EUROGUIDELINES IN CENTRAL AND EASTERN EUROPE NETWORK GROUP

Antiretroviral Resistance

in the INSTI Era

AIDS VE CYBH DERNEĞİ 1998

Mechanisms of Resistance in Human Immunodeficiency Virus

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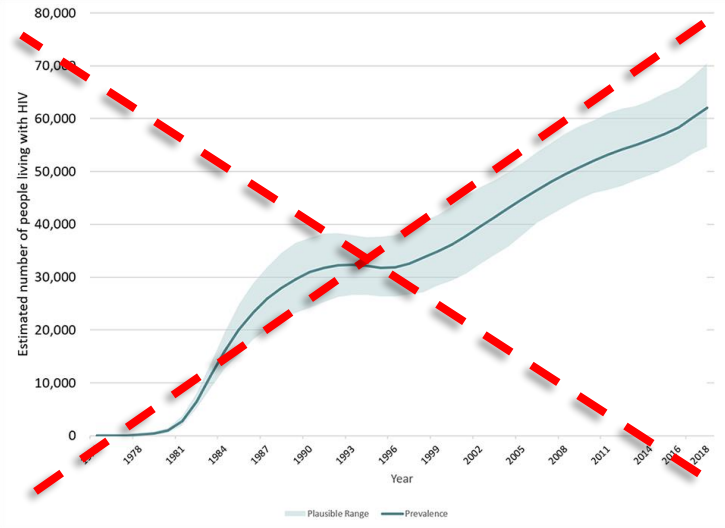
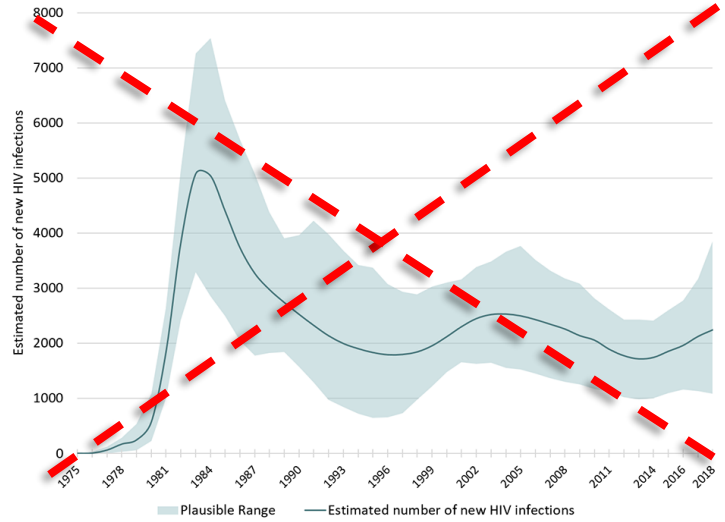
HIV drug resistance

Over the past decade, the world has witnessed an unprecedented increase in the use of antiretroviral therapy (ART), which has saved the lives of tens of millions of people living with HIV/AIDS. At the end of 2021, 28.7 million people, out of an estimated 38.4 million people living with HIV, were receiving ART globally.

Increased use of HIV medicines has been accompanied by the emergence of HIV drug resistance – the levels of which have steadily increased in recent years.

HIV drug resistance is caused by changes in the genetic structure of HIV that affect the ability of drugs to block the replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partly or fully inactive due to the emergence of drug-resistant virus strains. If not prevented, HIV drug resistance can jeopardize the efficacy of antiretroviral drugs, resulting in increased numbers of HIV infections and HIV-associated morbidity and mortality.





HIV drug resistance

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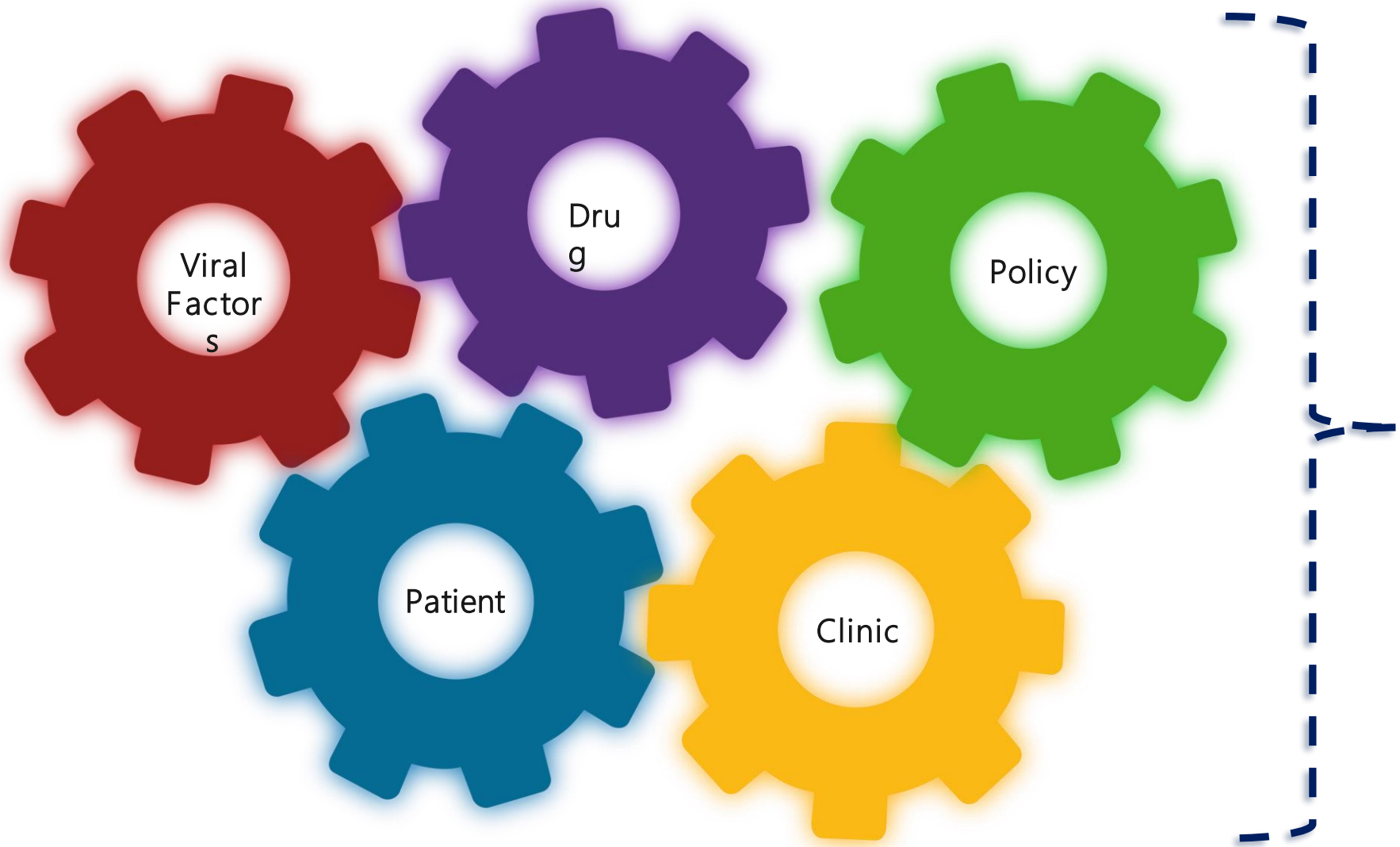
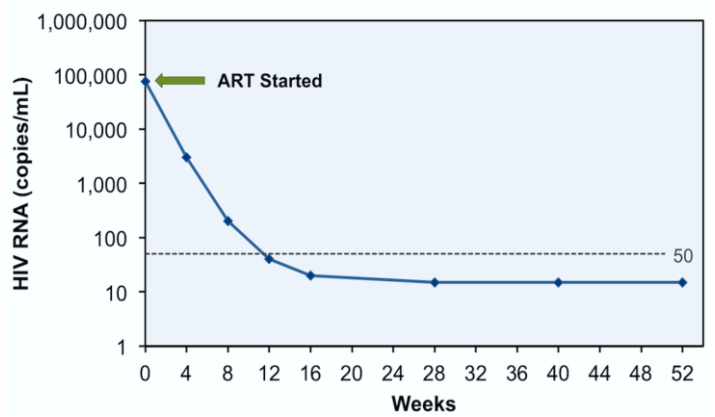
HIV Drug Resistance; Key Factors

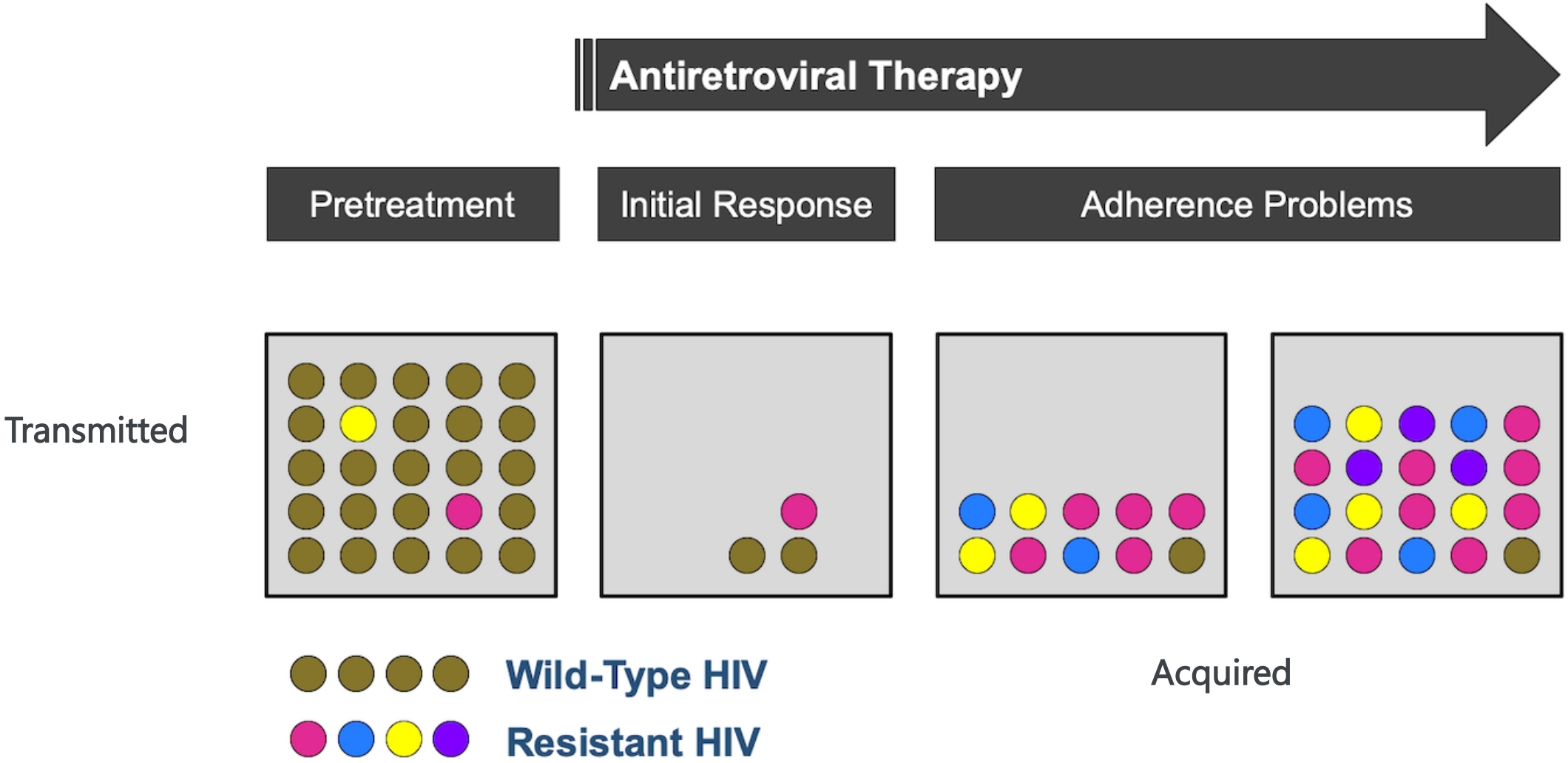


Main Goal

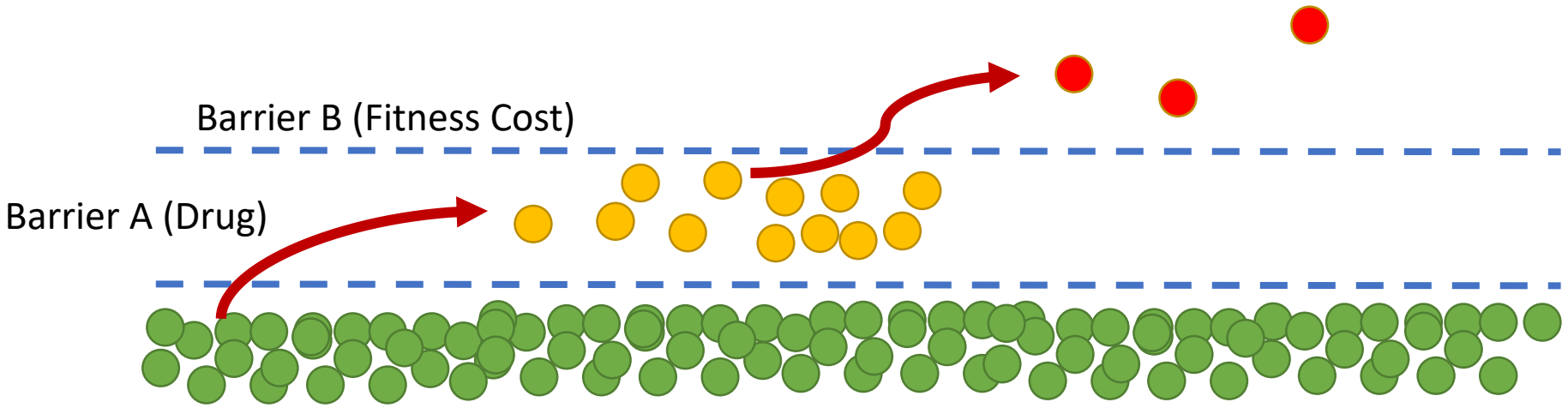


Main problem

HIV Drug Resistance, Basic Concepts



Selection of Mutants
Genetic Barrier & Fitness

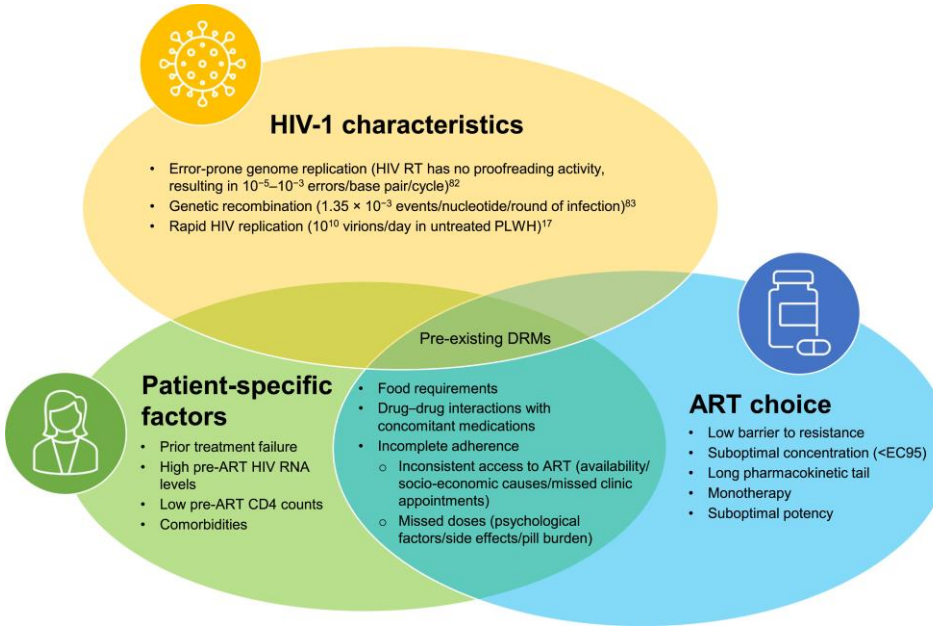


Wild Type

Mutant B
(COMPENSATORY mutation)

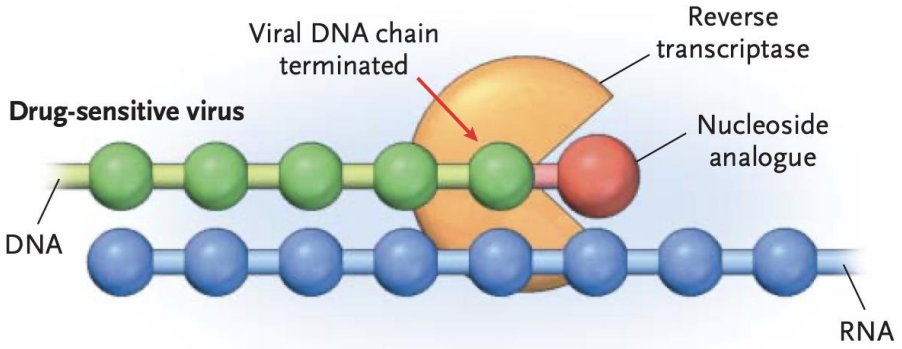
Fitness

Mutant A

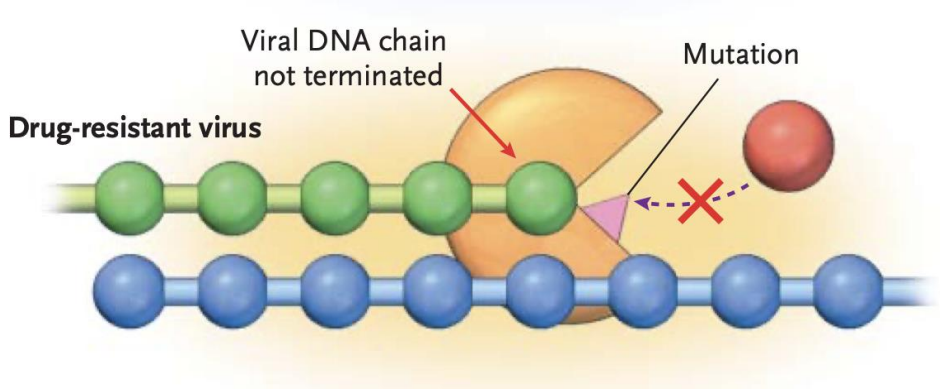


Mechanism of NRTI Resistance

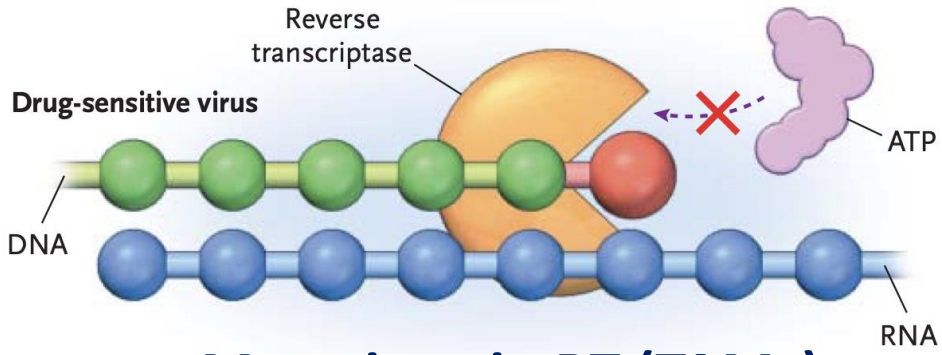
Resistance by Interference with the Incorporation of a Nucleoside Analogue



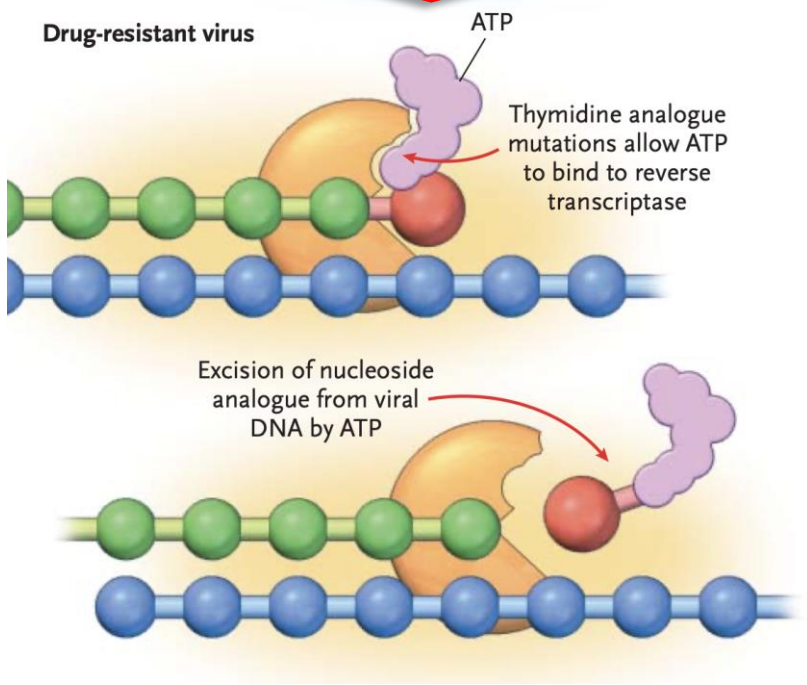
Mutations in RT



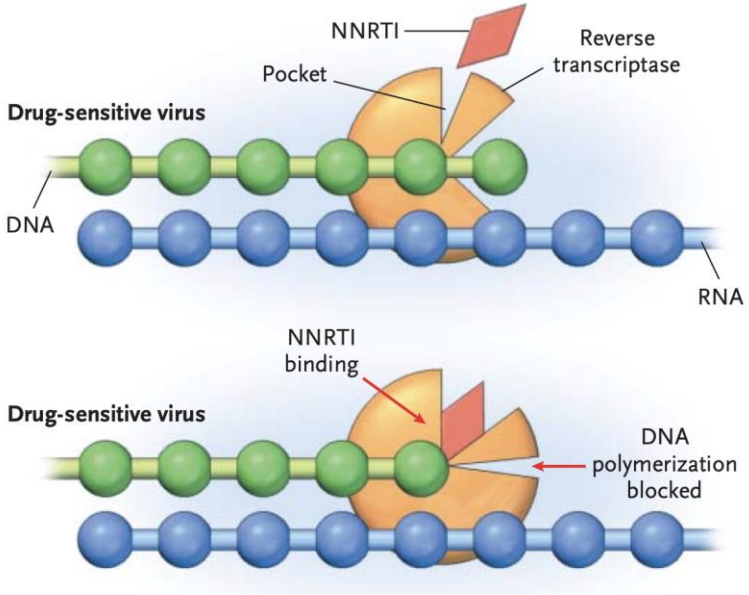
Resistance by ATP-Mediated Excision of the Nucleoside Analogue



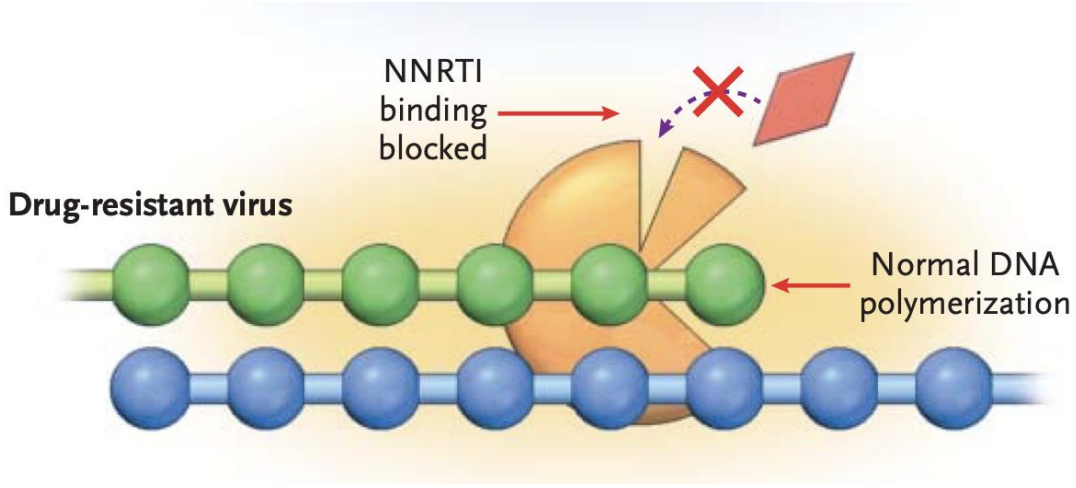
Mutations in RT (TAMs)



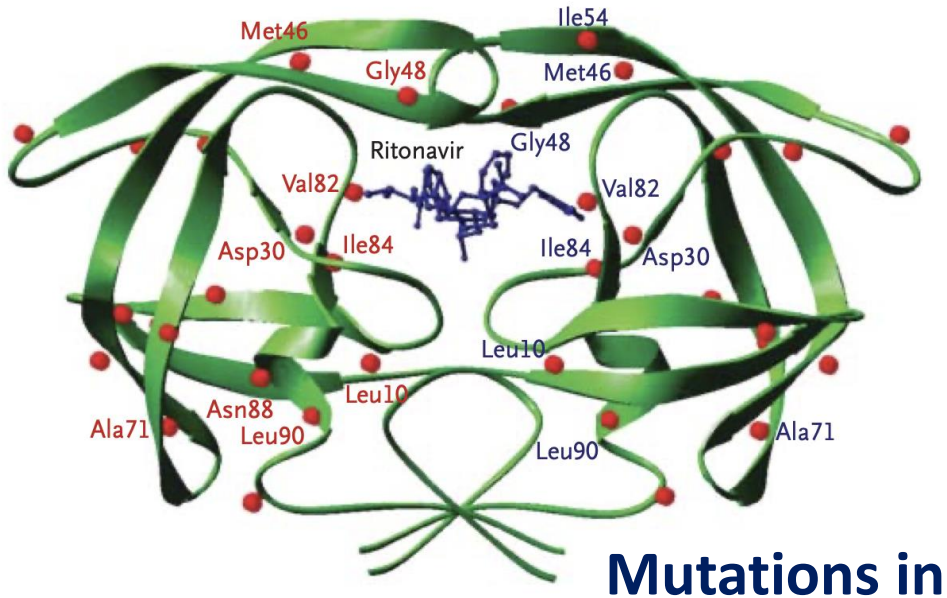
Mechanism of NNRTI Resistance



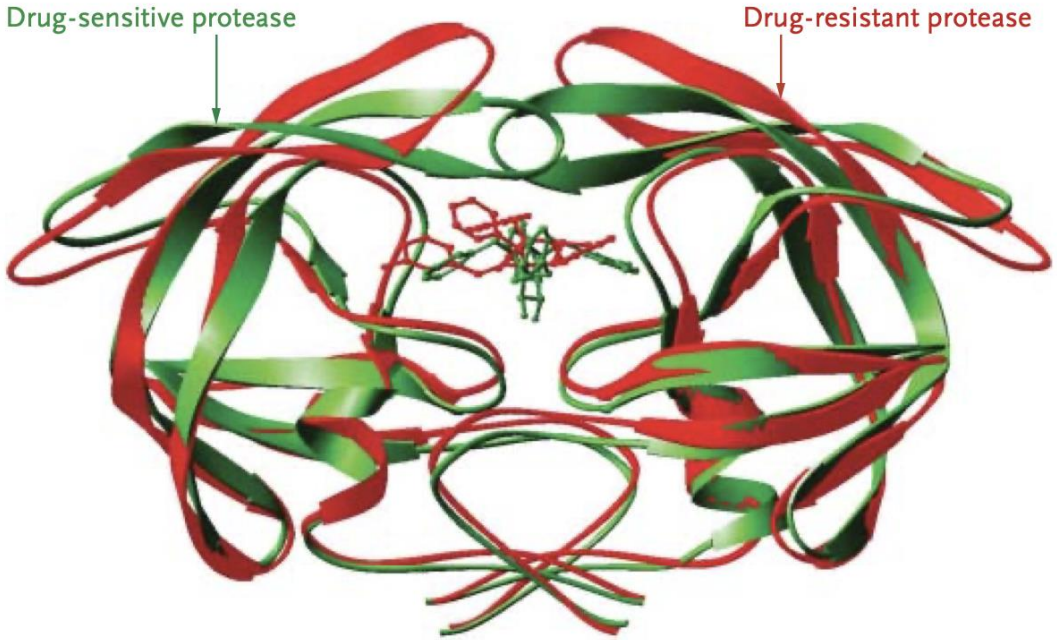
Mutations in RT



Mechanism of PI Resistance



Mutations in PI



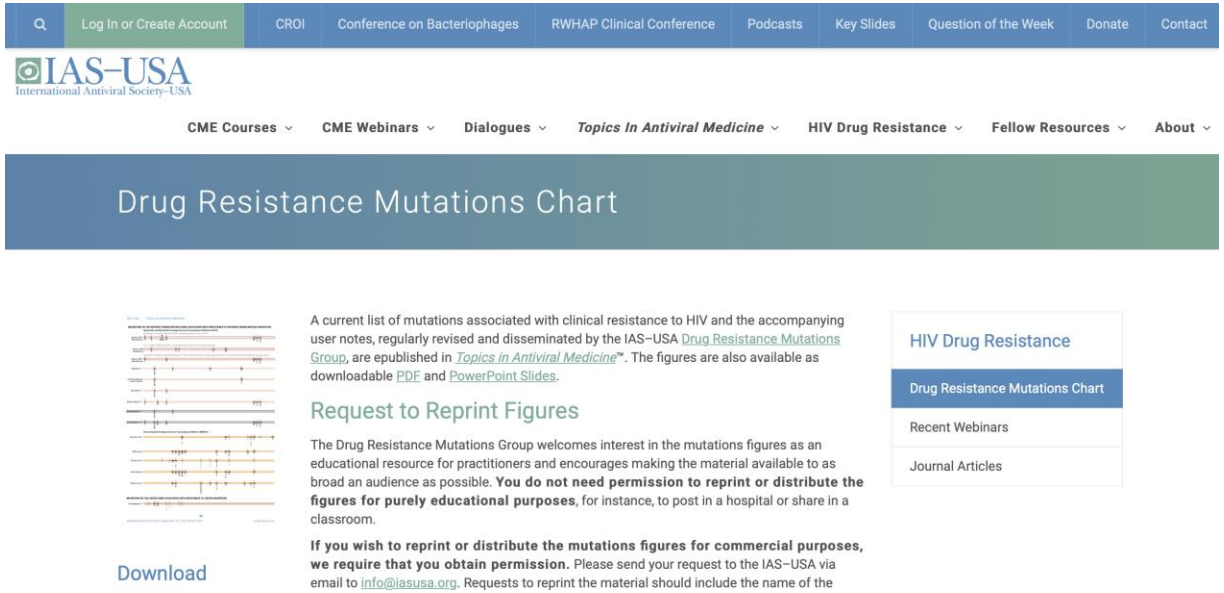
New Classes, New Problems

- Fostemsavir-CD4 attachment inhibitor
  - A study published in 2020 analyzed HIV-1 *env* gp120 sequences from both ART-naïve and ART-treated patients and identified several genomic positions with mutations associated with decreased susceptibility to fostemsavir, however, the BRIGHTE trial did not find consistent associations between virologic failure and gp120 substitutions

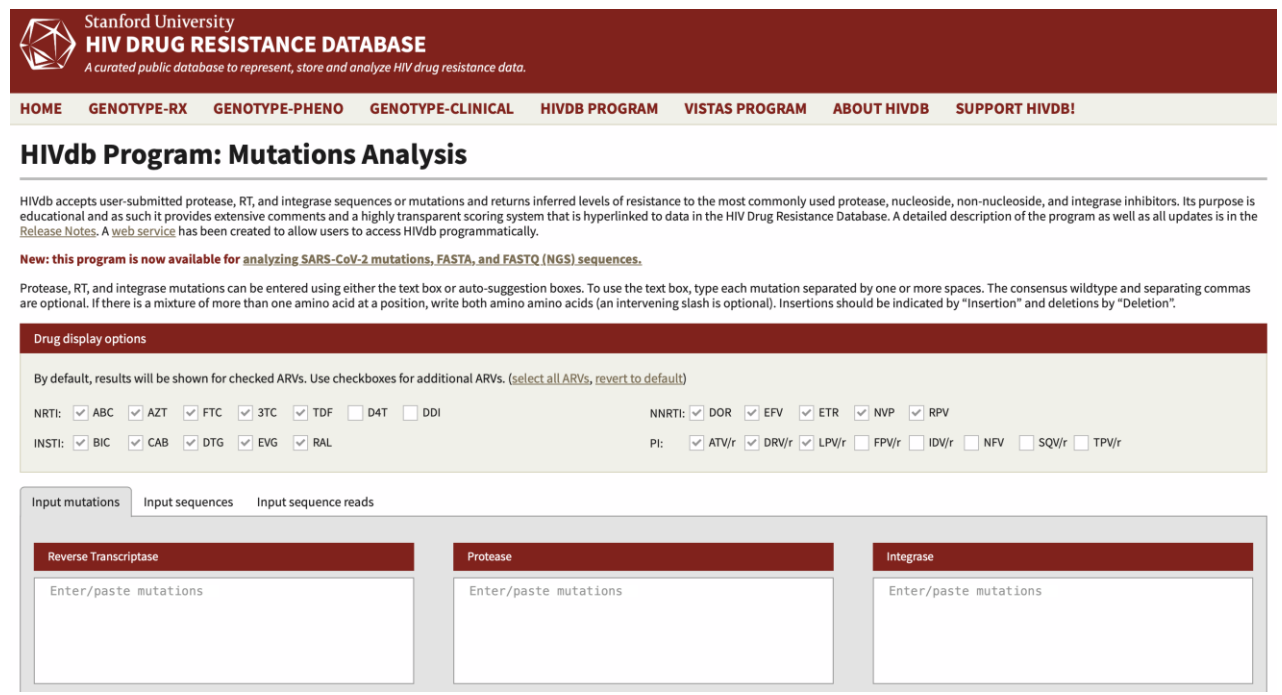
- Ibalizumab- post-attachment inhibitor
  - Resistance to ibalizumab is conferred by decreased viral expression of specific binding sites in the HIV gp120 envelope protein. This mechanism of resistance was observed in the TMB-301 study for 8 out of 10 patients who had virologic failure or rebound at week 25 and showed a lower degree of susceptibility to ibalizumab than at baseline

- Lenacapavir-long-acting capsid inhibitor
  - Studies showed viral escape strategies of M66I and Q67H, a highly LEN-resistant but fitness-impaired HIV-1 mutant.

https://www.iasusa.org/hiv-drug-resistance/hiv-drug-resistance-mutations/



https://hivdb.stanford.edu/hivdb/by-patterns/




ART resistance can lead to cases that are difficult to manage even in the
TASTE era...