

**A HIV reverz transzkriptáz (RT) és a proteáz (PR) szerepe a replikációban**

**Az RT/PR inhibítorok mint antiretrovirális anyagok hatásának molekuláris mechanizmusai**

**Antiretrovirális anyagok tesztelése**



**Orvosi N bel D j 1975:**

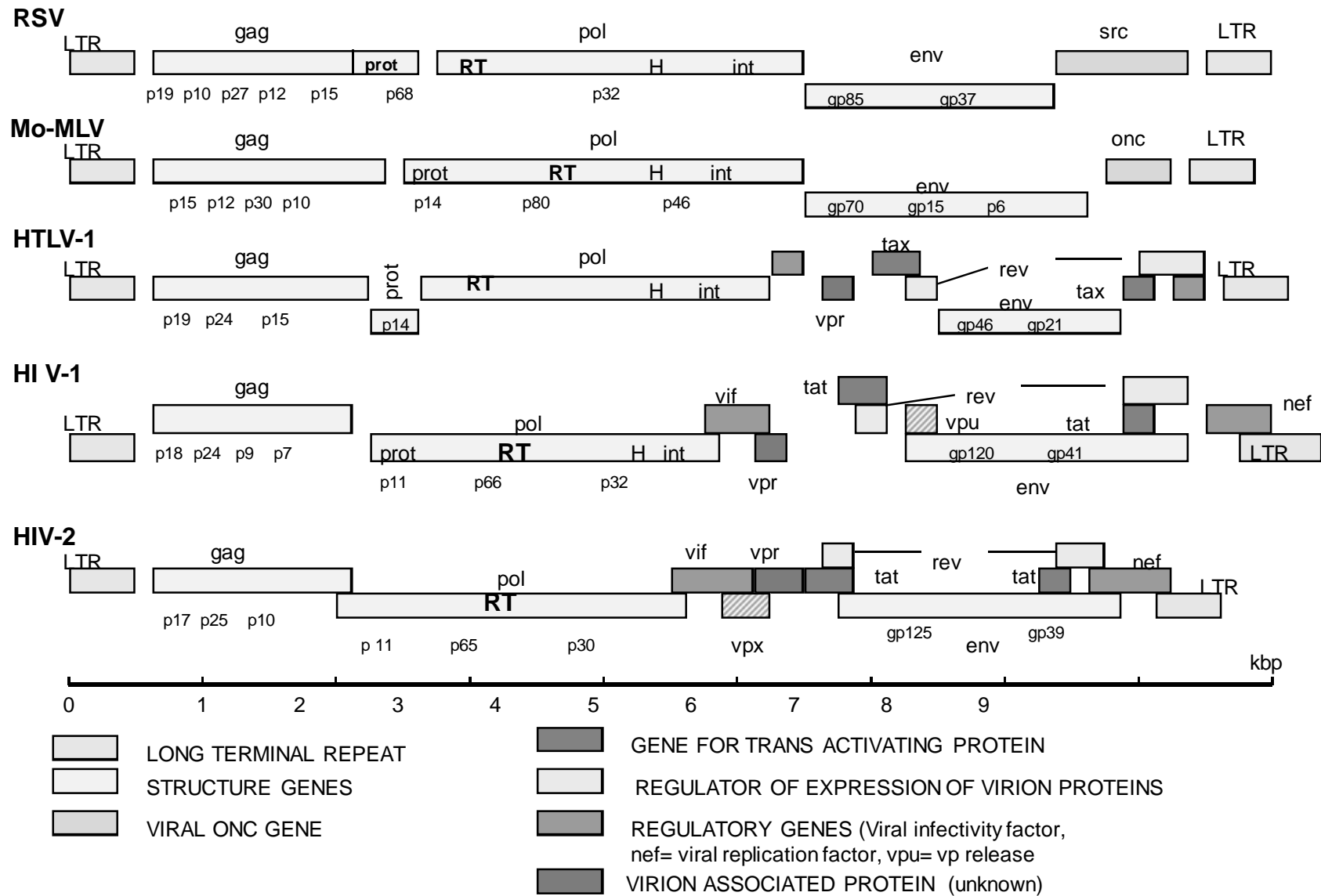
**Renato Dulbecco, Howard M. Temin, David Baltimore**

***„ For discoveries the interrelation between tumor virus and cellular germ plasm”***

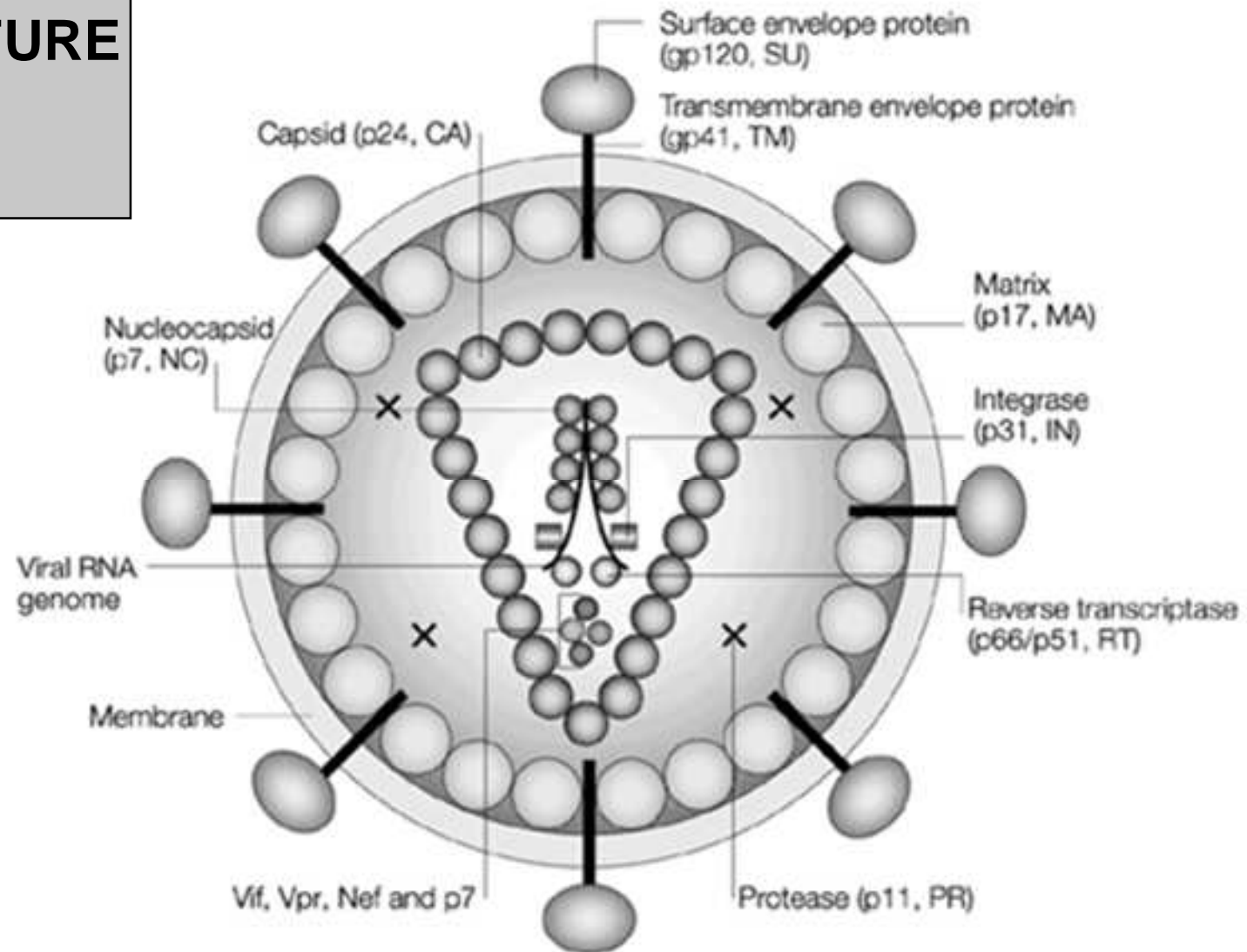


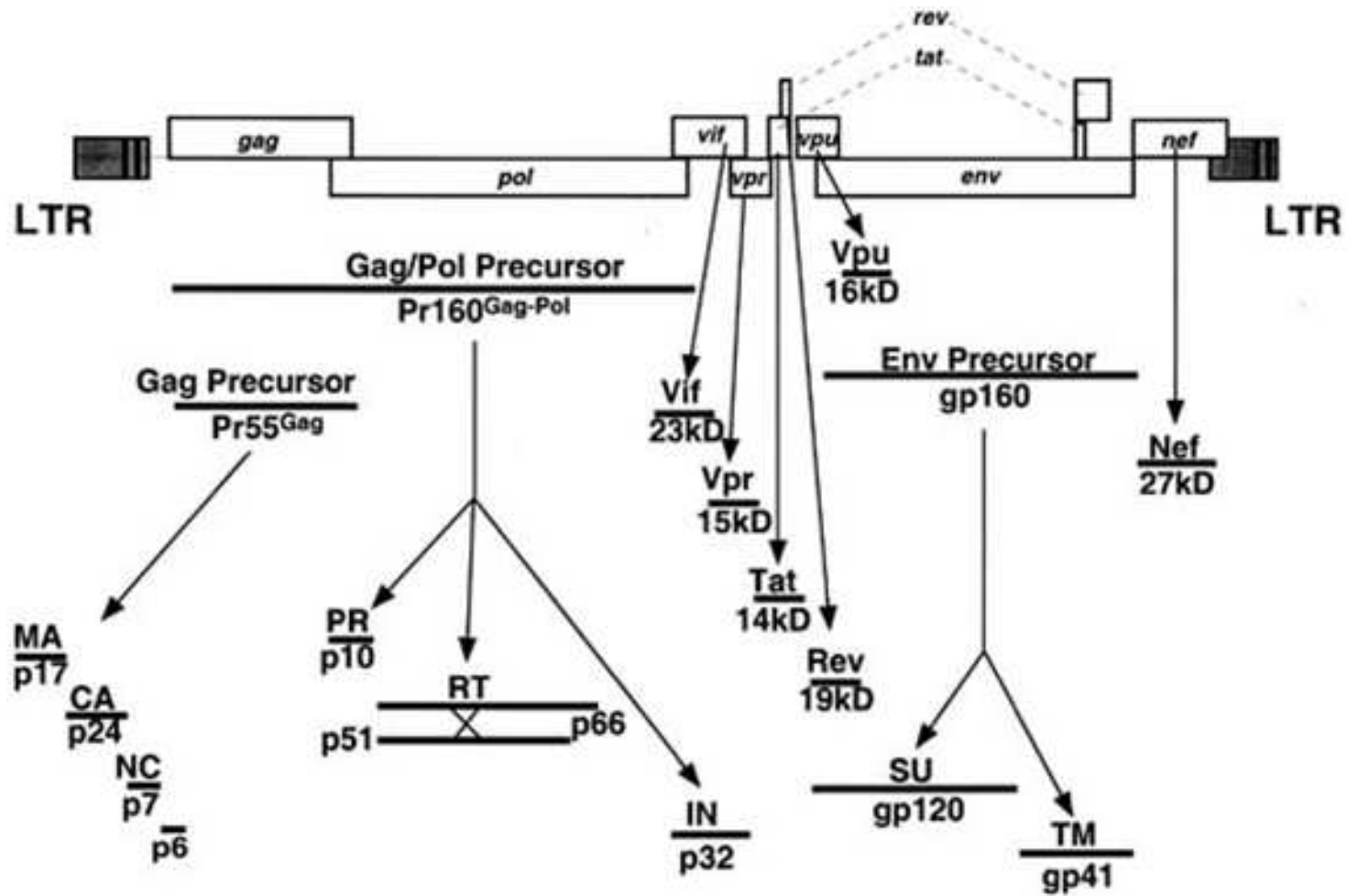
***David Baltimore (1938 -) Howard M. Temin (1934 – 1994)***

# GENOMIC ORGANISATION OF RETROVIRUSES

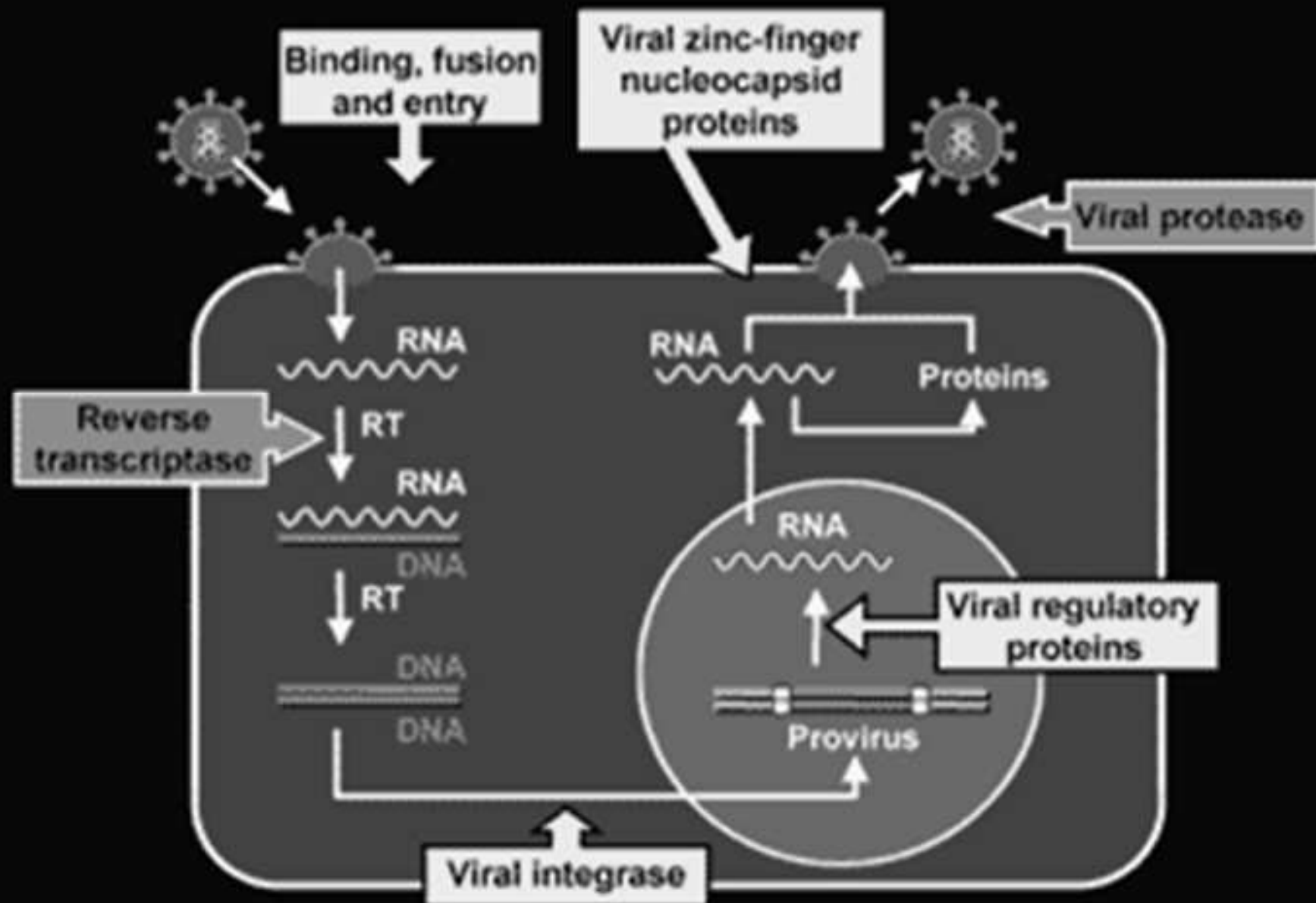


# STRUCTURE OF HIV



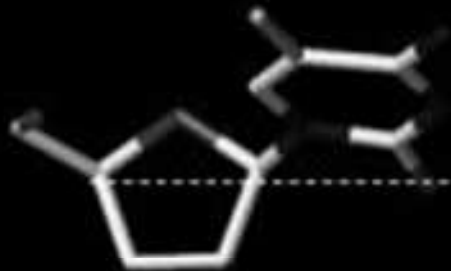


# Potential new targets

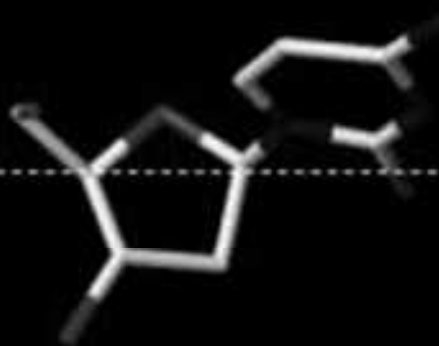


# Structure of AZT vs. other DDNs

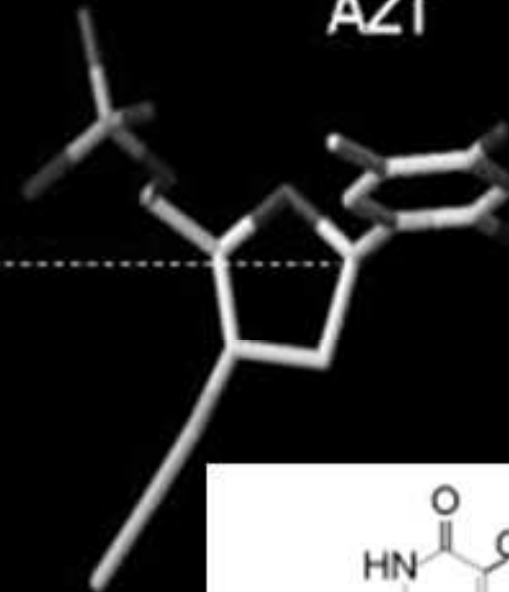
D-D4FC



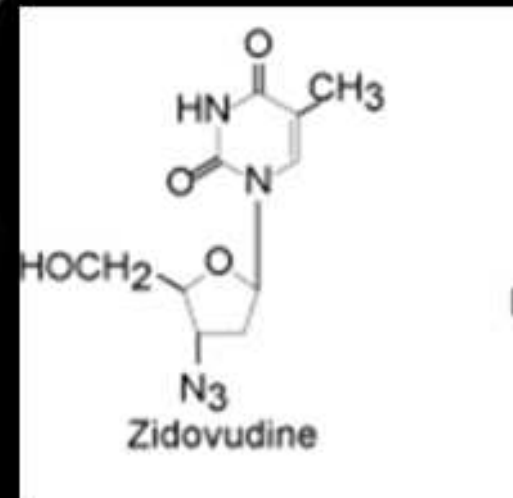
D-dC



AZT



3'Azido



AZT-vel elsőként kezelt hírességek



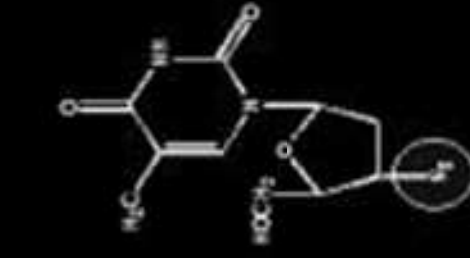
Rock Hudson



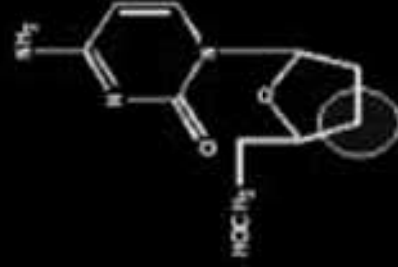
Magic Johnson



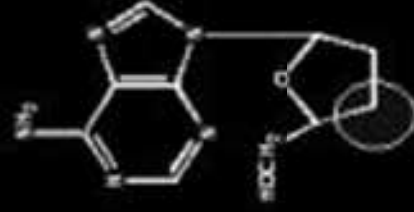
# 5 of 6 approved NRTI are D-nucleosides that vary by pseudosugar structure



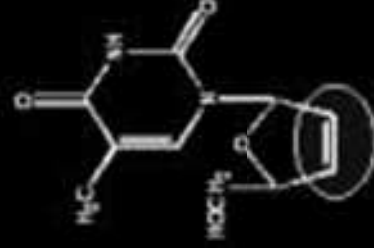
**AZT**  
(Zidovudine)



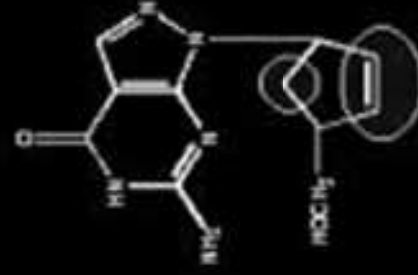
**ddC**  
(Zalcitabine)



**ddA**  
(Didanosine)

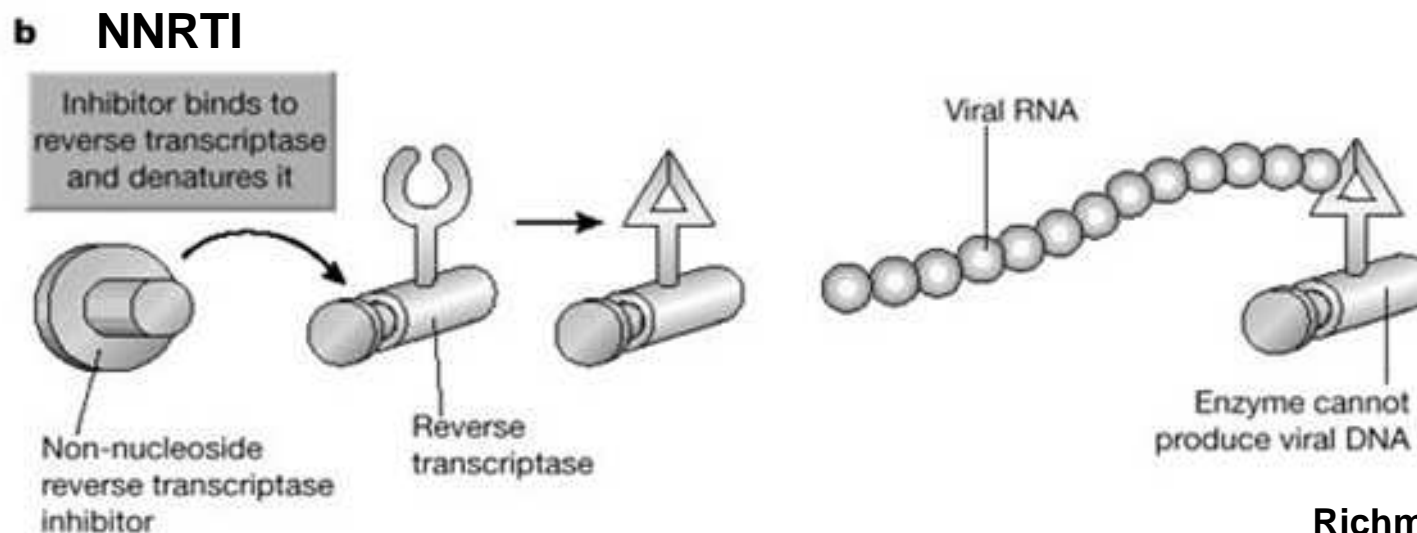
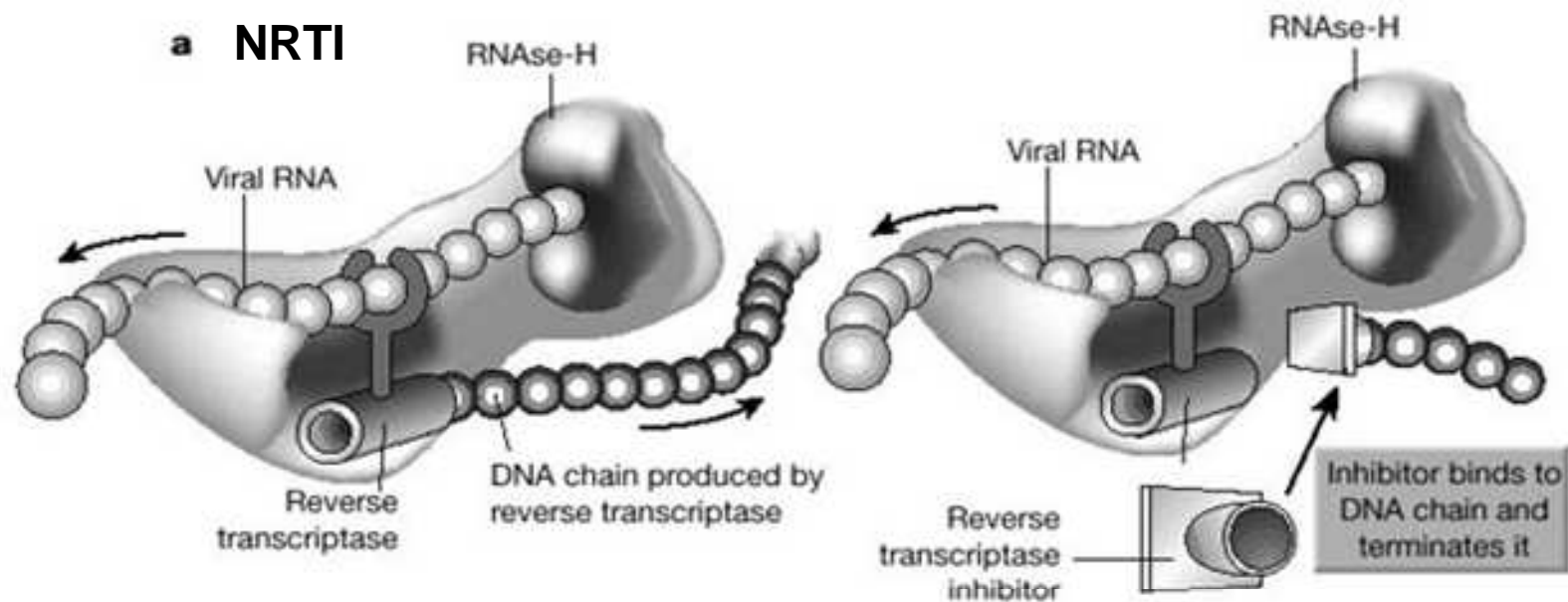


**d4T**  
(Stavudine)

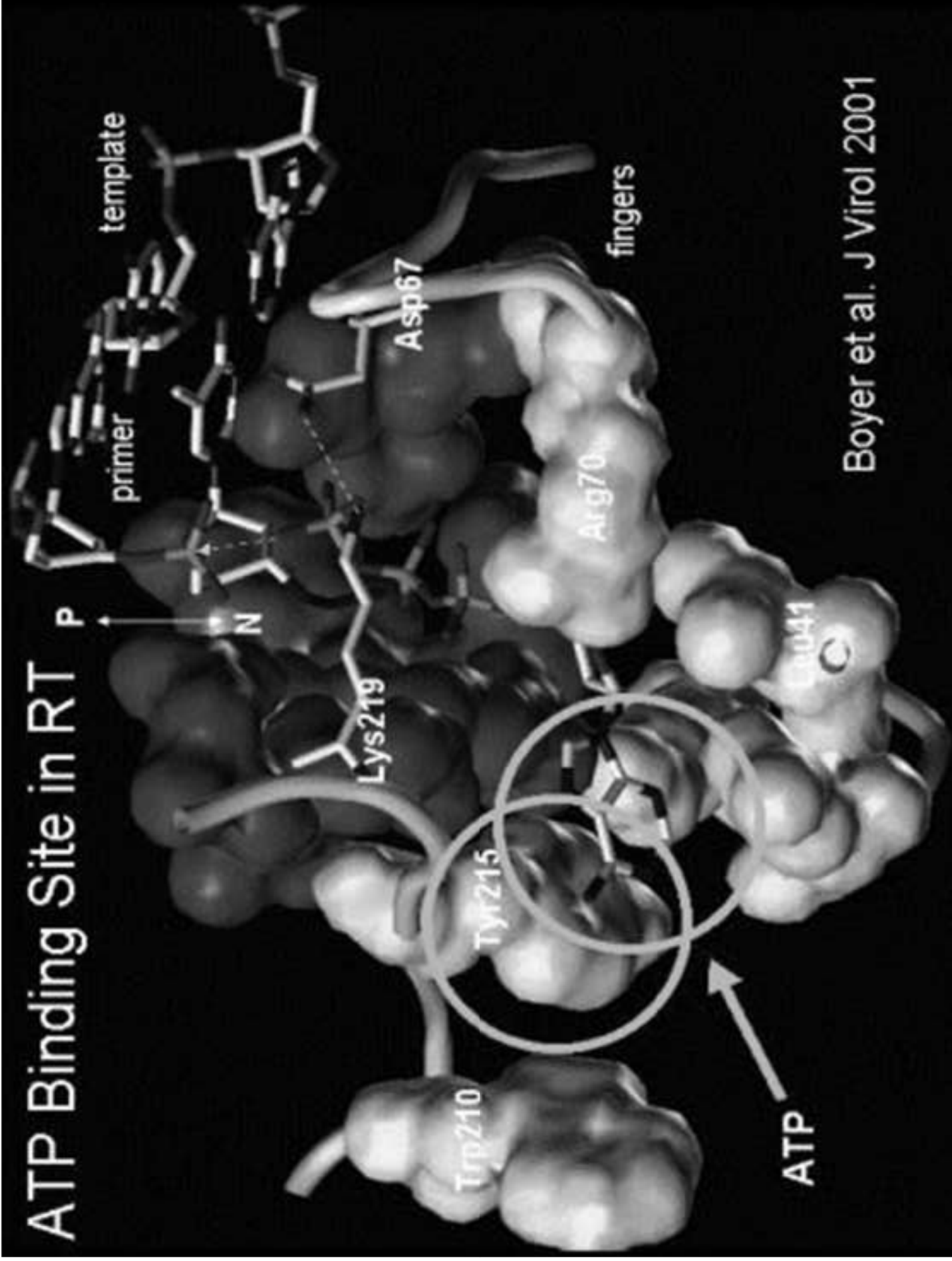


**Carbovir**  
(Abacavir)

# Mechanism of action of HIV RT inhibitors



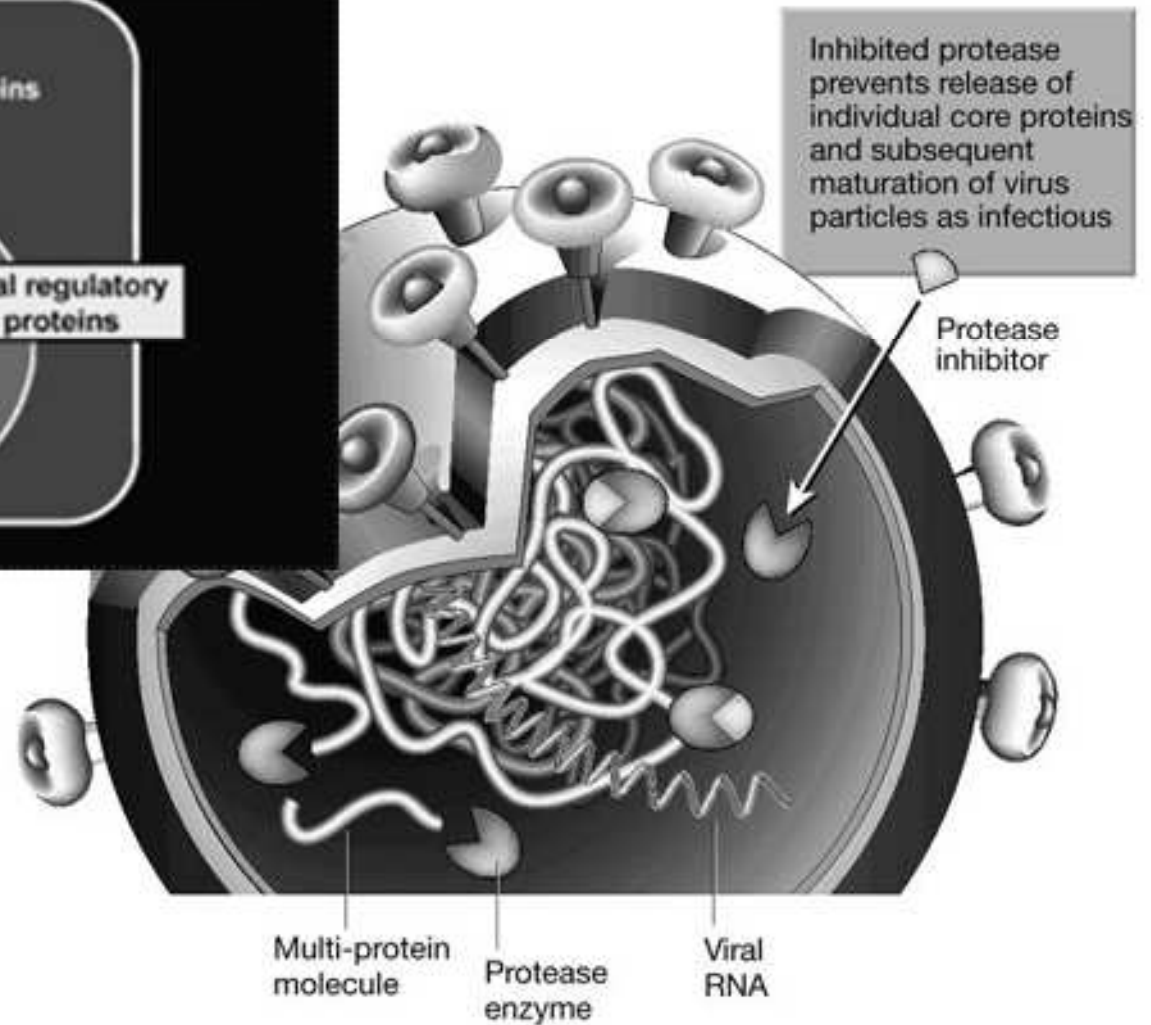
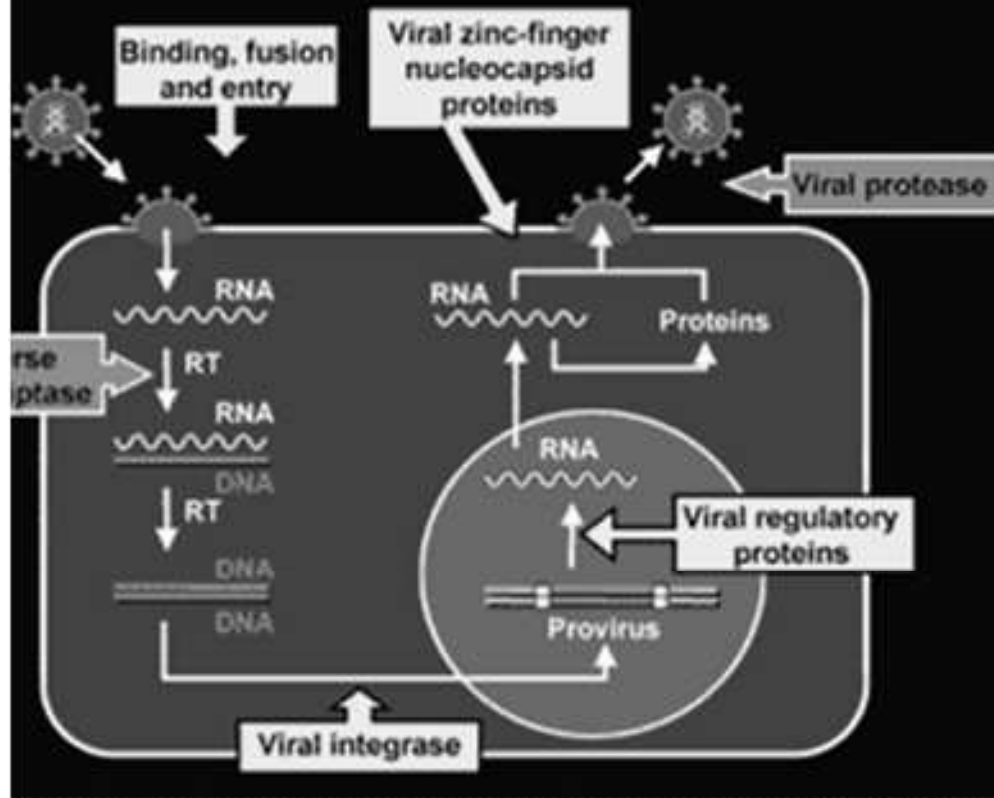
# ATP Binding Site in RT

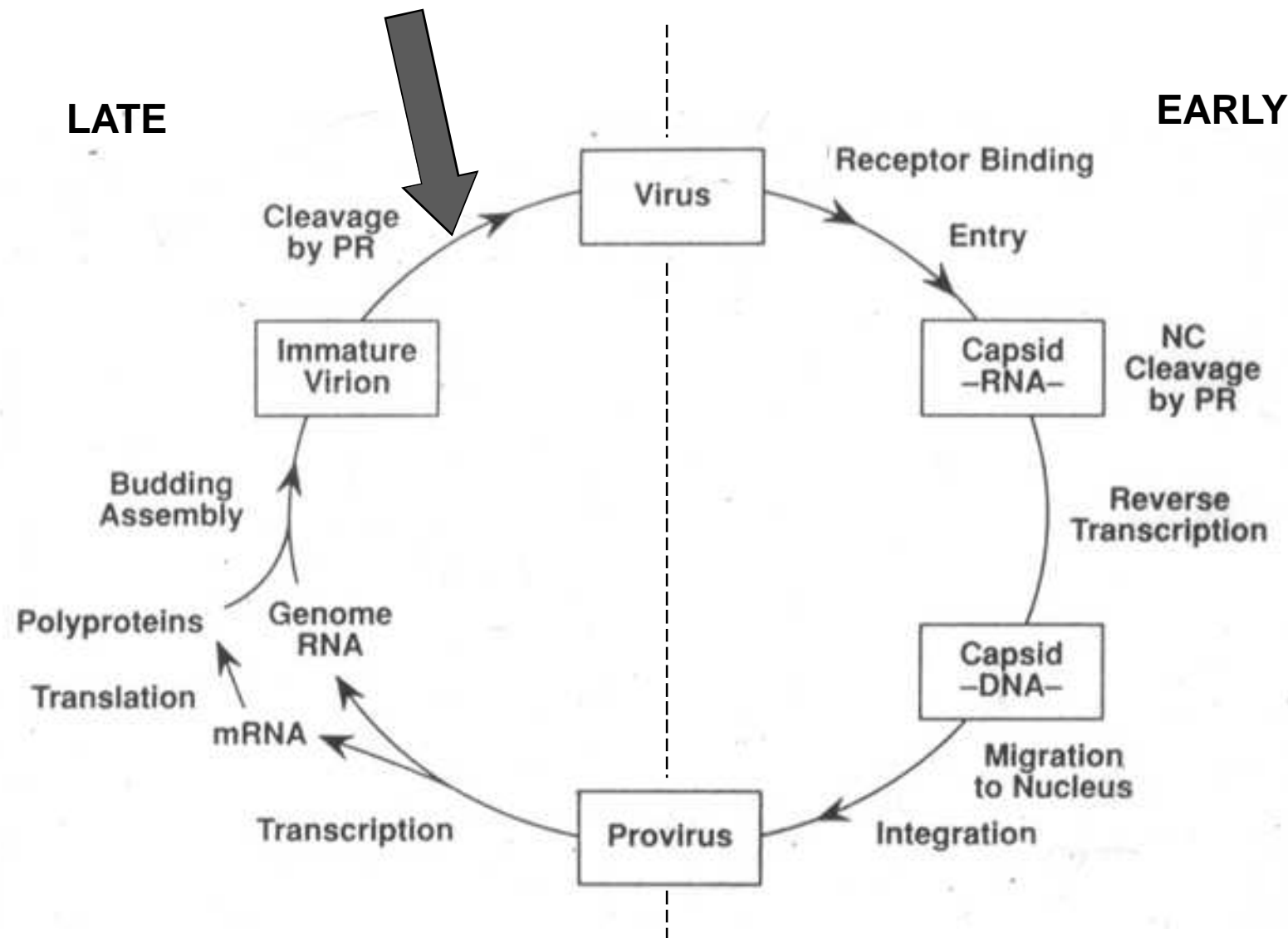


Boyer et al. J Virol 2001

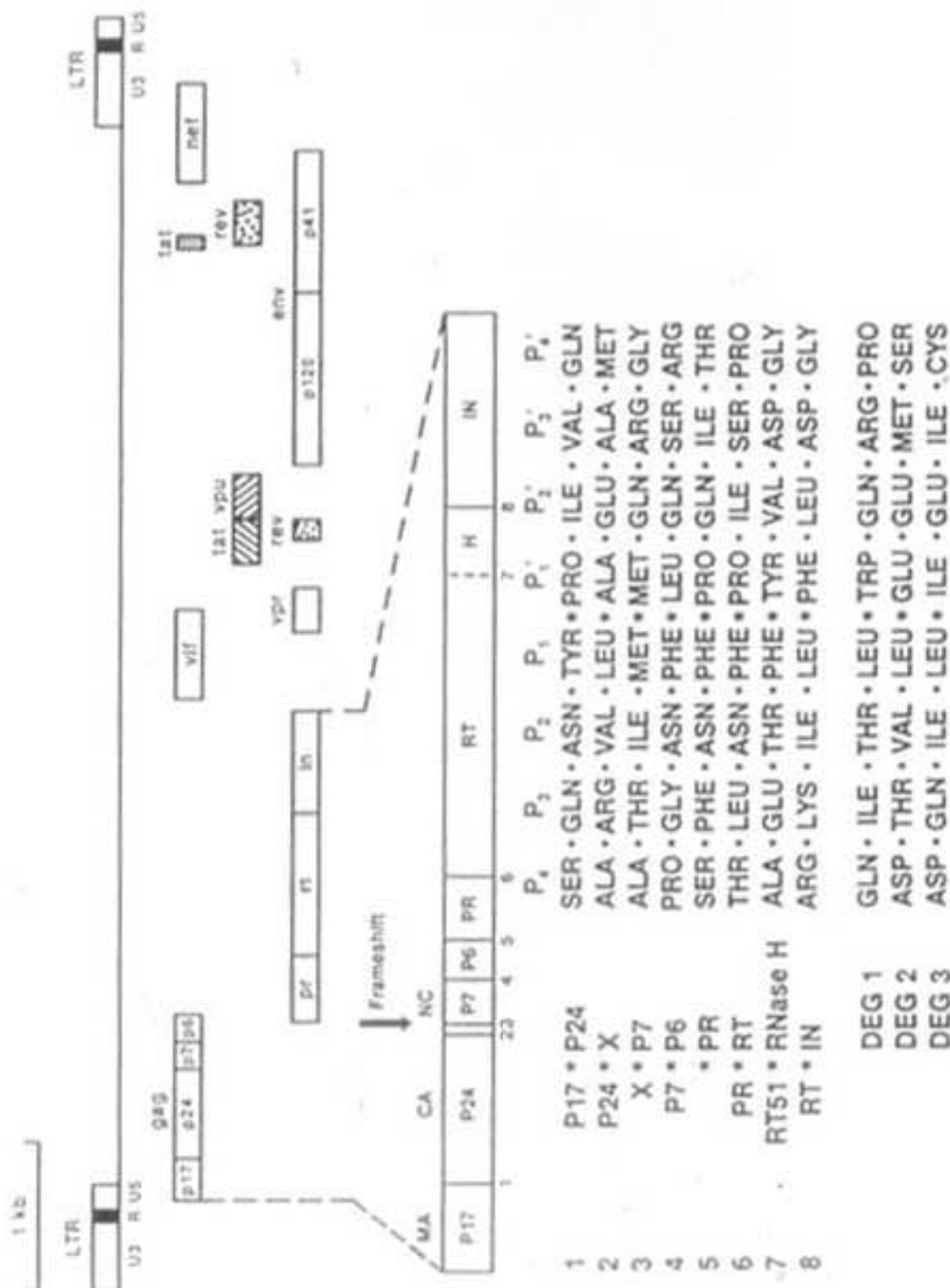
# PROTEÁZ GÁTLÓK

## Potential new targets

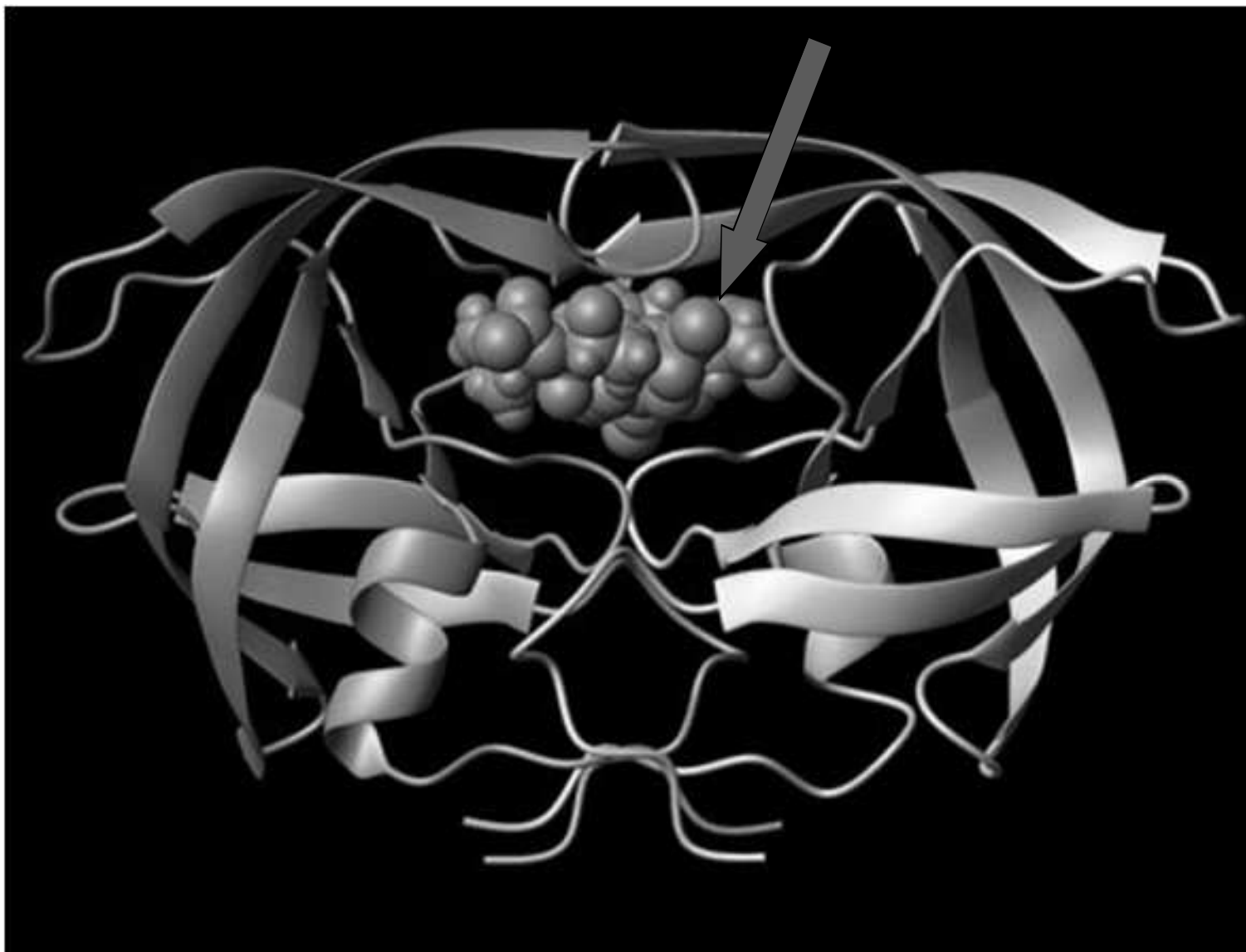




## HIV REPLICATION CYCLE

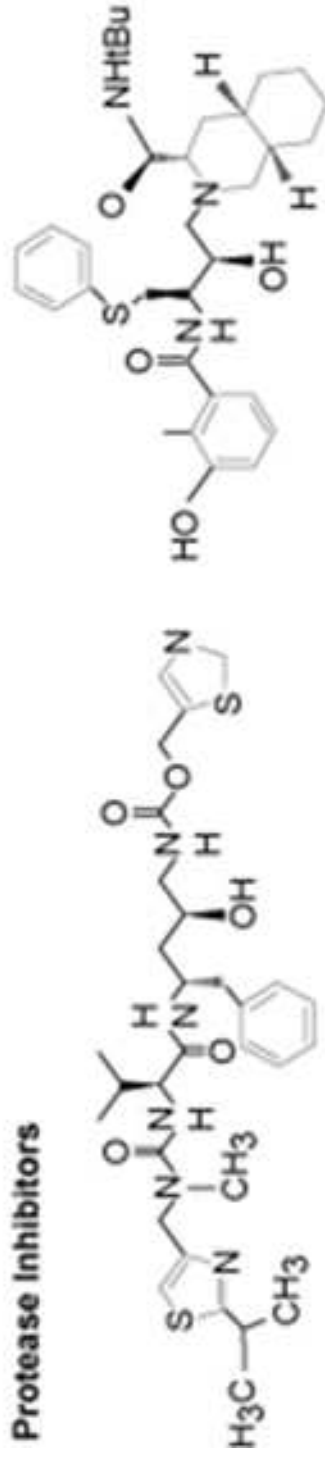


**HIV proteáz (dimer), inhibítorral az aktív helyen**



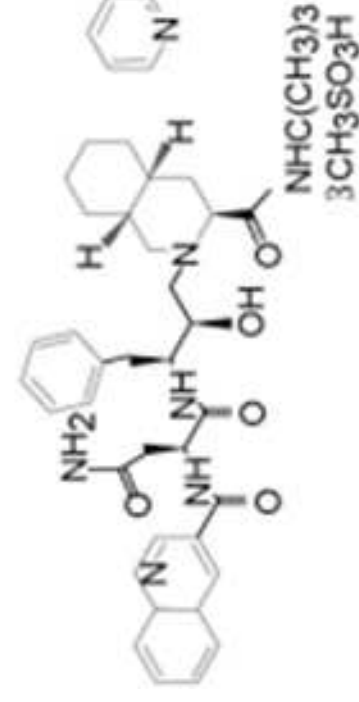


# Protease Inhibitors

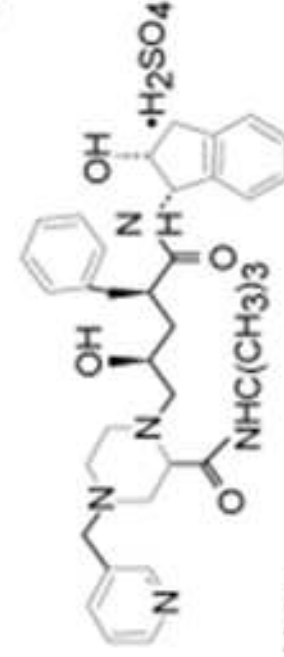


Ritonavir

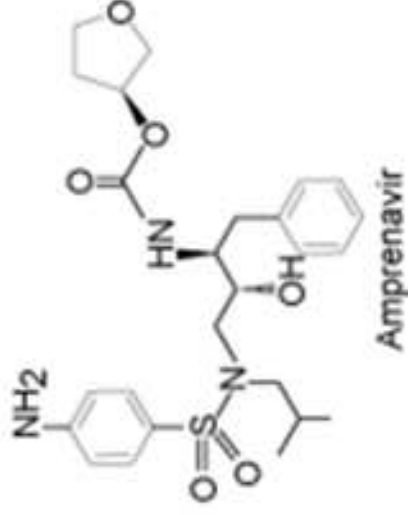
Nelfinavir mesylate



Saquinavir mesylate

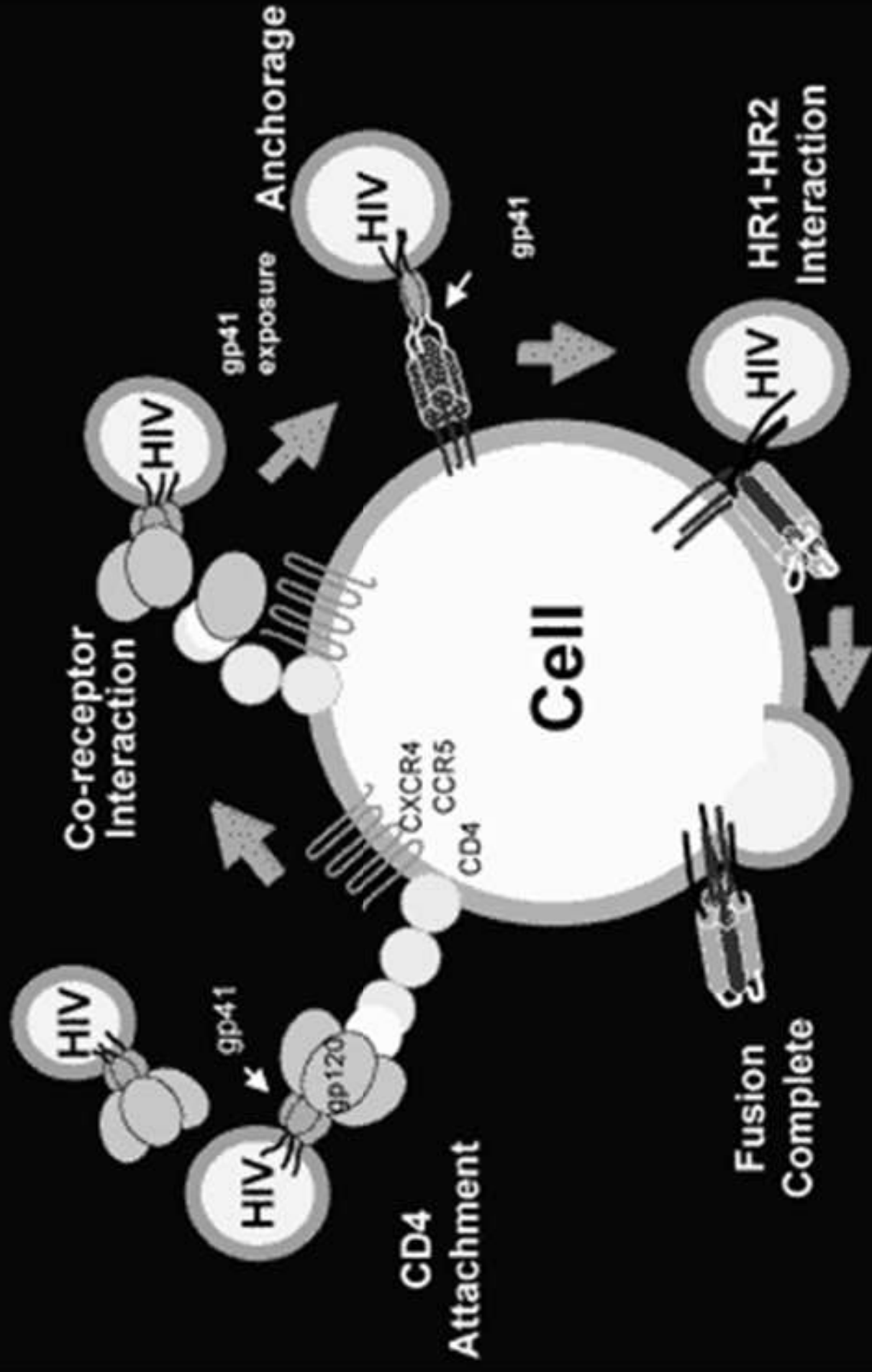


Indinavir sulfate



Amprenavir

# HIV interaction with CD4 cell



# Potential for targeting the coreceptor

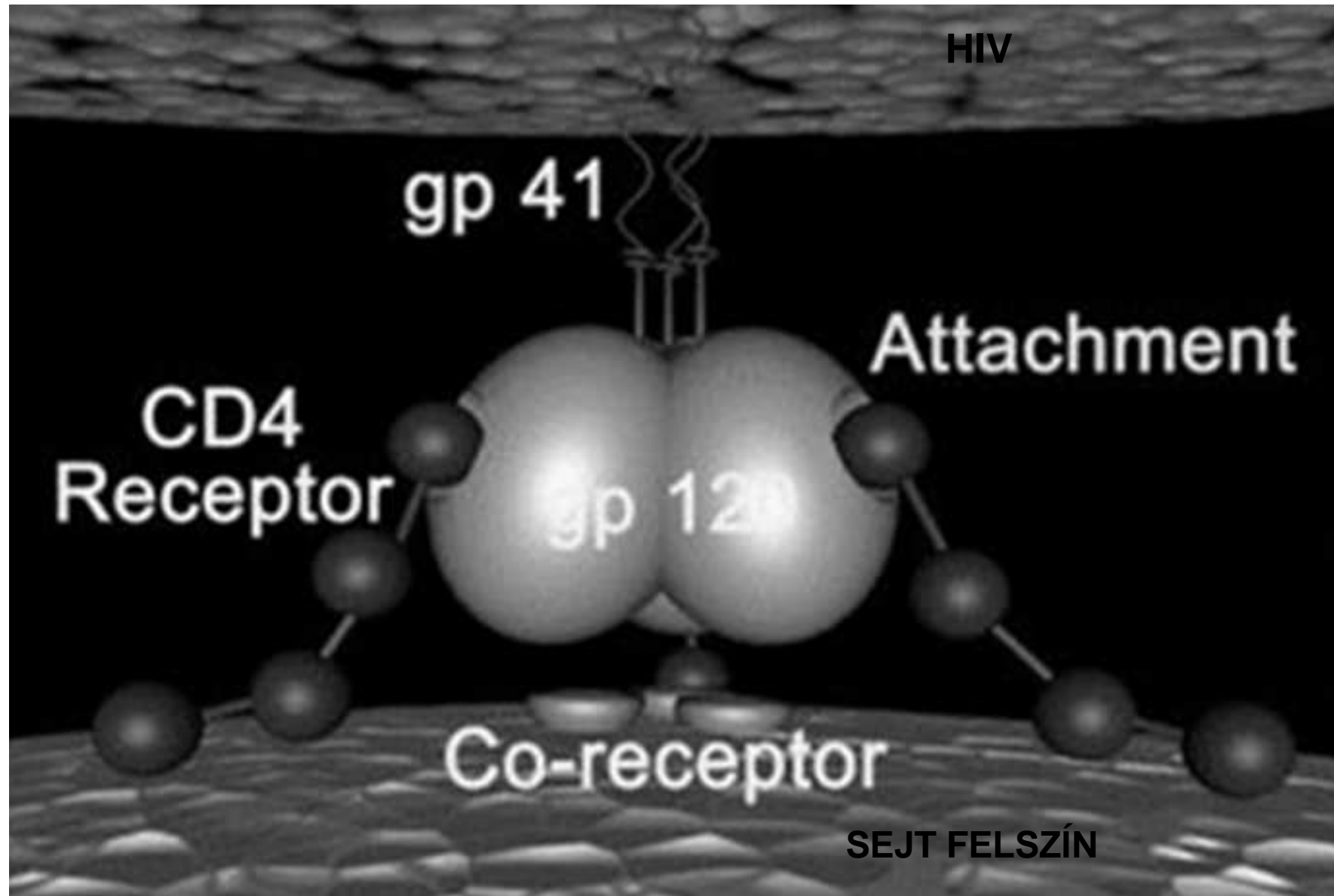
## Pluses

- Proof-of-concept *in vitro* since chemokines or chemokine derivatives can effectively inhibit HIV infection.
- Pharmaceutical experience with 7-transmembrane receptors.
- Potential to inhibit receptor without triggering functional activity.
- Individuals with deletions in the gene for CCR5 (delta32) highly resistant to HIV and have no significant side effects

## Minuses

- Potential for driving virus to different co-receptor usage? (Scarlatti. Nat Med 11:1259), but see Moore et al., this meeting -- LB05
- Unknown consequences of blocking chemokine pathways? (Importance of CXCR4 in vascularization and organogenesis - Tachibana. Nature 393:591)

# CCR-5 kemokin receptor gátlás

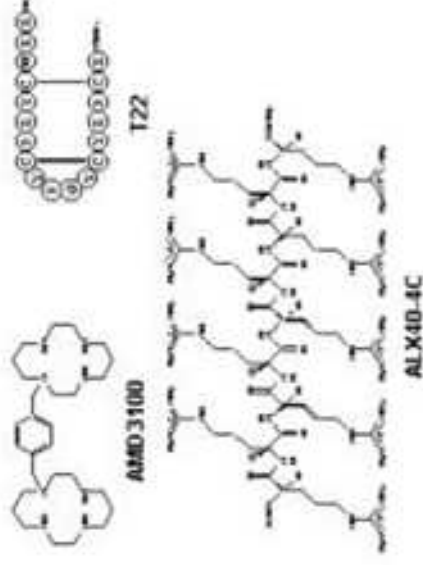


# Coreceptor Antagonists

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## CXCR4

ALX40-4C  
AMD3100  
T22



## CCR5

TAK779  
Schering C, D



HIV ENTRY

INHIBITORS



WEDNESDAY  
JULY 12, 2000  
BREAKFAST  
SYMPOSIUM  
06:30-08:45 AM

CONFERENCE  
TOPIC  
C  
F  
VII

Entry  
Inhibitors:

The Next Frontier  
in HIV Treatment

An Official Satellite Symposium of the  
XIII International AIDS Conference

# Fusion Inhibitors

## Peptides Derived From HR-2 sequence

HR2

COOH-YGLMNTINFENELSAWKDLLELEQENKEQCNQSEELSHILSTYNNIERDGEKSTNNWIQELSKN-

T20



T1249



T20 from HIV-1 sequence

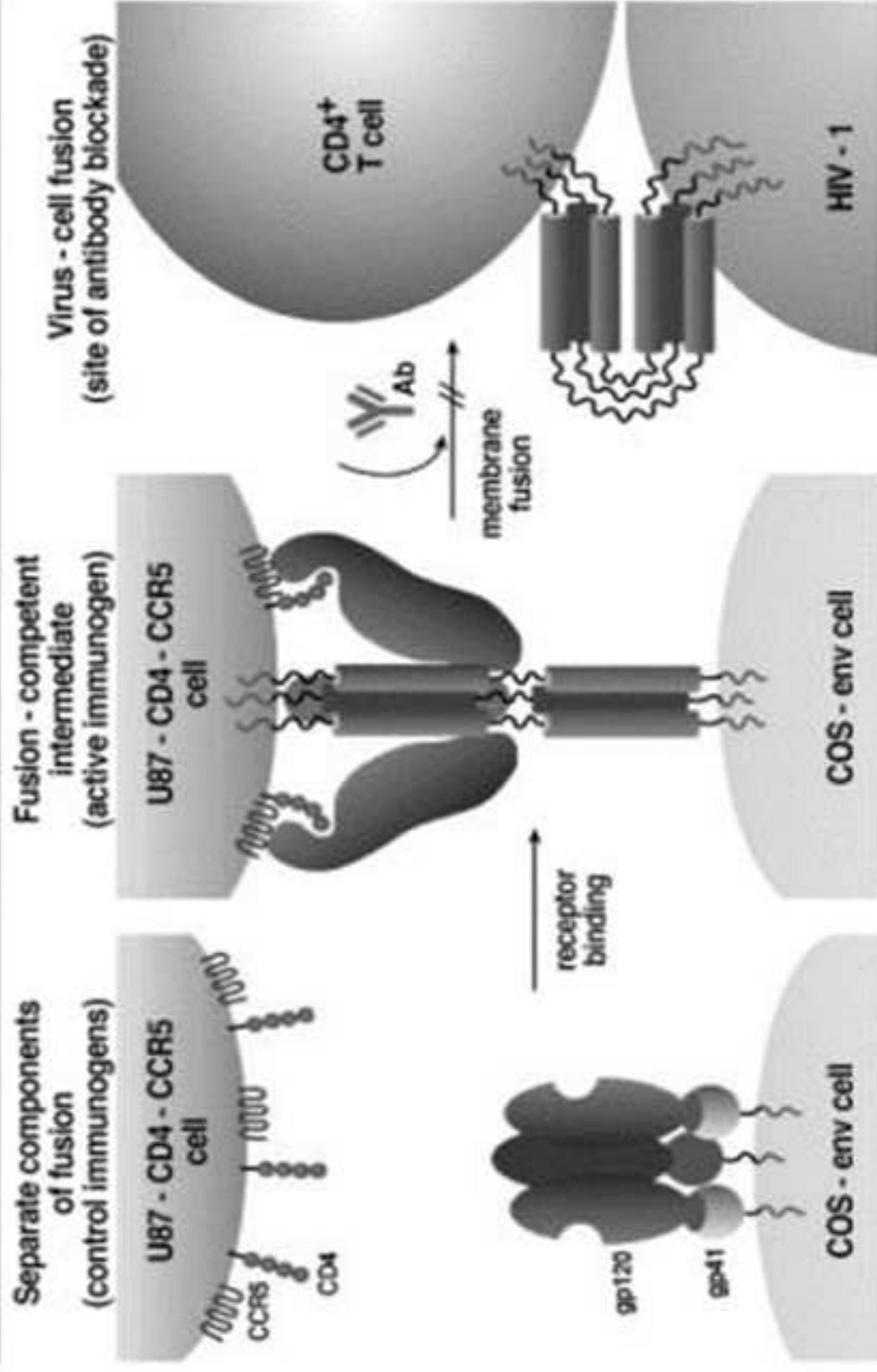
T1249 from HIV-1, HIV-2 and SIV

## T-20 Profile

- 36 amino acid peptide
- Inhibits gp41-mediated fusion
- ~1 ng/mL activity in T-cell lines
- Active against R5 and X4 viruses
- Synergistic with RTI's and PI's
- Administered by twice-daily injections
- Currently in phase 3 clinical trials



# Model of a Fusion-Competent Immunogen

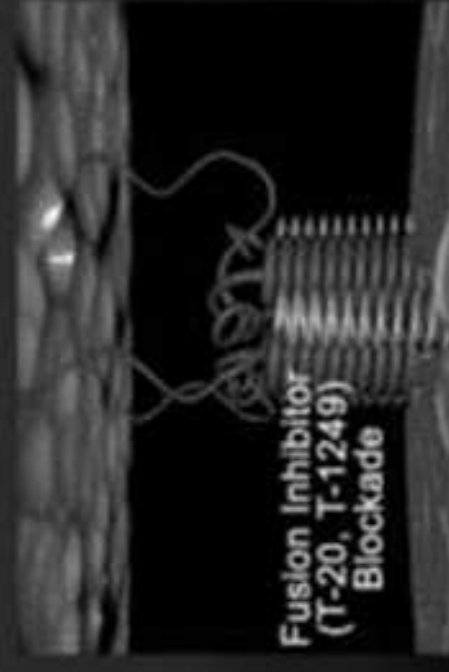


Source: DC Montelloni and JP Moore. Science 283:336, 1998.

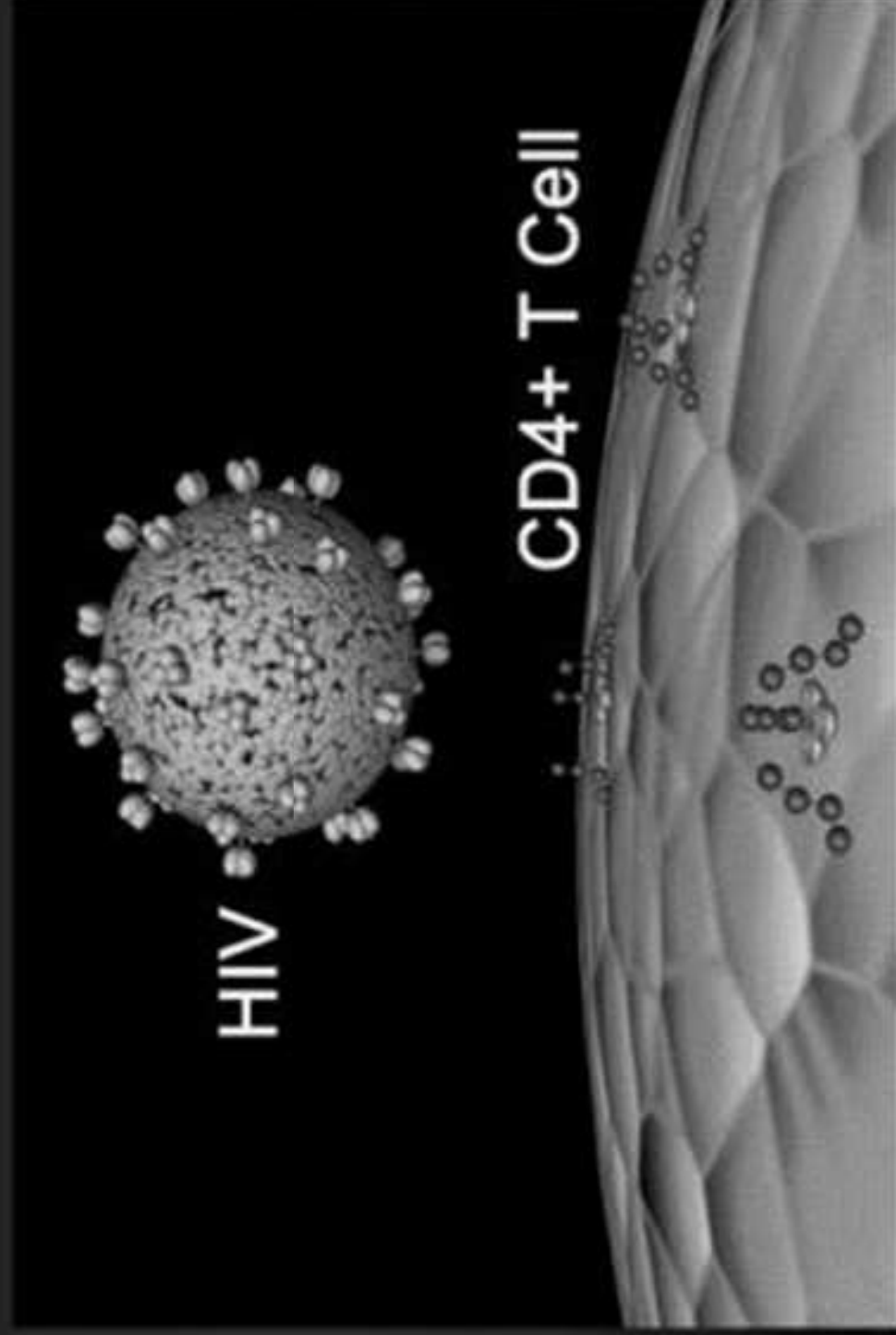
# C-Peptide Fusion Inhibition (T20, T1249)



+FI

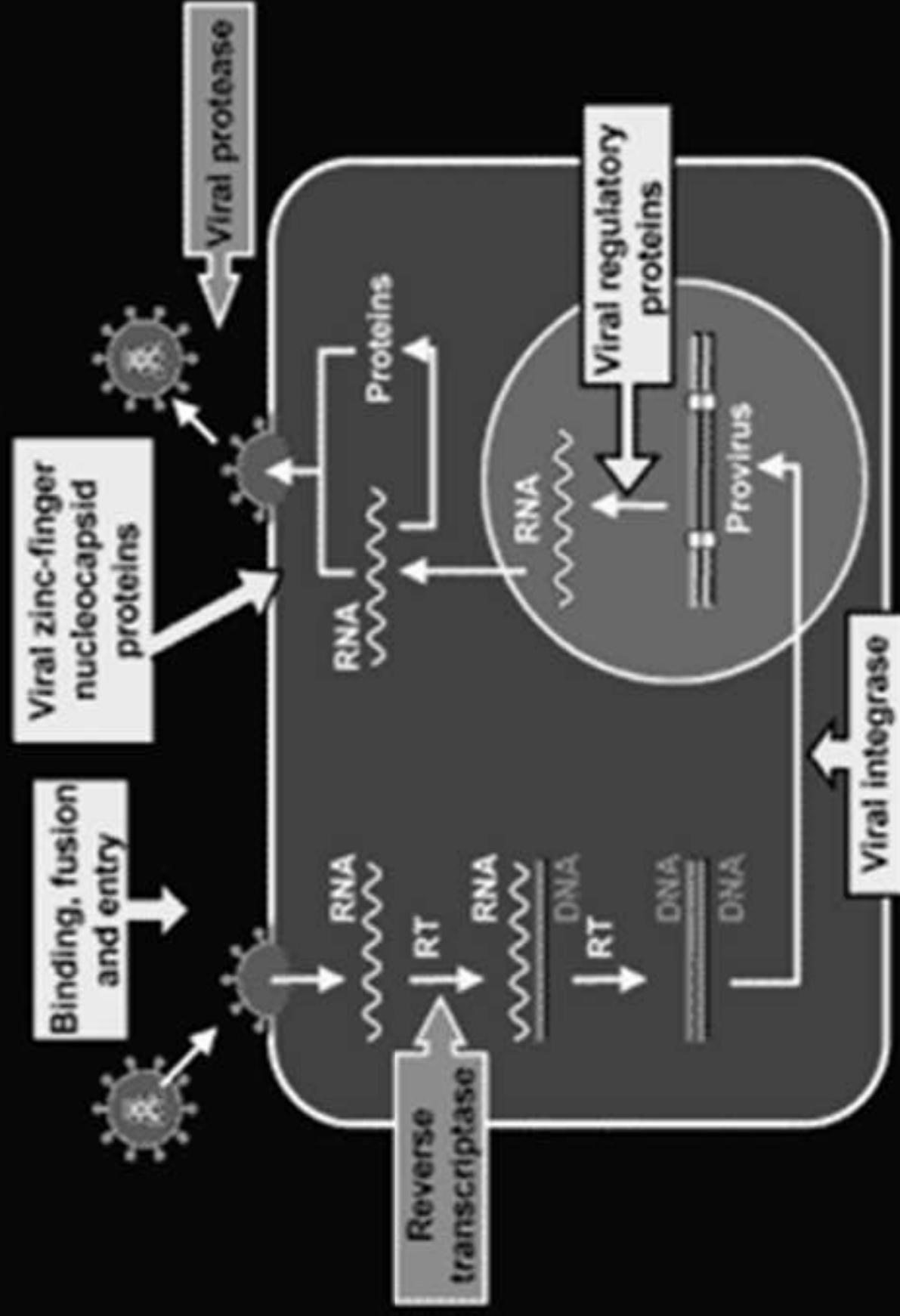


# HIV Attachment Inhibitors (gp120-CD4)

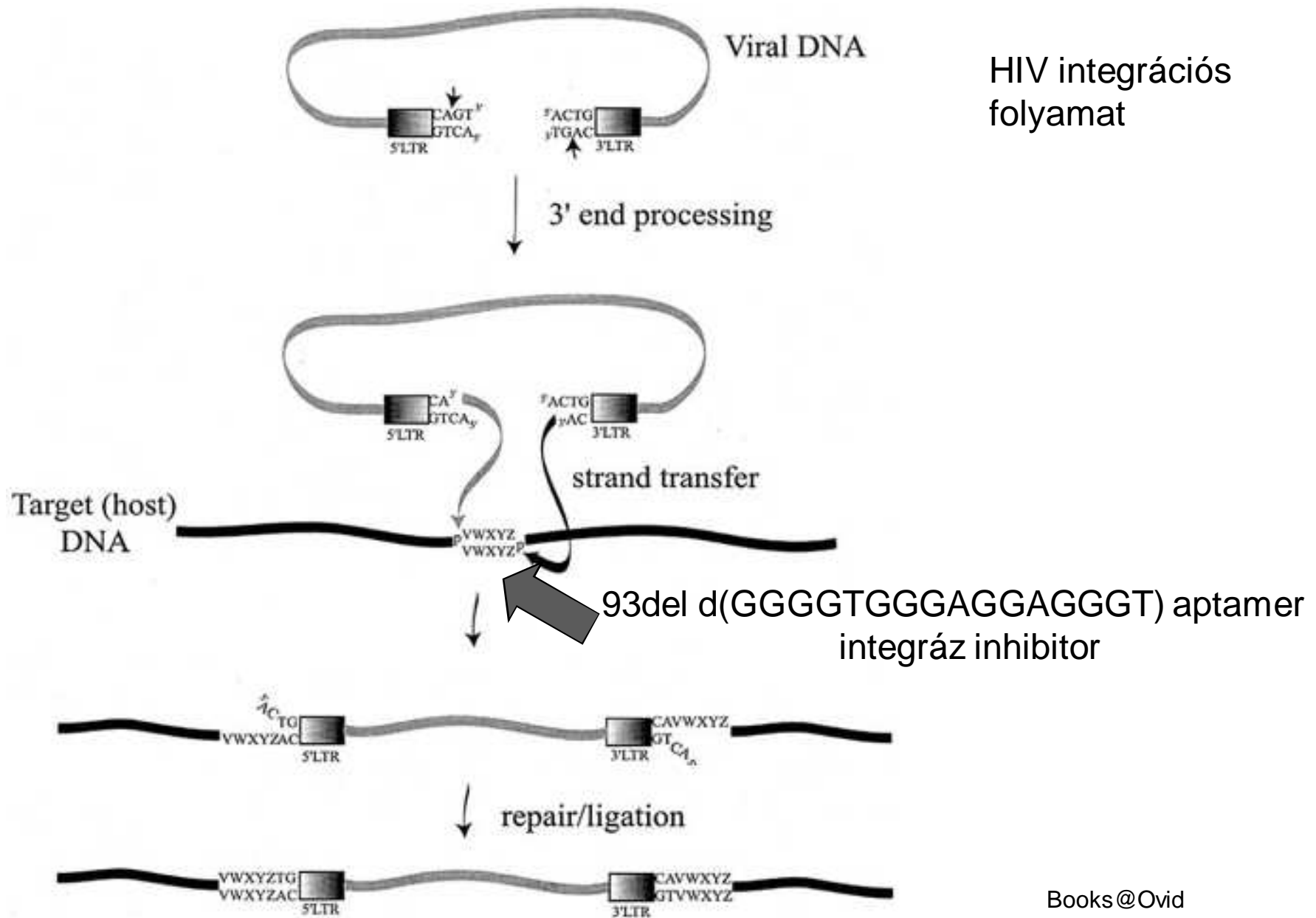


# HIV INTEGRÁZ GÁT LÓK

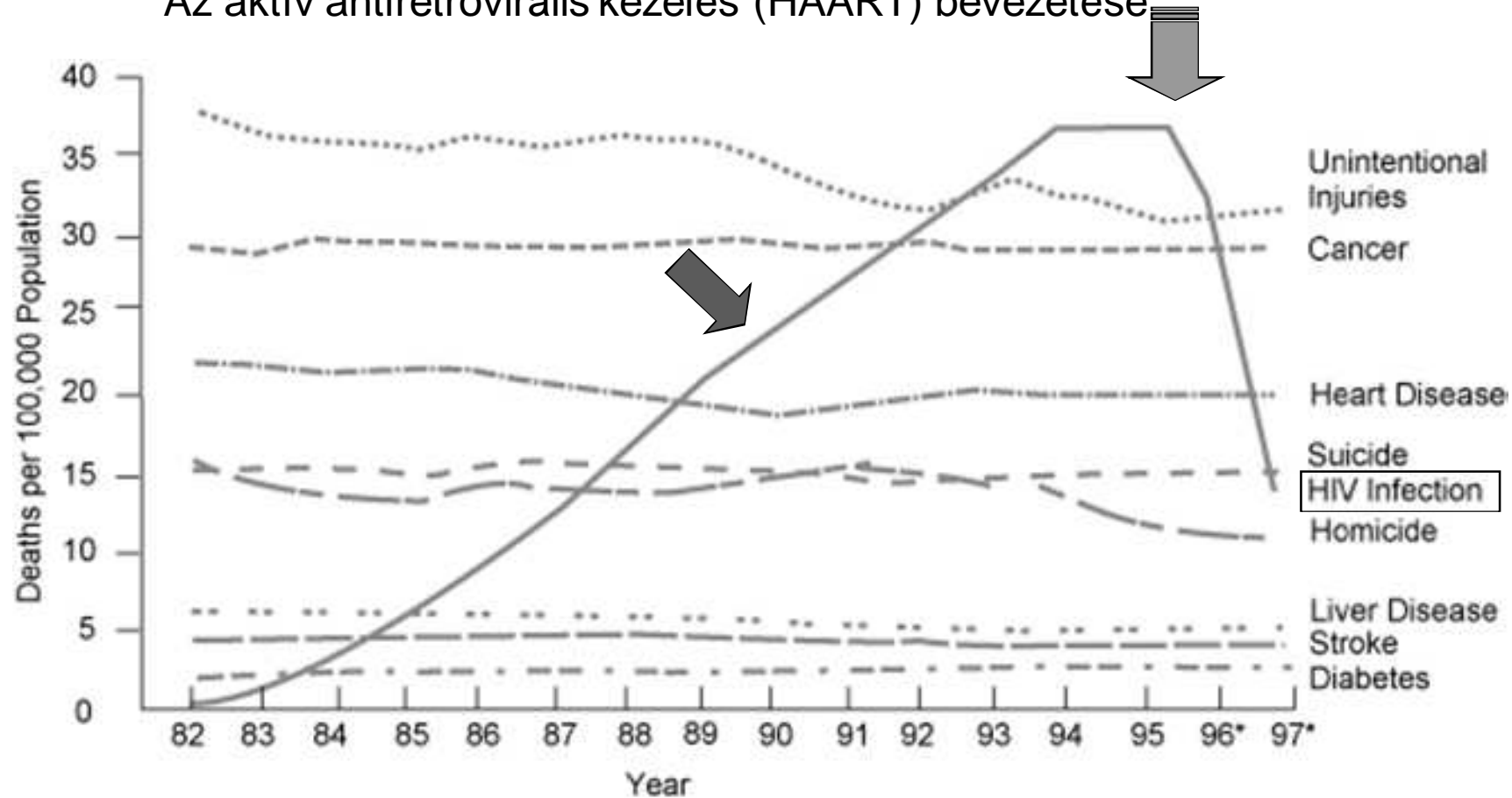
# Potential new targets



# HIV integrációs folyamat



Az aktív antiretrovirális kezelés (HAART) bevezetése



VEZETŐ HALÁLOKOK AZ USA-BAN