Demystifying virology: The link between the HIV life cycle and ART

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The virology of HIV and the basis of viral replication

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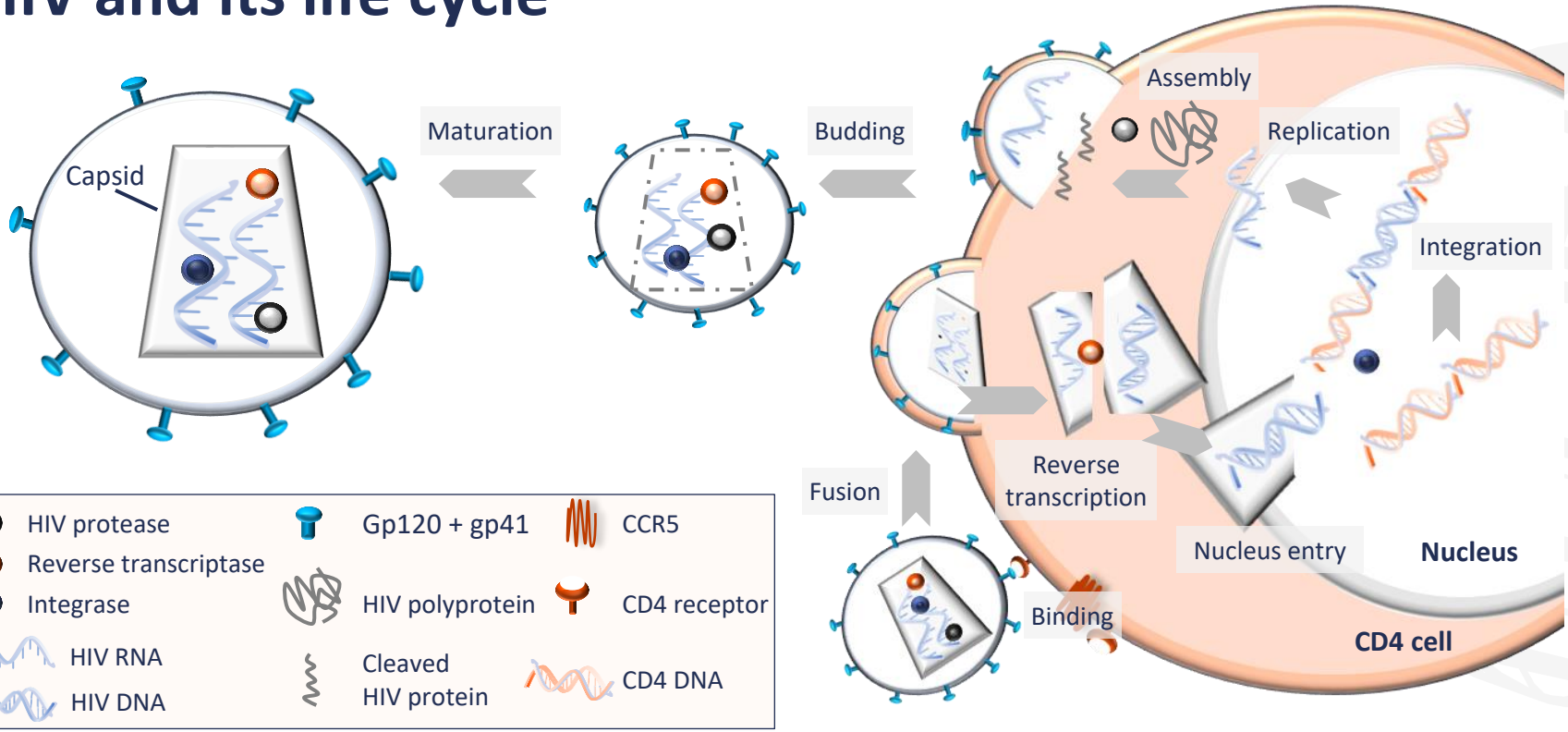
What are the key features of HIV and the steps of its life cycle?

HIV and its life cycle[1–4]



Adapted from: Fanales-Belasio E, et al. *Ann Ist Super Sanità*. 2010;46:5–14; HIVinfo.NIH.gov. The HIV life cycle. Available at: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle (accessed 2 July 2024).
CCR5, C-C chemokine receptor type 5; CD, cluster of differentiation; gp, glycoprotein.
1. Fanales-Belasio E, et al. *Ann Ist Super Sanità*. 2010;46:5–14; 2. Le Hingrat Q, et al. *Front Immunol*. 2021;12:695674; 3. Yang H, et al. *Cell Biosci*. 2012;2:32; 4. HIVinfo.NIH.gov. The HIV life cycle. Available at: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle (accessed 2 July 2024).

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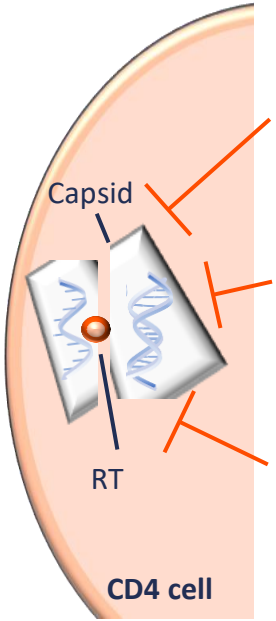
Which intracellular factors limit the integration and replication of the HIV?

Intracellular restriction of HIV



TRIM5α

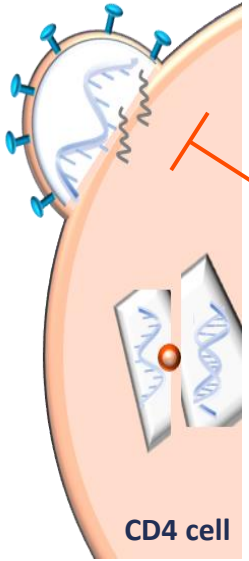
- Targets the capsids for proteasomal degradation and activates innate immune signalling

APOBEC3G

- Suppresses viral DNA synthesis and induces mutations in the viral DNA
- Counteracted by the HIV-1 protein Vif

SAMHD1

- Reduces the concentration of nucleotides below levels required for viral DNA synthesis



Tetherin

- Inhibits viral release
- Counteracted by the HIV-1 protein Vpu

Interplay between cellular restriction factors and HIV-1 occurs at every stage of its life cycle; the virus uses a combination of evasion and antagonism to achieve infection and replication

APOBEC3, apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3 proteins; CD, cluster of differentiation; RT, reverse transcriptase; SAMHD1, sterile alpha motif and histidine-aspartate domain-containing protein 1; TRIM, tripartite motif protein 5; Vif, viral infectivity factor; Vpu, viral protein U.

Sumner RP, et al. *Front Immunol*. 2017;8:1246.

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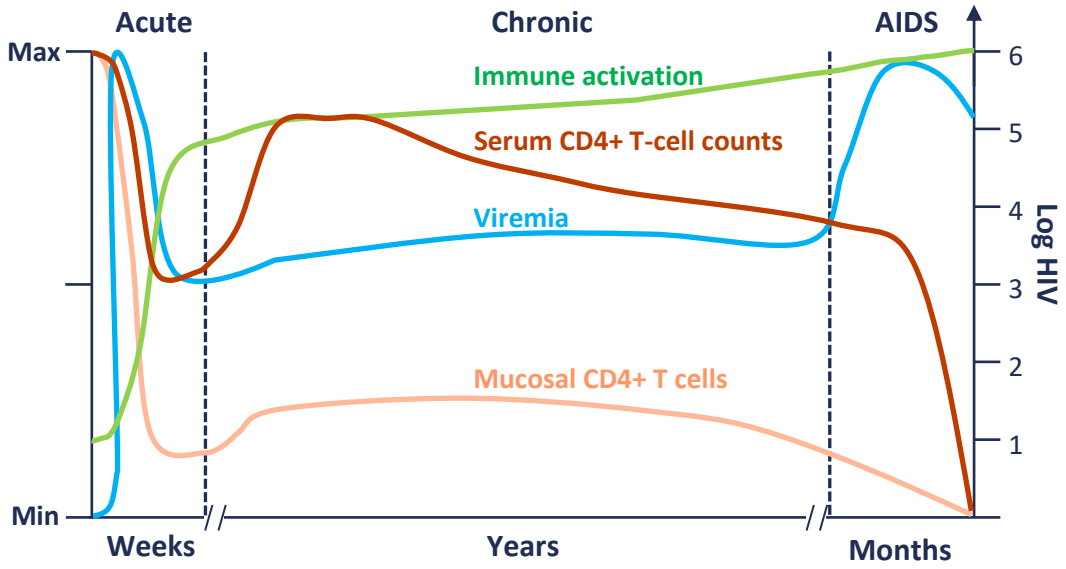
What is the natural course of HIV infection and why is early treatment important?

The dynamics of untreated HIV infection[1,2]



HIV pathogenesis is driven by:

- CD4 T-cell depletion
- Inflammation/immune activation

Early ART initiation has the potential to:

- Favour the restoration of the CD4 T-cell pool in the gut mucosa
- Limit the size and genetic diversity[3] of the viral reservoir
- Preserve immune function[4]

Adapted from: Grossman Z, et al. *Nat Med*. 2006;12:289–95. Reproduced with permission from Springer Nature.
ART, antiretroviral therapy; CD, cluster of differentiation.
1. Grossman Z, et al. *Nat Med*. 2006;12:289–95; 2. Le Hingrat Q, et al. *Front Immunol*. 2021;12:695674;
3. Simonetti FR, Kearney MF. *Curr Opin HIV AIDS*. 2015;10:49–54; 4. Moir S, et al. *Blood*. 2010;116:5571–9.

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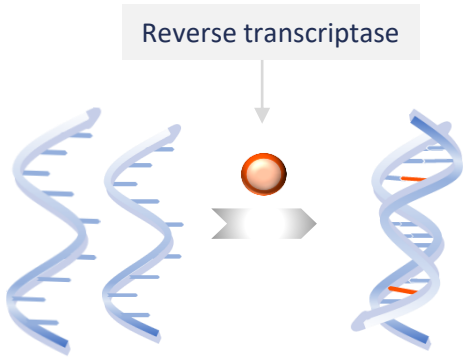
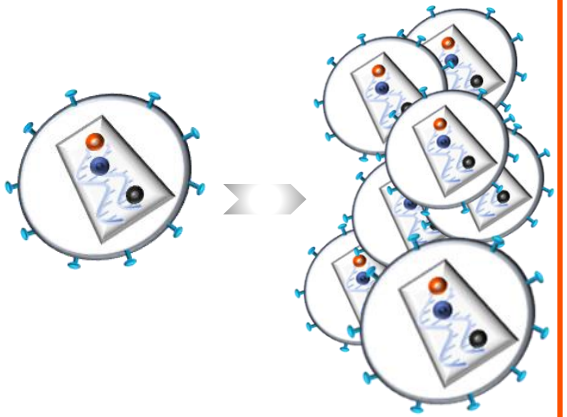
What are the challenges in achieving sustained viral suppression?

Processes leading to genetic diversity in HIV

Error-prone reverse transcription



Rapid viral replication



Viral recombination

After years of infection, substantial genetic diversity accumulates, and this highly diverse population can rapidly respond to selective pressures, facilitating immune escape and resistance to antiviral drugs

Maldarelli F, et al. *J Virol*. 2013;87:10313–23.

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The biological basis and rationale for multidrug ART regimens

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What is the main goal of ART when managing people living with HIV?

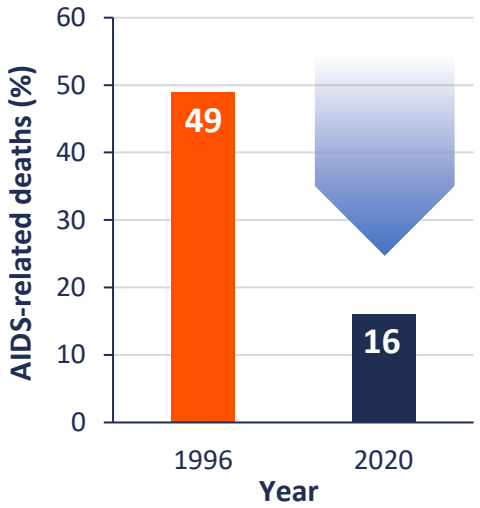
Impact of ART on individuals with HIV

The Antiretroviral Therapy Cohort Collaboration (ART-CC)

Multicentre study of 3-year survival and life expectancy of patients starting ART between 1996 and 2020[1]

- Data from 17 European and North American HIV cohorts
- N=189,301 people living with HIV included in this study

Change in AIDS-related mortality[1]



- ART is highly effective and has low toxicity[2]
- Important issues that remain to be addressed include:[2]
  - ART adherence
  - Non-AIDS mortality
  - Diagnosis and treatment of comorbidities

ART, antiretroviral therapy.

1. Trickey A, et al. *Lancet HIV*. 2024;11:e176–85; 2. The Antiretroviral Therapy Cohort Collaboration. *Lancet HIV*. 2017;4:e349–56.

Impact of viral load on the risk of HIV transmission

PARTNER study (2010–2014)[1,2]

- International, observational, multicentre study of HIV transmission following condomless sex between serodifferent partners:
  - N=888; median follow-up, 1.3 years
  - HIV-positive partner on ART (target VL <50 copies/mL)

- Median frequency of condomless sex = 37 times/year
- Condomless sex acts:
  - MSM, n=22,000
  - Heterosexual, n=36,000

HIV-negative partners becoming HIV-positive, n=11 (MSM, 10; heterosexual, 1)

Within-couple transmissions, n=0

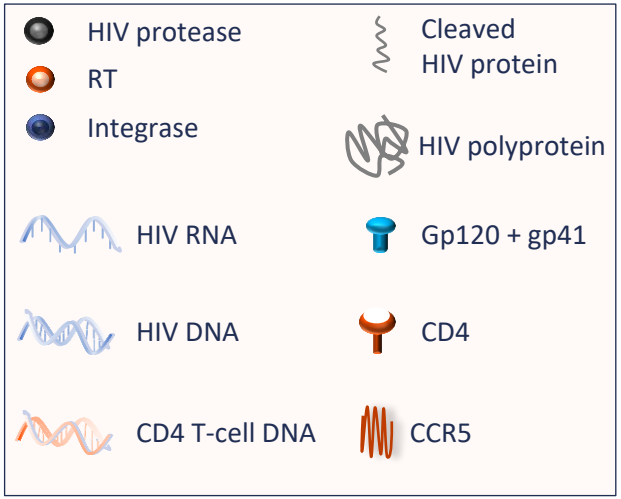
When HIV VL is suppressed, risk of HIV transmission through condomless sex is effectively zero, supporting the U=U (Undetectable = Untransmissible) campaign and the benefits of early testing and treatment for HIV[3]

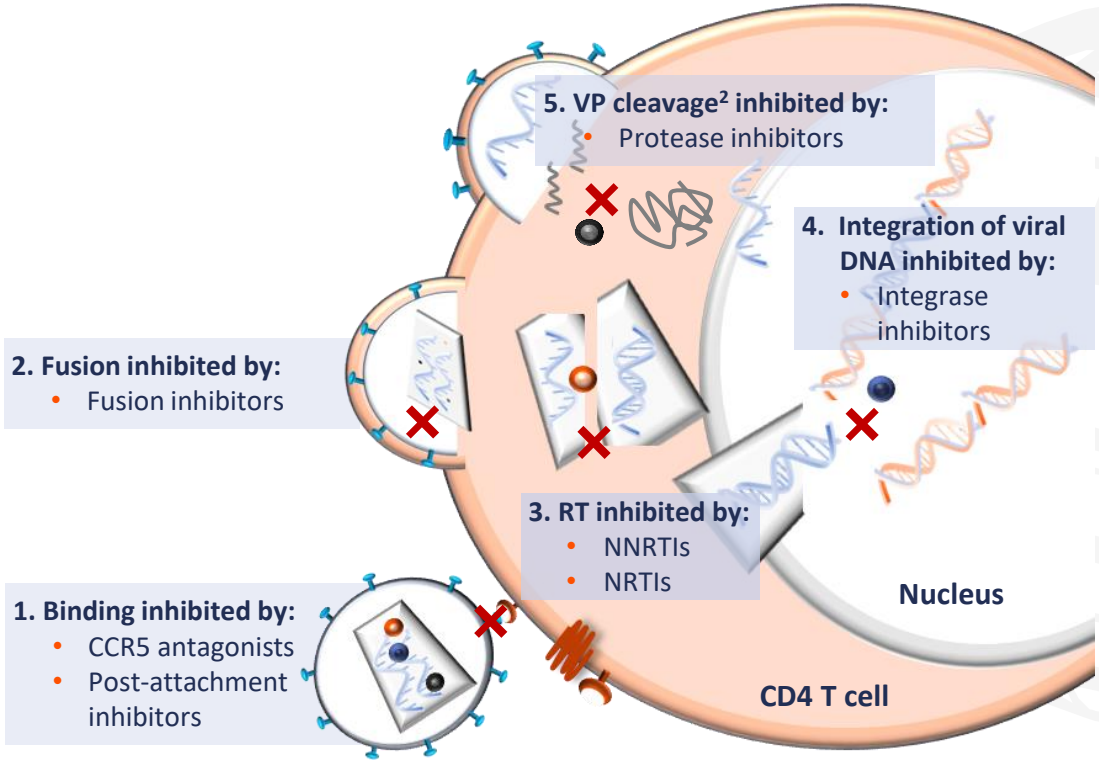
ART, antiretroviral therapy; MSM, men who have sex with men; VL, viral load.

1. Rodger A, et al. *BMC Public Health*. 2012;12:296; 2. Rodger AJ, et al. *JAMA*. 2016;316:171–81; 3. Rodger AJ, et al. *Lancet*. 2019;393:2428–38.

How do different antiretroviral drug classes inhibit HIV replication?

Therapeutic strategies to inhibit HIV replication[1]





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CCR5, C-C chemokine receptor type 5; CD, cluster of differentiation; gp, glycoprotein; NNRTI, non-nucleoside RT inhibitor; NRTI, nucleos(t)ide RT inhibitor; RT, reverse transcriptase; VP, viral polyprotein.
1. HIVinfo.NIH.gov. The HIV life cycle. Available at: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-life-cycle (accessed 2 July 2024);
2. Yang H, et al. *Cell Biosci*. 2012;2:32.

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What is the rationale for combining antiretroviral drug classes and what combinations are currently recommended?

EACS (2023): Regimens for ART-naive adults

Recommended regimens

	Drug classes	Combinations
Three-drug	2x NRTIs + 1x INSTI	ABC/3TC/DTG ABC/3TC + DTG TAF/FTC/BIC TAF/FTC + DTG TDF/XTC + DTG TAF/FTC + RAL TDF/XTC + RAL
Three-drug	2x NRTIs + 1x NNRTI	TDF/3TC/DOR TAF/FTC + DOR TDF/XTC + DOR
Two-drug	1x NRTI + 1x INSTI	3TC/DTG or XTC + DTG

Alternative regimens

	Drug classes	Combinations
Three-drug	2x NRTIs + 1x NNRTI	TDF/FTC/EFV TAF/FTC + EFV TDF/XTC + EFV
		TAF/FTC/RPV TAF/FTC + RPV TDF/FTC/RPV TDF/XTC + RPV
	2x NRTIs + 1x PI/r or PI/c	TAF/FTC/DRV/c TAF/FTC + DRV/c TAF/FTC + DRV/r TDF/XTC + DRV/c TDF/XTC + DRV/r

3TC, lamivudine; /c, co-formulated with cobistat; /r, boosted with ritonavir; ABC, abacavir; ART, antiretroviral therapy; BIC, bictegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitors; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; XTC, 3TC or FTC.

EACS Guidelines Version 12.0, October 2023. Available at: www.eacsociety.org/media/guidelines-12.0.pdf (accessed 2 July 2024).

What antiretroviral agents are currently in development and how do you see them integrating into the treatment paradigm?

Antiretrovirals in clinical development (phase II and III)

Cell binding (bNAbs)

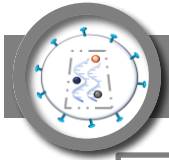
- **VH3810109**
  EMBRACE (NCT05996471)[1]
- **Teropavimab + zinlirvimab + lenacapavir†**
  NCT05729568[2]

Viral maturation (maturation inhibitors)

- **VH3739937**
  NCT06061081[8]

Integration with cell DNA (integrase inhibitors)

- **VH4524184**
  NCT06214052[3]
- **Islatravir + ulonivirine**
  NCT04564547[4]
- **Bictegravir + lenacapavir‡**
  ARTISTRY-1 (NCT05502341)[6]
- **Islatravir + lenacapavir**
  NCT05052996[7]



Capsid formation* (capsid protein inhibitors)

- **VH4004280 and VH4011499**
  NCT06039579[5]

*In addition to playing an essential role in HIV maturation, the HIV capsid also plays a role in trafficking HIV RNA into the cell nucleus.[9] †Lencapavir is approved for multidrug resistance.[10,11] ‡The combination bictegravir + lenacapavir (ARTISTRY-1; NCT05502341) is in phase II/III clinical trial, the remaining therapeutic strategies are in phase II clinical trials. bNAb, broadly neutralizing antibody. 1. ClinicalTrials.gov. NCT05996471; 2. ClinicalTrials.gov. NCT05729568; 3. ClinicalTrials.gov. NCT06214052; 4. ClinicalTrials.gov. NCT04564547; 5. ClinicalTrials.gov. NCT06039579; 6. ClinicalTrials.gov. NCT05502341; 7. ClinicalTrials.gov. NCT05052996; 8. ClinicalTrials.gov. NCT06061081; 9. Rossi E et al. *Life (Basel)*. 2021;11:100; 10. FDA. Lenacapavir. PI, 2022. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (accessed 2 July 2024); 11. EMA. Lenacapivir. SPC 2023. Available at: https://bit.ly/3zv8YzO (accessed 2 July 2024). All clinical trials are available at: https://ClinicalTrials.gov using the study identifier (accessed 2 July 2024).

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Understanding resistance to ART and how to manage it

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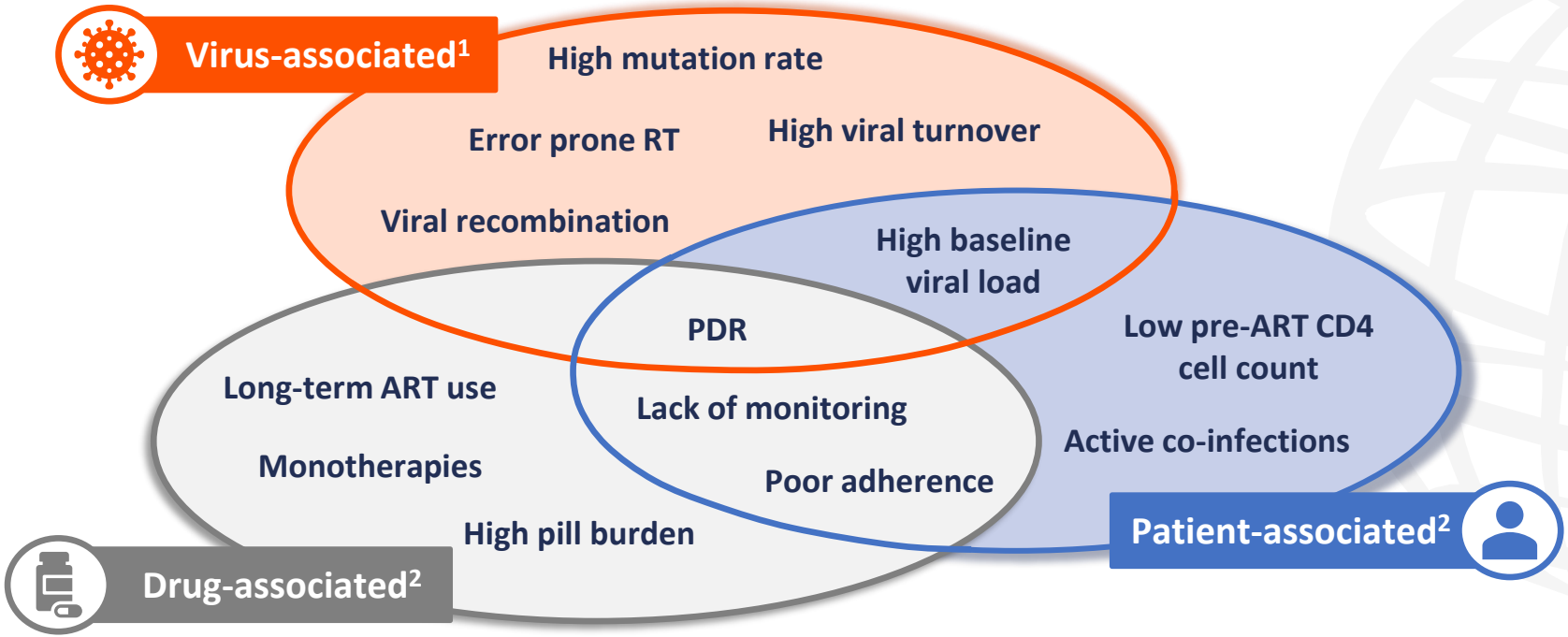
How does resistance to antiretrovirals emerge and what are the implications for patient management?

Factors contributing to ART resistance



ART, antiretroviral therapy; CD, cluster of differentiation; PDR, pre-treatment drug resistance; RT, reverse transcriptase.
1. Cilento ME, et al. *Chem Rev.* 2021;121:3271–96; 2. SeyedAlinaghi S, et al. *AIDS Res Ther.* 2023;20:74.

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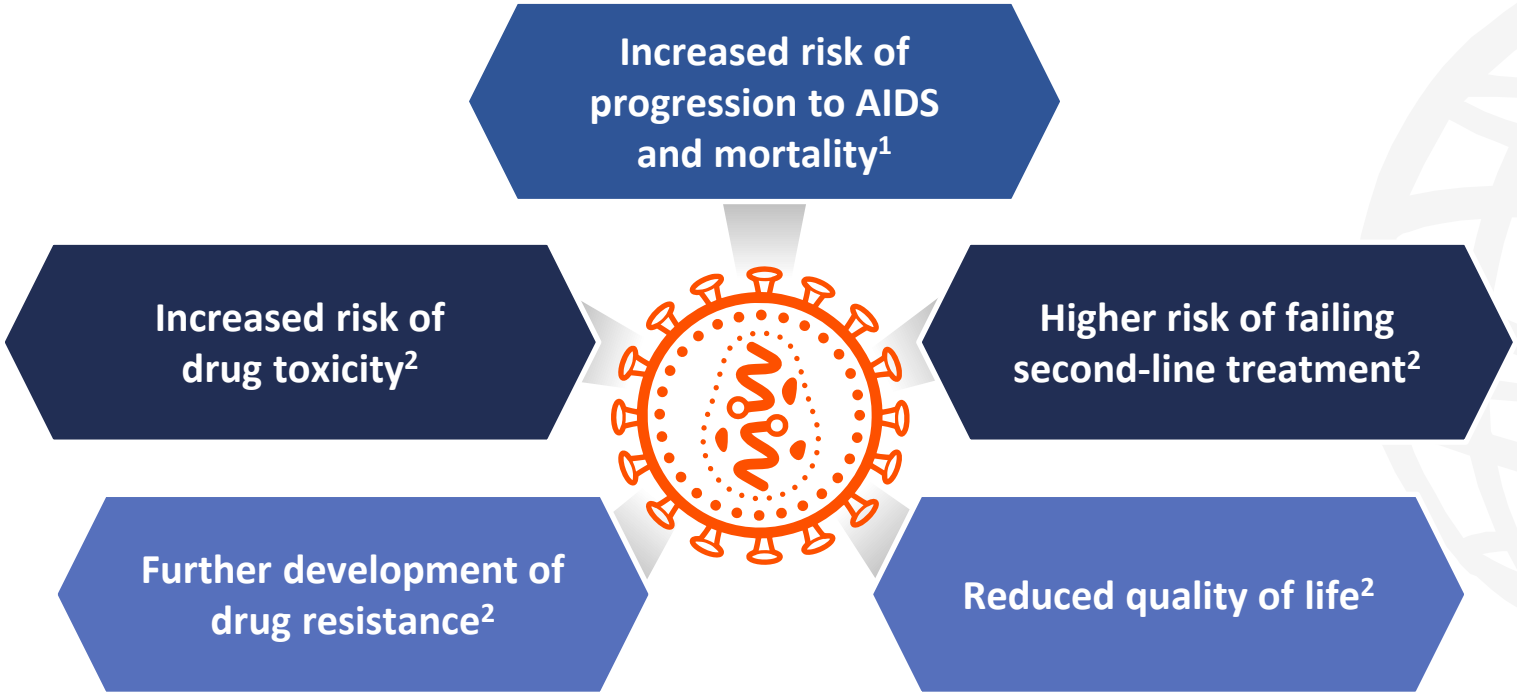
- What is the importance of identifying ART resistance both before and during ART treatment?

Impact of ART failure



ART, antiretroviral therapy.
1. Negash H, et al. *Infect Drug Resist.* 2020;13:1863–72; 2. SeyedAlinaghi S, et al. *AIDS Res Ther.* 2023;20:74

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What do the current guidelines recommend with regards to testing and monitoring for resistance to ART?

EACS guidelines for ART resistance testing

Diagnosis/pre-ART

Genotypic resistance testing prior to ART initiation, ideally at diagnosis

Testing should not delay initiation of ART

During ART

Genotypic resistance testing upon virological failure:

- **Incomplete suppression:** VL >50 copies/mL 6 months after starting ART (or longer if baseline VL >100,000 copies/mL)
- **Rebound:** VL >50 copies/mL in someone with previously undetectable VL

Evaluate adherence, tolerability, drug–drug and drug–food interactions and psychological issues

Special considerations

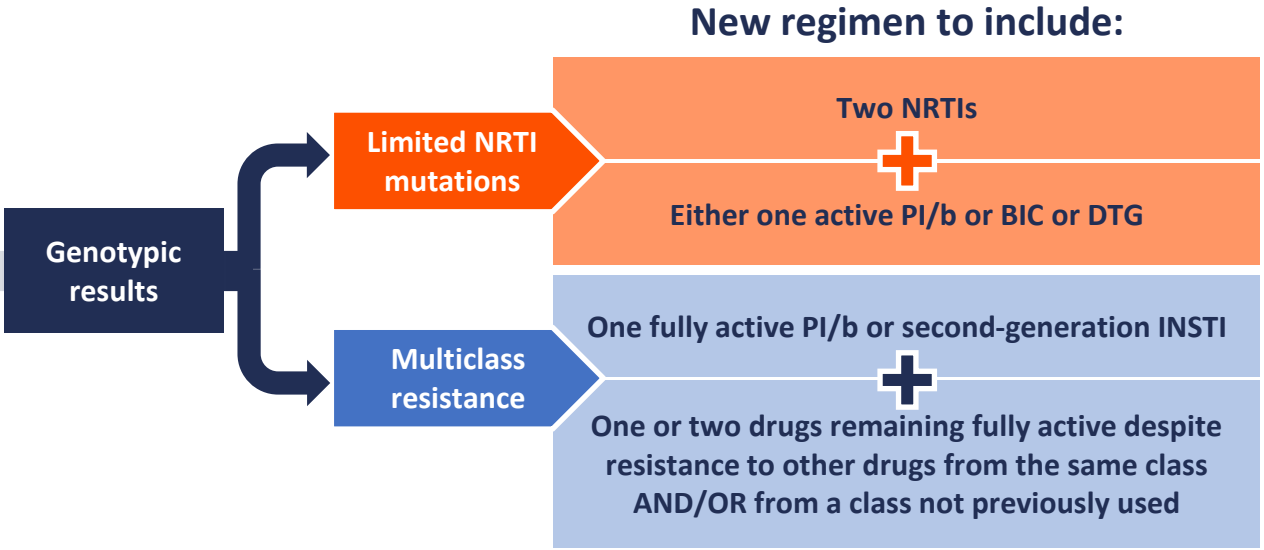
- **Genotypic resistance testing is recommended for pregnant women whose VL is not undetectable at the third trimester**
- **In the context of PEP, genotypic resistance testing of the source person is recommended if they are HIV positive, on ART and their VL is detectable**
- **HIV infections occurring in the context of PrEP failure may be associated with resistance-associated mutations**

ART, antiretroviral therapy; EACS, European AIDS Clinical Society; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; VL, viral load.
EACS Guidelines Version 12.0, October 2023. Available at: www.eacsociety.org/media/guidelines-12.0.pdf (accessed 2 July 2024).

What should clinicians do if ART-resistant mutations are identified?

Regimen changes in the presence of resistance

Use at least two, preferably three, fully active drugs in the new regimen (including active drug from previously used classes) based on resistance mutations



Other considerations

- If <2 active drugs are available, discuss on a case-by-case basis, deferring change
  - **Except** when CD4 count <100 cells/µL or there is a high risk of clinical deterioration
- Treatment interruption is not recommended
- Continuation of 3TC or FTC, even if there is documented resistance mutation, might be beneficial

3TC, lamivudine; BIC, bictegravir; CD, cluster of differentiation; DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI/b, protease inhibitor.

EACS Guidelines Version 12.0, October 2023. Available at: www.eacsociety.org/media/guidelines-12.0.pdf (accessed 2 July 2024).

Regimen changes in the presence of resistance

Use at least two, preferably three, fully active drugs in the new regimen (including active drug from previously used classes) based on resistance mutations

If many options are available, treatment selection should consider:

Simplicity of the regimen

Toxicity risk evaluation

Drug–drug interactions

Sparing of future salvage therapy

EACS Guidelines Version 12.0, October 2023. Available at: www.eacsociety.org/media/guidelines-12.0.pdf (accessed 2 July 2024).

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