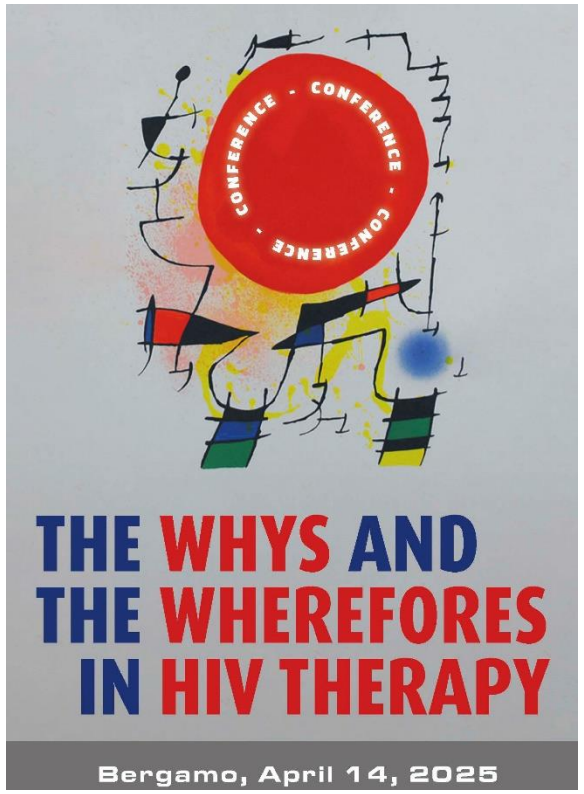


Monday 14 april

10.00-13.15 **I - LESSONS LEARNT FROM THE HIV CLINICAL TRIALS**

Convener: *A. Cattelan (Padua)*

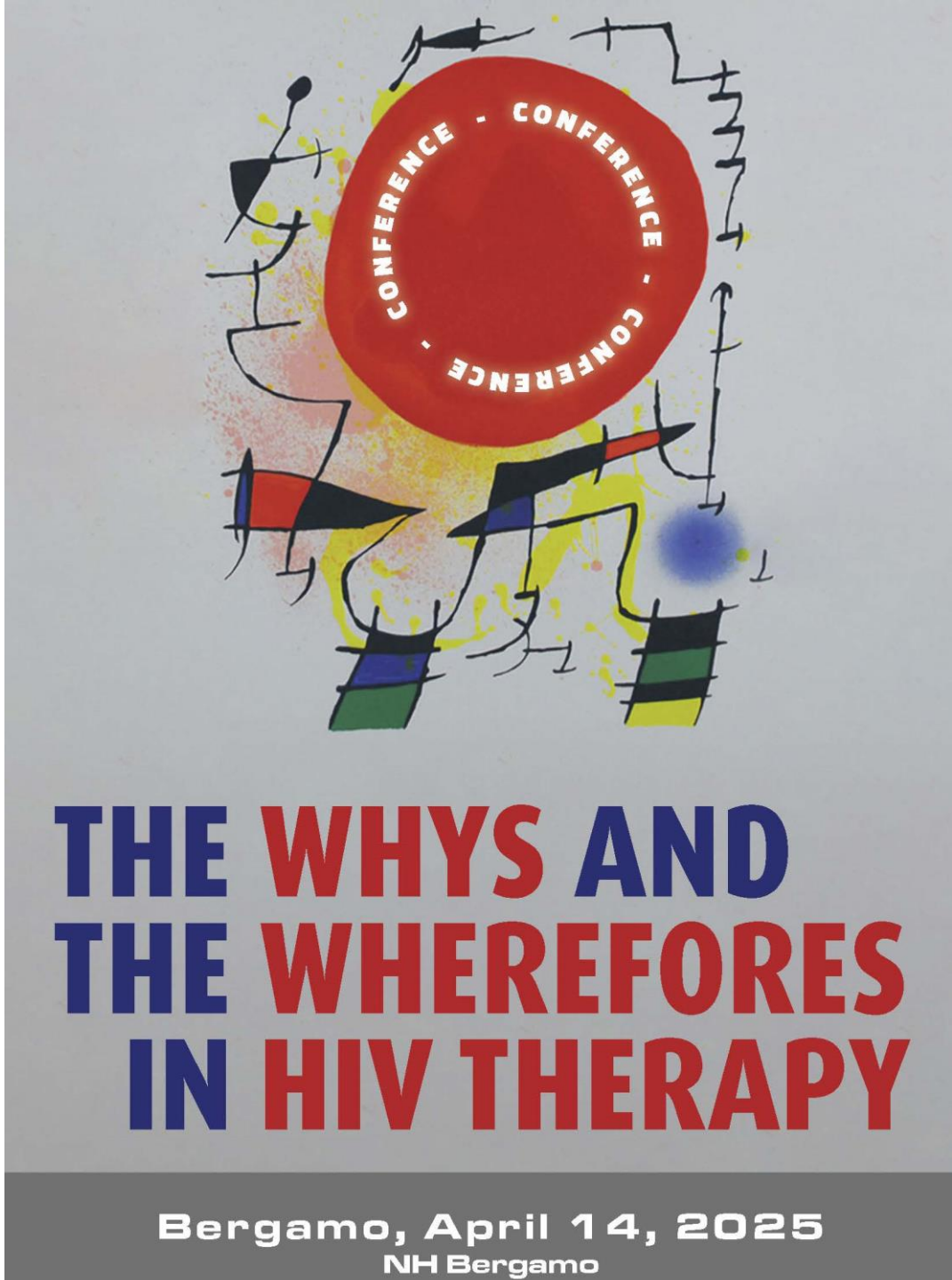
The residual antiviral activity of HIV agents: facts or myths?

M. Santoro (Rome)

The residual antiviral activity of HIV agents: facts or myths?

Università di Roma Tor Vergata

Santoro Maria

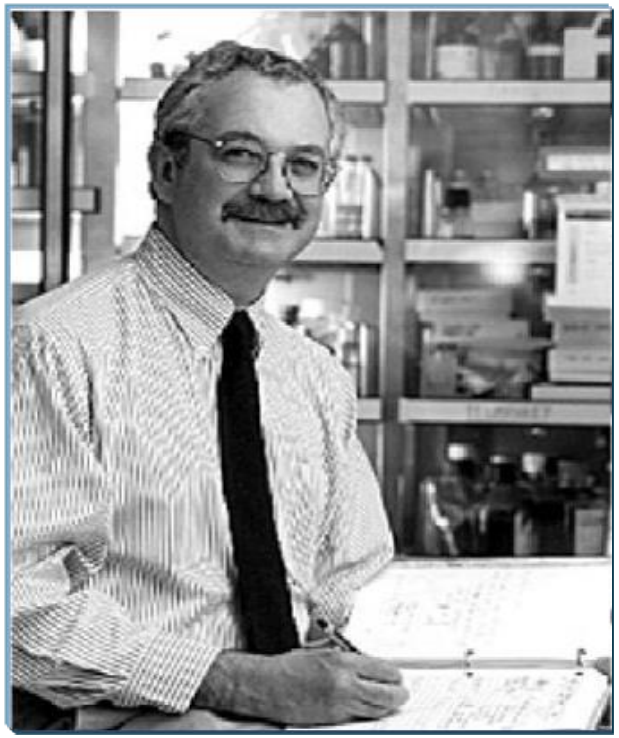


Disclosures

Santoro Maria has received funds for attending symposia, speaking and organizing educational activities from

- *Gilead Science*
- *MSD*
- *ViiV Healthcare*

ADMINISTRATION OF 3′-AZIDO-3′-DEOXYTHYMIDINE, AN INHIBITOR OF HTLV-III/LAV REPLICATION, TO PATIENTS WITH AIDS OR AIDS-RELATED COMPLEX

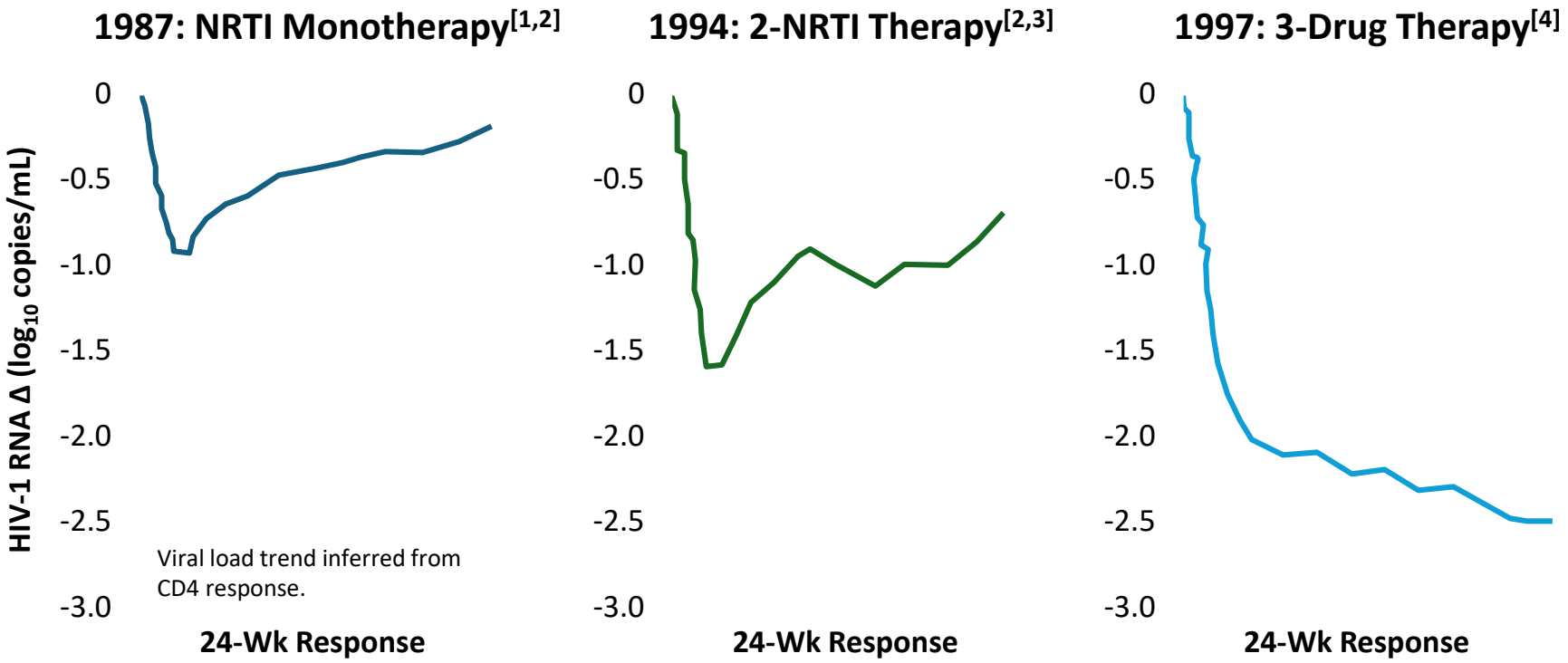


Although our findings suggest that AZT is virustatic at the highest dose examined, it should be recognised that only a small proportion of circulating cells in patients with ARC or AIDS express the HTLV-III virus[9] and that present technology does not permit precise measurement of the viral load, nor does it distinguish between cells bearing

long time, whether immunological improvements will be sustained, whether viral drug resistance will develop, or

R.Yarchoan et al ; Lancet 1986

Evolution of ART: 1987–1997



1. Fischl. NEJM. 1987;317:185. 2. Harrigan. J Acquir Immune Defic Syndr Hum Retrovirol. 1995;10 Suppl 1:S34.
3. Eron. NEJM. 1995;333:1662. 4. Gulick. NEJM. 1997;337:734.

Which is the principle that determined this big evolution of antiretroviral therapy?

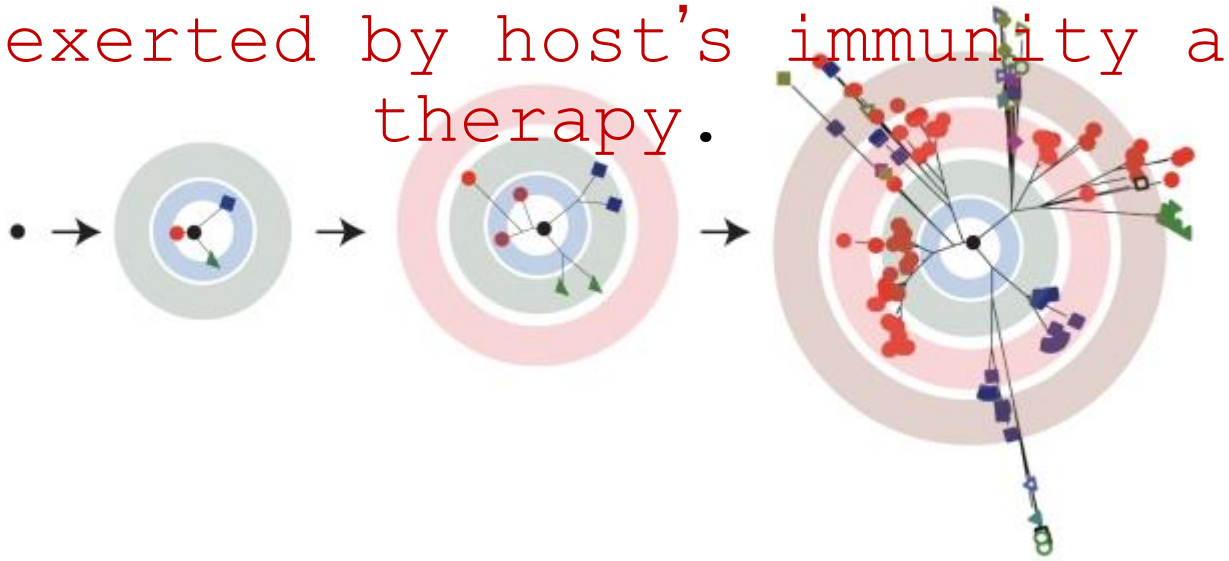
HIV shows considerable genetic and phenotypic variability

- Several factors are known to contribute to this variability:
- The high error rate of "transcription" and lack of "**proofreading**" function by RT enzyme.
- The **Recombination** made by RT during the process of viral DNA synthesis.
- The **high daily rate of viral production**.
- The **rapid selection** of quasispecies with different viral replicative capacity under immune and pharmacological pressure.

Santoro MM and Perno CF. ISRN Microbiol. 2013

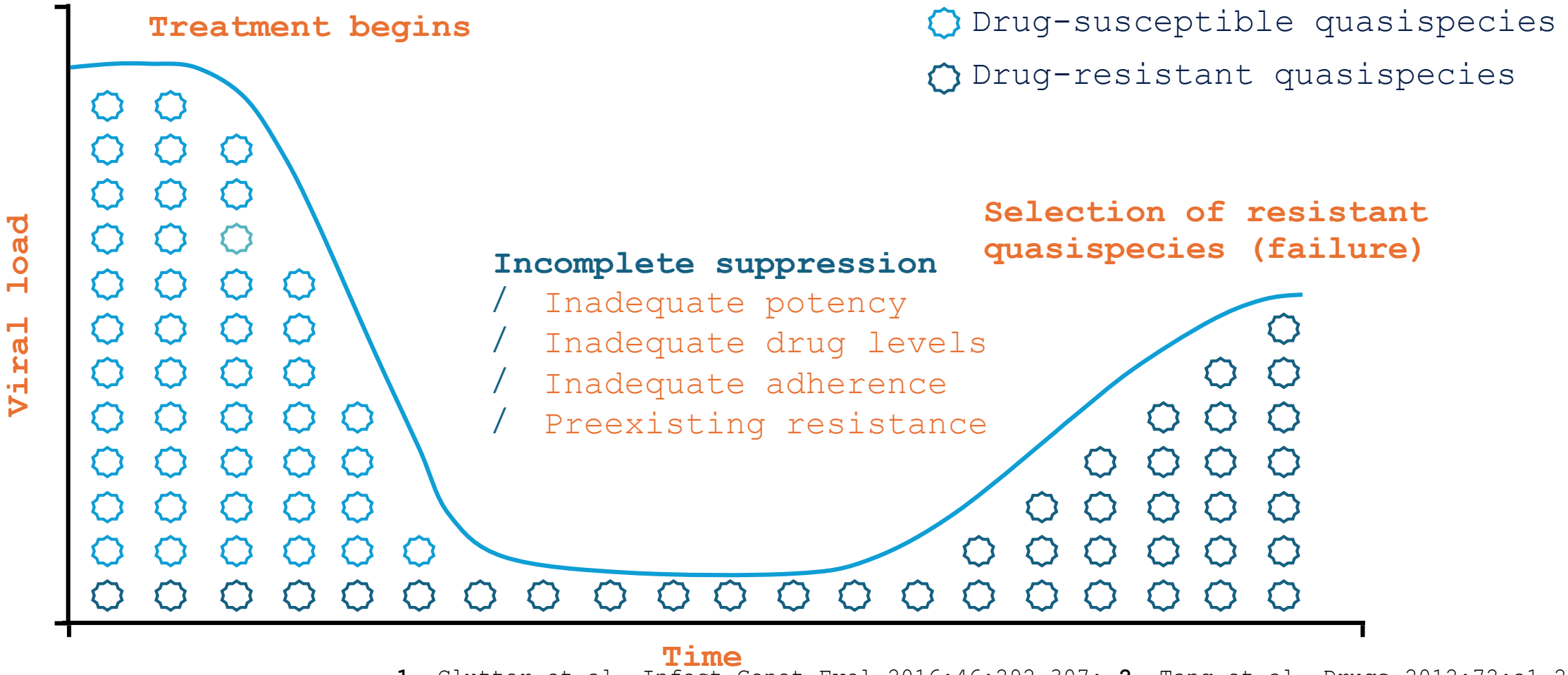
Viral quasispecies

It is a concept derived from the observation that, in an individual infected for a long time, there is a **continued evolution** of the virus, as a result of spontaneous mutations and selective pressures exerted by host's immunity and drug therapy.



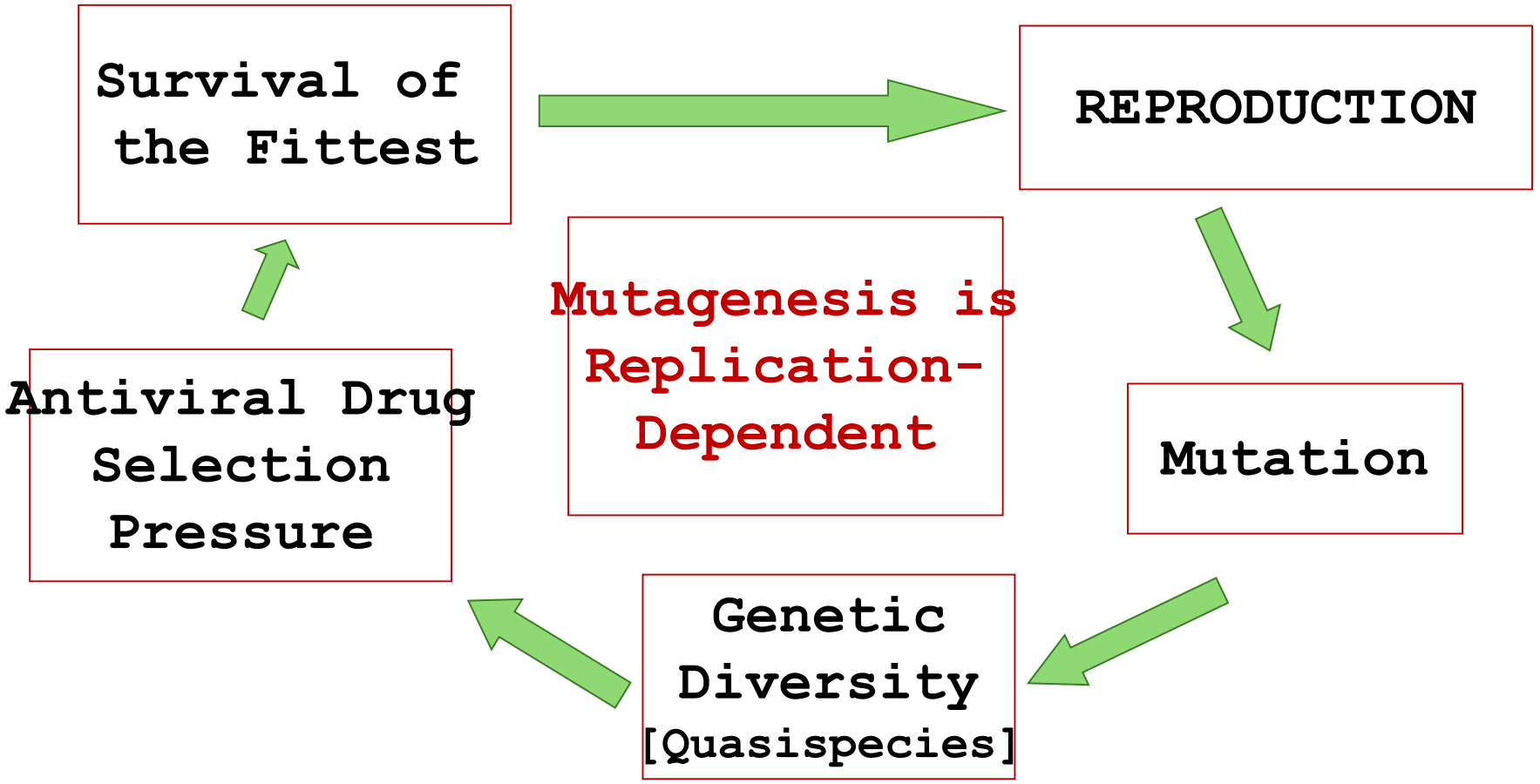
Lauring AS, Andino R. PLoS Pathog. 2010

HIV-1: Drug resistance development



1. Clutter et al. Infect Genet Evol 2016;46:292-307; **2.** Tang et al. Drugs 2012;72:e1-25; **3.** aidsmap. Resistance to anti-HIV drugs. Available at: https://www.aidsmap.com/about-hiv/resistance-anti-hiv-drugs.

Darwinian Principles in Viral Evolution and Drug Resistance



"An antiviral drug is a drug that selects for resistance" *Douglas D. Richman (2000) Hepatology 32:866*

The probability that three drug resistance mutations pre-exists in the same viral genome is very limited.

- ***This concept can be applied to HCV, HIV and HBV***

Base change	Expected N° in 10^8 HCV RNA	N° of possible variants	% existing (if viable)
1	9×10^6	3×10^4	100%
2	4.5×10^5	4.5×10^8	0.1%
3	1.5×10^3	4.5×10^{12}	**3×10^{-7}%**

This **principle** has been the **foundation of triple therapy** for over 20 years.

Modified from Perelson, CRO

Multiple Factors May Contribute to ART Resistance[1-3]

ART choice[1]

- Low barrier to resistance
- Suboptimal forgiveness[2,*]
- Monotherapy[†]
- Long pharmacokinetic tail
- Suboptimal concentration and potency
- Poor absorption
- Food requirements
- DDIs

Individual factors[1]

- Prior treatment failure
- Comorbidities
- High viral load pre-ART
- Low CD4 counts pre-ART
- Suboptimal adherence

HIV factors[1]

- Rapid error-prone replication
- Genetic recombination
- Pre-existing RAMs

Other[1]

- Inconsistent access to ART
- Socioeconomic causes

Drug resistance remains an important contributor to ART failure and is an obstacle to ending the HIV epidemic by 2030[4]

*Forgiveness describes the ability of a regimen to achieve and sustain virologic suppression despite suboptimal adherence; [†]There are no ARTs approved for use as monotherapy
DDI, drug-drug interaction

1. Carr A, et al. *Antiviral Ther.* 2023;28:13596535231201162; 2. Shuter J. *J Antimicrob Chemother.* 2008;61:769-73; 3. Benson C, et al. *AIDS Behav.* 2020;24:3562-72; 4. Temereanca A, Ruta S. *Front Microbiol.* 2023;14:1133407

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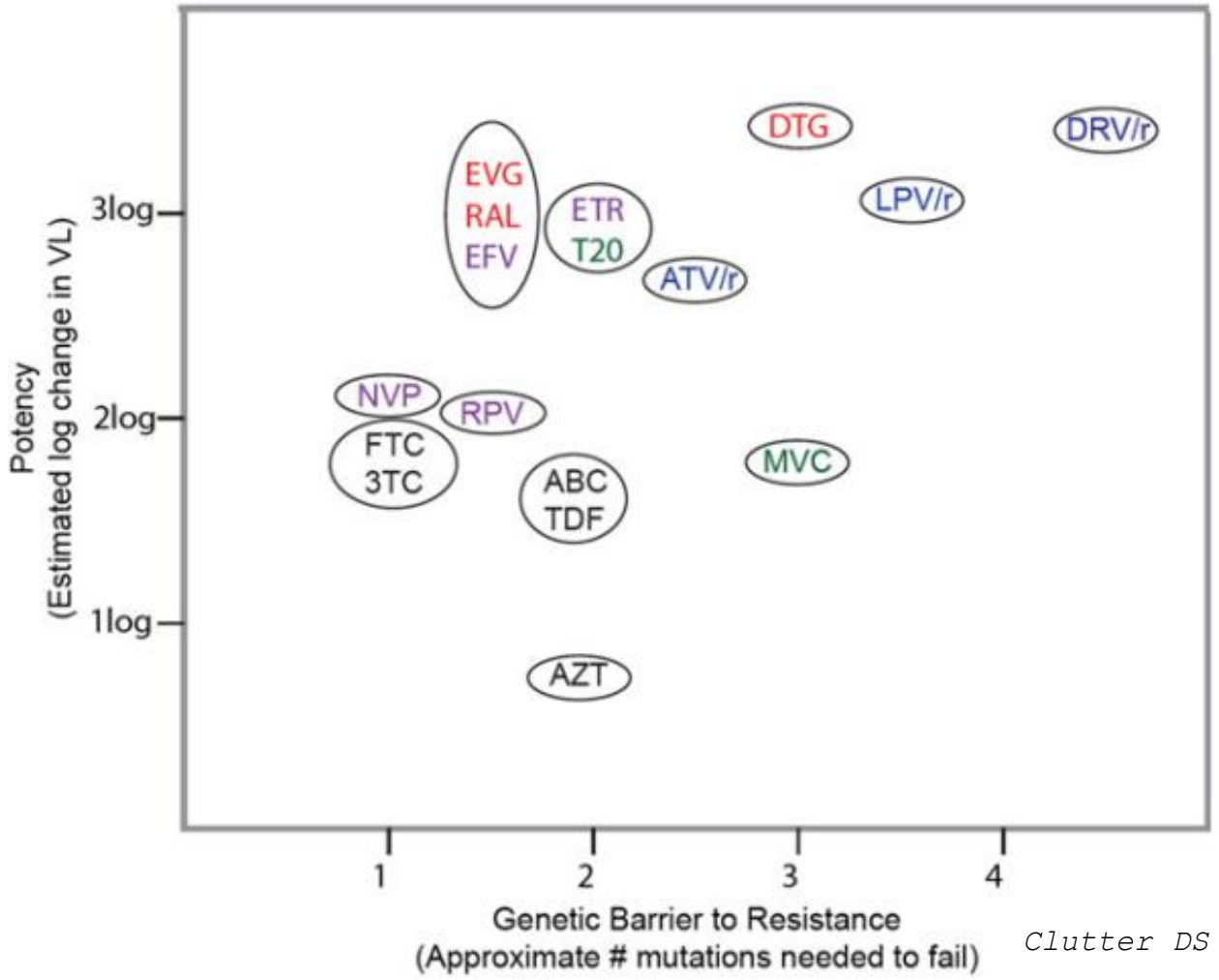
Explaining the Genetic Barrier to Resistance

- The 'barrier to resistance' of each ARV describes how 'easy' it is for HIV-1 to replicate *in vivo* in the drug's presence, and thus generate and select DRMs
- **The 'barrier to resistance' depends on several factors**
  - How many DRMs are required to reduce drug susceptibility
  - The impact of major DRMs on viral replicative capacity
  - The potency of the ARV
  - The concentration of the ARV in the plasma over the dosing period

ARV, antiretroviral; **DRM**, drug resistance mutation;

Clutter DS, et al. Infect Genet Evol 2016;46:292–307.

An ARV's intrinsic antiviral potency combined with its genetic barrier to resistance influences its ability to protect from virological failure



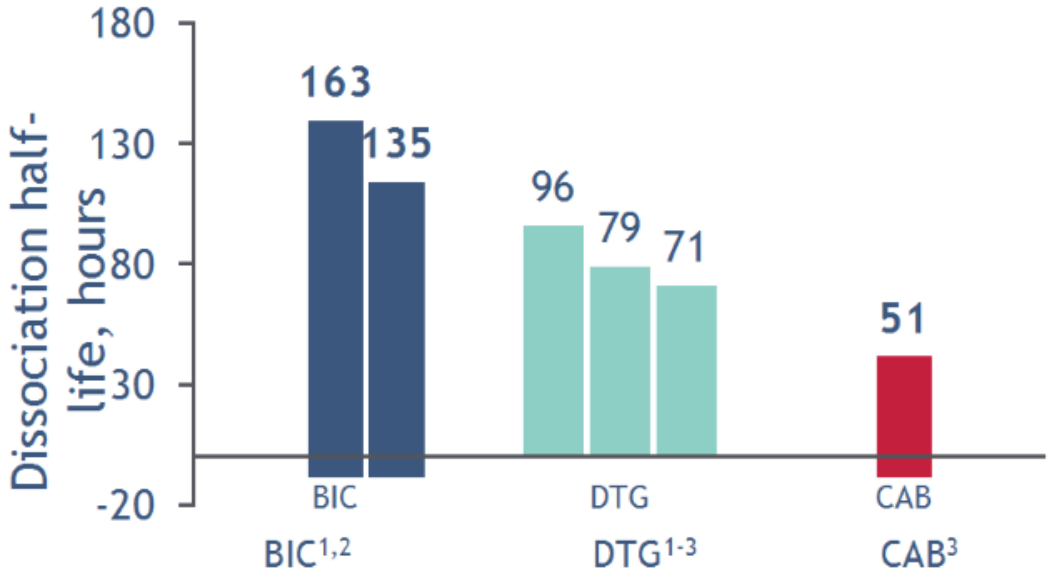
Orange font = nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)
Purple font = non-NRTIs (NNRTIs)
Blue font = protease inhibitors (PIs)
Red font = integrase strand transfer inhibitors (INSTIs)
Green font = entry inhibitors

ARVs appearing together in the same ellipse should be considered to have roughly equivalent potencies and genetic barriers to resistance

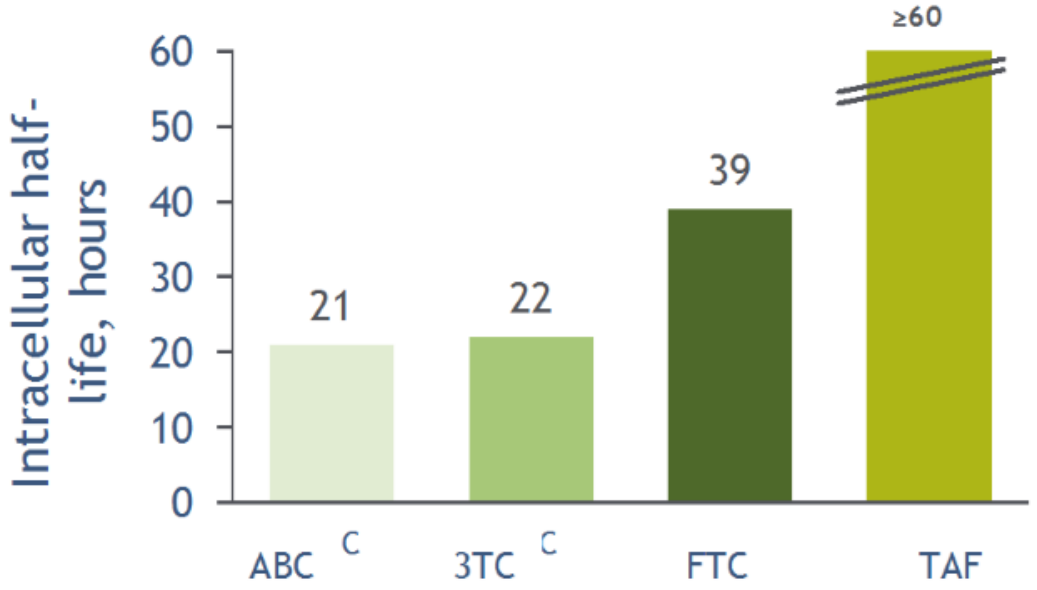
Clutter DS et al., Inf Gen Evol 2016. 46:292-307

Dissociation half-lives of 2° generation INSTIs and intracellular half-lives of NRTIs

Dissociation half-lives of 2nd generation INSTIs,[1-3]
across several distinct *in vitro* studies[a]



Intracellular half-lives of NRTIs,[4-6]
from distinct studies[a]



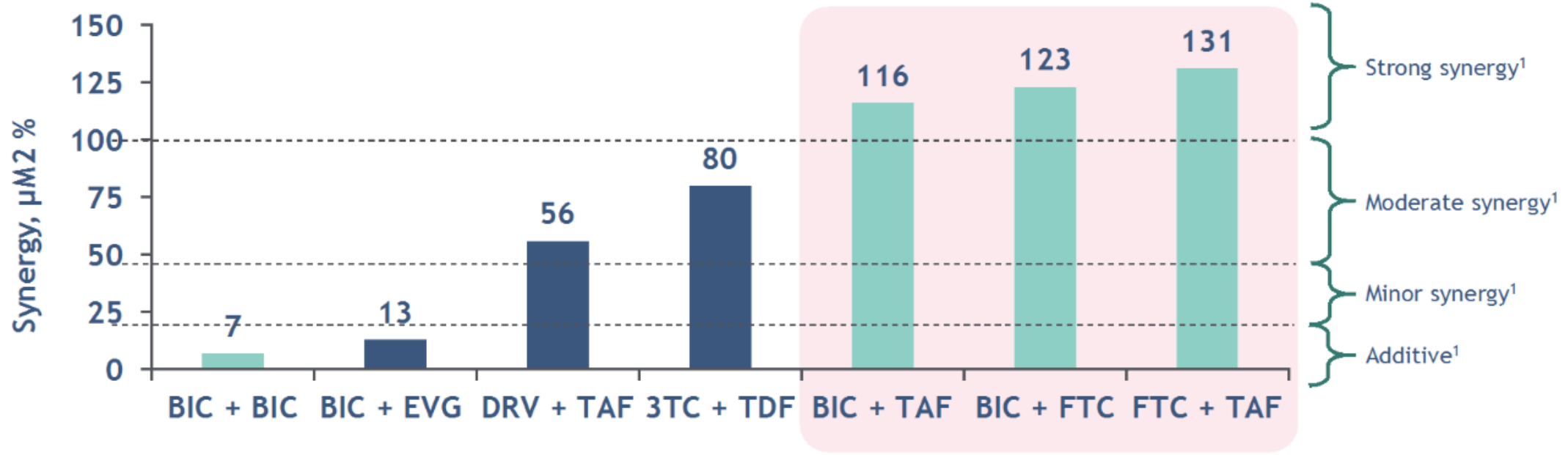
A long dissociation half-life may contribute to a high barrier to resistance and low likelihood of virologic breakthrough[1]

[a]These data are summarized from distinct studies and therefore results and conclusions drawn from comparisons may not be appropriate.
CAB: cabotegravir; TAF: tenofovir alafenamide fumarate

1. White KL, *et al. Antimicrob Agents Chemother* 2021;65:e02406-20; 2. White KL, et al. CROI 2017, Poster 497; 3. Dudas K, *et al.* CROI 2015, Conference report;
4. Piliero *PJ. J Acquir Immune Defic Syndr* 2004;37:S2-S12; 5. Anderson PL, *et al. AIDS* 2003; 17:2159-2168; 6. Mathias AA, *et al. J Acquir Immune Defic Syndr* 2007;46:167-173

Combinations of antiretrovirals show synergistic activity against HIV-1

Distinct *in vitro* studies[a] evaluating intracellular synergy in cell culture[1-3]

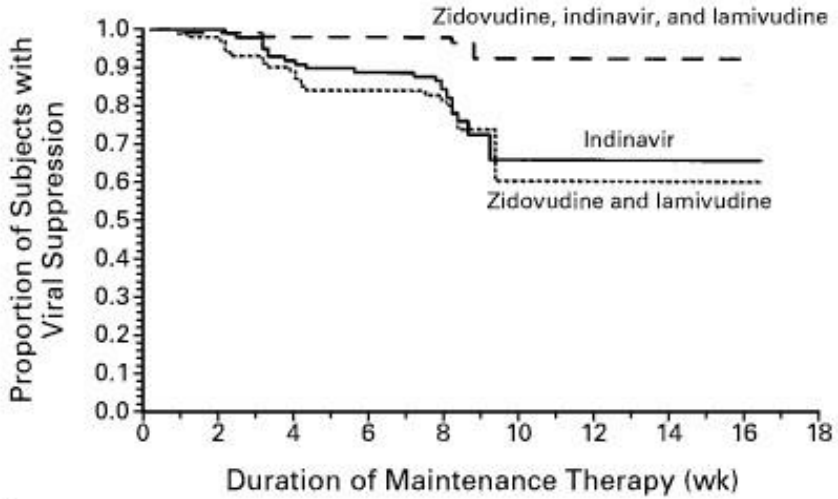


Combinations of BIC, FTC and TAF resulted in strong synergy in vitro, providing increased antiviral activity compared with BIC alone

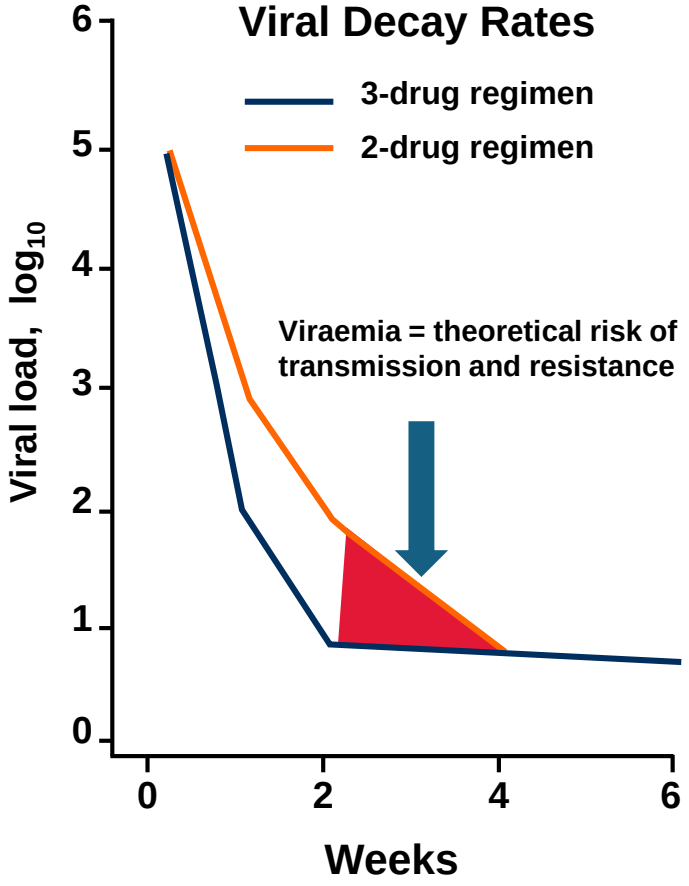
[a] These data are summarized from distinct in vitro studies and therefore results and conclusions drawn from comparisons may not be appropriate

1. Callebaut C, *et al. Antimicrob Agent Chemother* 2015;59:5909-5916. 2. Tsiang M, *et al. Antimicrob Agent Chemother* 2016;60:7086-7097.
3. Borroto-Esoda K, *et al. Antivir Ther* 2006;11:377-384

The dogma of 3DRs was based upon the characteristics (and limitations) of the first-generation antivirals available in the '90s (drugs with low potency and low genetic barrier)



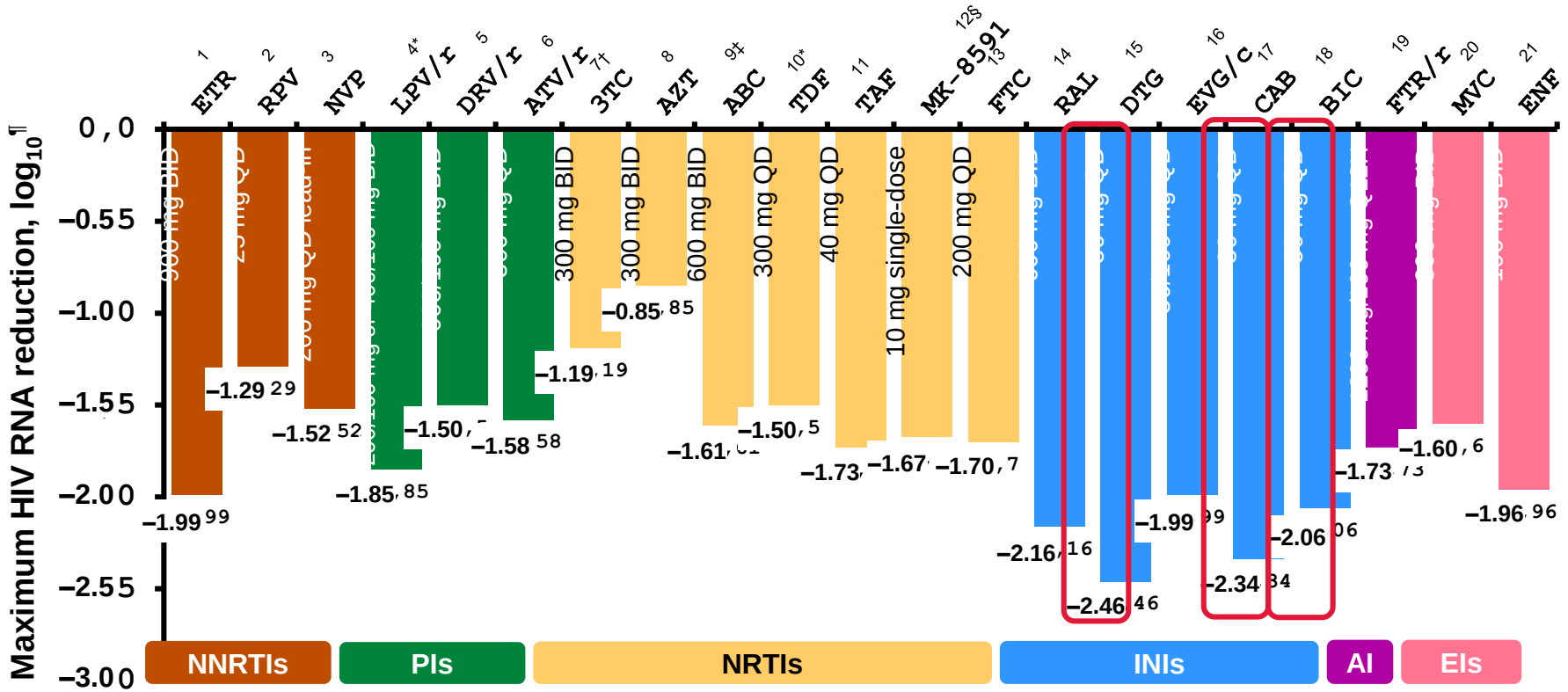
No. at Risk									
Zidovudine, indinavir, and lamivudine	105	101	98	94	44	6	3	2	0
Zidovudine and lamivudine	104	96	83	78	34	5	3	3	1
Indinavir	100	99	88	85	39	6	4	3	1



Havlir DV et al. N Engl J Med 1998;339:1261-1268.

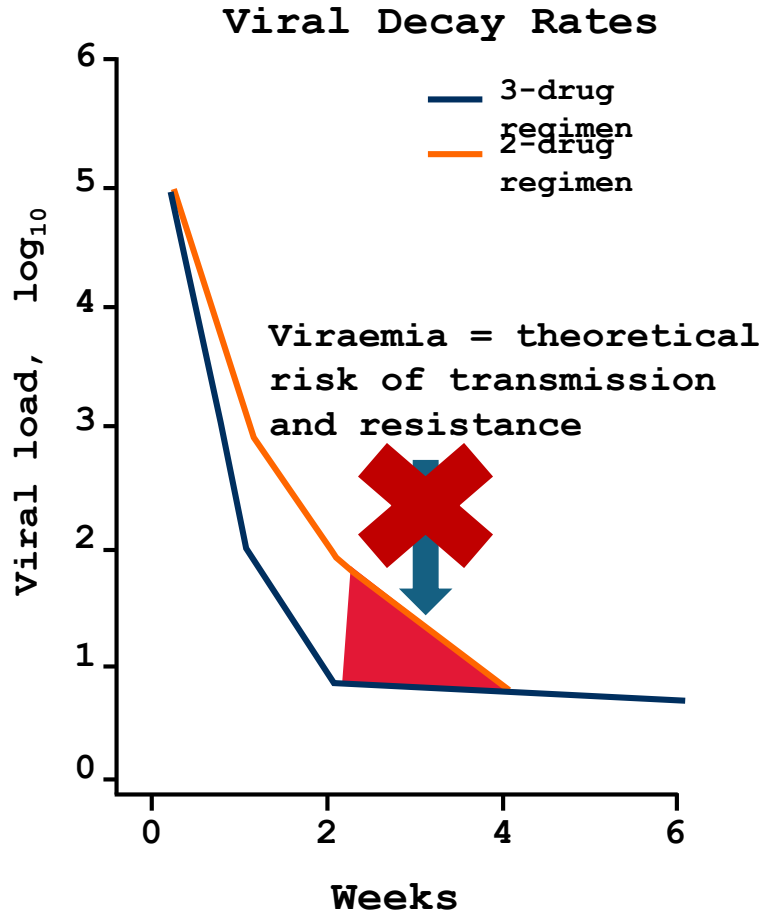
Second-Generation INIs Exhibit Higher Antiviral Activity versus Other Drug Classes

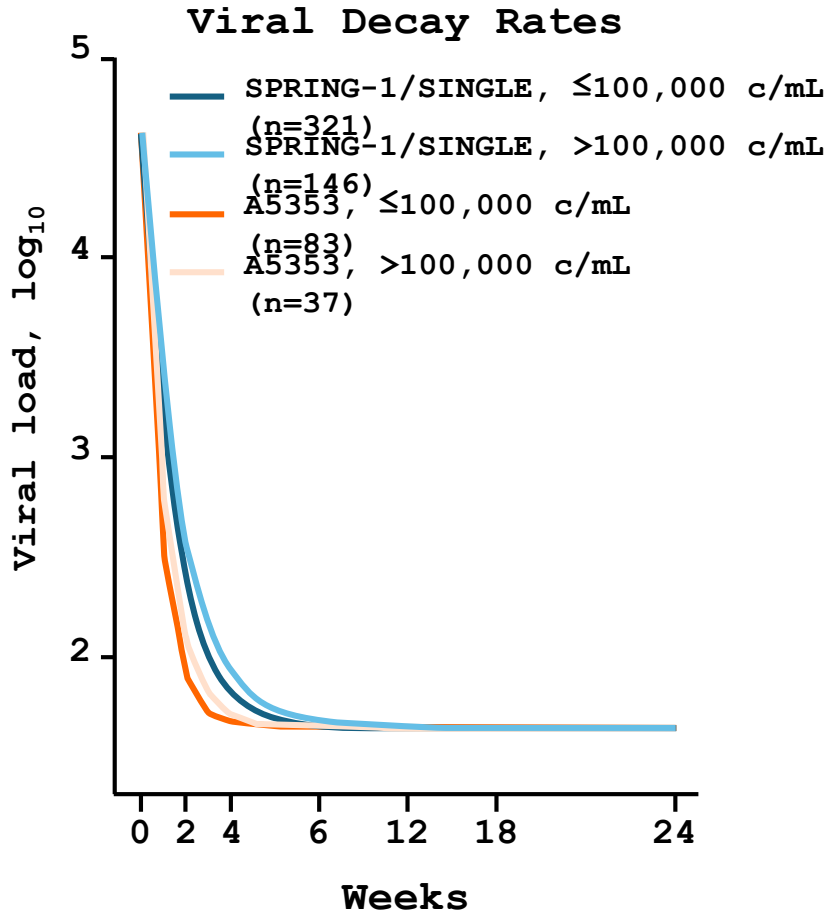
Proof-of-concept ART monotherapy: maximum change in HIV RNA (log_{10}) over 7–15 days



- **Day 21; †Greatest reduction over a 24-week period; ‡Day 28; §Single dose; ¶Mean/median value as available; BID, twice daily*

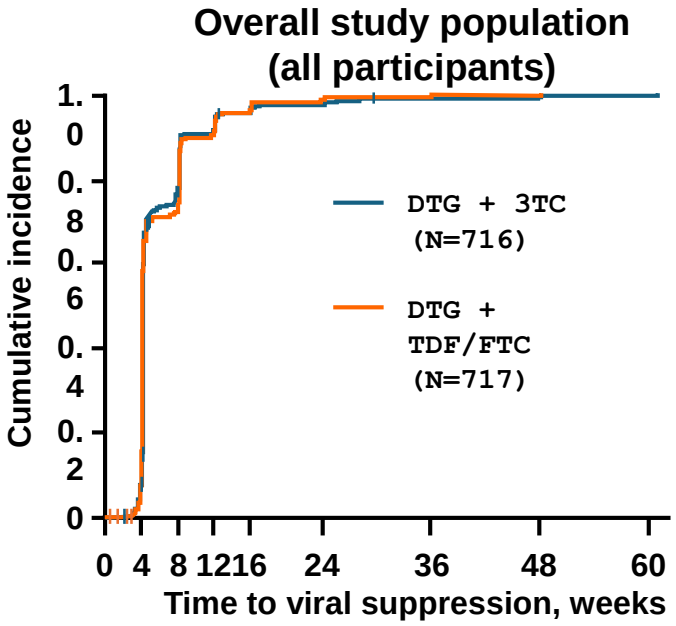
Dolutegravir plus lamivudine achieves viral suppression in a similar time frame to dolutegravir-based three-drug therapy



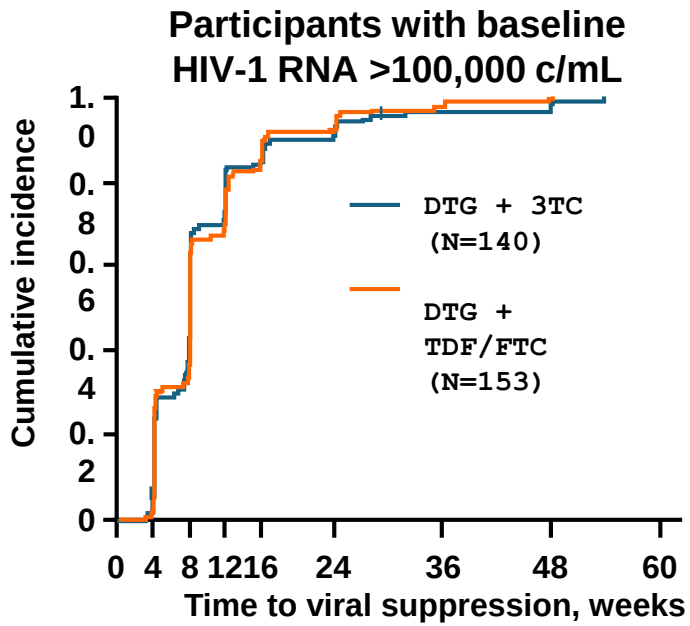


wo B, et al. HIV Glasgow 2018. Presentation O213; Gillman J. et al., J Antimic Chemother 2019

GEMINI-1 and -2: Time to Viral Suppression



Time to viral suppression	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Median (95% CI), days	29.0 (NE–NE)	29.0 (NE–NE)
Hazard ratio (95% CI)	1.01 (0.91–1.12)	



Time to viral suppression	DTG + 3TC (N=140)	DTG + TDF/FTC (N=153)
Median (95% CI), days	57.0 (56.0–57.0)	57.0 (NE–NE)
Hazard ratio (95% CI)	1.00 (0.79–1.26)	

- *95% CI for the quartile cannot be estimated*
  NE, not estimable

- *Eron J, et al. HIV DART and Emerging Viruses 2018. Ora*

Explaining the Genetic Barrier to Resistance

- The 'barrier to resistance' of each ARV describes how 'easy' it is for HIV-1 to replicate *in vivo* in the drug's presence, and thus generate and select DRMs
- **The 'barrier to resistance' depends on several factors**
  - How many DRMs are required to reduce drug susceptibility
  - The impact of major DRMs on viral replicative capacity
  - The potency of the ARV
  - The concentration of the ARV in the plasma over the

The emergence of drug resistance depends on the **combined barrier** imposed by the combination of **ARVs in the regimen**

ARV, antiretroviral; **DRM**, drug resistance mutation;

Clutter DS, et al. Infect Genet Evol 2016;46:292–307.

a) Three drugs with low genetic barrier to resistance: each of them completely loses its efficacy with a single mutation:

es: 3TC/FTC = M184V
EFV/NVP = K103N, G190A/S, Y181C, etc
RAL/EVG = Y143C/H/R, Q148H/K/R, N155H

b) One single drug with high genetic barrier to resistance that loses its efficacy with three different mutations:

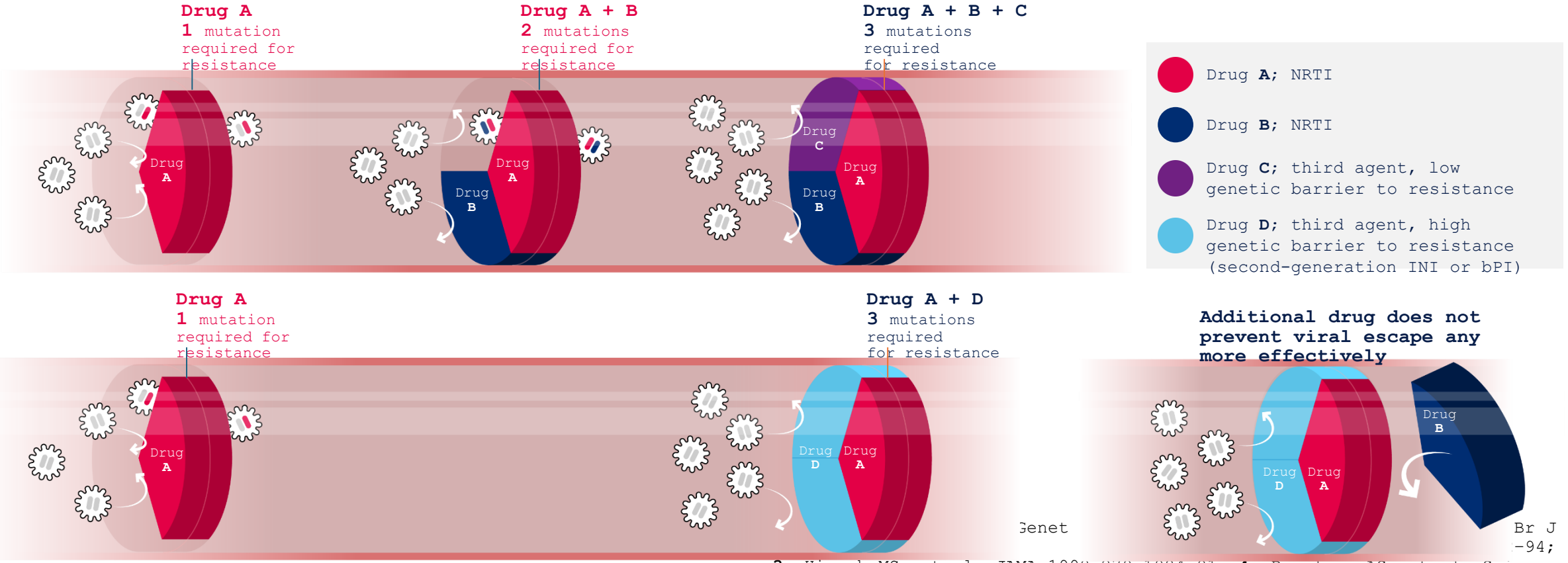
Boosted PIs = M46I + I54V + V82A
Dolutegravir/Bictegravir = Q148H/K/R + G140S + E138A

The keywords of combined anti-HIV therapy are not "(at least) three drugs", but "(at least) three mutations", i.e. the virus overcomes antiviral pressure only when at least three primary mutations will be generated and selected

Only drugs with high genetic barrier (such as boosted PIs, dolutegravir and bictegravir) have characteristics consistent with this concept

Two well-chosen agents can achieve a high genetic barrier to resistance[1–5]

An **HIV virus does not generate three resistance mutations** at once.[6] This **principle** has been the **foundation of triple therapy** for over 20 years. **Building on these foundations** with **well-chosen** ARVs that act at **two separate targets** in the replication cycle, the same **high genetic barrier to resistance** can be achieved with **two well-chosen agents**



Genet Br J -94;

3. Hirsch MS, et al. JAMA 1998;279:1984–91; **4.** Perelson AS, et al. Science 1996;271:1582–6;

5. Feng Q, et al. BMJ 2019;366:l4179; **6.** Perelson AS, et al. AIDS 1997;11(Suppl A):S17–24

bPI, boosted protease inhibitor

Conclusions

- Due to its high genetic variability, HIV continuously evolves and under suboptimal drug pressure (due to several factors such as inadequate drug potency, inadequate drug levels, inadequate adherence..) tends to develop drug resistance.
- Since1987 numerous antiretrovirals targeting several steps of HIV replication cycle have rendered the achievement of virological suppression and, therefore, the containment of resistance development possible goals.
- The introduction of three-drug regimens with two NRTIs and a core drug guaranteed not only the achievement of the virological suppression but also its maintenance.
- A durable virological suppression is today possible also with only two drugs that act at two separate HIV targets, thanks to the availability of antiretrovirals with high antiviral potency and high genetic barrier.
- With the arsenal of antiretrovirals available today, in view of a personalized management of HIV infection throughout life, it is therefore possible to carefully choose appropriate drug combinations that guarantee the maintenance of virological suppression.

Thank you for the attention!