

Mechanisms of Resistance in Human Immunodeficiency Virus

Dr. Mert A. Kuşkucu

Koç University School of Medicine,

Department of Medical Microbiology

Koç University İşbank Center for Infectious Diseases

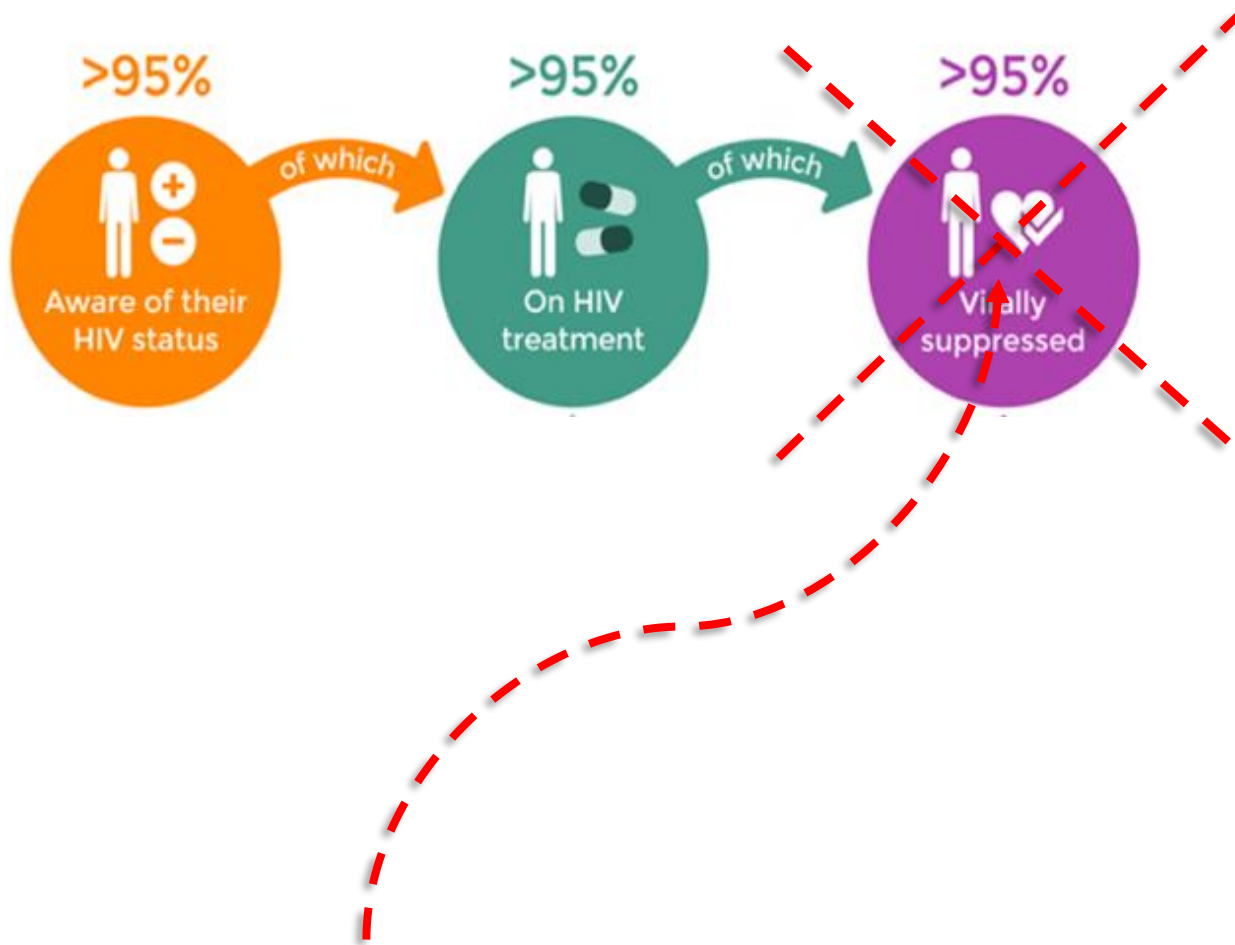
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HIV drug resistance

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.

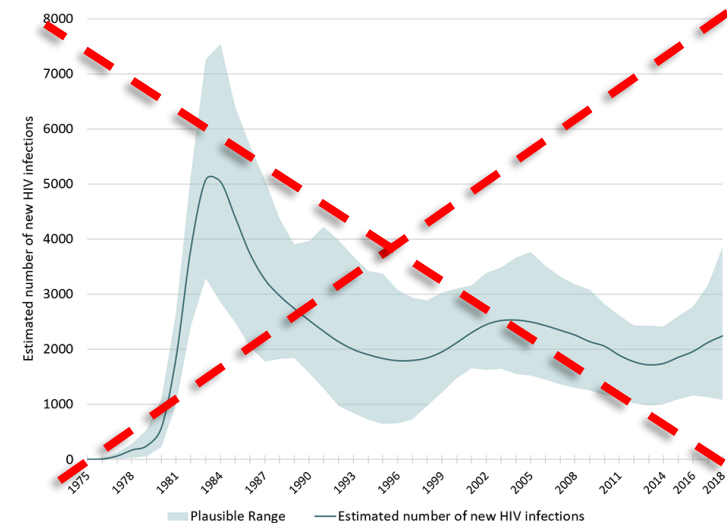
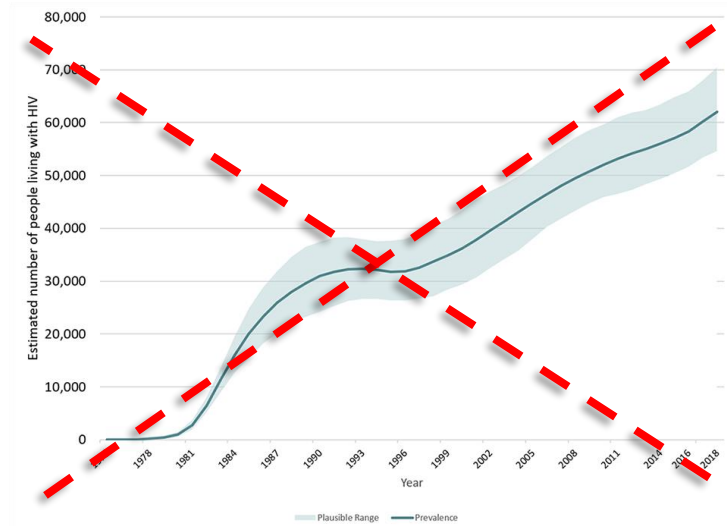
Increased use of HIV medicines has been accompanied by the emergence of HIV drug resistance – the levels of which have steadily increased in recent years.

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

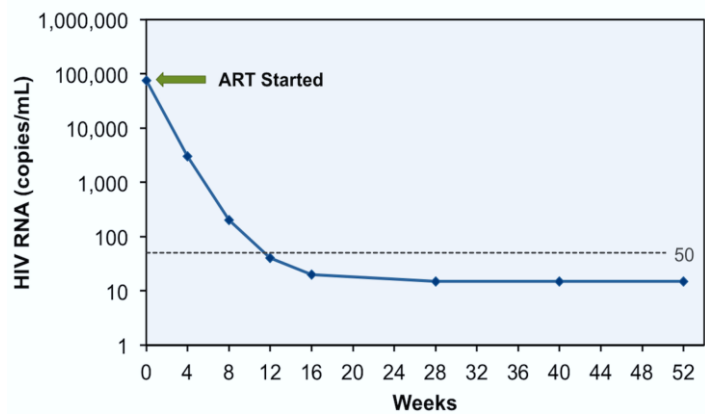
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HIV Drug Resistance; Key Factors



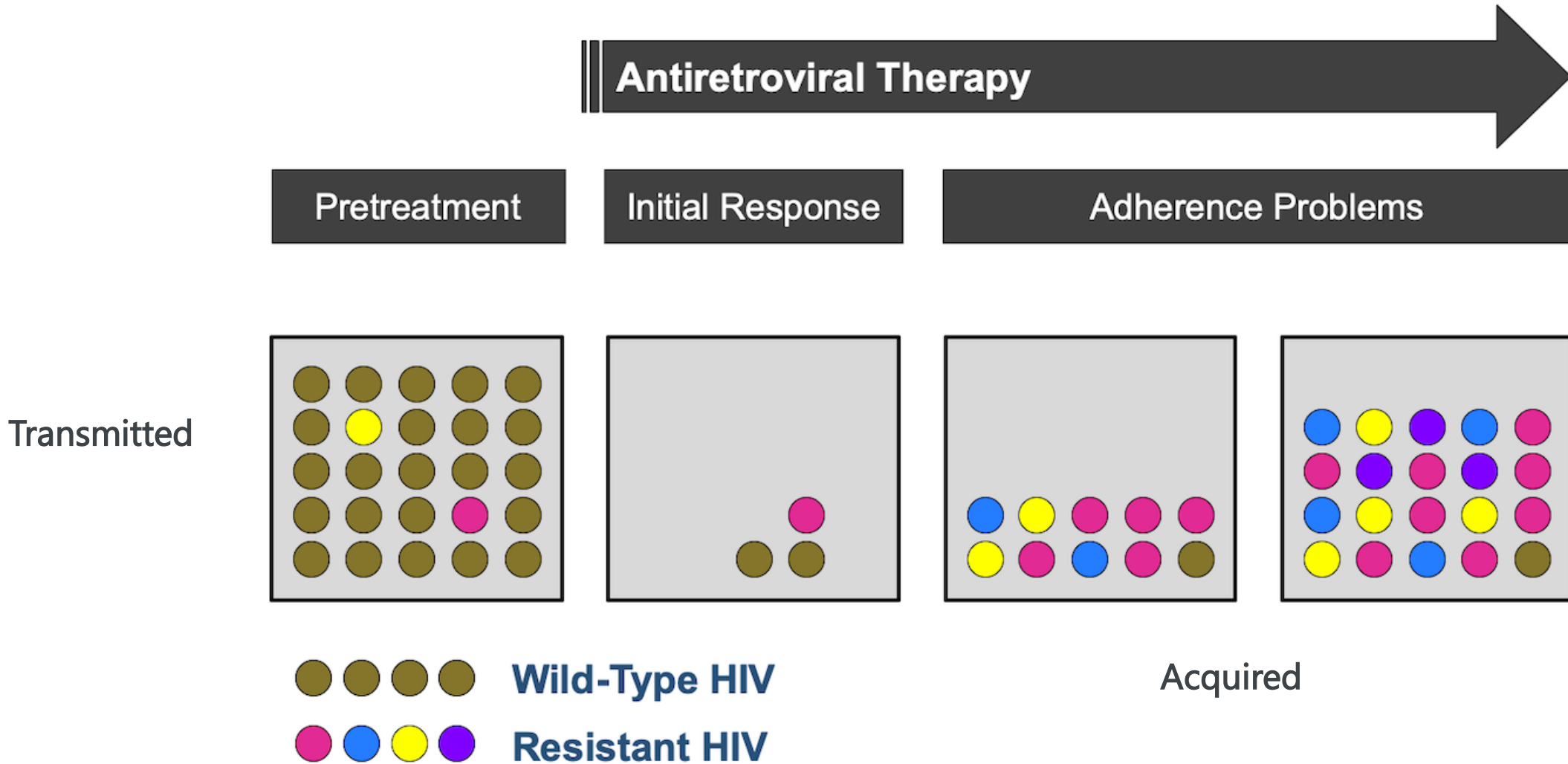
Main Goal



Main problem

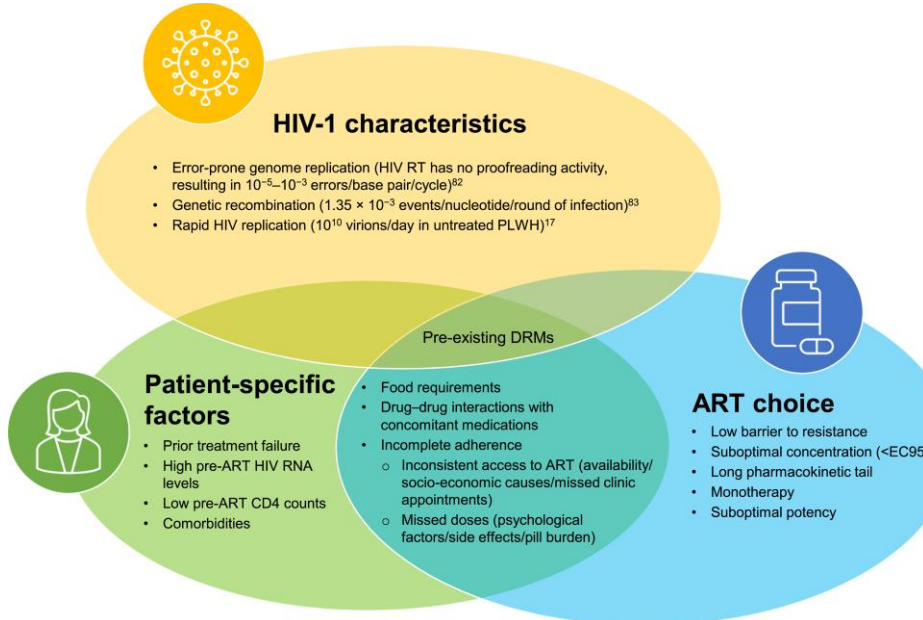
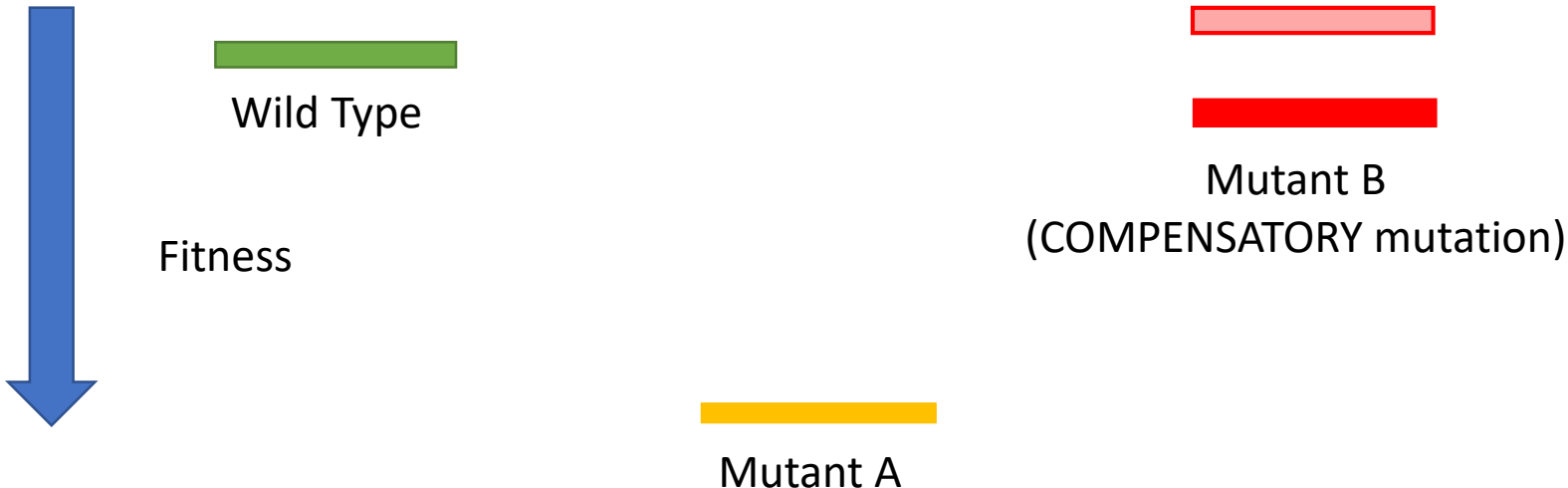
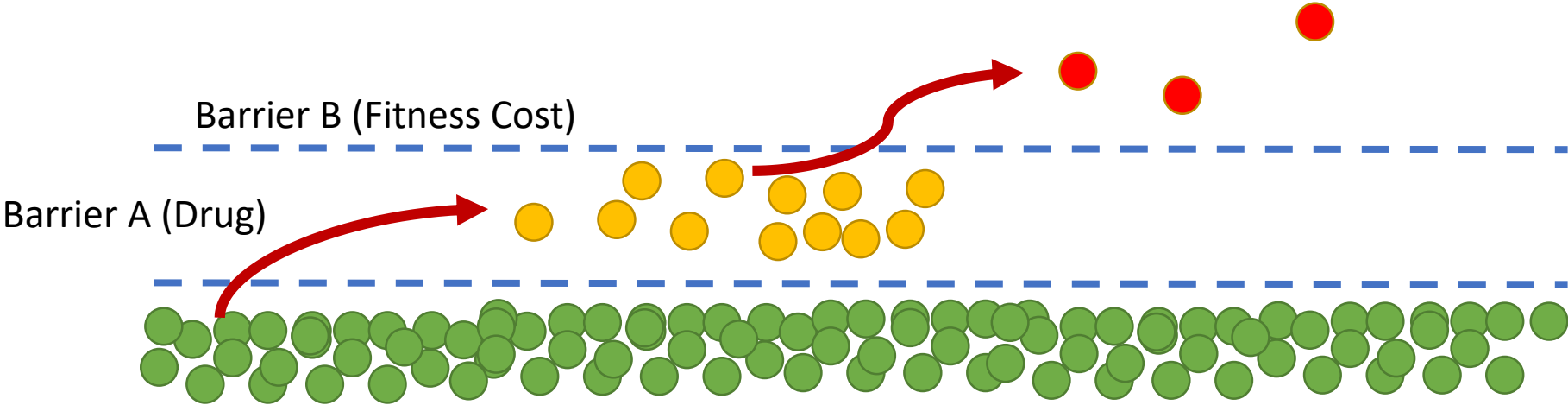


HIV Drug Resistance, Basic Concepts



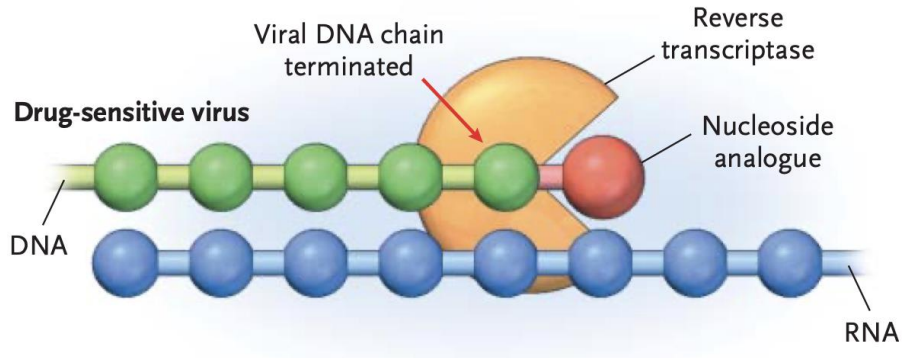
Selection of Mutants

Genetic Barrier & Fitness

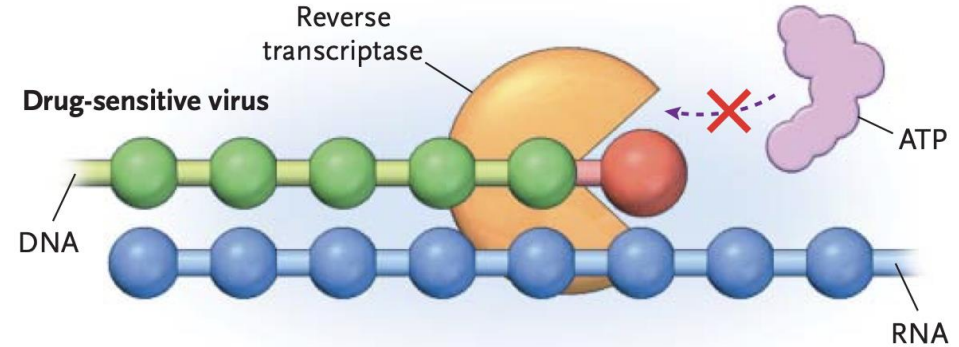


Mechanism of NRTI Resistance

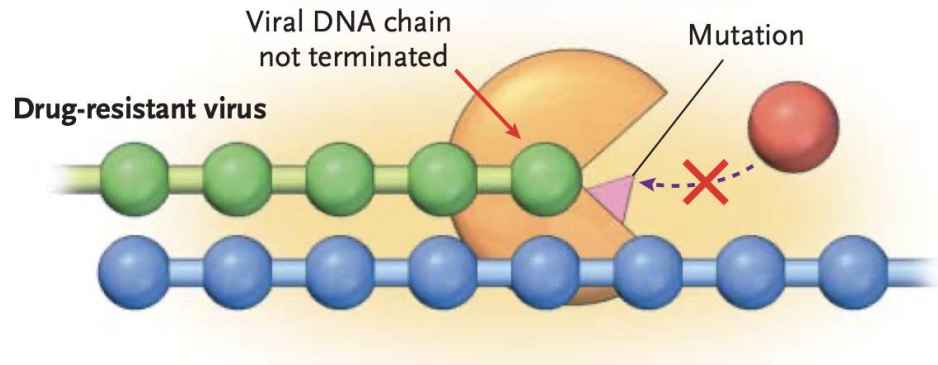
Resistance by Interference with the Incorporation of a Nucleoside Analogue



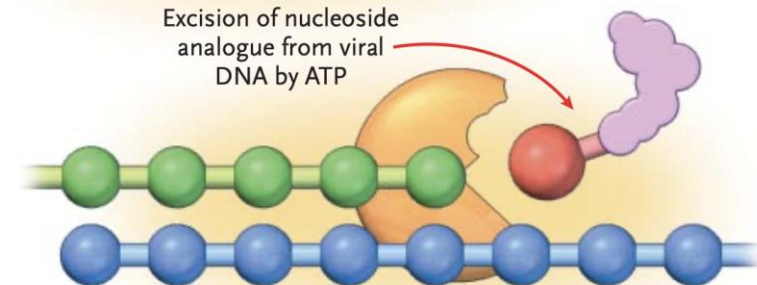
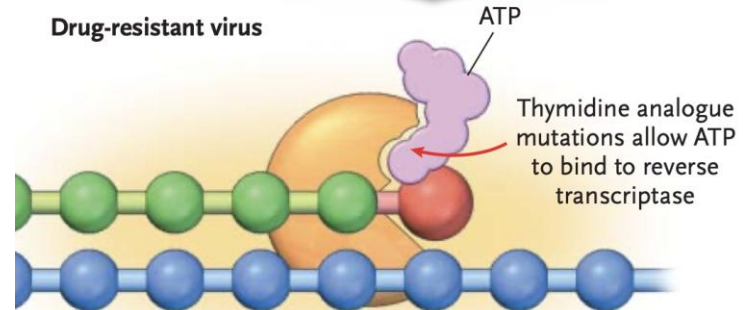
Resistance by ATP-Mediated Excision of the Nucleoside Analogue



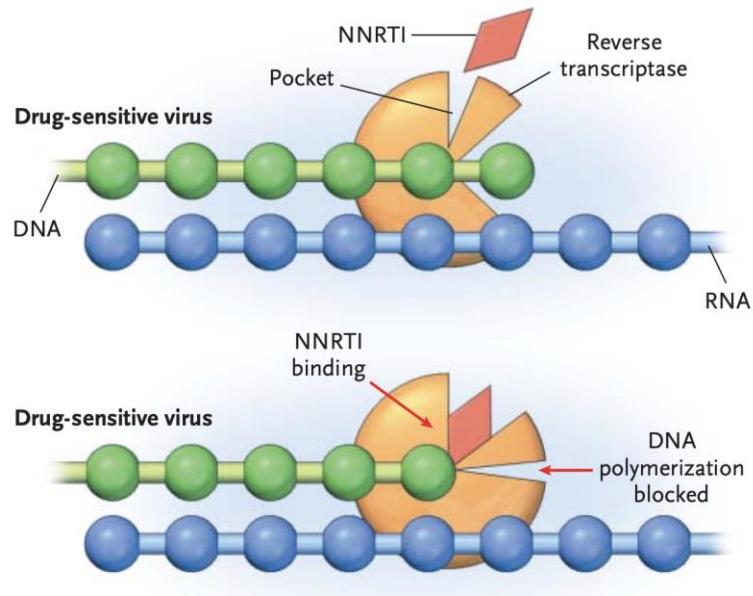
Mutations in RT



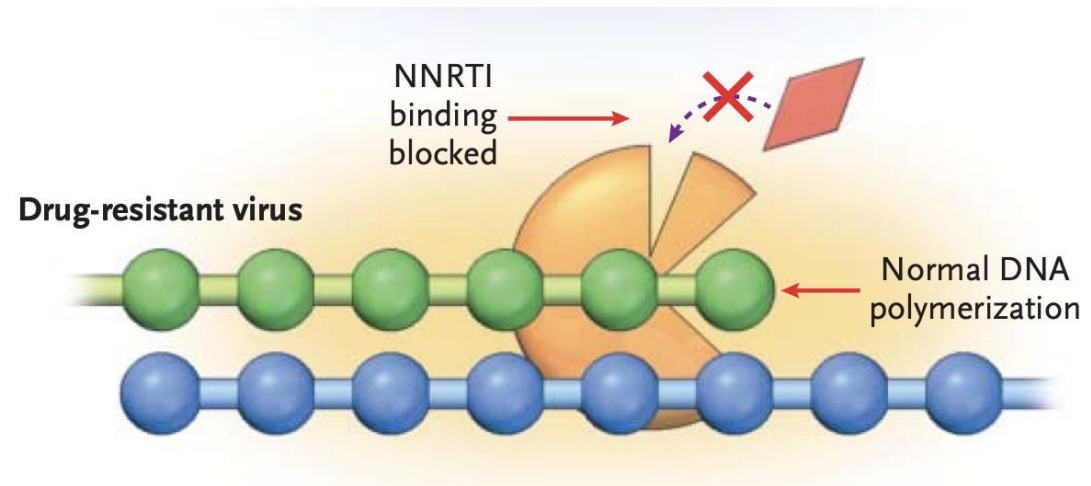
Mutations in RT (TAMs)



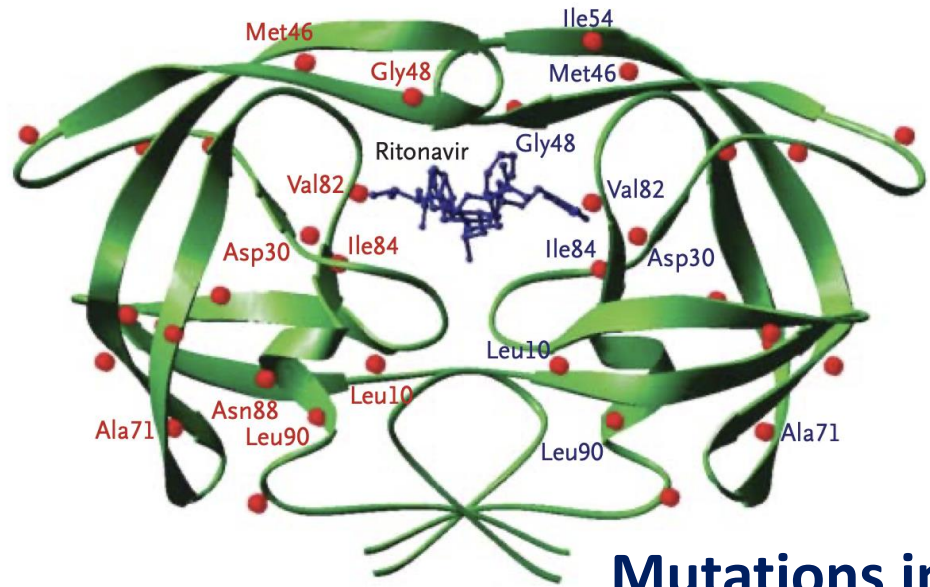
Mechanism of NNRTI Resistance



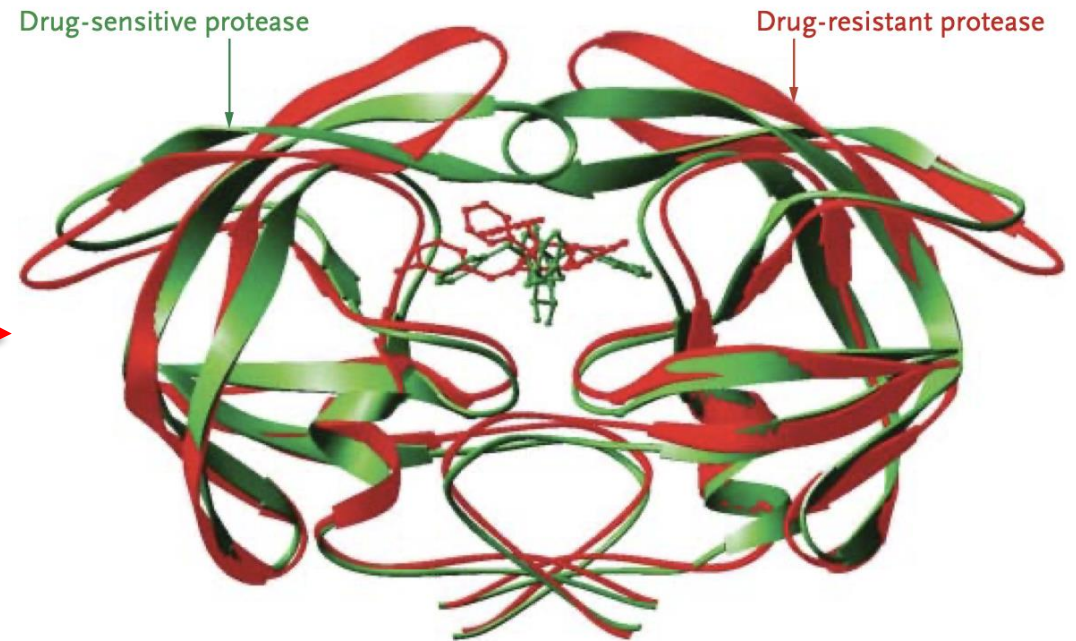
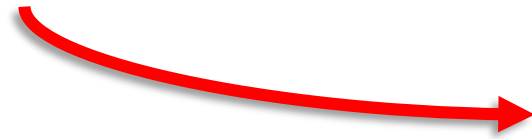
Mutations in RT



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 BRIGHTTE trial did not find consistent associations between virologic failure and gp120 substitutions

- **Ibalizumab- post-attachment inhibitor**

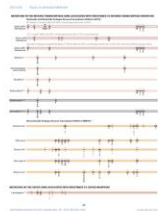
- Resistance to ibalizumab is conferred by decreased viral expression of specific binding sites in the HIV gp120 envelope protein. This mechanism of resistance was observed in the TMB-301 study for 8 out of 10 patients who had virologic failure or rebound at week 25 and showed a lower degree of susceptibility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



Drug Resistance Mutations Chart



A current list of mutations associated with clinical resistance to HIV and the accompanying user notes, regularly revised and disseminated by the IAS-USA Drug Resistance Mutations Group, are published in *Topics In Antiviral Medicine*. The figures are also available as downloadable PDF and PowerPoint Slides.

Request to Reprint Figures

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages making the material available to as broad an audience as possible. **You do not need permission to reprint or distribute the figures for purely educational purposes**, for instance, to post in a hospital or share in a classroom.

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HIV Drug Resistance

Drug Resistance Mutations Chart

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HIV DRUG RESISTANCE DATABASE

A curated public database to represent, store and analyze HIV drug resistance data.

HIVdb Program: Mutations Analysis

HIVdb accepts user-submitted protease, RT, and integrase sequences or mutations and returns inferred levels of resistance to the most commonly used protease, nucleoside, non-nucleoside, and integrase inhibitors. Its purpose is educational and as such it provides extensive comments and a highly transparent scoring system that is hyperlinked to data in the HIV Drug Resistance Database. A detailed description of the program as well as all updates is in the [Release Notes](#). A [web service](#) has been created to allow users to access HIVdb programmatically.

New: this program is now available for analyzing SARS-CoV-2 mutations, FASTA, and FASTQ (NGS) sequences.

Protease, RT, and integrase mutations can be entered using either the text box or auto-suggestion boxes. To use the text box, type each mutation separated by one or more spaces. The consensus wildtype and separating commas are optional. If there is a mixture of more than one amino acid at a position, write both amino acids (an intervening slash is optional). Insertions should be indicated by "Insertion" and deletions by "Deletion".

Drug display options

By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. (select all ARVs, revert to default)

NRTI: ABC AZT FTC 3TC TDF D4T DDI

NNRTI: DOR EFV ETR NVP RPV

INSTI: BIC CAB DTG EVG RAL

PI: ATV/r DRV/r LPV/r FPV/r IDV/r NFV SQV/r TPV/r

Input mutations

Input sequences

Input sequence reads

Reverse Transcriptase

Enter/paste mutations

Protease

Enter/paste mutations

Integrase

Enter/paste mutations



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