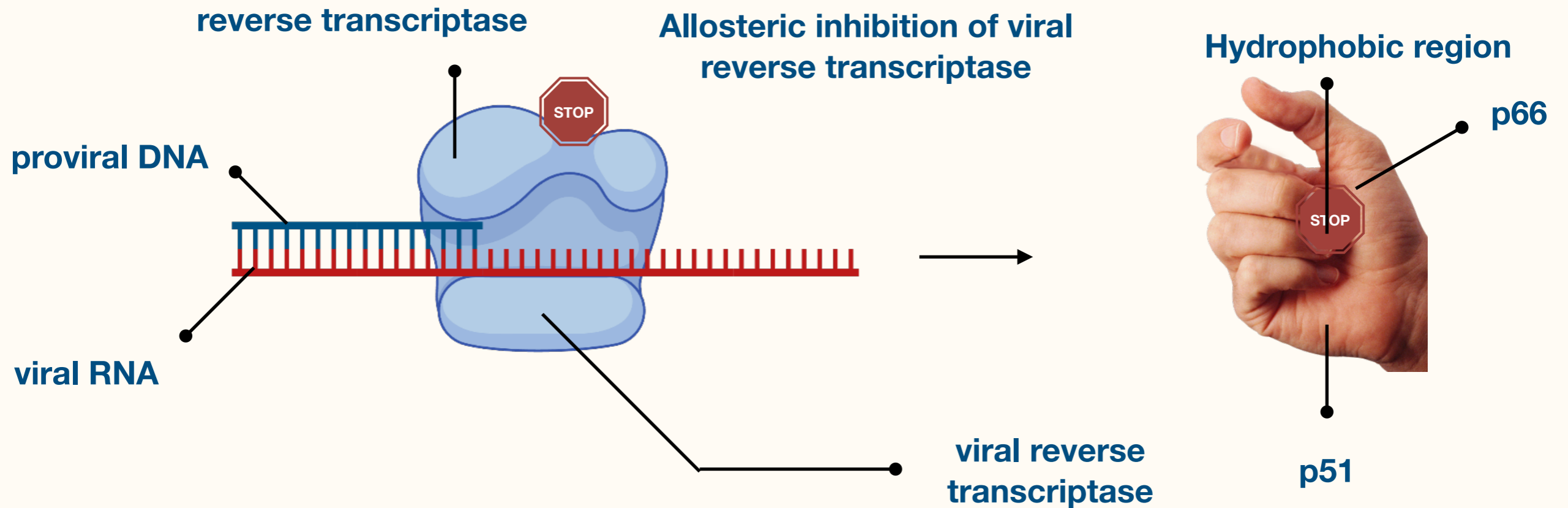
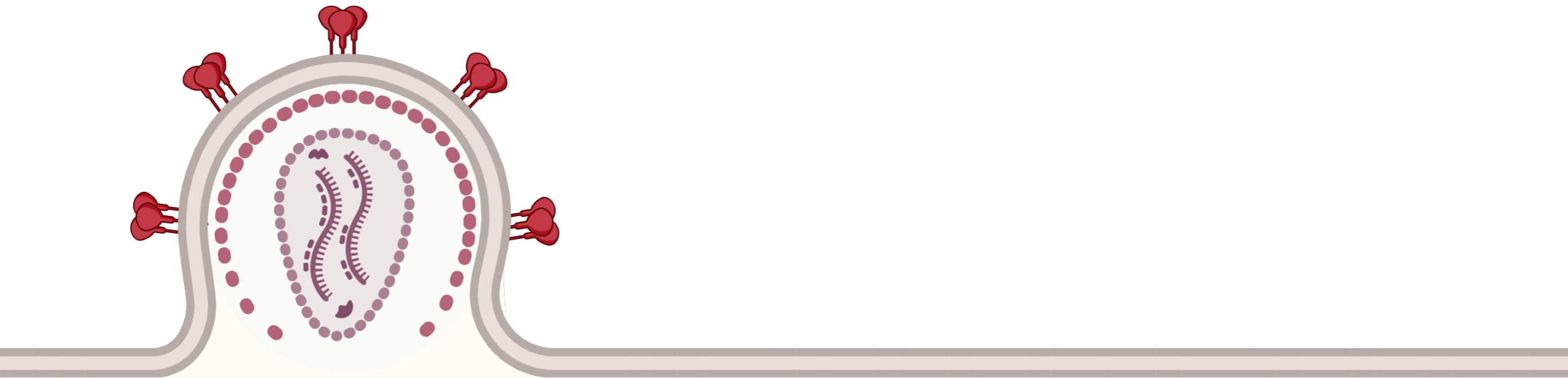
1)  $(\text{TMS})_2\text{-cytosine}$   
 $\text{SnCl}_4$

2) TBAF

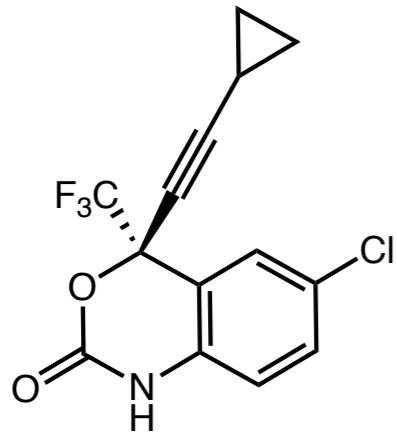


**Lamivudine**  
 $\beta:\alpha > 300:1$

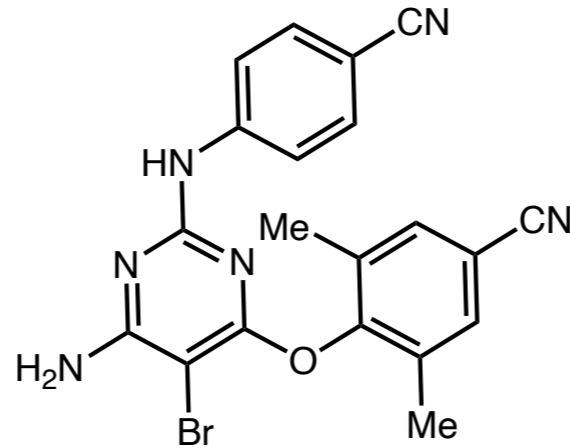
# Mechanism of Action - NNRTIs



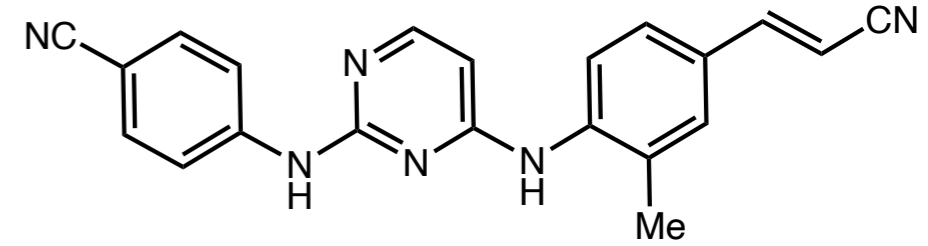
## Mechanism of Action - NNRTIs



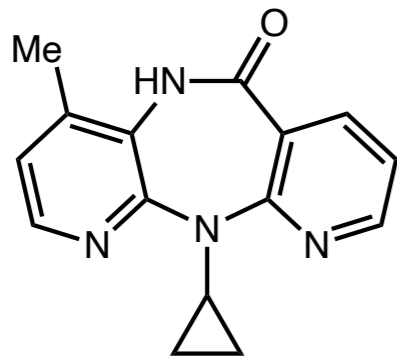
**Efavirenz**



**Etravirine**

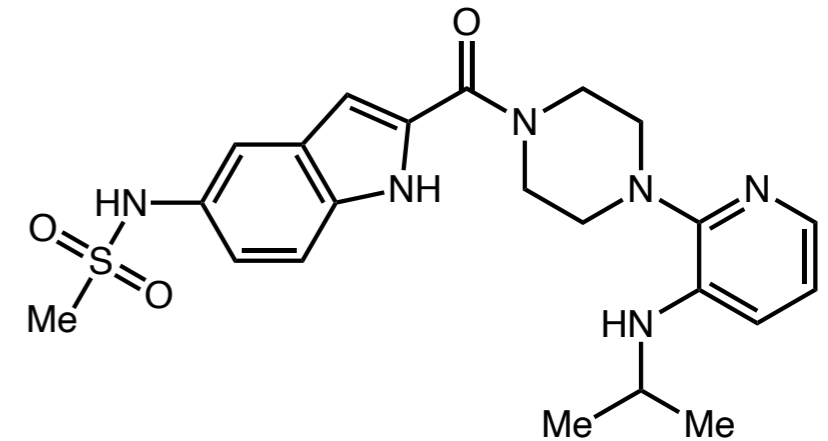


**Rilpivirine**



**Nevirapine**

**Despite chemical diversity,  
they all bind at  
the same site in the  
reverse transcriptase.**

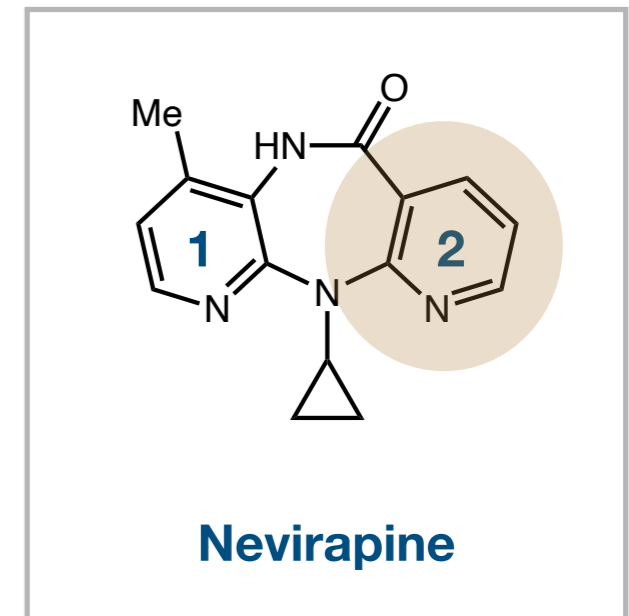
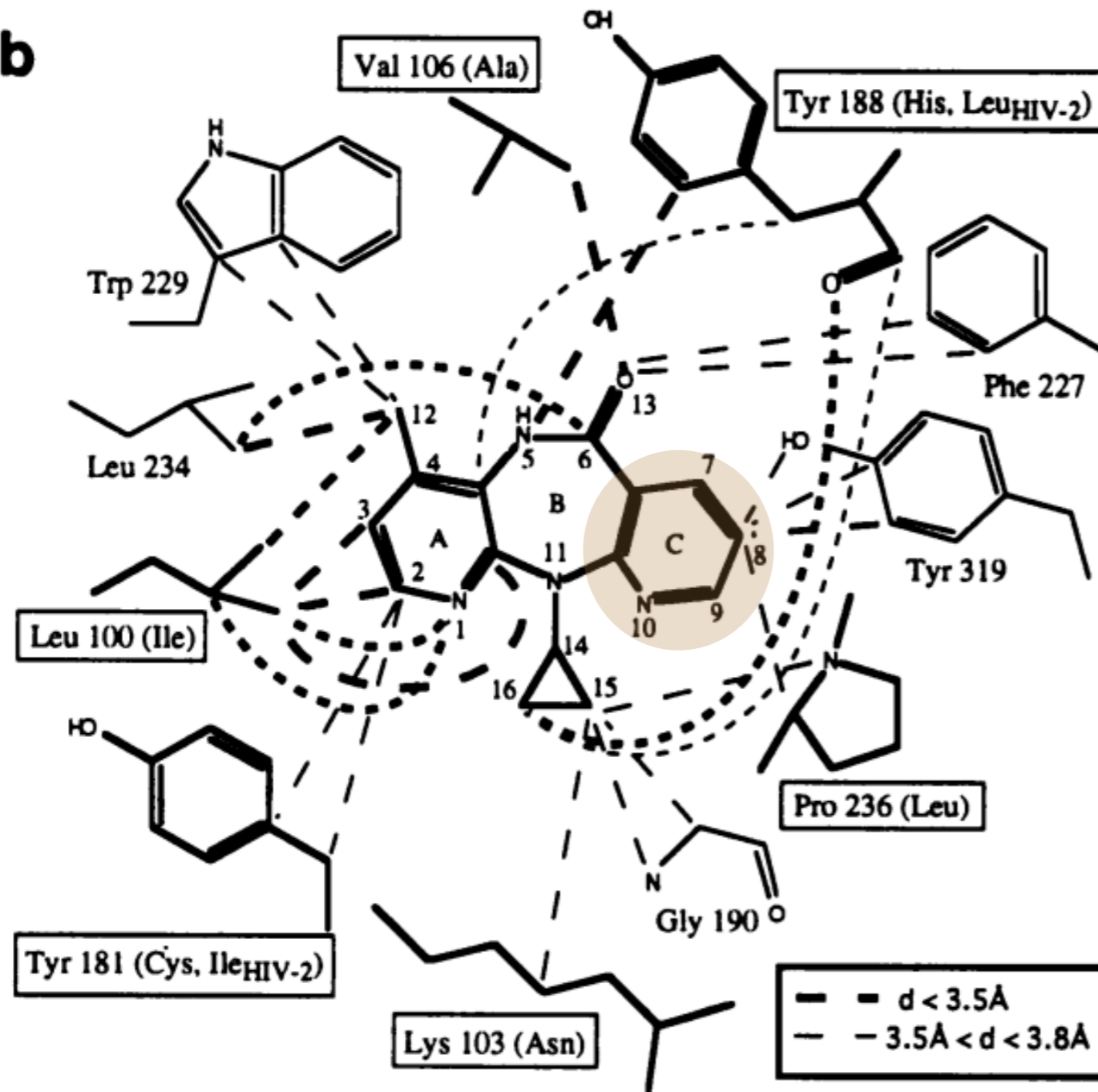


**Delavirdine**

**Each non-nucleoside reverse transcriptase inhibitor interacts with different amino acid residues**

# Mechanism of Action - NNRTIs

**b**

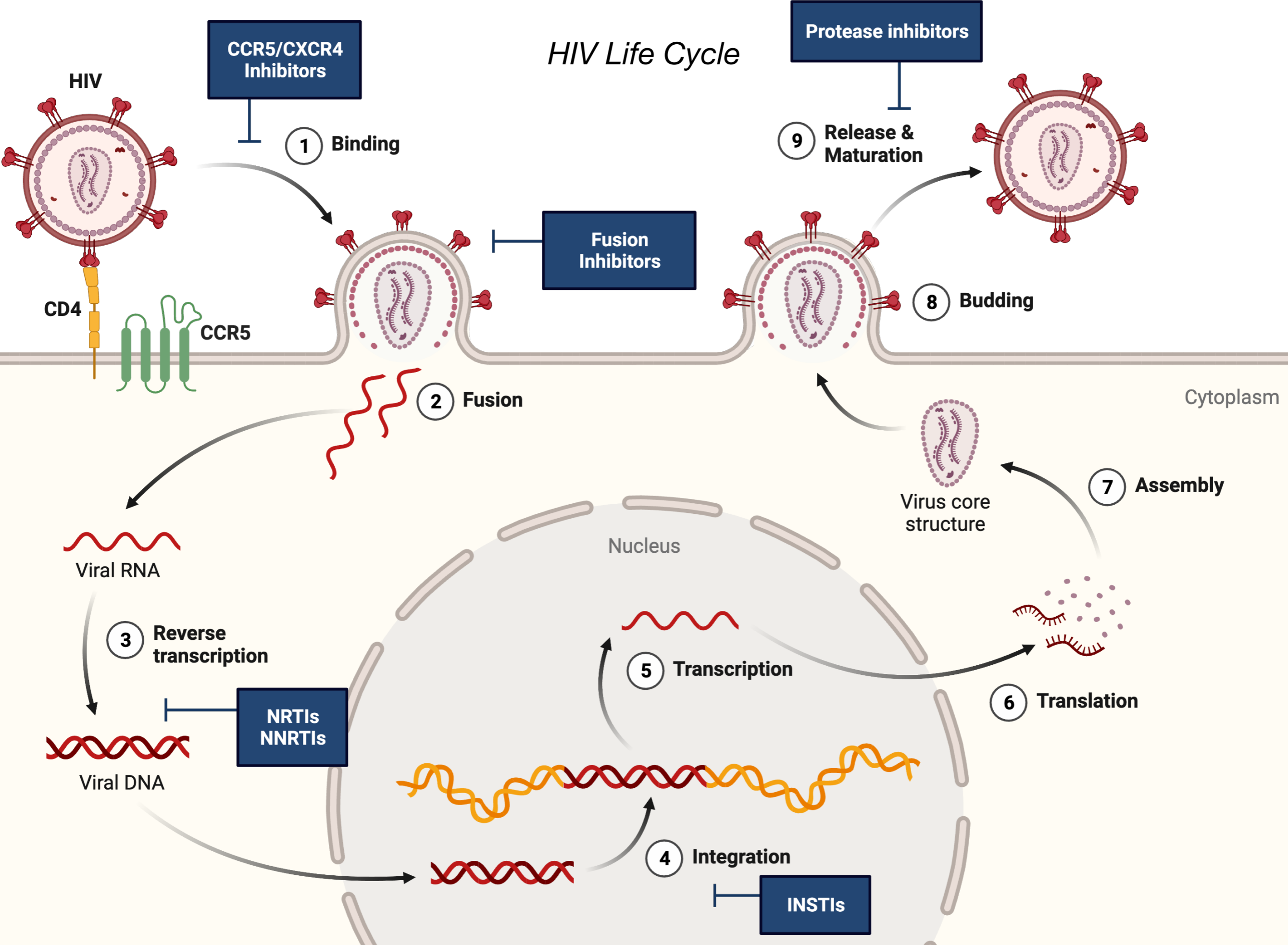


**'butterfly-like'**

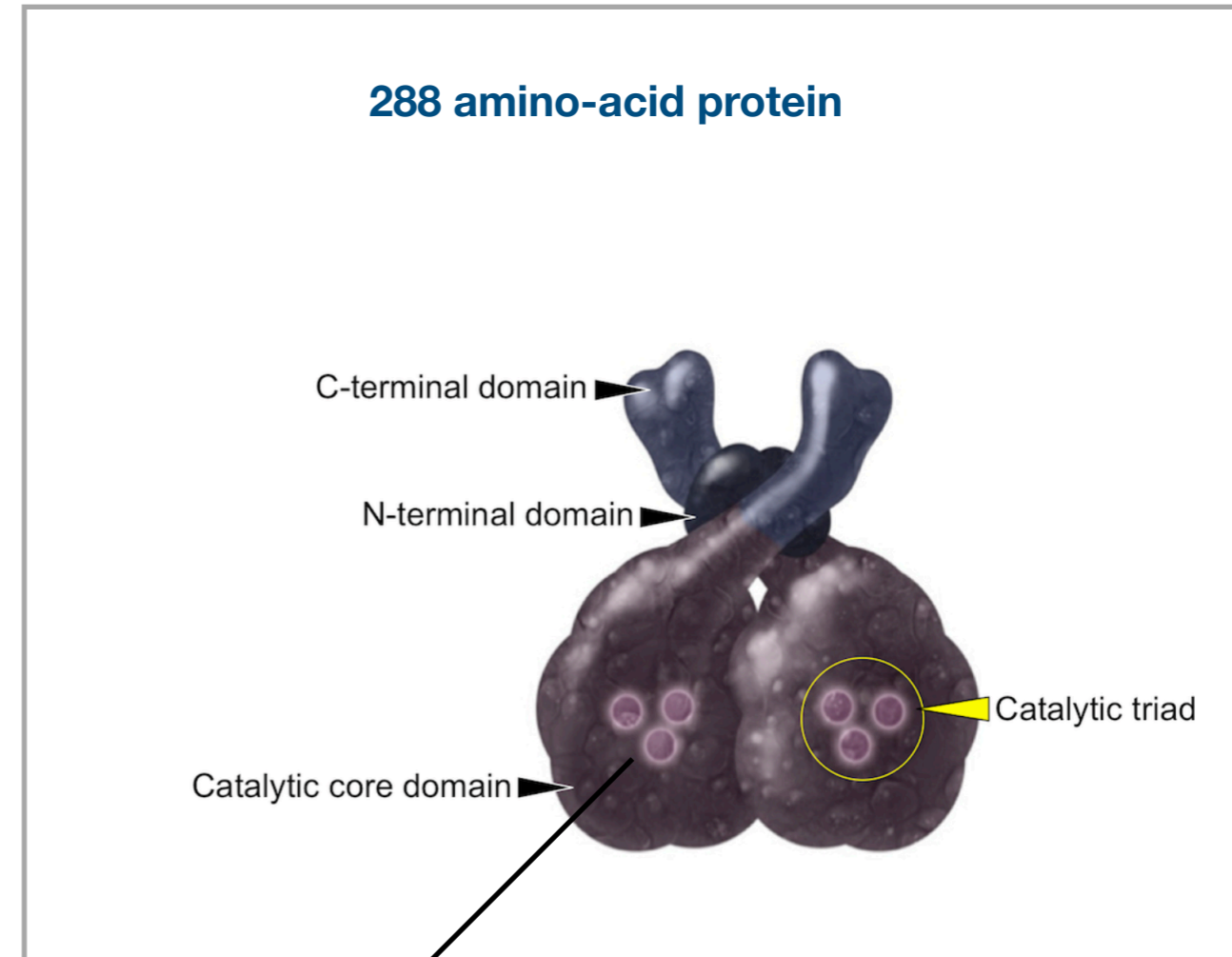
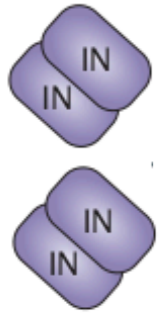
- 'Body': Hydrophilic center**
- 'Wing 1': heteroaromatic**
- 'Wing 2': phenyl or allyl substituent**

**Over 38 amino acid interactions**

# HIV Life Cycle

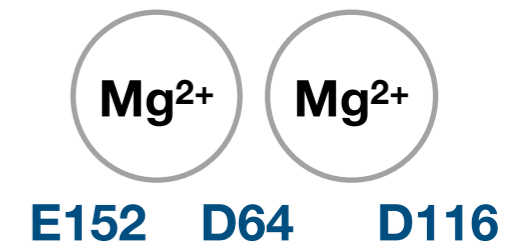
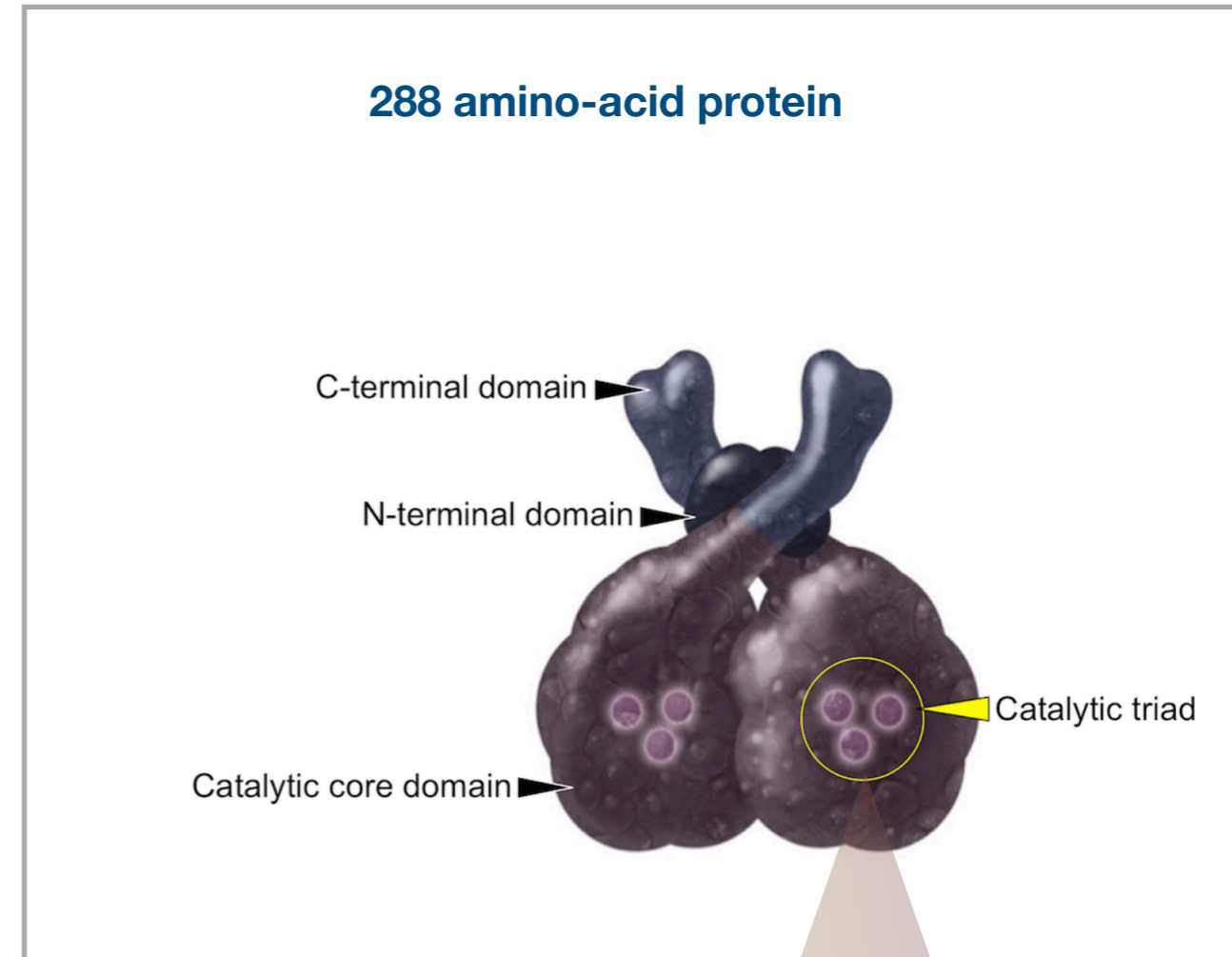
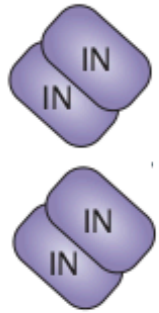


# HIV Integrase



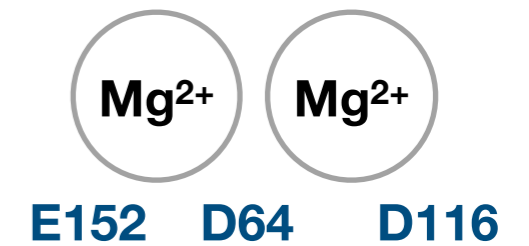
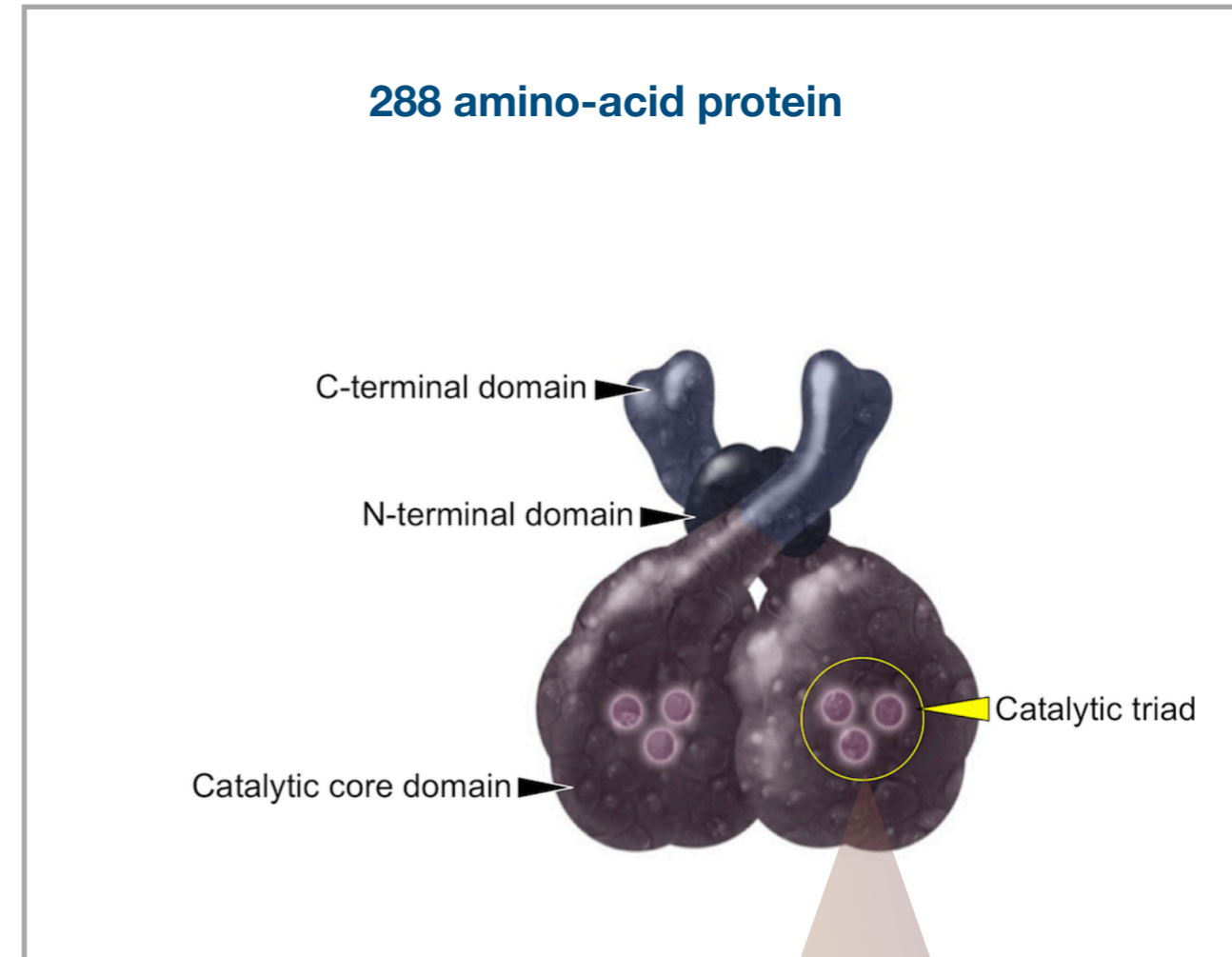
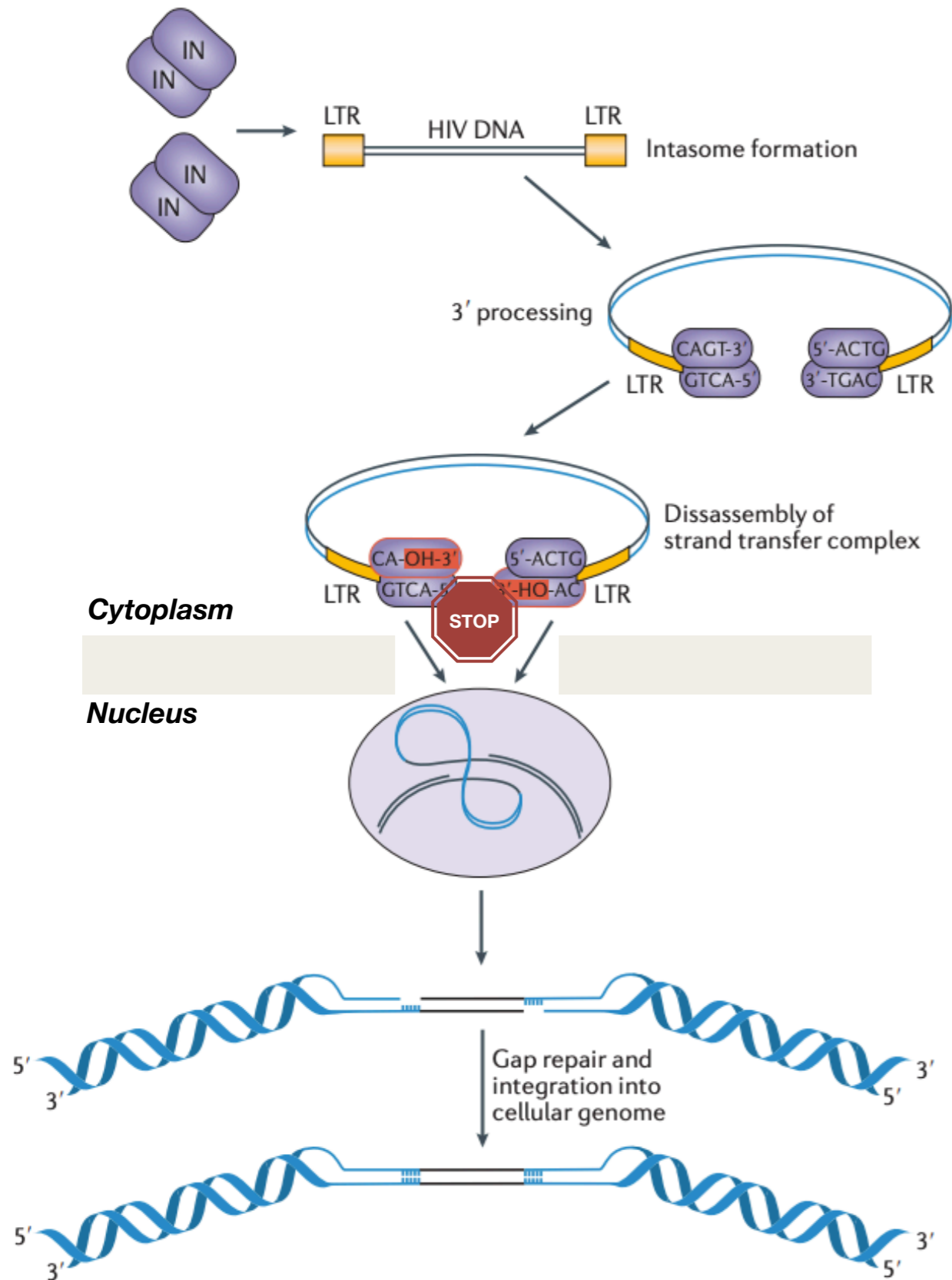
divalent metal ions ( $Mg^{2+}$  or  $Mn^{2+}$ )

# HIV Integrase

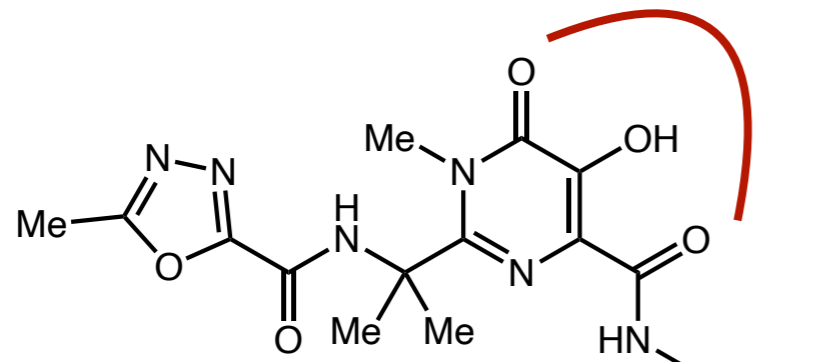




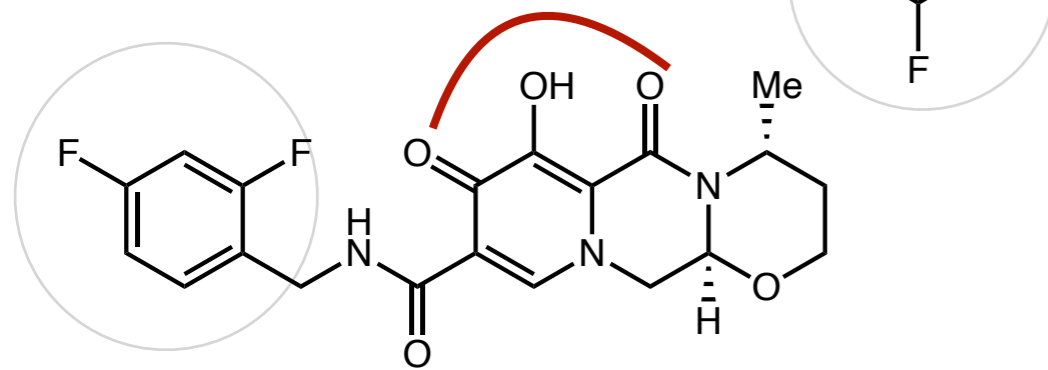
# HIV Integrase



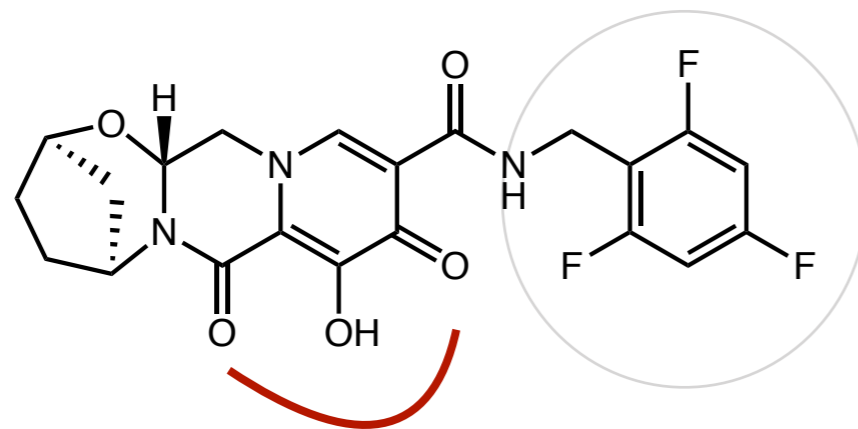
# INTSIs



**Raltegravir**

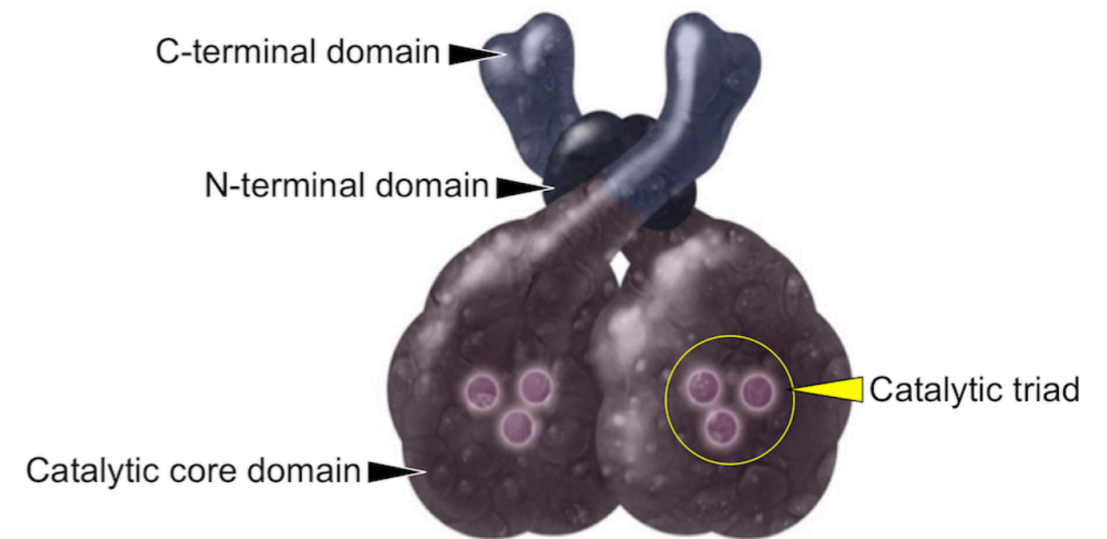


**Dolutegravir**

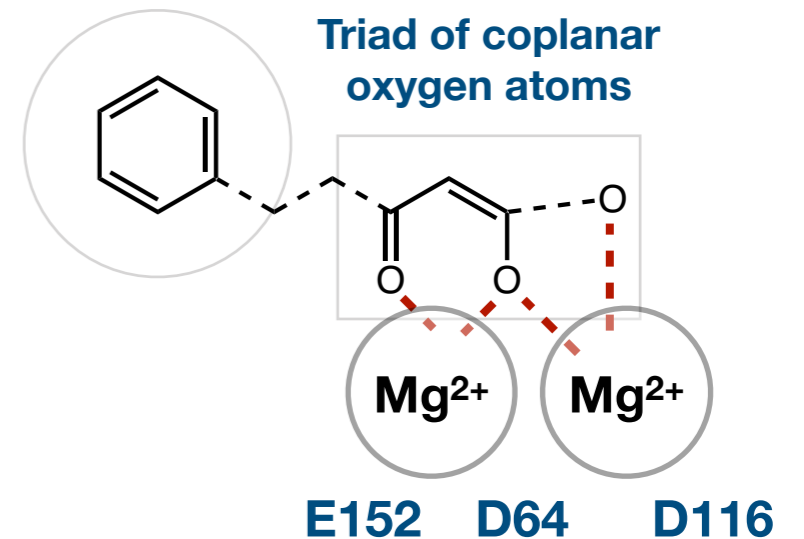


**Bictegravir**

**288 amino-acid protein**



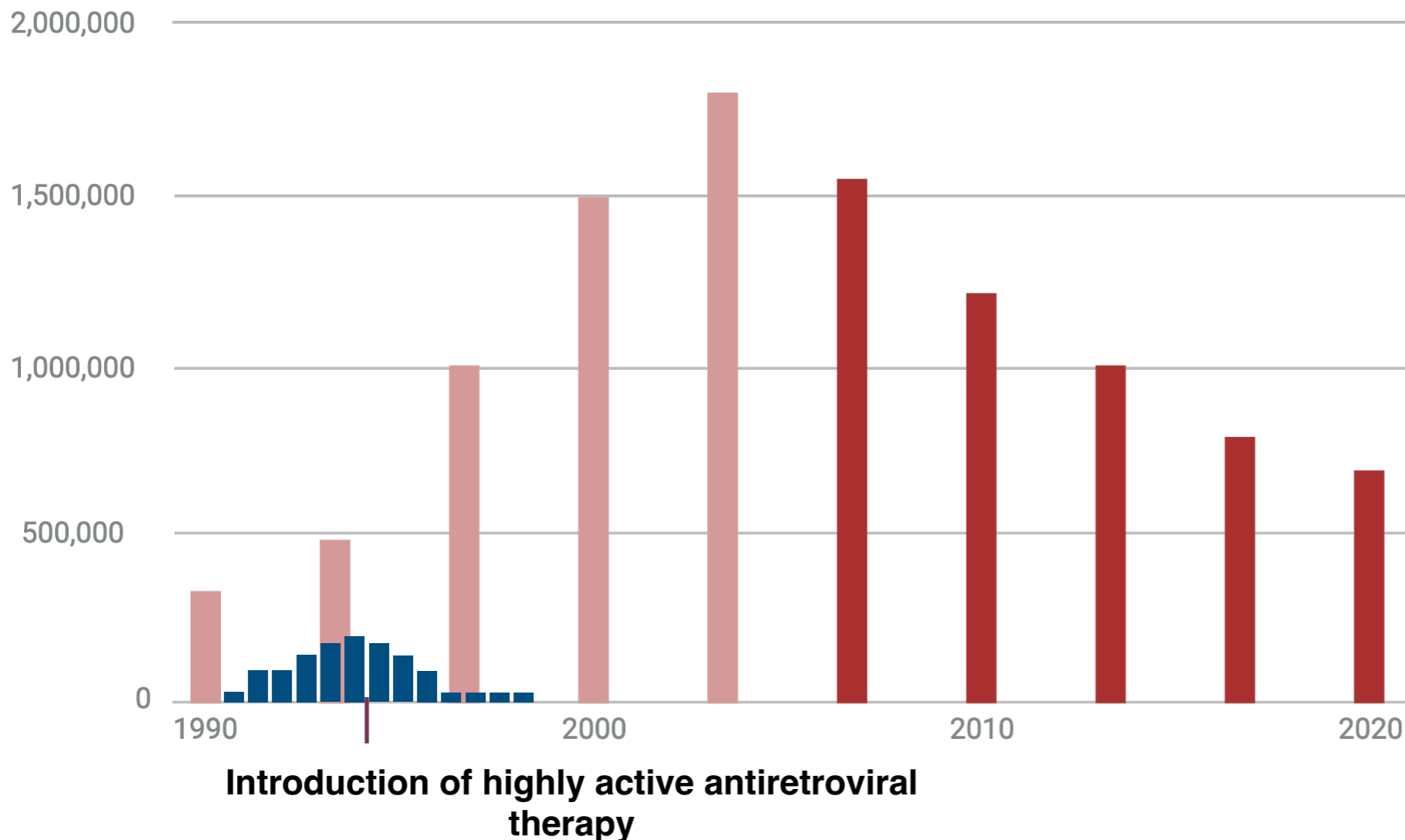
**Halogenated phenyl ring**



**E152 D64 D116**

# What is HIV/AIDS?

## Estimated Number of AIDS-related deaths worldwide/US



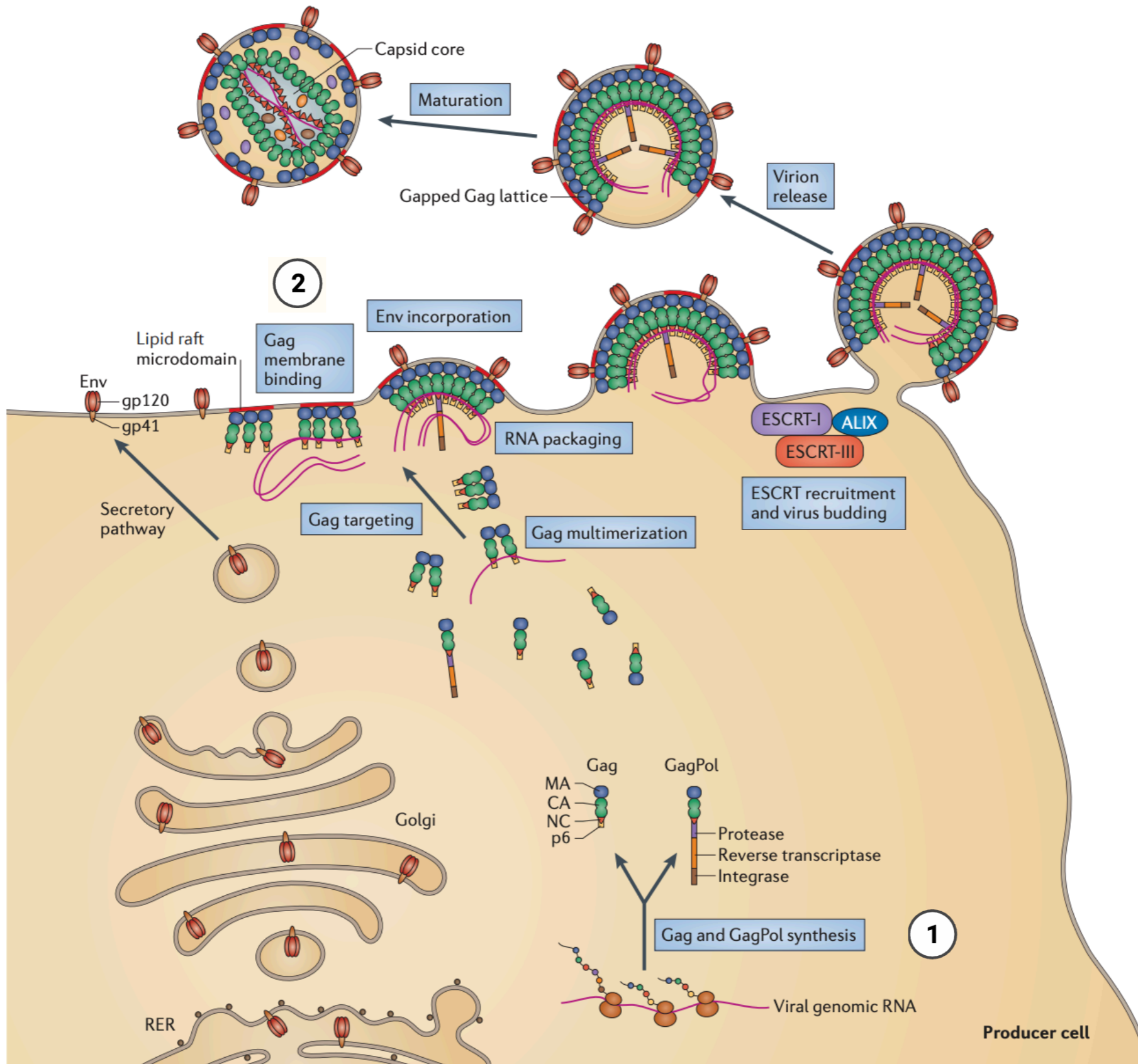
**HIV in 1980s**  
Lifespan upon exposure: **10-13 years**

**HIV in 2023**  
Lifespan upon exposure with proper treatment: **normal lifespan**

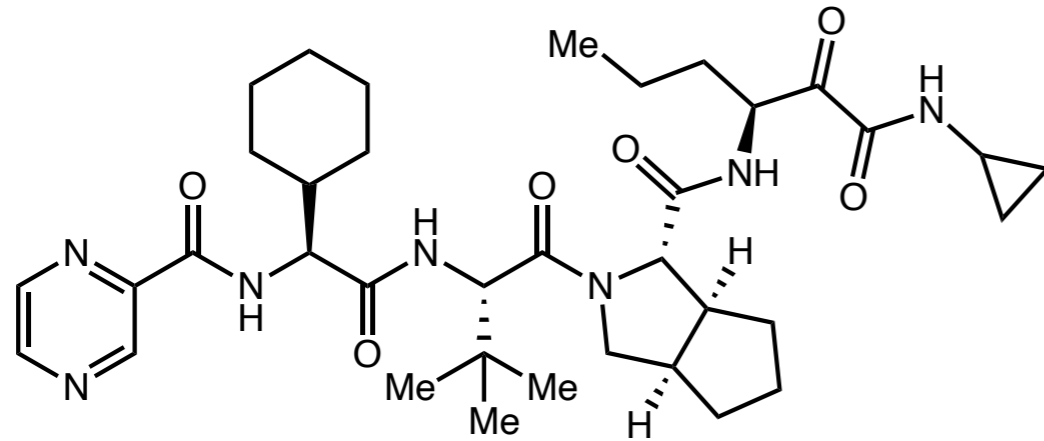


**How did we get to this point?**

# HIV Assembly, Budding, and Maturation

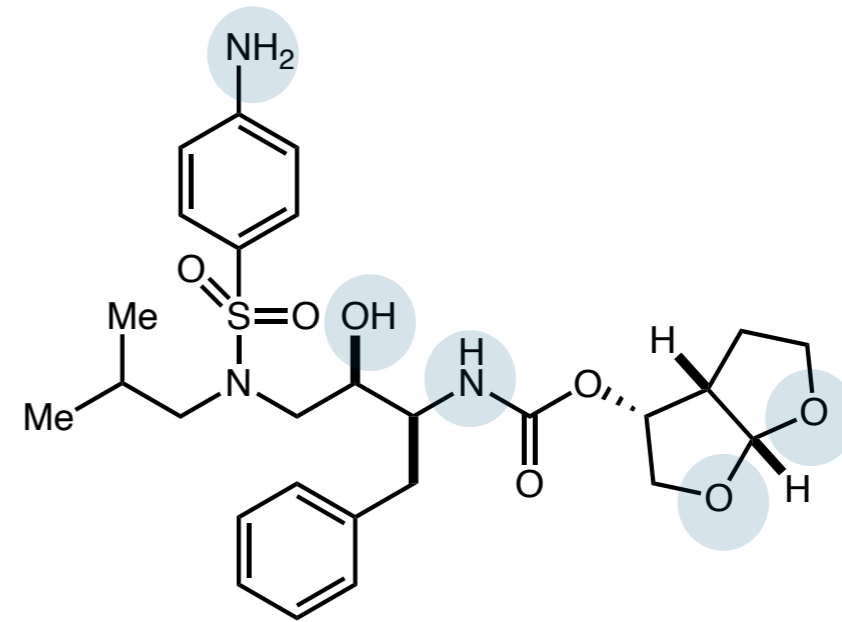


# Protease Inhibitors



**Telaprevir**

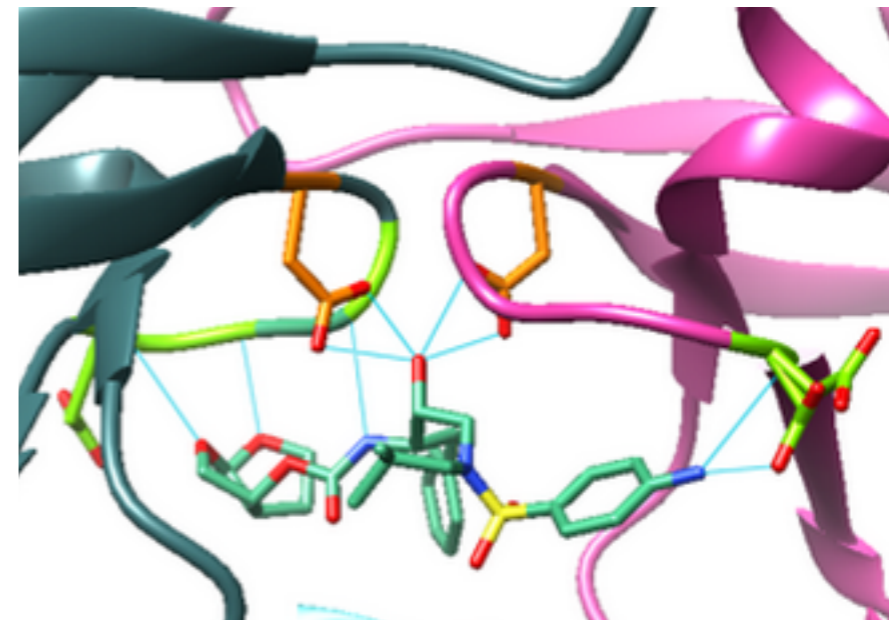
**Back box warning**



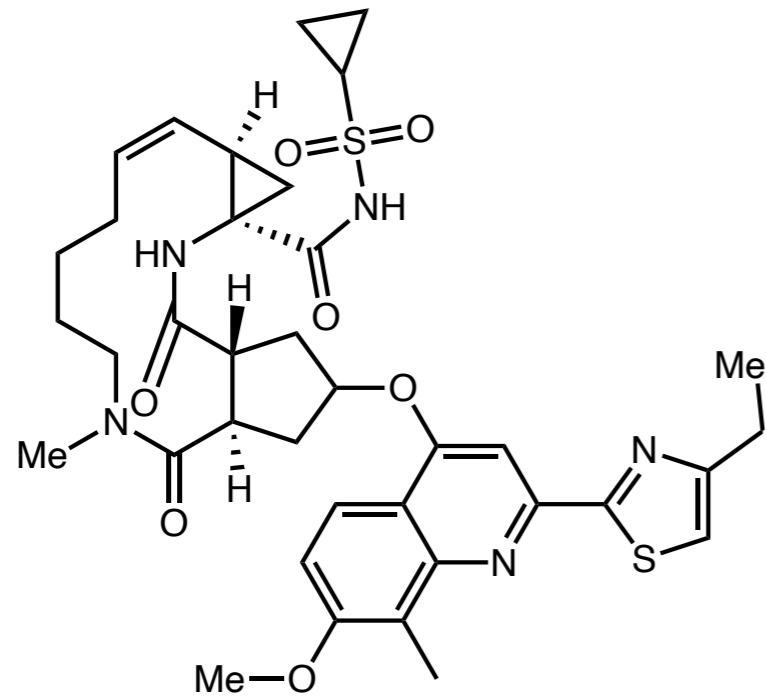
**Darunavir**

**FDA 2006**

**Darunavir interacts with Asp25 and Asp25'**



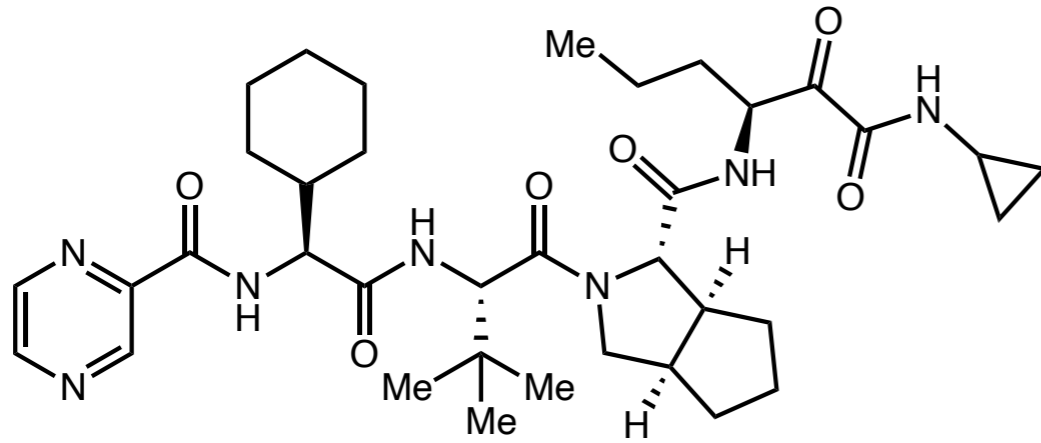
**$K_d = 4.5 \times 10^{-12} \text{ M}$**



**Simeprevir**

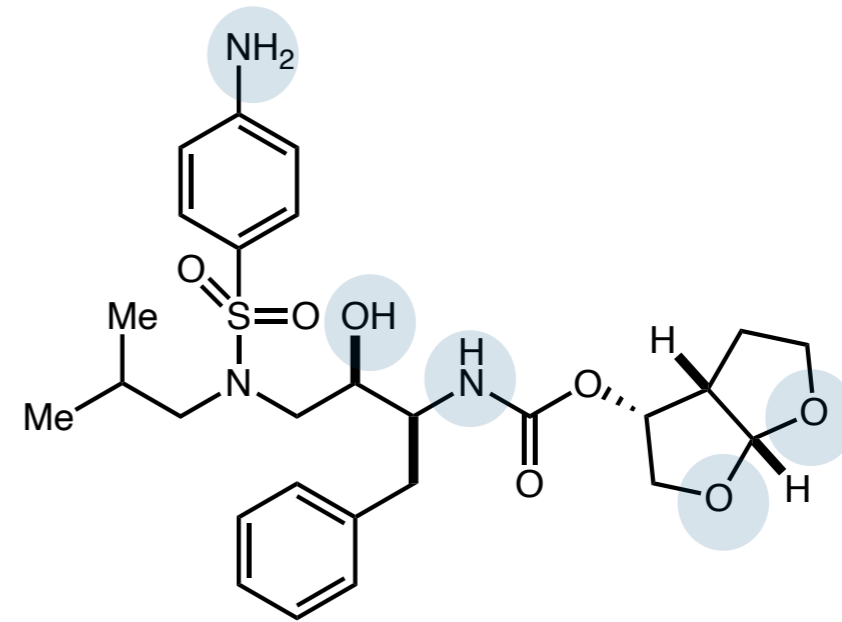
**FDA 2013**

# Protease Inhibitors



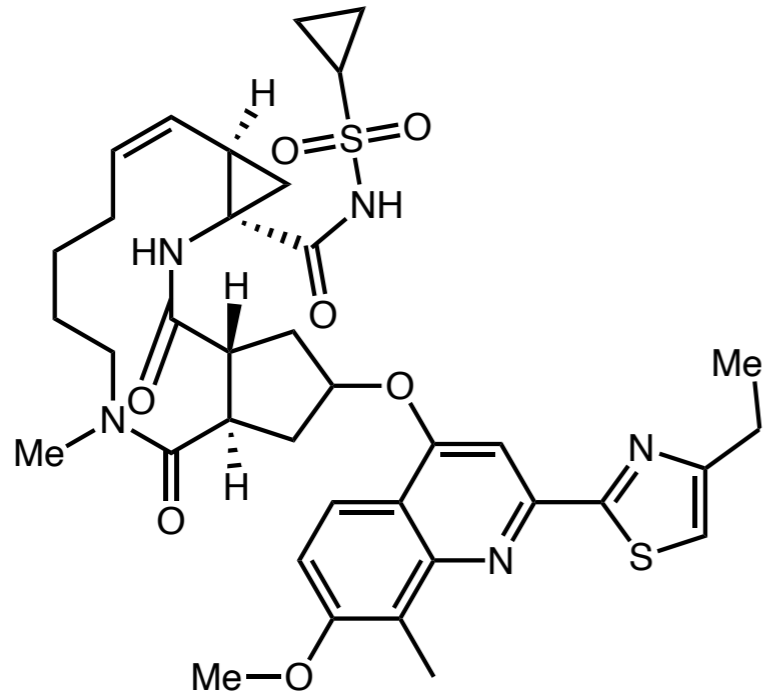
**Telaprevir**

**Back box warning**



**Darunavir**

**FDA 2006**



**Simeprevir**

**FDA 2013**

**> 12**

**FDA approved**

**PIs**

# Outlook

## Modern Day

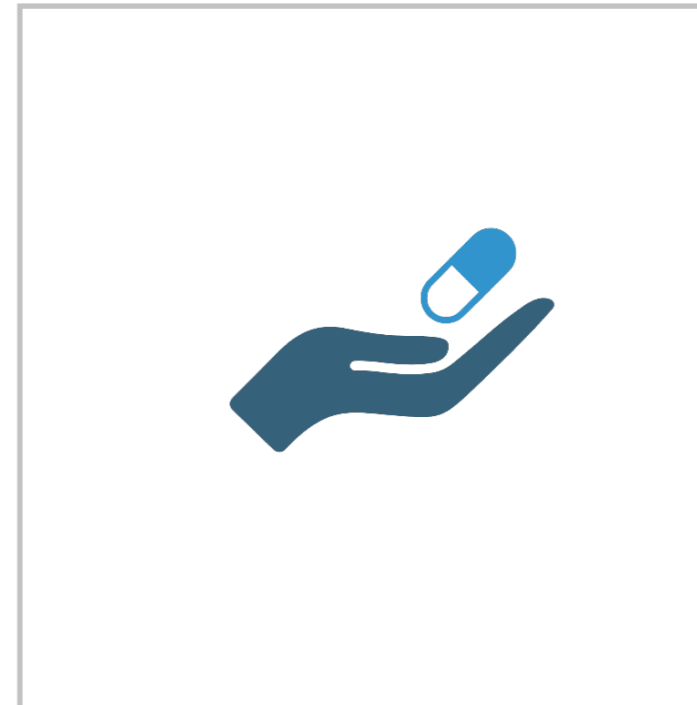


**Perpetual need to refill medication**

**Barriers to medical access**

**Daily pills**

## Hypothetical

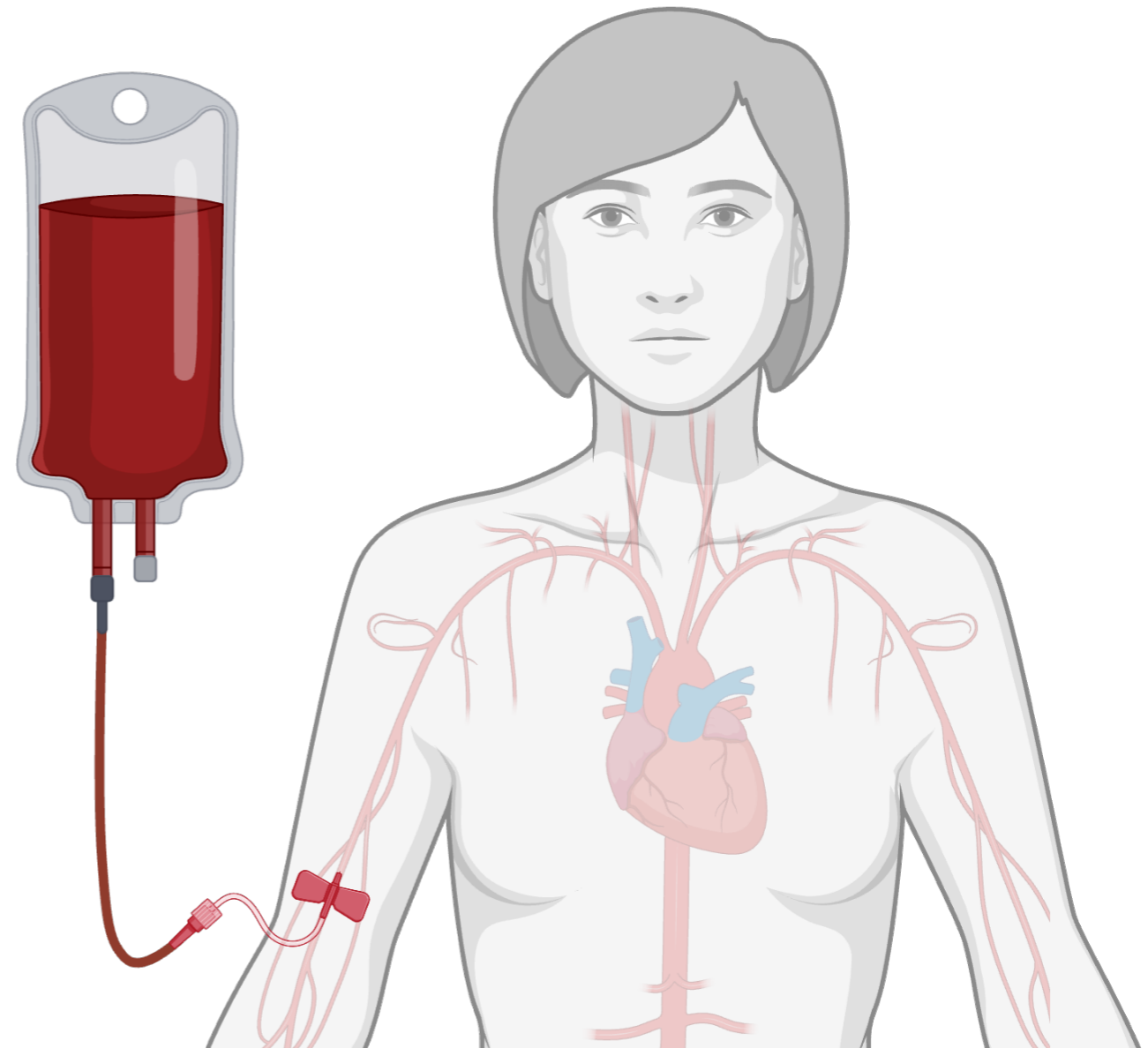
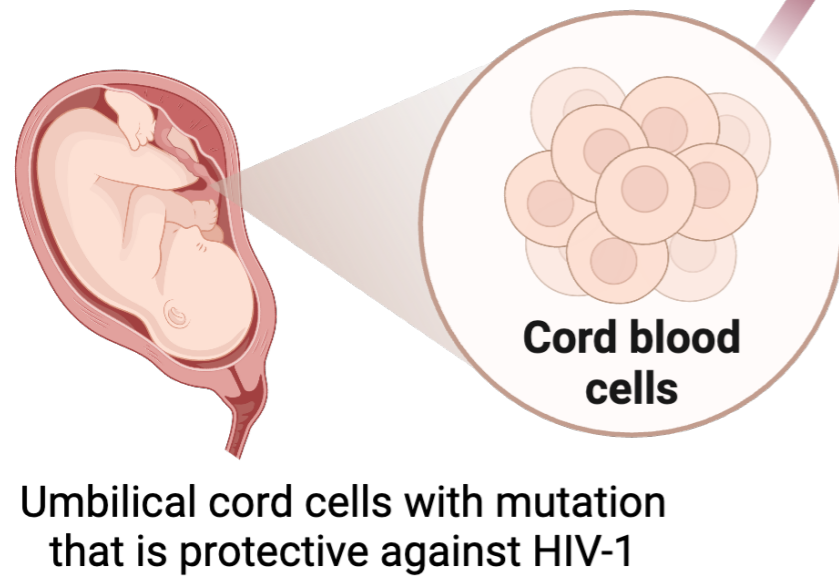
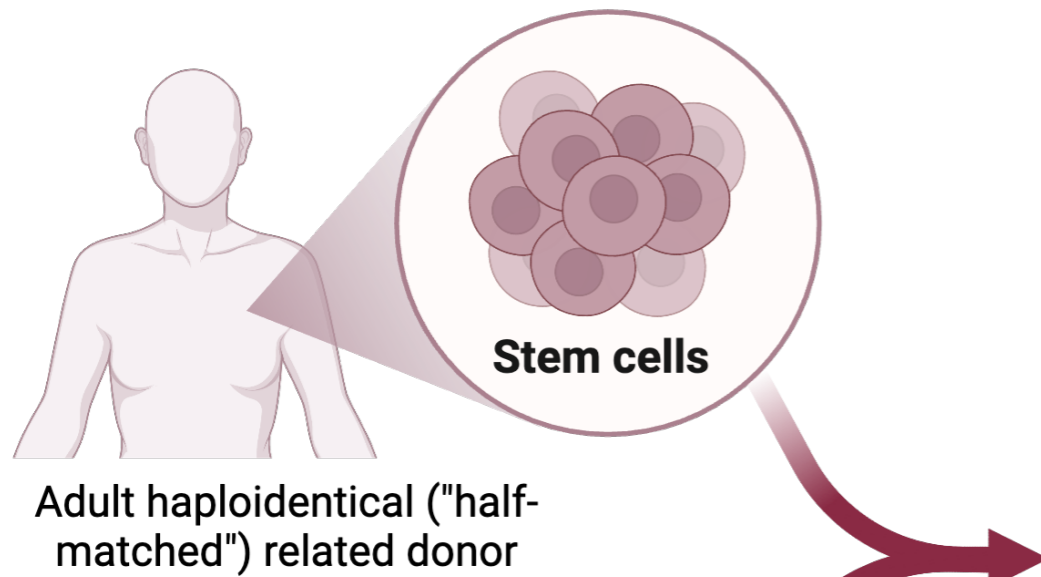


**One pill to cure**

*Is there a cure?*

## The New York Patient

Administration of combined stem cell graft to patient pre-treated with chemotherapy and/or radiation therapy



**Stem cell donors all carried two copies of CCR5  $\Delta$ 32 which confers resistance to HIV**



*Is there a cure?*

## 5th person confirmed to be cured of HIV

The Dusseldorf patient is latest to be rid of HIV with no signs of return.

By [Dr. Kaviya Sathyakumar](#)

February 20, 2023, 11:01 AM



**Do we need a cure?**

*Is there a cure?*

## 5th person confirmed to be cured of HIV

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February 20, 2023, 11:01 AM



**Do we need a cure?**