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Medical-biological groundwork of HIV's resistance

GENERAL MEDICINE FACULTY

044-1,2 GROUP

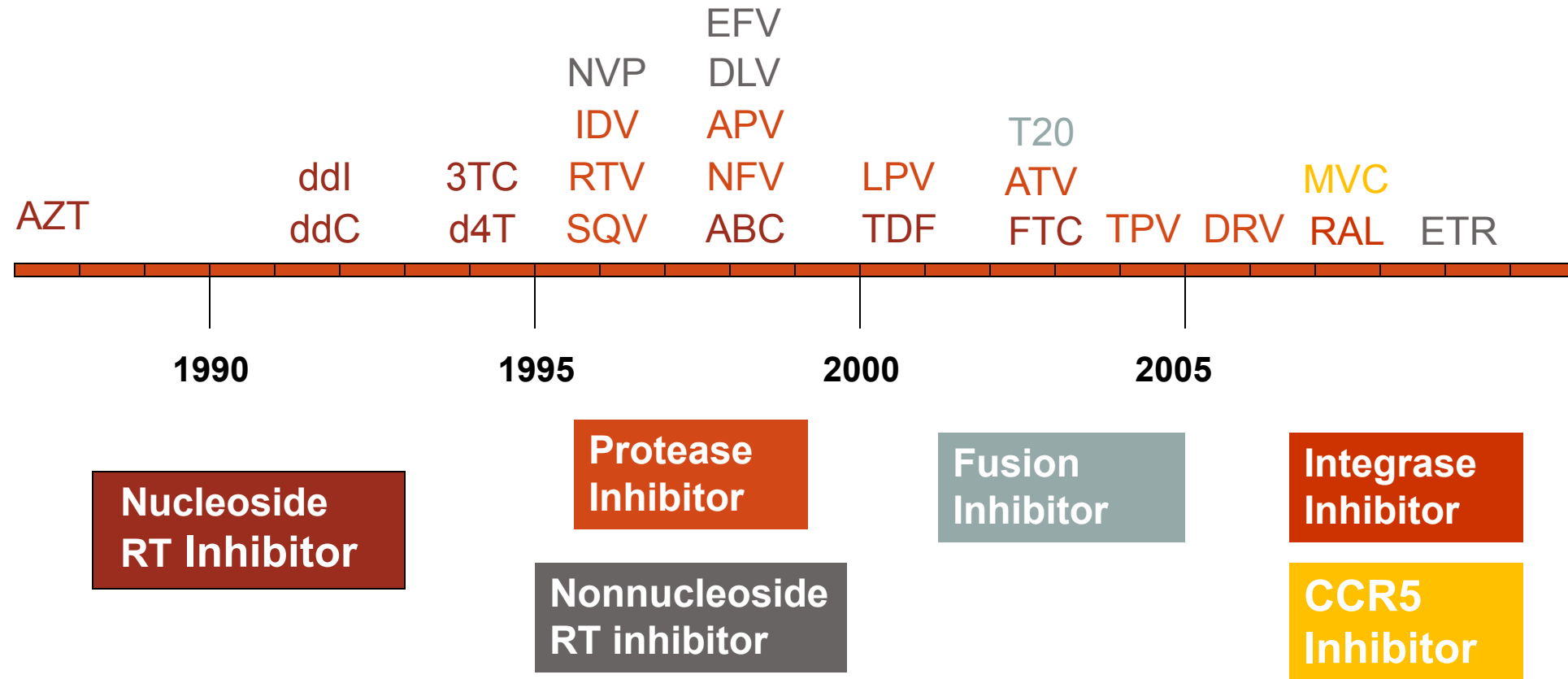
Key facts:

- HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2015, 1.1 (940 000–1.3 million) million people died from HIV-related causes globally.
- There is no cure for HIV infection. However, effective antiretroviral (ARV) drugs can control the virus and help prevent transmission so that people with HIV, and those at substantial risk, can enjoy healthy, long and productive lives.

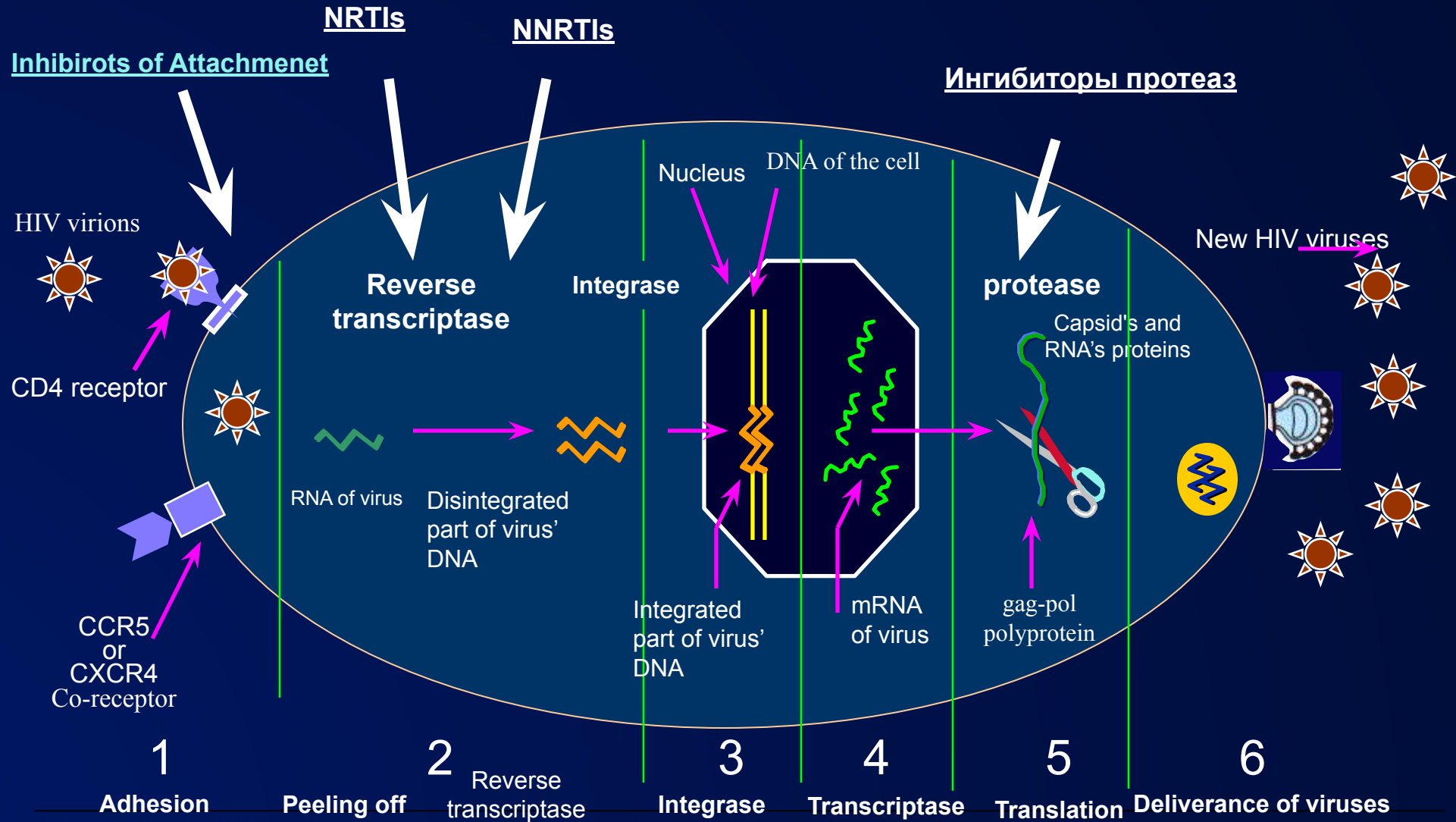
What are antiretroviral drugs?

Antiretroviral drugs are used in the treatment and prevention of HIV infection. They fight HIV by stopping or interfering with the reproduction of the virus in the body, reducing the amount of virus in the body.

Antiretroviral Inhibitors (ARVs)



ВИЧ-репликация и места воздействия АРВ препаратов



Antiviral Drug
Resistance

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graph TD; A[Antiviral Drug Resistance] --> B[Its Causes]; B --> C[Biological causes]; B --> D[Medical causes];
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Its Causes

Biological
causes

Medical
causes

Evolution of Viral Mutations

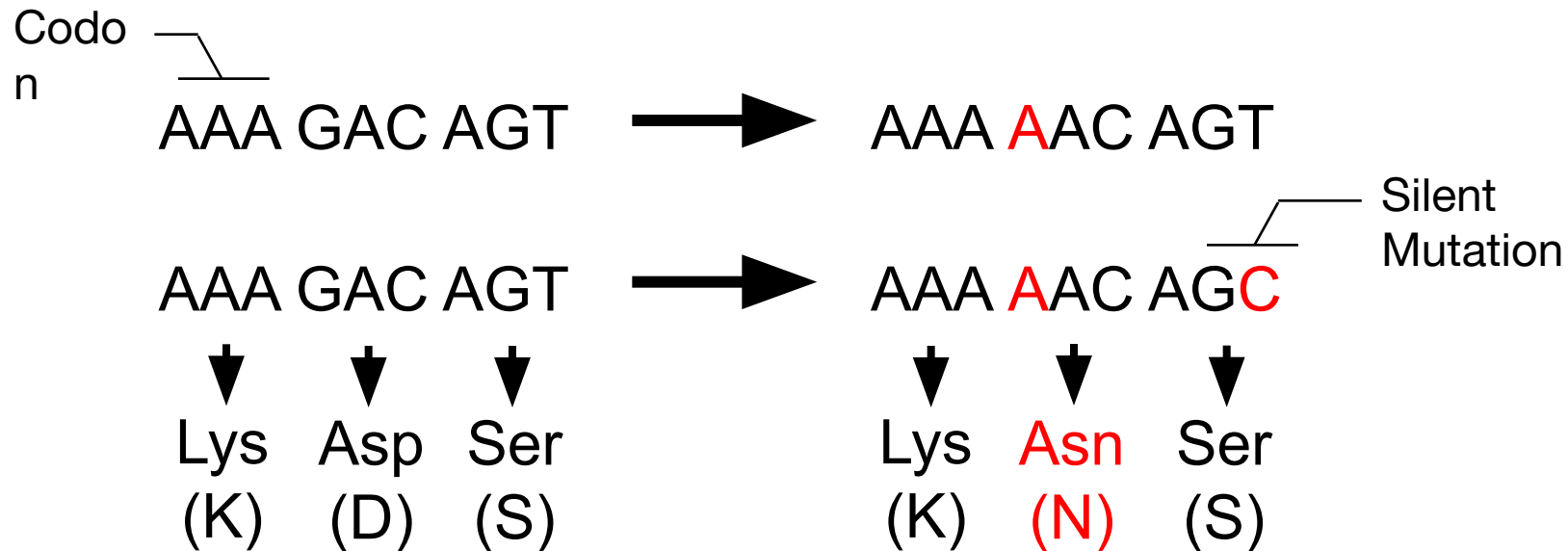
- Mutations arise because HIV-1 RT makes spontaneous errors (1 in 10^4)
- HIV-1 genome is 10 000 (10^4) bases long, therefore 1 error each time the genome is replicated
- Production of virus = 10^9 to 10^{10} virions per day → quasispecies
- Every possible mutation present in quasispecies before ARV therapy

Biological causes

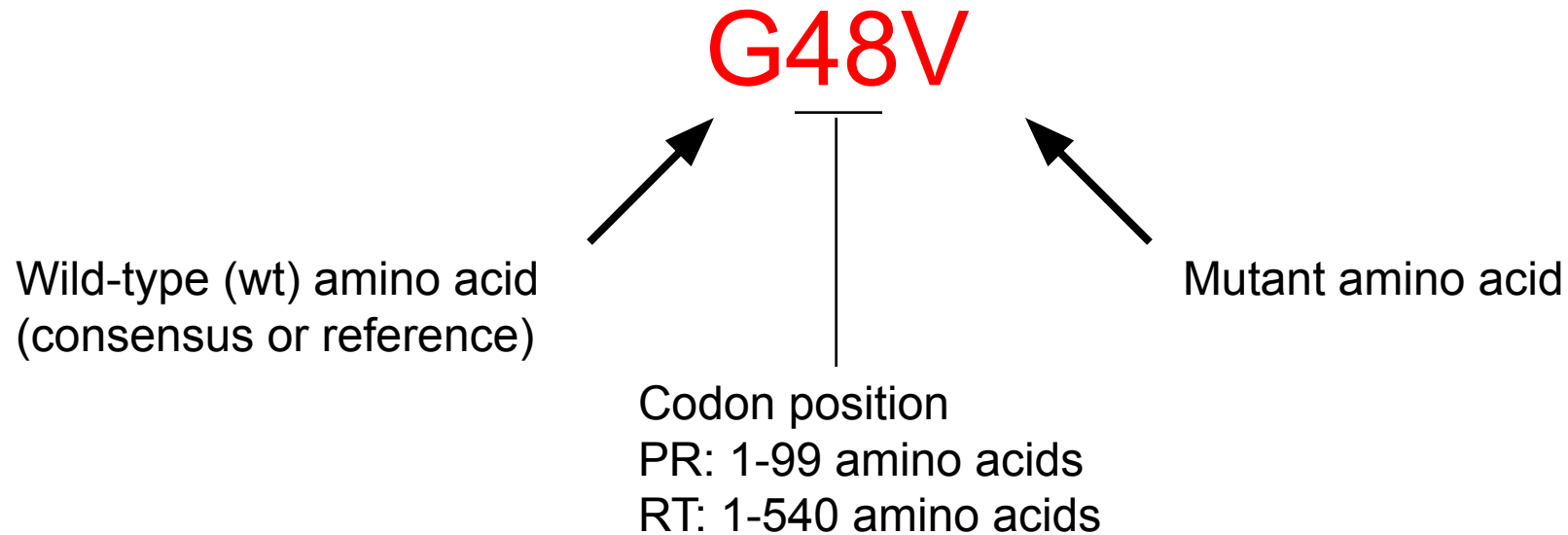
Mutation

Molecular definition: change in nucleic acid sequence compared to a reference sequence

Biological definition: change in nucleic acid sequence that results in a change in structure or function of the nucleic acid or a resulting protein



Mutational Nomenclature



L10L/I (mix of wt and mutant)

V82A/F (mix of 2 mutants)

Effect of Nucleotide Changes

Nucleotide changes (mutations)



Changes in amino acid sequence of a protein



Changes in structure/function of the protein (e.g. PR or RT)



Changes in ability of drug to inhibit target enzyme (resistance)

Types of Mutations

Polymorphisms

- Naturally occurring mutations, not selected by drugs (but can influence susceptibility)

“Primary” mutations

- Directly affect drug binding, present near active site
- Appear first in pathway to resistance
- Not present in virus not exposed to drug pressure

“Secondary” mutations

- Compensate for fitness defects
- Do not usually confer resistance on their own but modulate susceptibility
- May include polymorphisms that are found more frequently in resistant viruses

HIV Drug Resistance is Inevitable

HIV DR is an inevitable consequence of ART, influenced by:

- Ability of regimens to suppress replication completely
- Adherence and tolerability of regimens
- "Genetic barrier" to resistance
- Relative fitness of resistant variant(s)
- Pharmacokinetics (IQ)
- Availability/continuity of drug supply
- Removal of barriers to access to care

Therefore, efforts to minimize HIVDR should be focused on these factors

Medical factors in DR's emergence

Treatment with <3 drugs

Inappropriate selection of drugs

Adding one drug to a failing regimen

Interruption of treatment (even for a few days)

Prolonging a failing regimen



Systematic Medical factors in DR's emergence

Limited number of regimens

Trained personnel, low turnover

Supervision and monitoring

Adequate lab services

Drug supply and delivery systems



Caused by patients' negligence factors in DR's emergence

Adherence to treatment regimen

Avoiding interruption of treatment, even if only a few days

Regular follow-up (going to clinic)

Staying on uninterrupted first-line ART as long as possible

Caused by patients' inability factors in DR's emergence

Cost of treatment to patient

Distance patient must travel to get treatment

Supply interruptions

Availability of second-line regimens for patients whose first-line regimens fail

Timing of use of second-line regimens



Thank you for your
attention!

Q+A