17th Residential Course on Clinical Pharmacology of Antiretrovirals

January 19-21, 2022

SESSION I: TWO-DRUG REGIMENS FOR HIV INFECTION: OPPORTUNITY OR PARADIGM?

Clinical Pharmacology of 2DRs Regimens: what Clinicians should know

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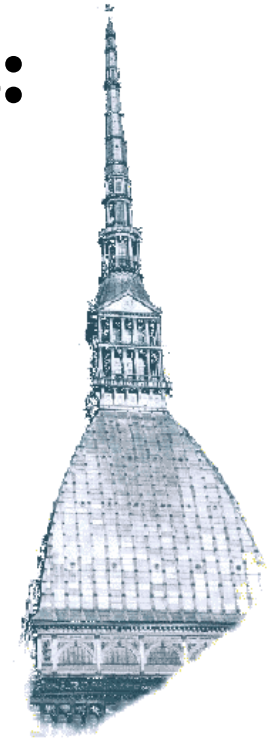

Ospedale Amedeo di Savoia

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- Abbvie
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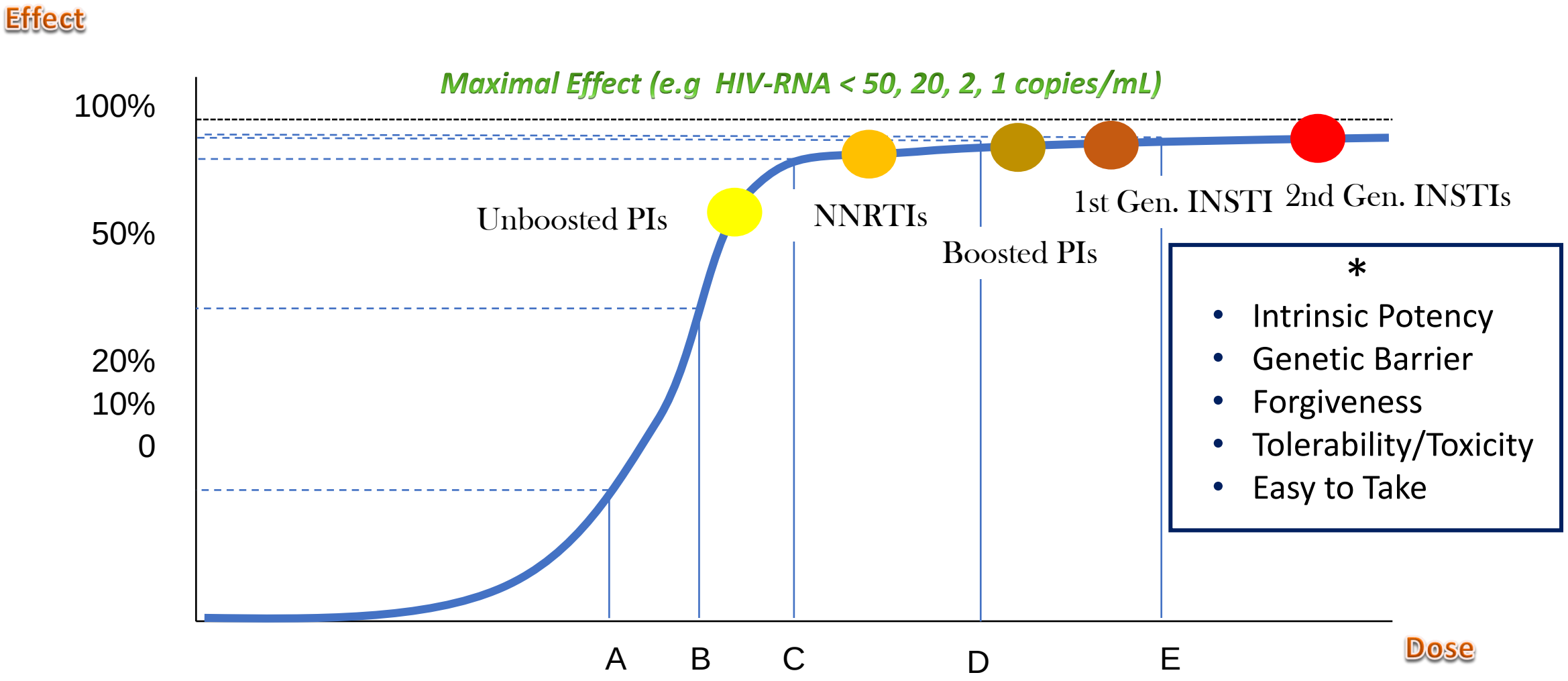
- Astellas
- Basilea
- Zambon
- Correvio
- Angelini

Emax Model



Coloured dots represent **my perception** of the overall ranking of triple regimens*

Recommendations for Initiation of ART in PLWH with Chronic Infection without prior ART Exposure

Version 10.0
November 2019

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + DTG		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) III Weight increase
TAF/FTC/BIC		
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
DTG + 3TC	HBsAg negative HIV-VL < 500,000 copies/mL CD4 count > 200 cells/µL	
2 NRTIs + NNRTI		
TAF/FTC or TDF/FTC or TDF/3TC + DOR TDF/3TC/DOR		
TAF/FTC or TDF/FTC or TDF/3TC + RPV TAF/FTC/RPV TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r TAF/FTC/DRV/c	With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (DRV/r: cardiovascular risk)

3

2

3

Switch Strategies for Virologically Suppressed Persons

Dual therapies

Dual therapies supported by large randomized clinical trials or meta-analyses

DTG + RPV
3TC + DTG
3TC + DRV/b
3TC + ATV/b

2

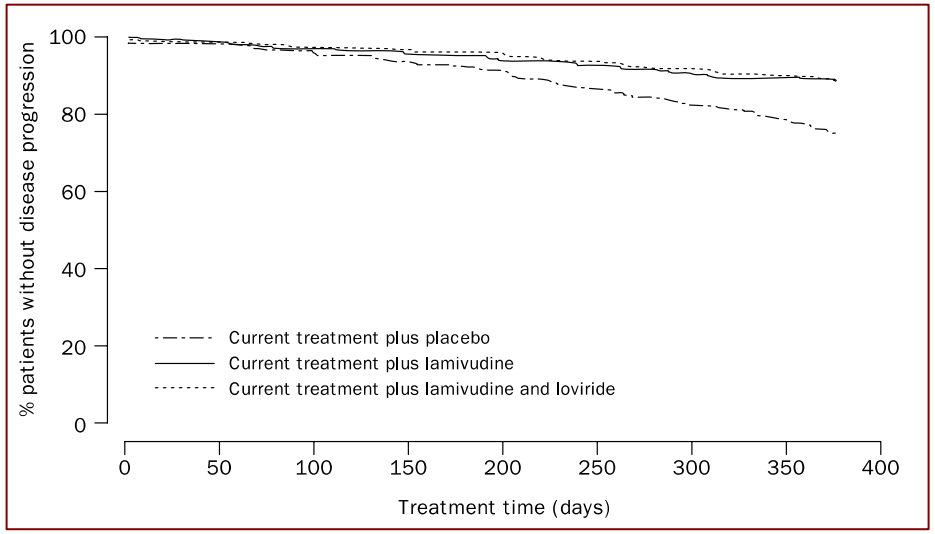
The short but important story of the (first) dual therapy: first signs that the pathway to multidrug regimens was the right one

THE LANCET

Articles

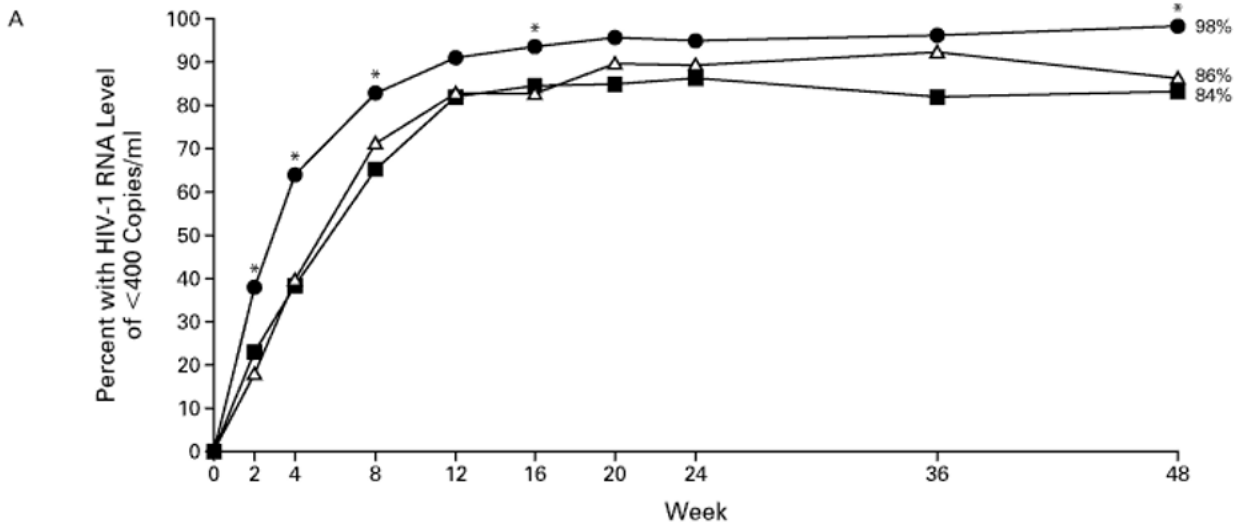
Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial

*CAESAR Coordinating Committee**



Lancet 1997; 349: 1413-1421

Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, and Indinavir plus Zidovudine and Lamivudine in the Treatment of HIV-1 Infection in Adults. *Schlomo Staszewski, et al.* NEJM 1999; 341:1865-1873



AZT
AZT + ddI or ddC

1. **Placebo**
2. **3TC**
3. **3TC + Loviride**

Primary endpoints:
Death
Progression to AIDS

3TC, PIs & NNRTIs
Naïve pts

1. **EFV + IDV**
2. **EFV + AZT + 3TC**
3. **IDV + AZT + 3TC**

Primary endpoint:
% of pts. With HIV-RNA < 400 copies/mL

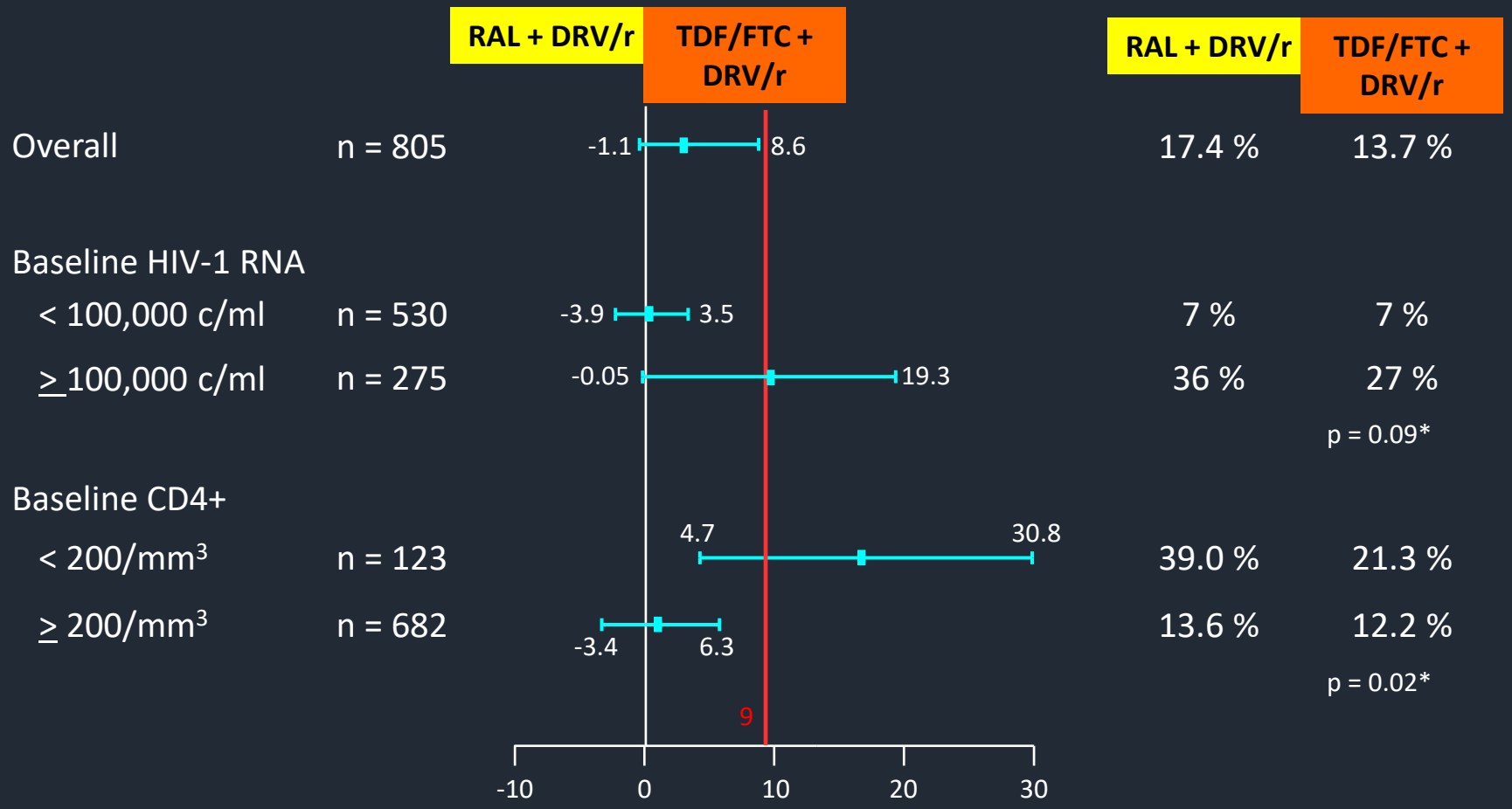
2DR Studies - overview

	Initiating ART	Suppressed Switch
bPI + 3TC	**GARDEL** (416) LPVr+3TC ANDES (145) DRVr+3TC	**ATLAS-M** (266) ATVr+3TC **SALT** (273) ATVr+3TC **OLE** (250) LPVr+3TC **DUAL** (257) DRVr+3TC **MOBIDIP** (265) DRVr/LPVr+3TC***
INSTI + 3TC	PADDLE (20) DTG+3TC **ACTG5353** (120) DTG+3TC R **GEMINI** (700) DTG+3TC	LAMIDOL/ANRS167 (104) DTG+3TC DOLULAM (27) DTG+3TC **(TANGO** DTG+3TC)
bPI + INSTI	PROGRESS (206) LPVr+RAL **NEAT001** (805) DRVr+RAL	KITE (60) LPVr+RAL **HARNESS** (108) ATVr+RAL SPARE (59) DRVr+RAL DUALIS (320) DRVb + DTG
other	R **LATTE-2** (286) CAB+RPV **MODERN** (804) DRVr+MVC	R **SWORD** (1024) DTG+RPV LATTE (243) CAB+RPV PROBE (60) DRVr+RPV Multineka (67) LPVr+NVP **GUSTA** (133) DRVr+MVC **MARCH** (395) bPI+MVC

Primary endpoint at W96 by baseline characteristics

NEAT 001/ANRS 143

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r



* Test for homogeneity

Timing of the Components of the HIV Life Cycle in Productively Infected CD4$^+$ T Cells in a Population of HIV-Infected Individuals$^{\nabla}$

John M. Murray,[1,2]* Anthony D. Kelleher,[2,3] and David A. Cooper[2,3]

JOURNAL OF VIROLOGY, Oct. 2011, p. 10798–10805

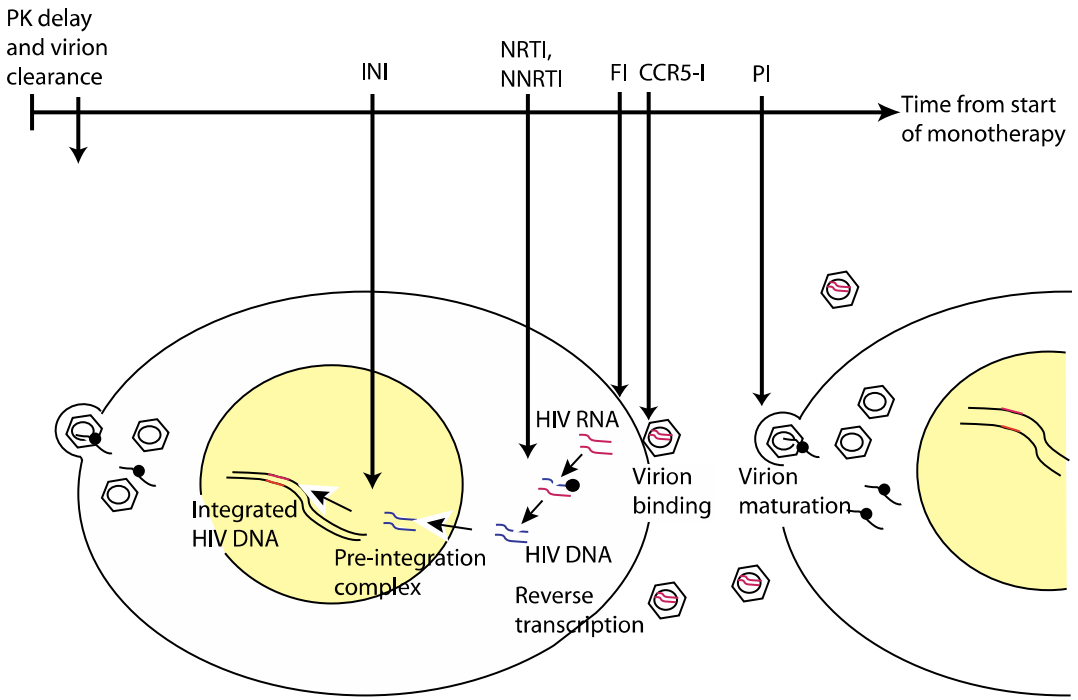


FIG. 1. The positions in the HIV life cycle affected by each drug class and their relative timing in terms of when they impact HIV RNA levels in blood.

HIV requires an average of 52 h between two sequential generations;

Most of this time is taken by reverse transcription (RT, 33 h)

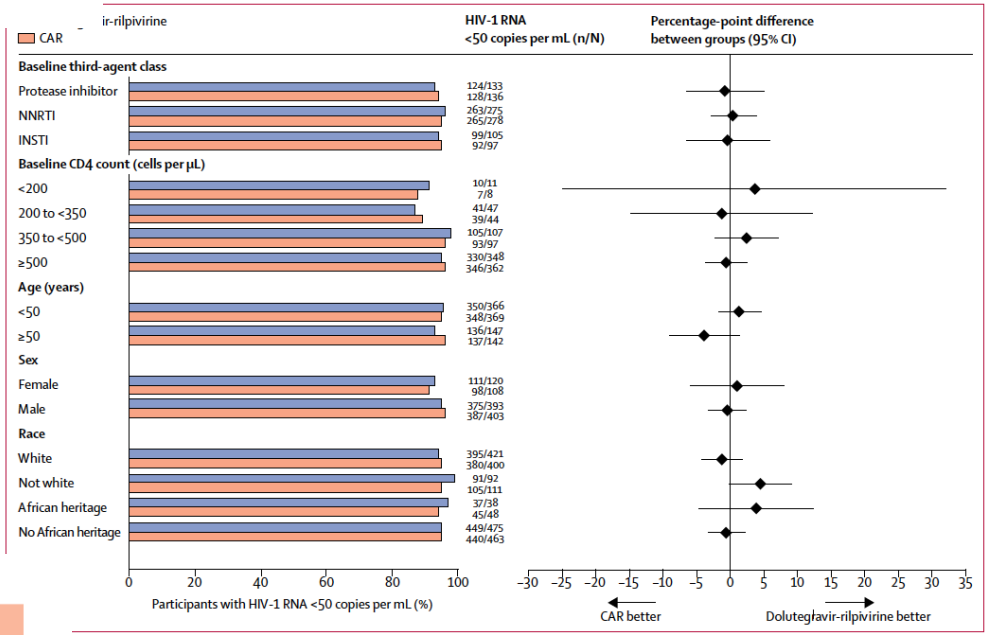
In HIV infection, until 2019 the recognized successful paradigm has been the use of 3 drugs, although the introduction of more potent drugs has improved the Pk/PD performance of antiretroviral therapy

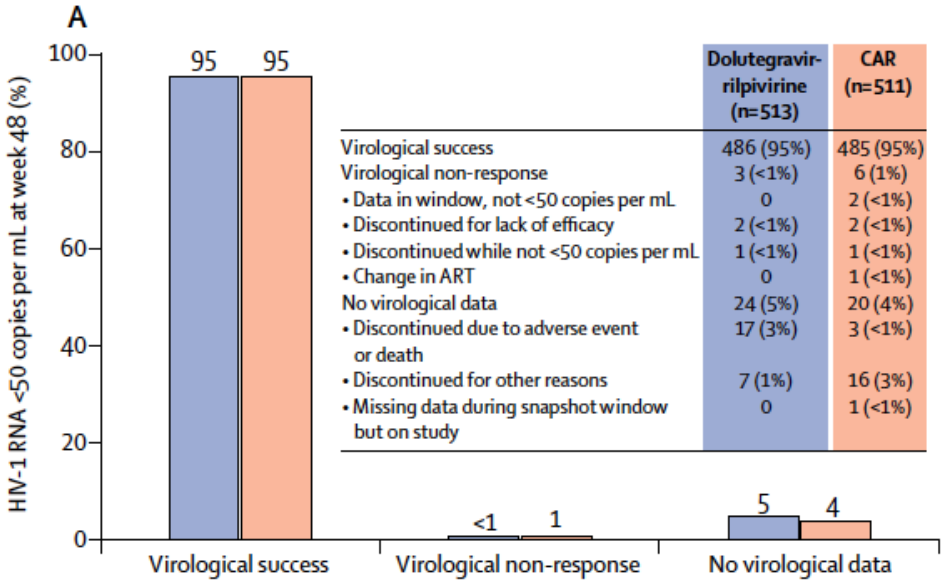
Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies

Lancet 2018; 391: 839–49

Josep M Llibre, Chien-Ching Hung, Cynthia Brinson, Francesco Castelli, Pierre-Marie Girard, Lesley P Kahl, Elizabeth A Blair, Kostas Angelis, Brian Wynne, Kati Vandermeulen, Mark Underwood, Kim Smith, Martin Gartland, Michael Aboud

We included participants aged 18 years or older who were on first or second ART with stable plasma HIV-1 RNA (viral load <50 copies per mL) for 6 months or longer at screening.





	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	0	1 (<1%)
No virological data	24 (5%)	20 (4%)
• Discontinued due to adverse event or death	17 (3%)	3 (<1%)
• Discontinued for other reasons	7 (1%)	16 (3%)
• Missing data during snapshot window but on study	0	1 (<1%)

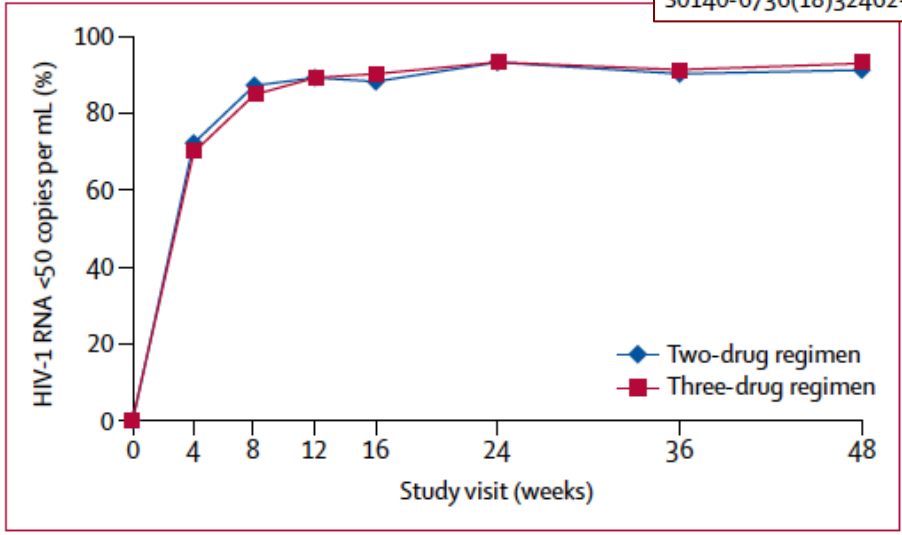
Dolutegravir-rilpivirine was non-inferior to CAR over 48 weeks in participants with HIV suppression and showed a safety profile consistent with its components. Results support the use of this two-drug regimen to maintain HIV suppression.

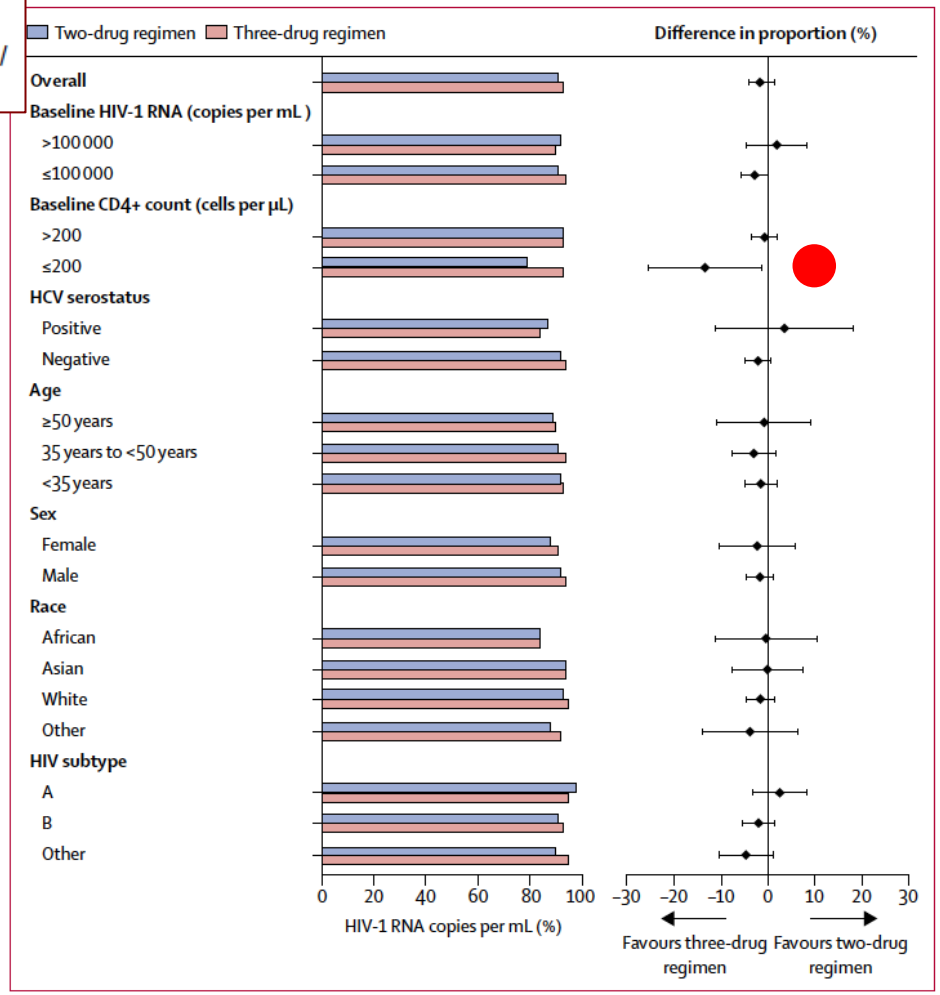
Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials

Pedro Cahn, Juan Sierra Madero, José Ramón Arribas, Andrea Antinori, Roberto Ortiz, Amanda E Clarke, Chien-Ching Hung, Jürgen K Rockstroh, Pierre-Marie Girard, Jörg Sievers, Choy Man, Alexander Currie, Mark Underwood, Allan R Tenorio, Keith Pappa, Brian Wynne, Anna Fettiplace, Martin Gartland, Michael Aboud, Kimberly Smith, and the GEMINI Study Team

Published Online
November 9, 2018
http://dx.doi.org/10.1016/S0140-6736(18)32462-0

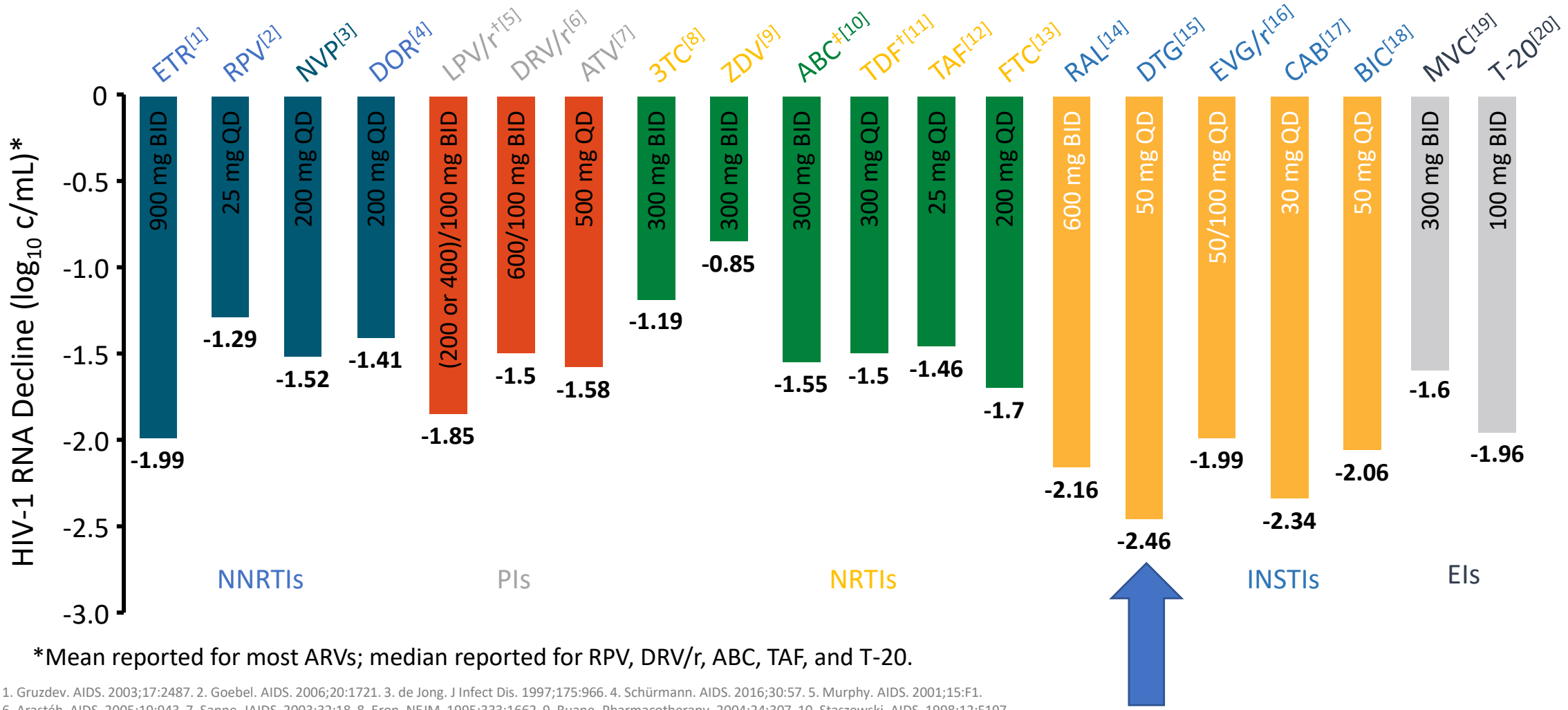
We included participants (≥18 years) with HIV-1 infection and a screening HIV-1 RNA of 500.000 copies per mL or less, and who were naive to ART.





The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a guideline recommended three-drug regimen at 48 weeks in ART-naive adults supports its use as initial therapy for patients with HIV-1 infection.

Why INSTIs?
Antiviral Activity After 7-14 Days of Monotherapy



*Mean reported for most ARVs; median reported for RPV, DRV/r, ABC, TAF, and T-20.

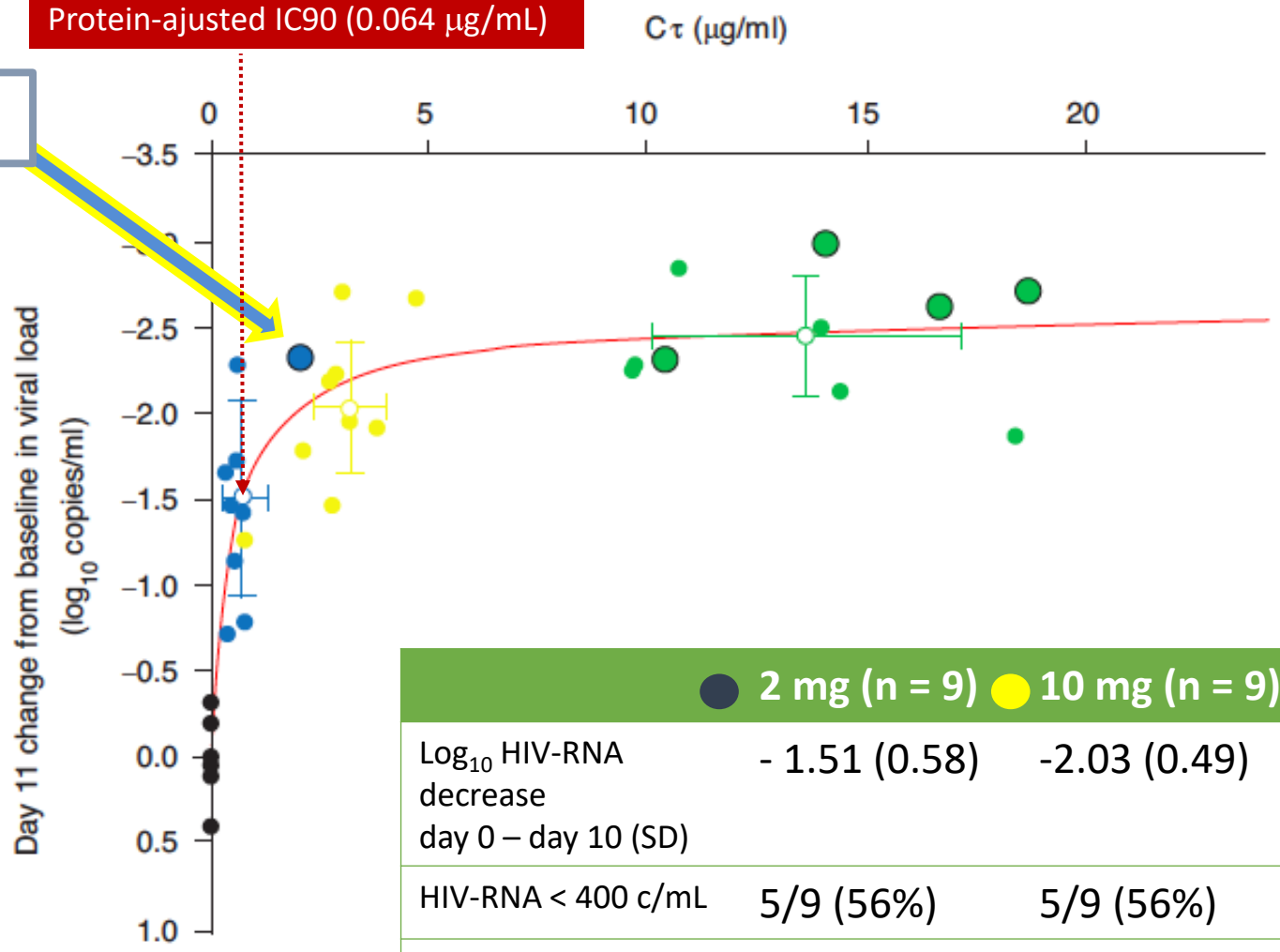
1. Gruzdev. AIDS. 2003;17:2487. 2. Goebel. AIDS. 2006;20:1721. 3. de Jong. J Infect Dis. 1997;175:966. 4. Schürmann. AIDS. 2016;30:57. 5. Murphy. AIDS. 2001;15:F1.
6. Arasteh. AIDS. 2005;19:943. 7. Sanne. JAIDS. 2003;32:18. 8. Eron. NEJM. 1995;333:1662. 9. Ruane. Pharmacotherapy. 2004;24:307. 10. Staszewski. AIDS. 1998;12:F197.
11. Louie. AIDS. 2003;17:1151. 12. Ruane. JAIDS. 2013;63:449. 13. Rousseau. J Infect Dis. 2003;188:1652. 14. Markowitz. JAIDS. 2006;43:509. 15. Min. AIDS. 2011;25:1737.
16. DeJesus. JAIDS. 2006;43:1. 17. Spreen. HIV Clin Trials. 2013;14:192. 18. Gallant. JAIDS. 2017;75:61. 19. Fätkenheuer. Nat Med. 2005;11:1170. 20. Kilby. Nat Med. 1998;4:1302.

Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults

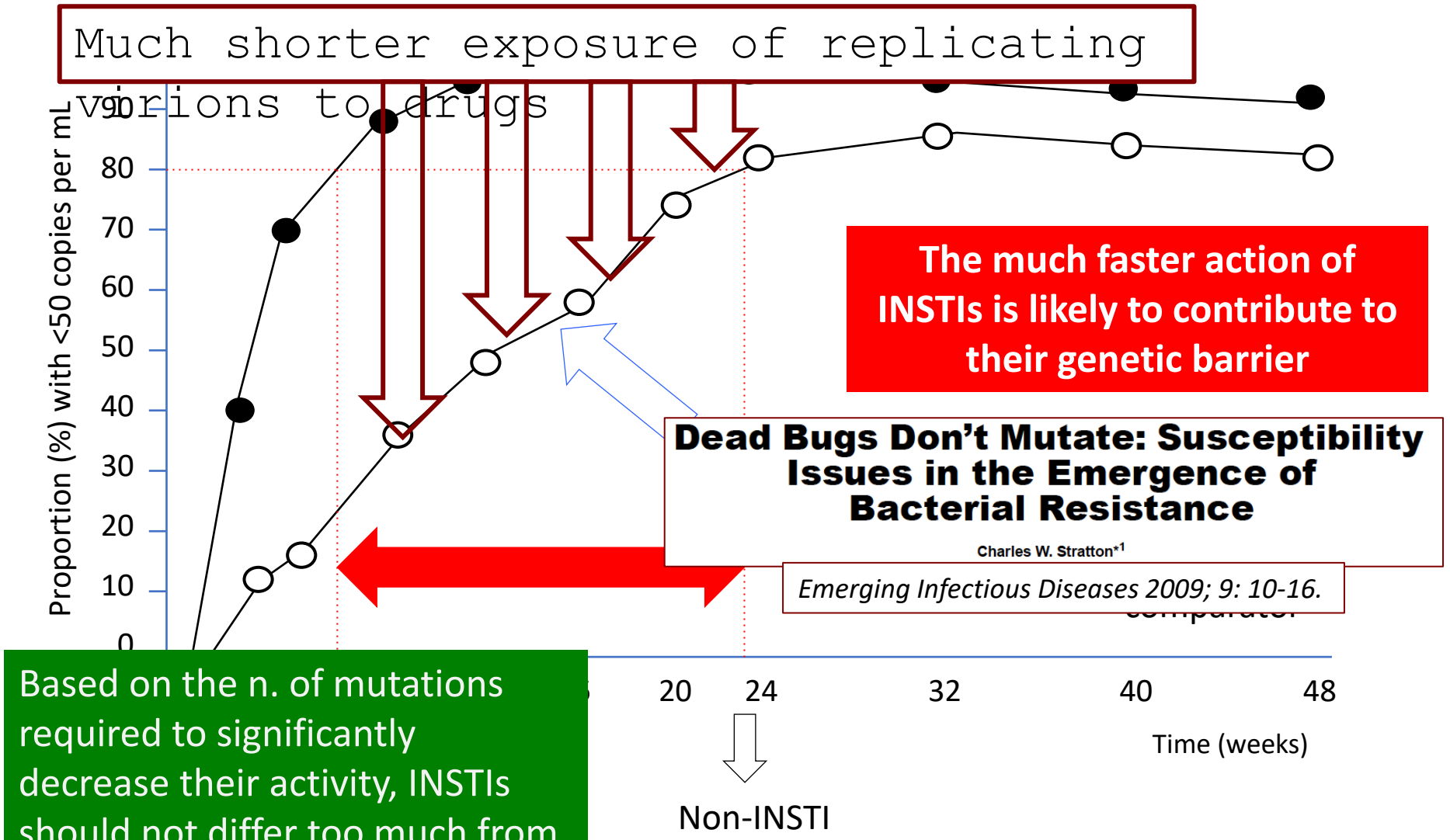
Min S, et al.
AIDS 2011, 25:1737–1745

Protein-ajusted IC90 (0.064 µg/mL)

2 mg dose



	2 mg (n = 9)	10 mg (n = 9)	50 mg (n = 10)
Log_{10} HIV-RNA decrease day 0 – day 10 (SD)	- 1.51 (0.58)	-2.03 (0.49)	-2.46 (0.35)
HIV-RNA < 400 c/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
HIV-RNA < 50 c/mL	1/9 (11%)	0	7/10 (70%)



e comparison between the viral decay associated to INSTIs and the one seen with a non-INSTI 3rd drug.. The double arrow identifies the different time required to achieve 80% of viral suppression; a much shorter exposure of the viral biomass to treatment drugs is seen with INSTIs (6 weeks) as compared to a non-INSTI 3rd drug (nearly 24 weeks). Di Perri G, et al. Teaching material

Snedecor SJ, et al. BMC Infect Dis. 2019; 19: 484

NMA study

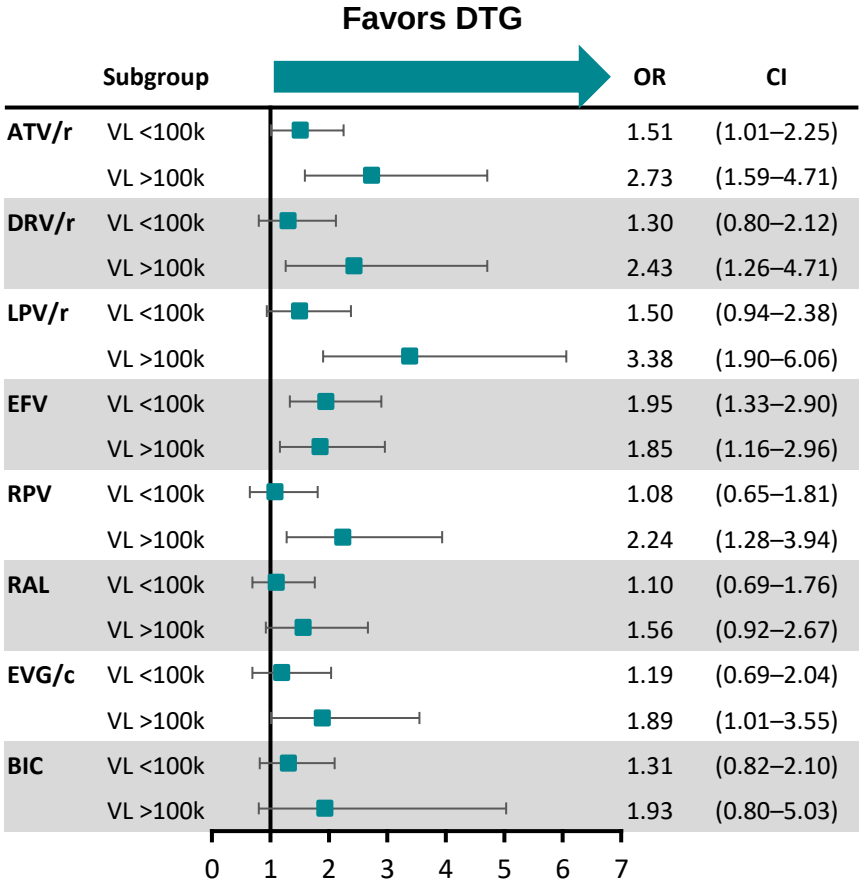
Network…… Meta…….. Analysis

The aim of this study was to compare the efficacy and safety of different 3rd-agent ARVs for treatment-naïve patients using a network meta-analysis (NMA)

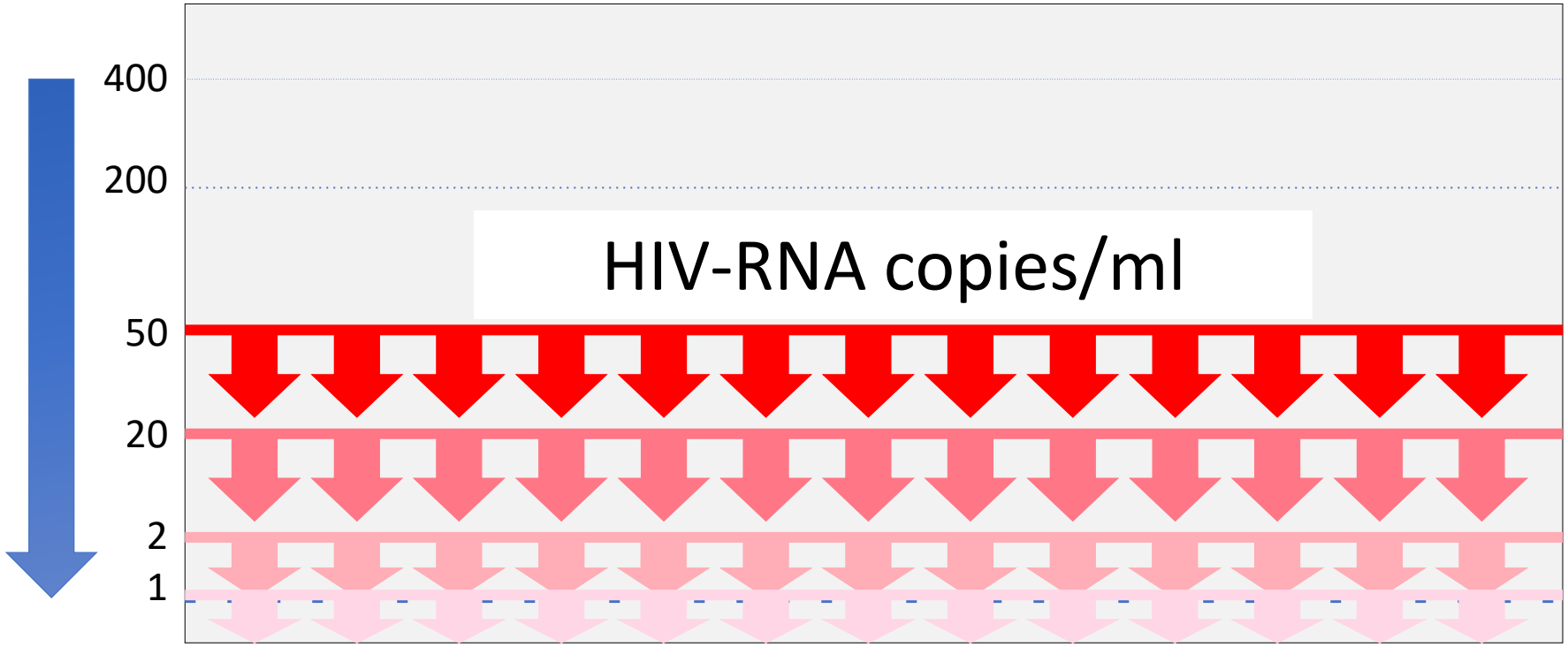
The NMA was based on a systematic review of the literature to identify relevant RCTs for inclusion

"Indirect comparisons are not randomized comparisons, and cannot be interpreted as such. They are essentially observational findings across trials, and may suffer the biases of observational studies, for example due to confounding."

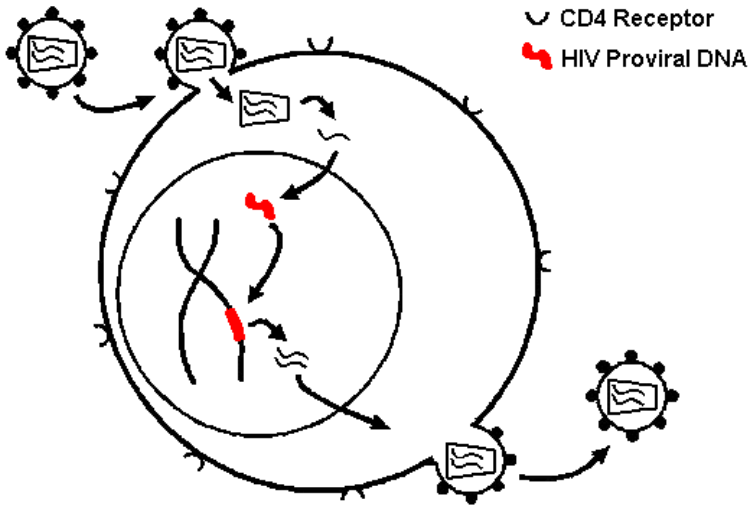
- High and low VL



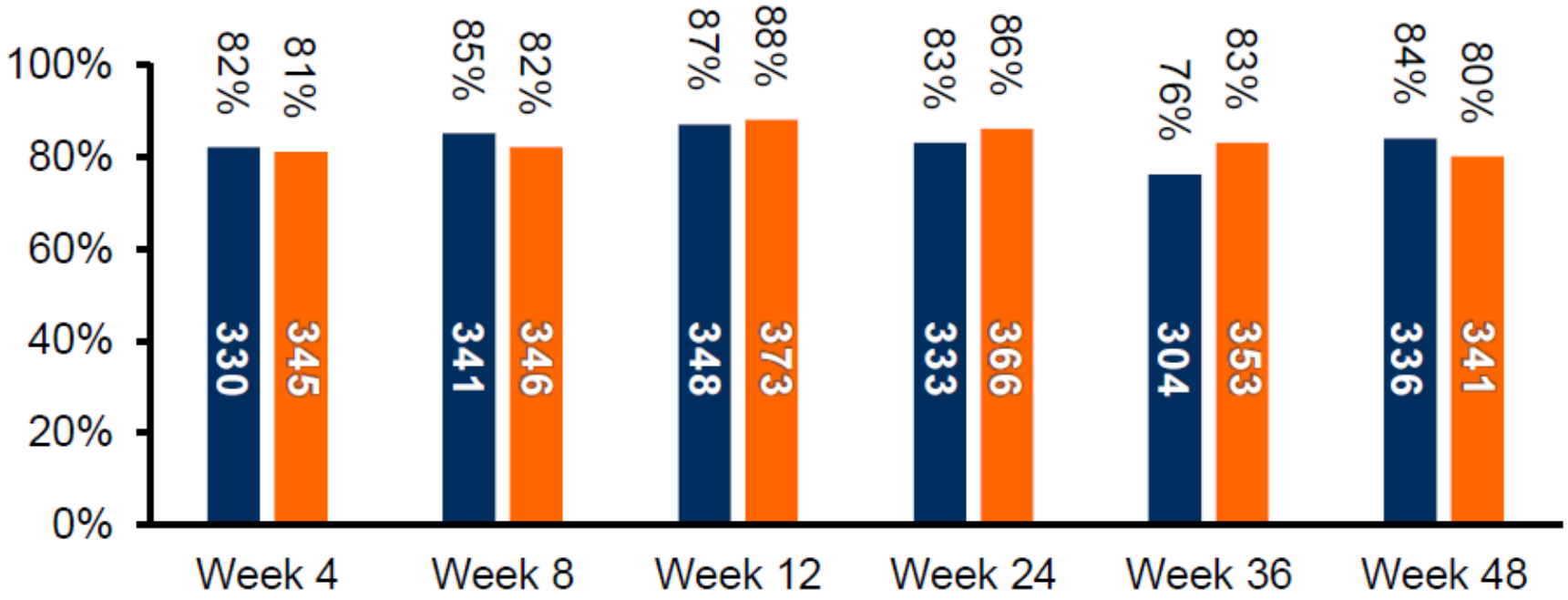
- ATV, atazanavir; BIC, bictegravir; c, cobicistat; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; LPV, lopinavir; OR, odds ratio; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; VL, viral load.



PROVIRAL HIV-DNA MEASUREMENT as a clinical tool to quantify HIV reservoir



Proportions of TND by Week for Participants With Baseline TND



- Similar proportions of participants with TND were observed at each visit in the DTG + RPV and CAR arms through Week 48 among participants with TND at Baseline

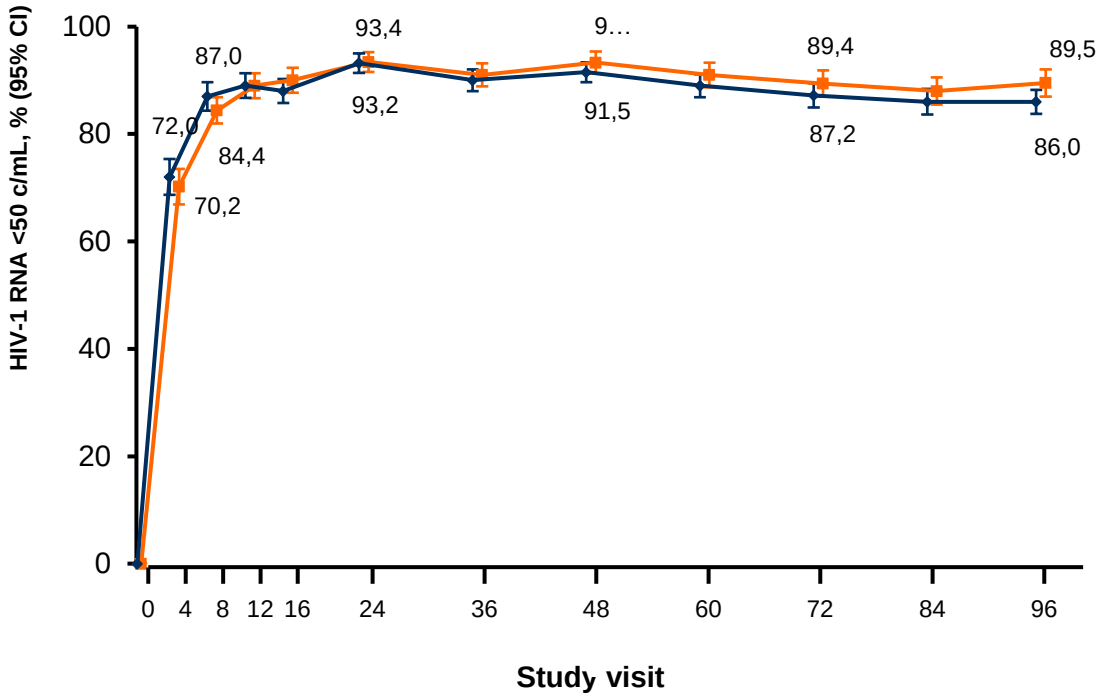
DTG + RPV

Current Antiretroviral Regimen (CAR)

Underwood et al. HIV Glasgow; Glasgow, UK. Poster P311.

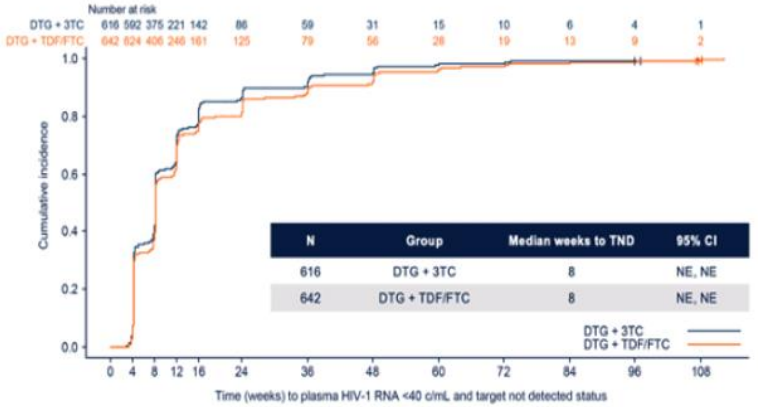
ASSESSMENTS OF VERY-LOW-LEVEL HIV REPLICATION FOR DOLUTEGRAVIR + LAMIVUDINE (DTG + 3TC) VS DOLUTEGRAVIR + TENOFOVIR DISOPROXIL/EMTRICITABINE (DTG + TDF/FTC) IN THE GEMINI-1&-2 STUDIES THROUGH WEEK 96

Mark Underwood, Rimgaile Urbaityte, Ruolan Wang, et al. 17th EACS 2019 Nov 6-9 Basel



	Treatment	Responders, n (%)	Adjusted difference, % (95% CI)[a]
Snapshot	DTG + 3TC	616/716 (86.0)	−3.4 (−6.7, 0.0)
	DTG + TDF/FTC	642/717 (89.5)	
TRDF	DTG + 3TC	692/716 (96.6)	0.2 (−1.8, 2.2)
	DTG + TDF/FTC	691/717 (96.4)	

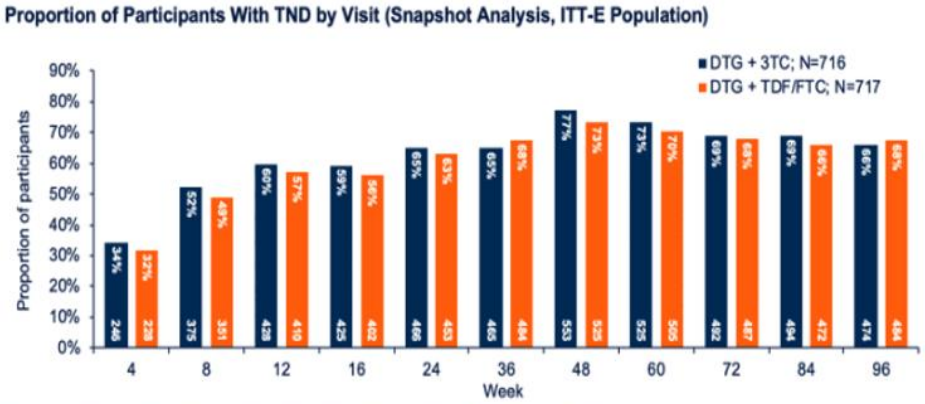
Similar Median Weeks to TND Across Groups in Observed Analysis



- Median 8 weeks to TND across groups was also seen by Snapshot analysis at Week 96 and was previously demonstrated for Week 48[1]

NE, not evaluable.
1. Underwood et al. CROI 2019; Seattle, WA. Poster 490.

Proportions With TND Were Similar Between Groups at All Visits

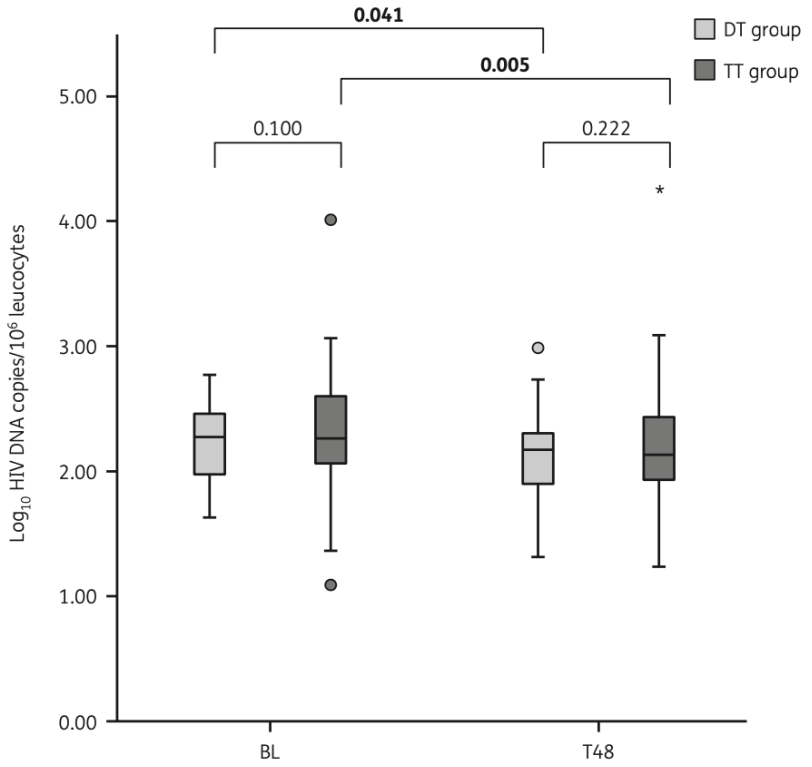


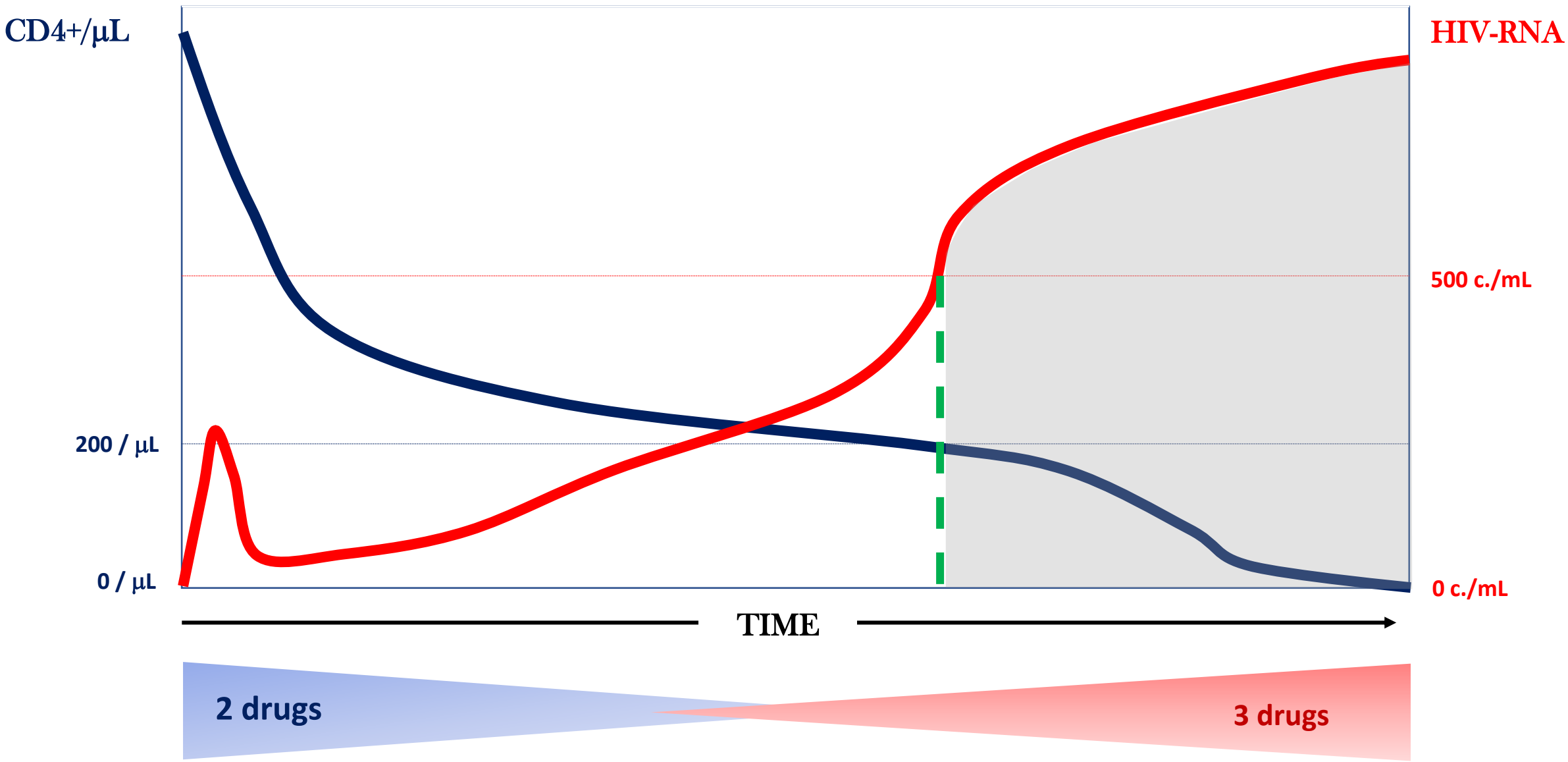
Number at base of bars is number of participants reaching TND at week visit

Evolution of cellular HIV DNA levels in virologically suppressed patients switching to dolutegravir/lamivudine versus maintaining a triple regimen: a prospective, longitudinal, matched, controlled study

Francesca Lombardi[1]*, Simone Belmonti[1], Alberto Borghetti[2], Massimiliano Fabbiani[3], Simona Marchetti[4], Enrica Tamburrini[1,2], Roberto Cauda[1,2] and Simona di Giambenedetto[1,2]

- We enrolled 40 patients in the DT group and 40 in the TT group; the two groups were homogeneous for all main characteristics except nadir CD4 cell count.
- Total blood- associated HIV DNA levels were assessed by droplet digital PCR at BL and after 48 weeks (T48). Results were expressed as log_{10} HIV DNA copies/10_6 leucocytes.
- Change in HIV DNA load from BL to T48 was -0.105 (IQR -0.384 to 0.121, P = 0.041) in the DT group and #0.132 (IQR -0.362 to 0.046, P = 0.005) in the TT group, with a comparable decline observed between the two groups (P = 0.821). A higher HIV DNA decline was associated with higher BL CD4/CD8 ratio.




CD4+/µL
HIV-RNA
500 c./mL
200 / µL
0 / µL
0 c./mL
TIME
2 drugs
3 drugs

Assessing Barrier to Resistance: *In Vitro* Methodology

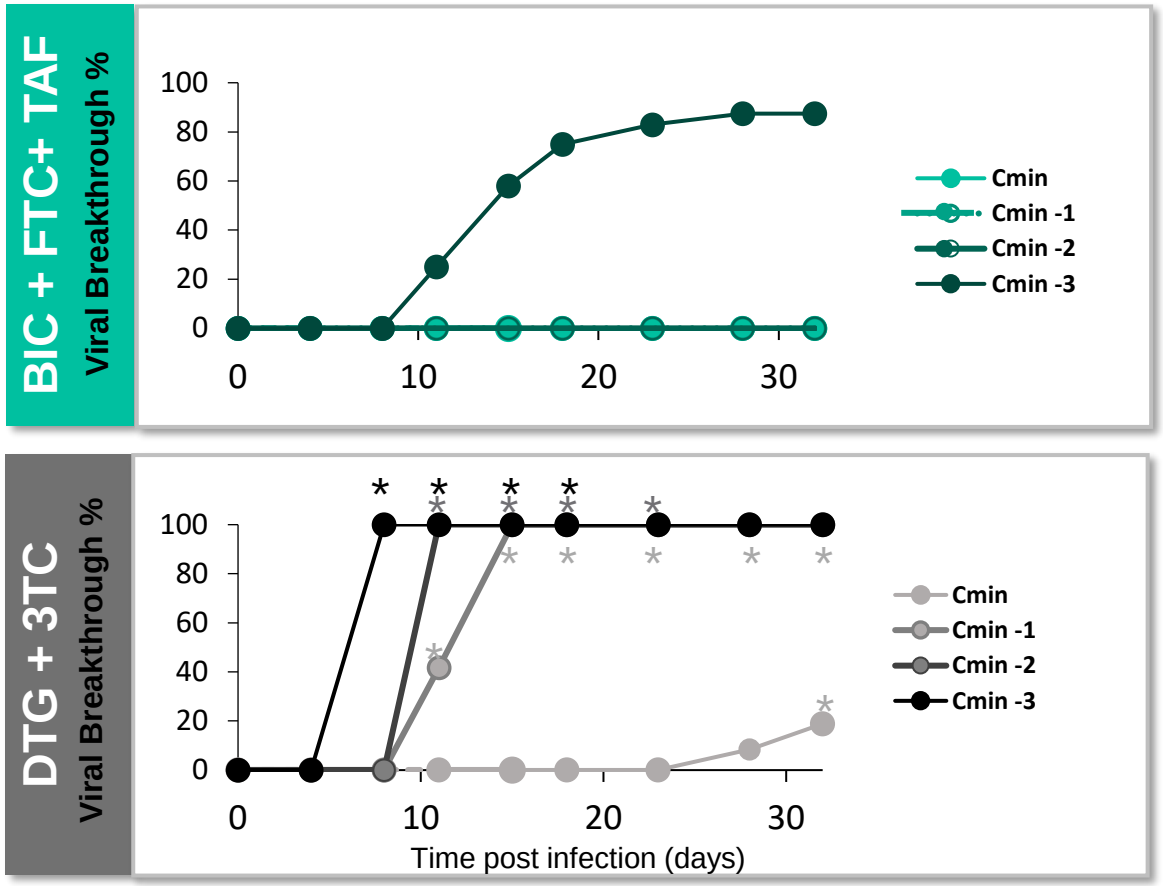
2 or 3 drugs ?

Which is the main doubt in HIV Doctor's mind ?

Mulato A, et al. IDWeek 2020. Poster #1448

Speed of Viral Breakthrough

Time to Viral Breakthroughs



Time to first viral breakthrough

	BIC + FTC + TAF	DTG + 3TC
Cmin	-	D23
Cmin - 1	-	D8
Cmin -2	-	D8
Cmin -3	D8	D4

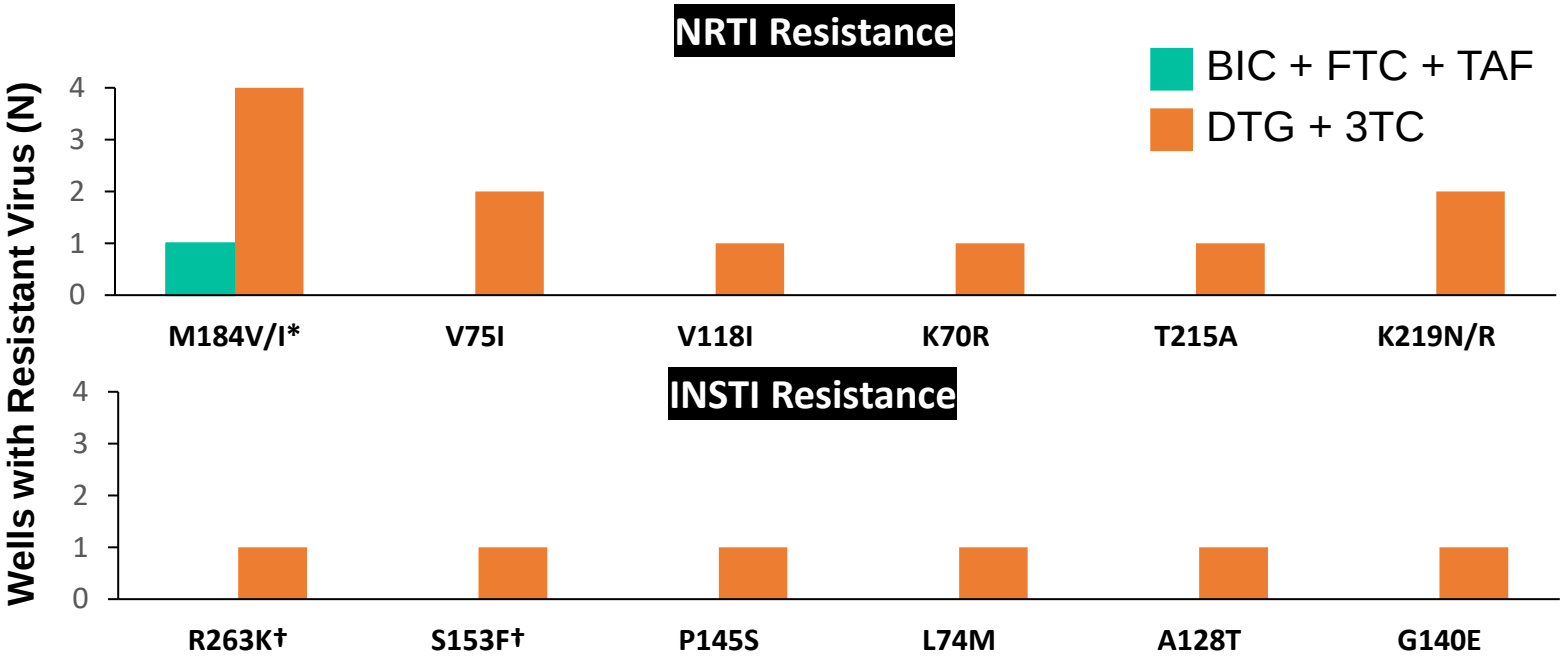
There was a lower threshold for viral breakthrough with missed doses for DTG + 3TC compared to BIC + FTC + TAF *in vitro* with wild-type HIV

Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

* P-value < 0.05 (Fisher’s Exact test, comparing BIC+FTC+TAF and DTG+3TC); ** HIV IIIb strain

In Vitro “Forgiveness” Studies: BIC+FTC+TAF vs DTG+3TC – WT virus**

Consequence of Viral Breakthrough: Emergent Resistance



Resistance Emergence in BIC + FTC + TAF wells

M184V/I (RT) occurred once (1/144) at Cmin-3

Resistance Emergence in DTG + 3TC wells

More resistance emergence with DTG+3TC (15/144) from Cmin to Cmin-2

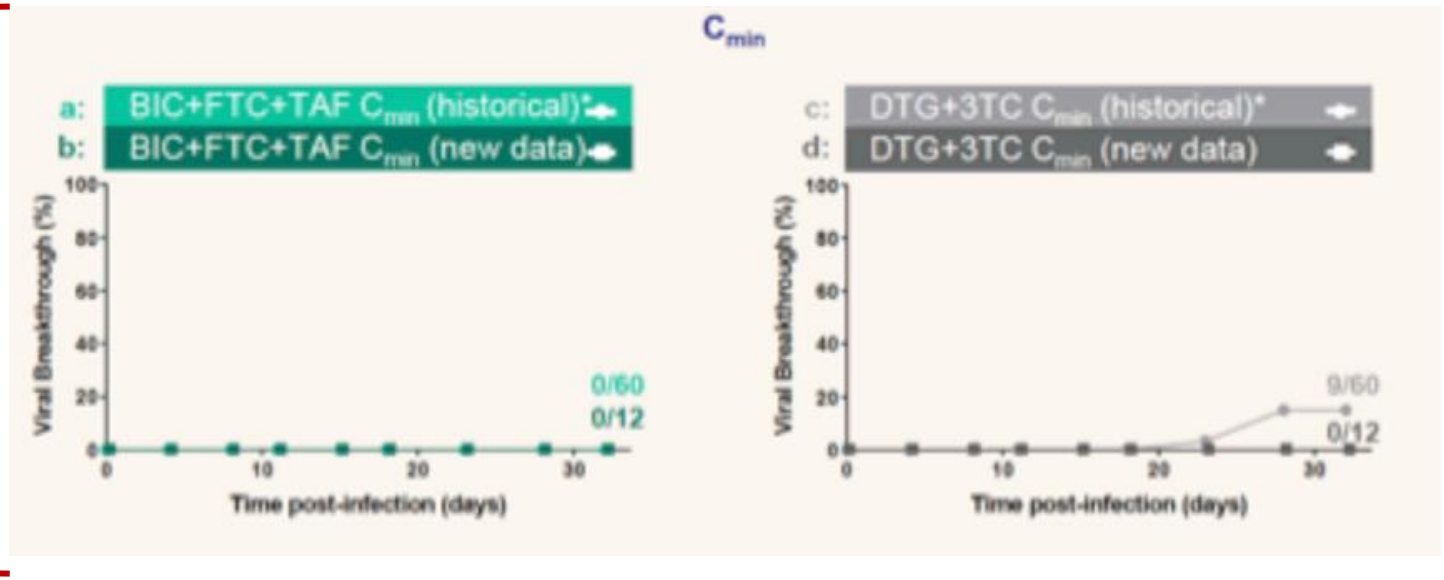
Emergence of both INSTI and NRTI resistance

***In vitro* emergent drug resistance was less common with BIC+FTC+TAF compared to DTG+3TC in wild-type HIV**

* M184V and M184I cause high-level resistance to FTC and 3TC and increased sensitivity to TAF; ** HIV IIIb strain
† R263K and S153F have been previously selected by DTG and cause reduced susceptibility to DTG. The well with R263K in IN also had T215A and K219R present.
Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

- The “in vitro” simulation of decreasing adherence might not include the complete interplay of “in vivo” factors
- The dynamic environment of ”in vivo” situation might compensate for decreased drug exposure of the target (e.g. dissociation time)
- The effect of long-term HIV suppression cannot be easily translated into an “in vitro” simulation
- Inspite adjustment for protein binding, plasma half-lives of the different drugs and their metabolites, other “in vivo” variables might not be entirely reproducible “in vitro” (e.g. broadly neutralizing antibodies, CD4+, T-cells)

The late viral breakthrough seen in control plates with DTG + 3TC is an unlikely event “in vivo”

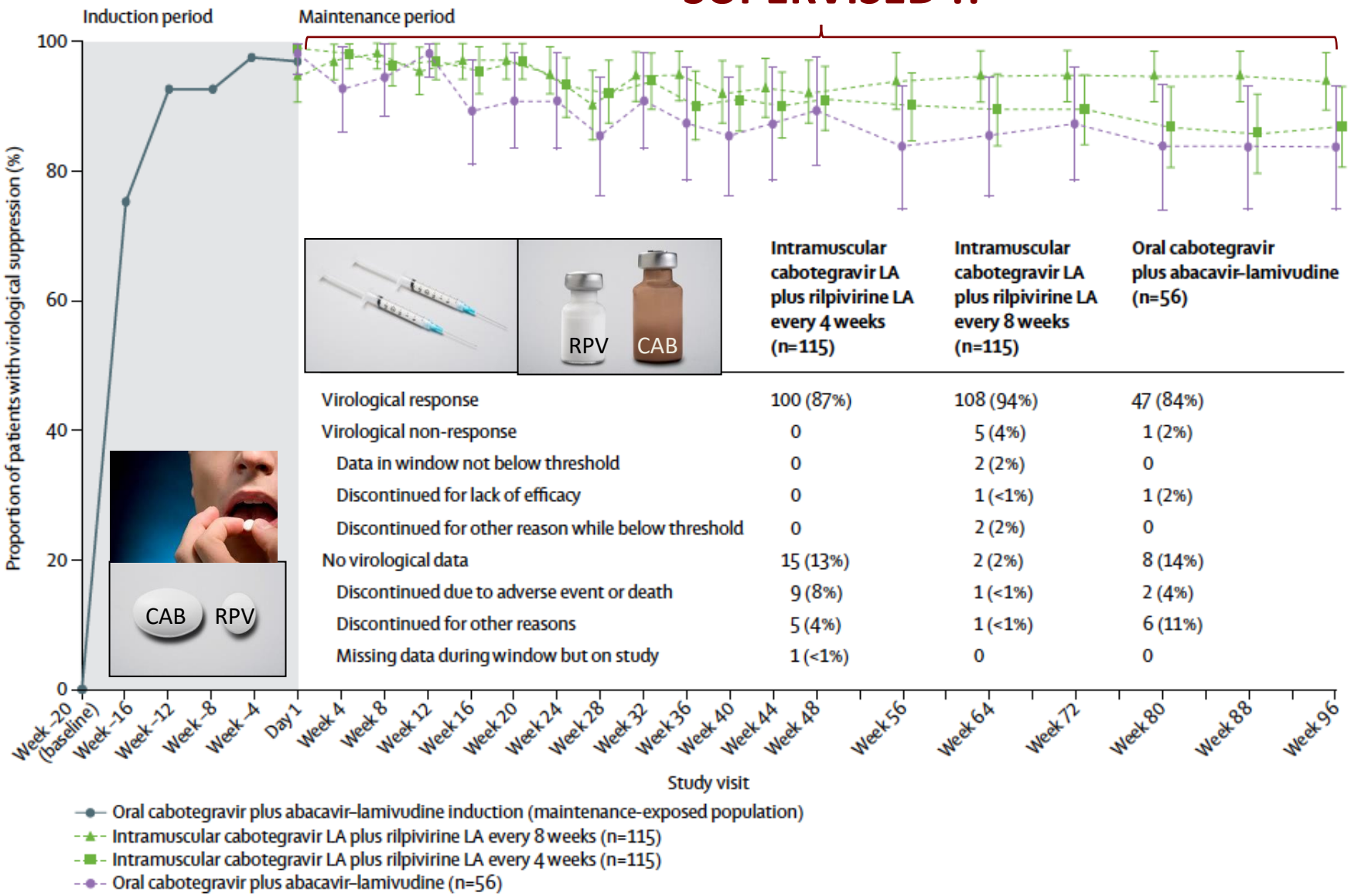


Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al

Lancet 2017; 390: 1499–510

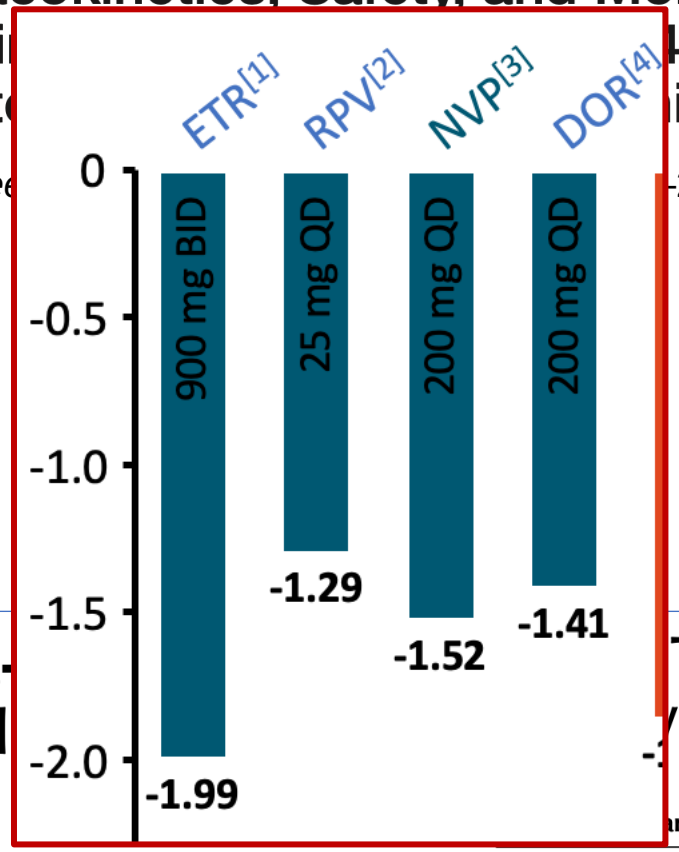
SUPERVISED !!

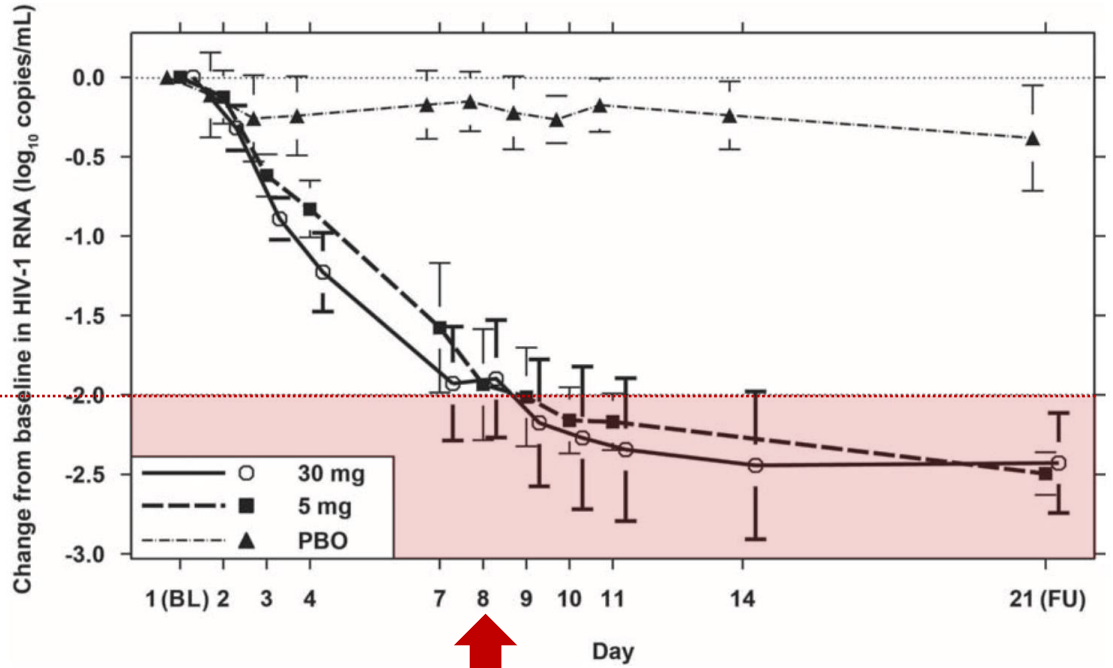


	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

Pharmacokinetics, Safety, and Monotherapy Antivi… …4, an HIV Int… …ibitor

W. Spree… …-203





Short-… NNRTI… …TMC278 – a novel …-1-infected subjects

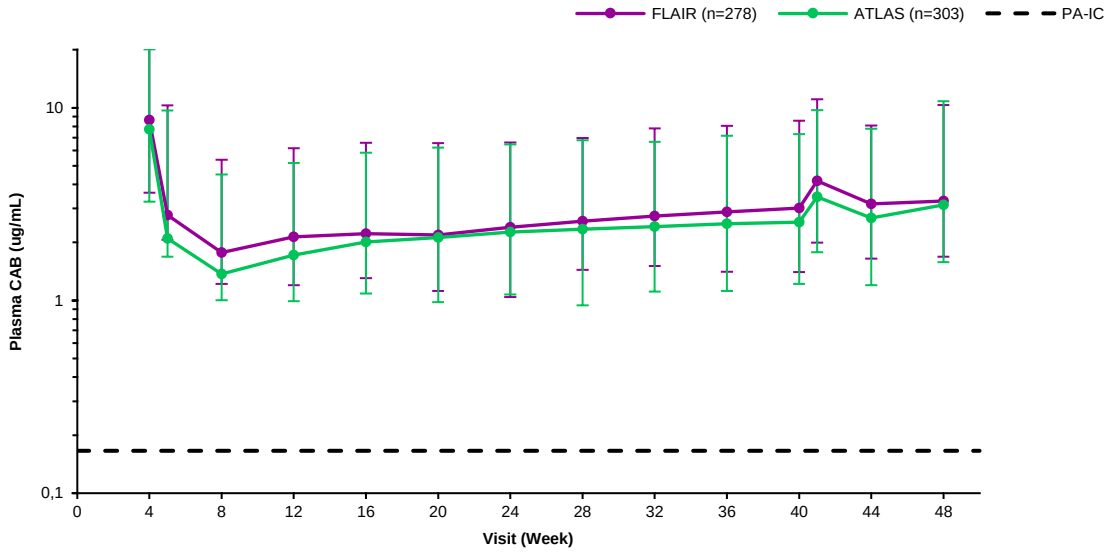
Frank Goebel, et al. AIDS 2006, 20:1721–1726

…n changes from baseline in log_{10} HIV-1 RNA viral load on day 8.

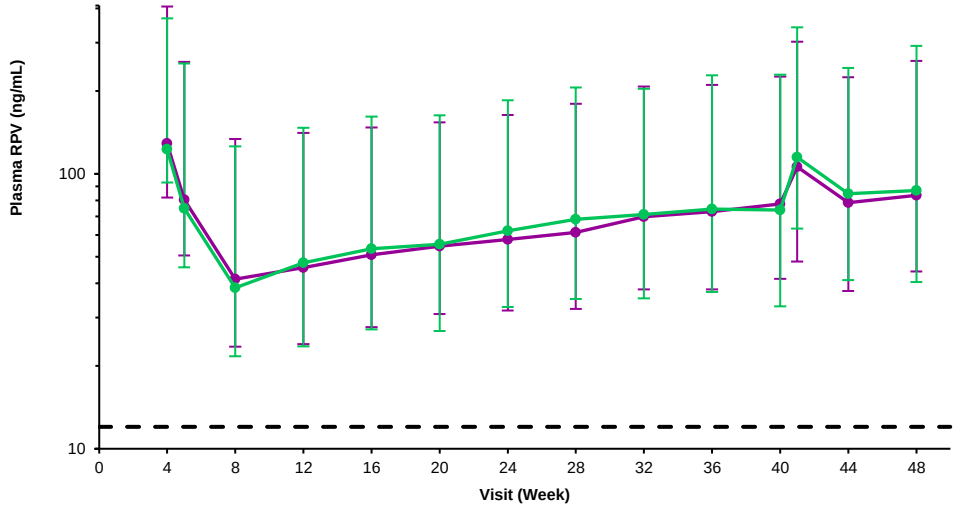
	TMC278					
	25 mg q.d.	50 mg q.d.	100 mg q.d.	150 mg q.d.	Placebo	All groups
Patients (n)	9	9	9	9	11	36
Viral load reduction from baseline to day 8 (log_{10} copies/ml) [median (range)]	−1.287* (−0.93 to −1.86)	−1.225* (−0.77 to −1.50)	−1.067* (−0.89 to −1.54)	−1.172* (−0.66 to −1.53)	+0.002 (−0.97 to +0.28)	−1.199* (−0.66 to −1.86)
Median viral load reduction at nadir (log_{10} copies/ml)	−1.30**	−1.23**	−1.17**	−1.27**	−0.34	
Patients with a decrease in viral load > 1 log_{10} (n)	6***	6***	7***	6***	0	25***

LA CAB and RPV PK Q4W

Median (5th and 95th centile) plasma CAB



Median (5th and 95th centile) plasma RPV PK



Oral lead-in period	Initiation dose (Week 4b)	Continuation dose Week 8 and every 4 weeks thereafter
CAB 30 mg once daily	CAB LA 600 mg IM (3 mL x 1)	CAB LA 400 mg IM (2 m L x 1)§
RPV 25 mg once daily	RPV LA 900 mg IM (3 mL x 1)	RPV LA 600 mg IM (2 mL x 1)§

LA = long-acting; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

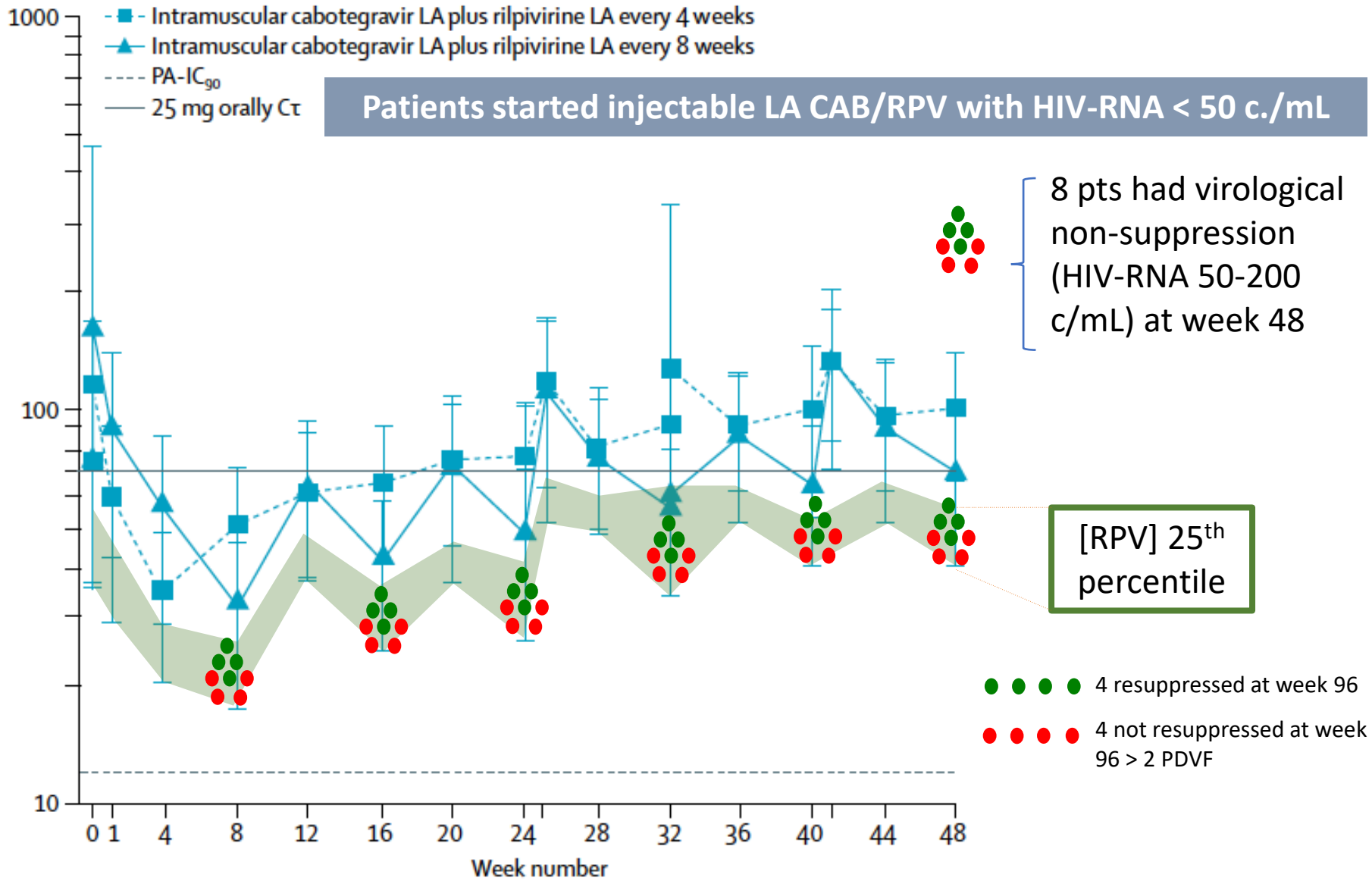
Patel et al. IDWeek 2019

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al

Lancet 2017; 390: 1499–510

SUPERVISED ADMINISTRATION !



Patients started injectable LA CAB/RPV with HIV-RNA < 50 c./mL

8 pts had virological non-suppression (HIV-RNA 50-200 c/mL) at week 48

[RPV] 25th percentile

4 resuppressed at week 96

4 not resuppressed at week 96 > 2 PDVF

A COMBINATION OF VIRAL AND PARTICIPANT FACTORS INFLUENCE VIROLOGIC OUTCOME TO LONG-ACTING CABOTEGRAVIR + RILPIVIRINE: MULTIVARIABLE AND BASELINE FACTOR ANALYSES ACROSS ATLAS, FLAIR AND ATLAS-2M PHASE 3 STUDIES

Margolis et al. HIV Glasgow 2020; Virtual. Slides 0442.

Multivariable Analysis: The Majority of CVFs* had Multiple Potential Factors

Study	ID	CAB PK† ≤Q1	RPV PK† ≤Q1	Subtype A6/A1	Baseline IN L74I‡	Baseline INSTI mutation	Baseline RPV RAM	Baseline NNRTI RAM	Female at birth	BMI ≥30	Q8W
ATLAS-2M	1	√	√		√	√	√	√	√	√	√
ATLAS-2M	2	√	√	√	√				√	√	√
ATLAS	3	√	√	√	√		√		√		
ATLAS	4	√	√				√	√	√	√	
FLAIR	5	√	√	√	√			√		√	
FLAIR	6	√	√	√	√				√	√	
FLAIR	7	√	√	√	√				√	√	
ATLAS-2M	8			√	√		√	√	√	√	√
ATLAS-2M	9	√	√								
ATLAS	10		√	√	√						
ATLAS-2M	11						√	√		√	√
ATLAS-2M	12		√								√
ATLAS-2M	13							√			

ISLATRAVIR, a First-in-Class NRTTI With Multiple MOAs

The 3'OH group of the last incorporated nucleotide binds with the tri-P group of the incoming…

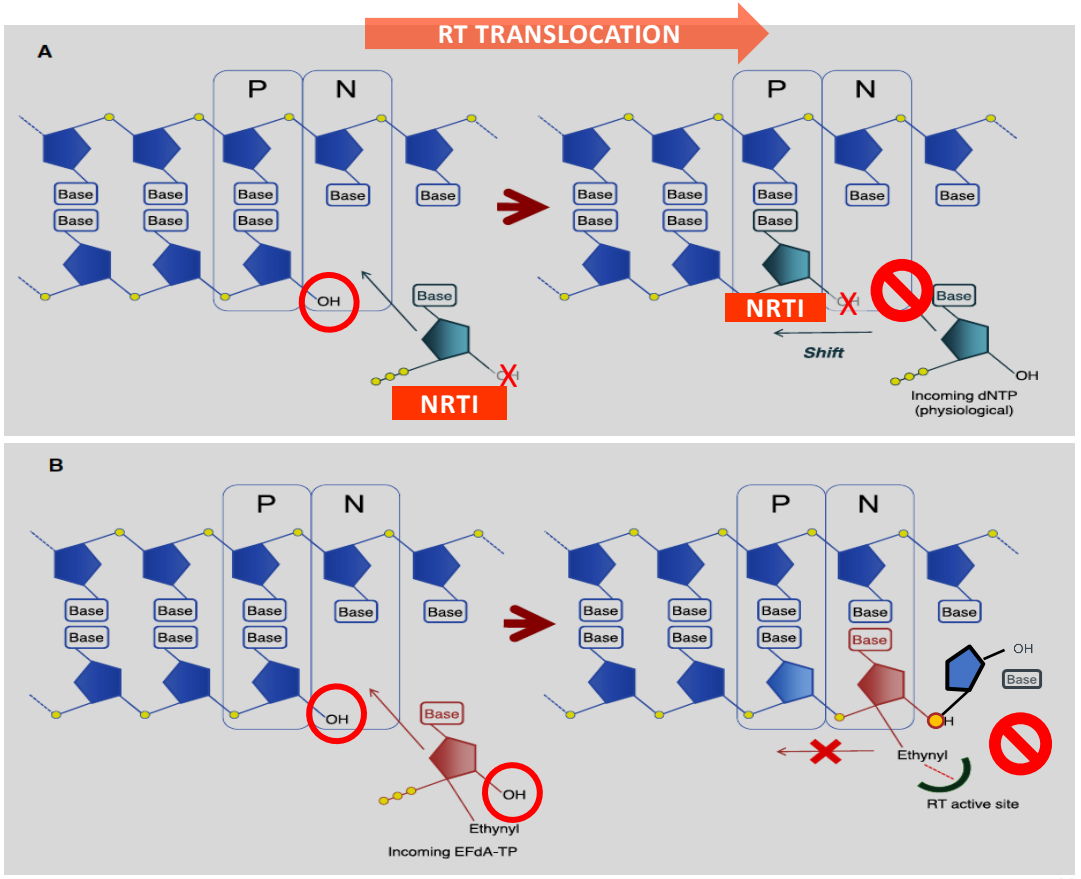
NRTI

- Translocation occurs for further nucleotide incorporation
- Immediate chains termination occurs due to the lack of 3'OH group of the incorporated NRTI

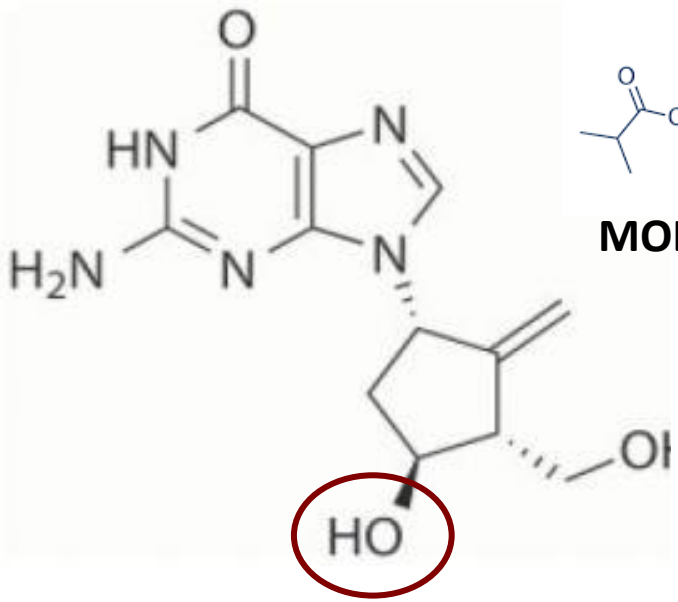
ISL

- **Translocation inhibition**: Translocation is inhibited by the strong interactions of the hydrophobic 4´-ethynyl group with the hydrophobic pocket of the RT active site. Immediate inhibition of further nucleotide incorporation.

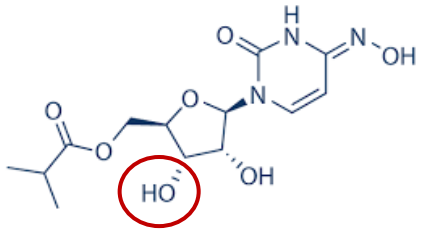
- **Delayed chain termination:** In the event that RT translocation does occur…. A new nucleotide is added to the 3'OH group of the incorporated EFdA, but the steric crowding by the 4'-ethynyl group OH group distorts the structural conformation of the cDNA, leading to delayed chain termination.
- EFdA is not longer susceptible to resistance-conferring mutations, once out of the active site.



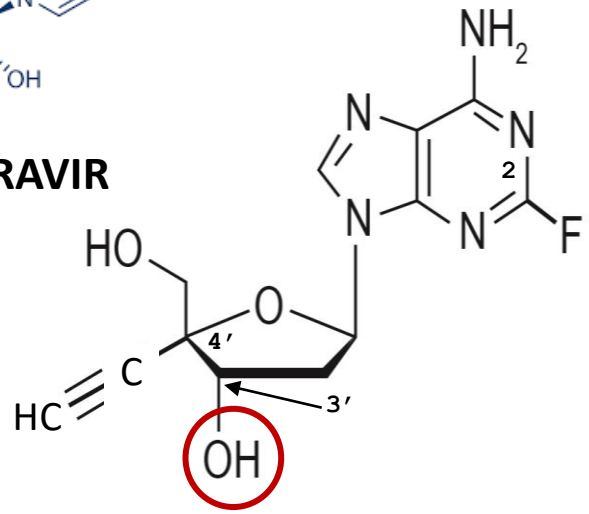
D'après JC TARDY – Synergie et Résistances 2018
Salie et al. PNAS 2016. Michailidis E et al. J Biol Chem. 2014;289(35):24533-24548



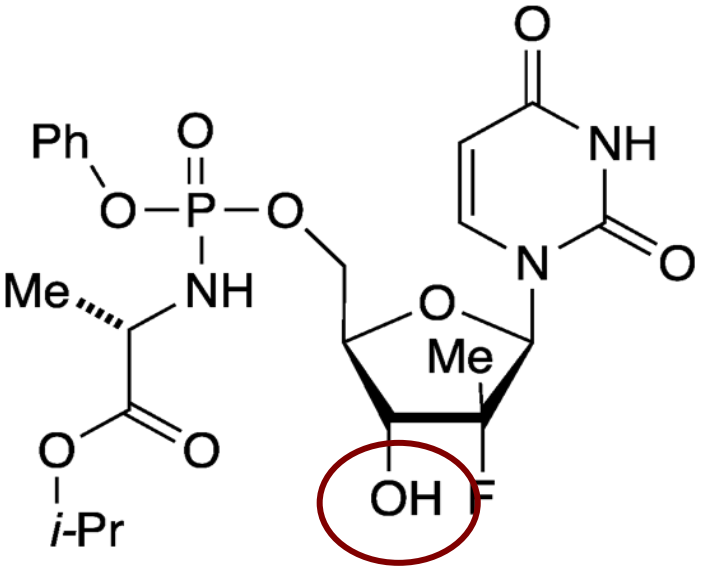
ENTECAVIR



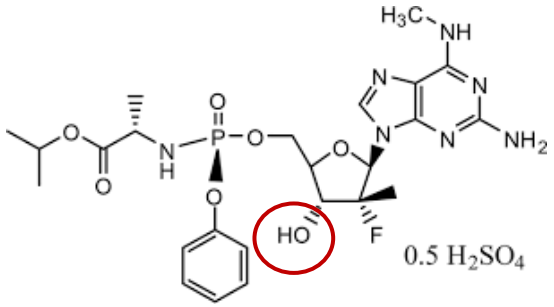
MOLNUPIRAVIR



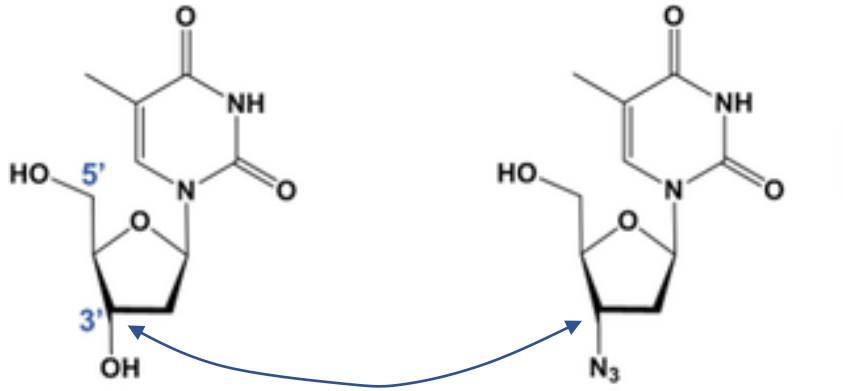
ISLATRAVIR



SOFOSBUVIR

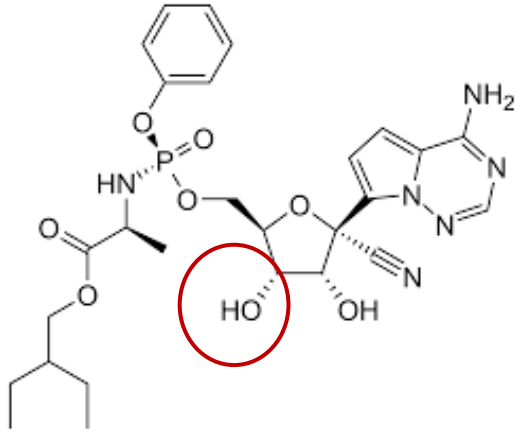


AT - 527



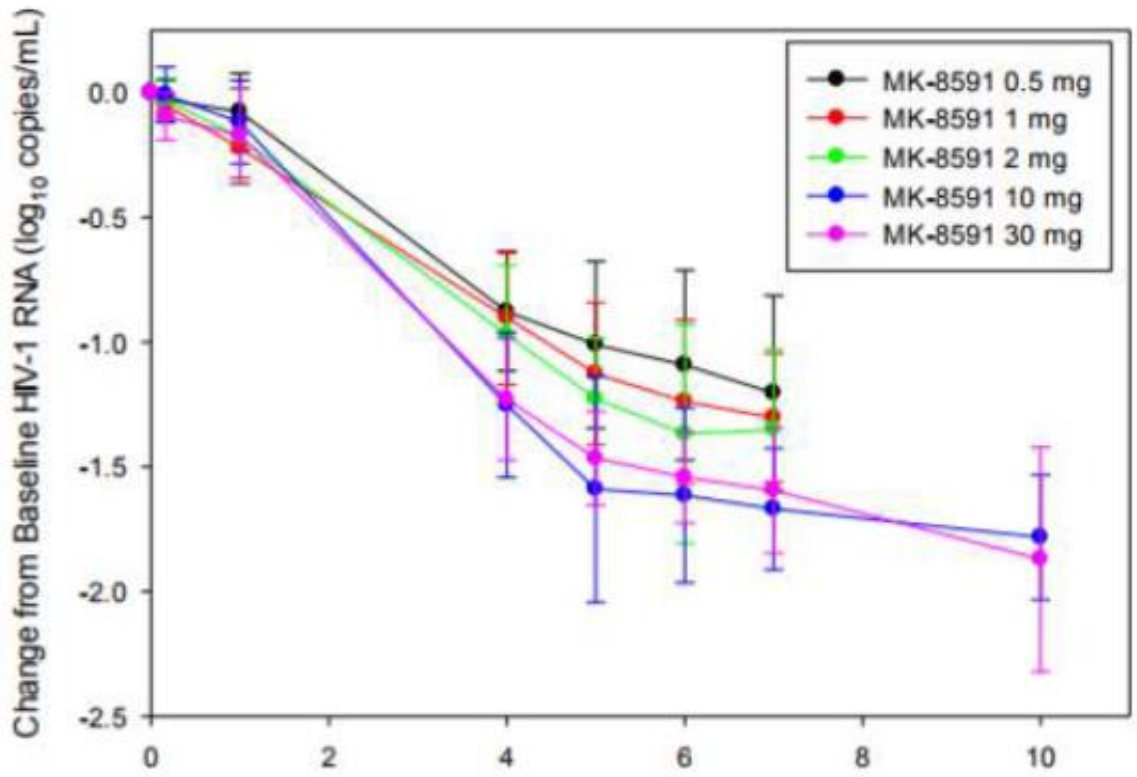
Thymidine

Azidothymidine (AZT)
Zidovudine



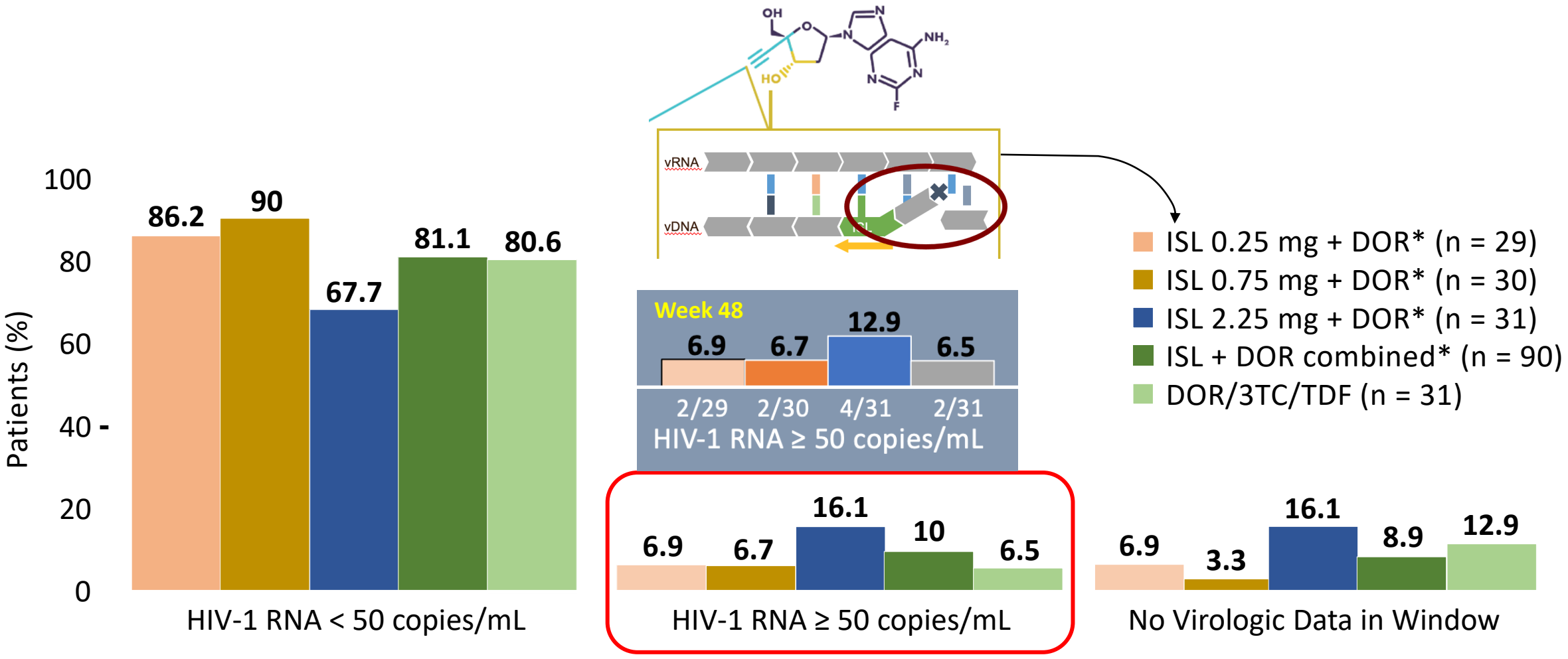
REMDESIVIR

MK-8591: Single-dose (!) Pharmacodynamic Study



Matthews RP, et al. Paris IAS 2017, TUPDB0202LB.

P011: Virologic Outcomes at Wk 96 by FDA Snapshot



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR for the Wk 24-96 period of the study.

Molina. HIV Glasgow 2020. Abstr O415.

Trials of long-acting islatravir for HIV treatment and prevention placed on hold

Liz Highleyman | 21 December 2021

On **December 13**, the US Food and Drug Administration (**FDA**) placed a clinical hold on **islatravir**, a long-acting experimental antiretroviral from Merck that is being developed for HIV treatment and prevention.

The move came after HIV-positive participants in treatment trials and HIV-negative volunteers in pre-exposure prophylaxis (PrEP) studies experienced **declining CD4 cell** or **total lymphocyte counts**. The reason for the apparent side effect is not well understood at this time, nor is the fate of islatravir going forward.

Islatravir has shown good activity in a once-daily combination with Merck's approved NNRTI doravirine .
At the recent European AIDS Conference, researchers reported that the regimen led to sustained viral suppression for 144 weeks in people new to treatment.
In addition, data from the phase III ILLUMINATE SWITCH trials showed than the combination maintained viral suppression for 48 weeks in people who switched from their current regimen to islatravir plus doravirine.

However, doravirine is not suitable for long-acting therapy, so Merck paired islatravir with its experimental long-acting NNRTI MK-8507 in a once-weekly regimen evaluated in the phase II IMAGINE-DR trial.

But a couple weeks after the conference, Merck announced that it was halting IMAGINE-DR after participants randomised to receive once-weekly islatravir plus MK-8507 experienced a **decline in CD4 cells**.

Trials of long-acting islatravir for HIV treatment and prevention placed on hold

Liz Highleyman | 21 December 2021

While islatravir plus MK-8507 had an additive effect on CD4 counts, with the greatest decreases seen in those who received the **highest doses of MK-8507**, declines were also seen when islatravir was used in **combination with doravirine or alone. So far, an additive effect has not been seen with lenacapavir.**

Declines in CD4 counts were very **small** and **subtle** in trials of **once-daily islatravir** but **larger in studies of monthly dosing**. Starting treatment for the first time typically leads to a gain in CD4 cells, which could mask a small drug-related decline in treatment-naive people.

In switch studies, in which people taking daily **islatravir plus doravirine** experienced about a **40-cell decrease** while those in the **control group saw about a 30-cell increase**. But in an individual with around 700 CD4 cells, that change initially didn't look clinically meaningful,

Among those who received **higher doses** of **islatravir once weekly**, the effect was **larger** and **more apparent**, with some study participants seeing a **50% drop in their CD4 cells** and some falling below the 200 cells/mm^3 threshold. However, there have been no cases of virological failure,

In the PrEP programme, lymphocyte counts **fell by about 20%,** but levels remained within the normal range. **CD4 cell levels** specifically **are not usually measured in healthy HIV-negative study participants**. The islatravir **implant** releases a daily **drug level below that of once-daily dosing**, and hopeful its development can continue.

Trials of long-acting islatravir for HIV treatment and prevention placed on hold

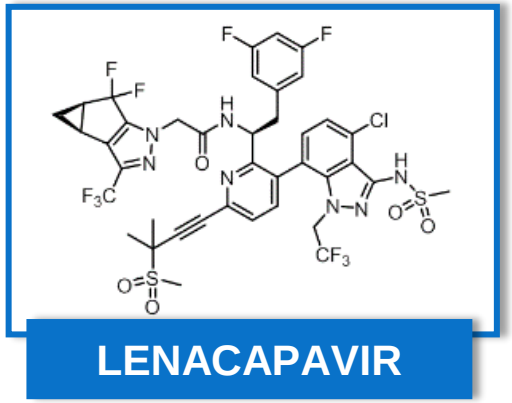
Liz Highleyman | 21 December 2021

Merck did extensive **animal studies** prior to human trials and saw no signal of this adverse effect, but the drug is metabolized very differently in animals and people, he explained. Once the mechanism and its relation to drug levels becomes clearer, it may be possible to resume development of islatravir, **perhaps with different dosing**.

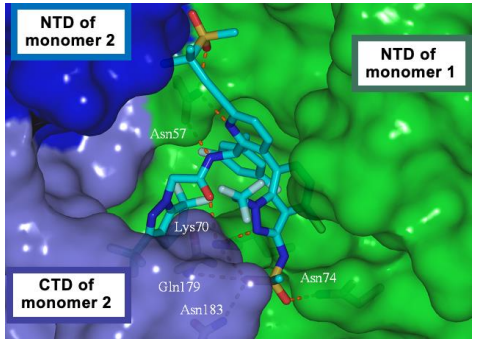
"*We don't have a full explanation right now*," Dr Michael Robertson, executive director of Merck Research Laboratories, said during a December 16 virtual meeting with HIV community advocates. "*The CD4 count is concerning, but **the overall safety profile [of islatravir] has been really excellent**, so we don't want to throw the baby out with the bathwater.... We're going to do everything we can to understand that and see if there's a path forward, but it's going to take some time.*"

Lenacapavir (LEN): Capsid Inhibitor

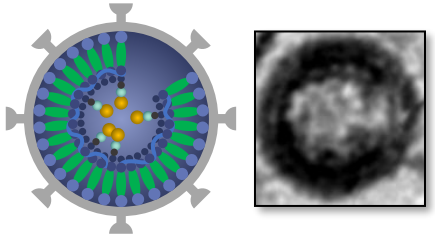
Capsid Assembly

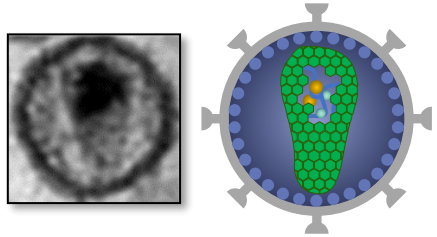


LEN binds at the interface of two adjacent capsid monomers
Pocket naturally binds nuclear import factors necessary for virus replication

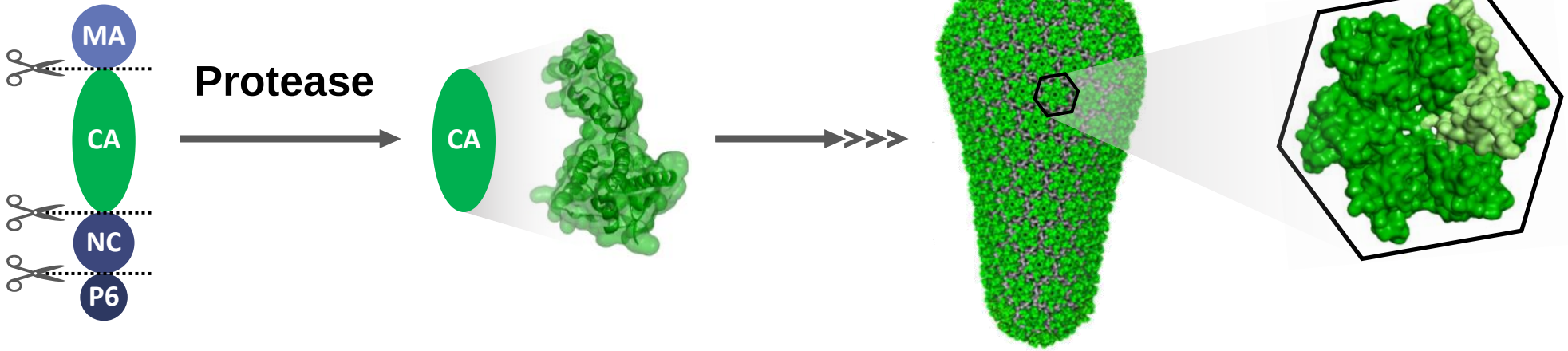


Immature virion





Mature virion



Gag (p55) | **Capsid protein (p24) (monomer)** | **Capsid core** | **Capsid hexamer**

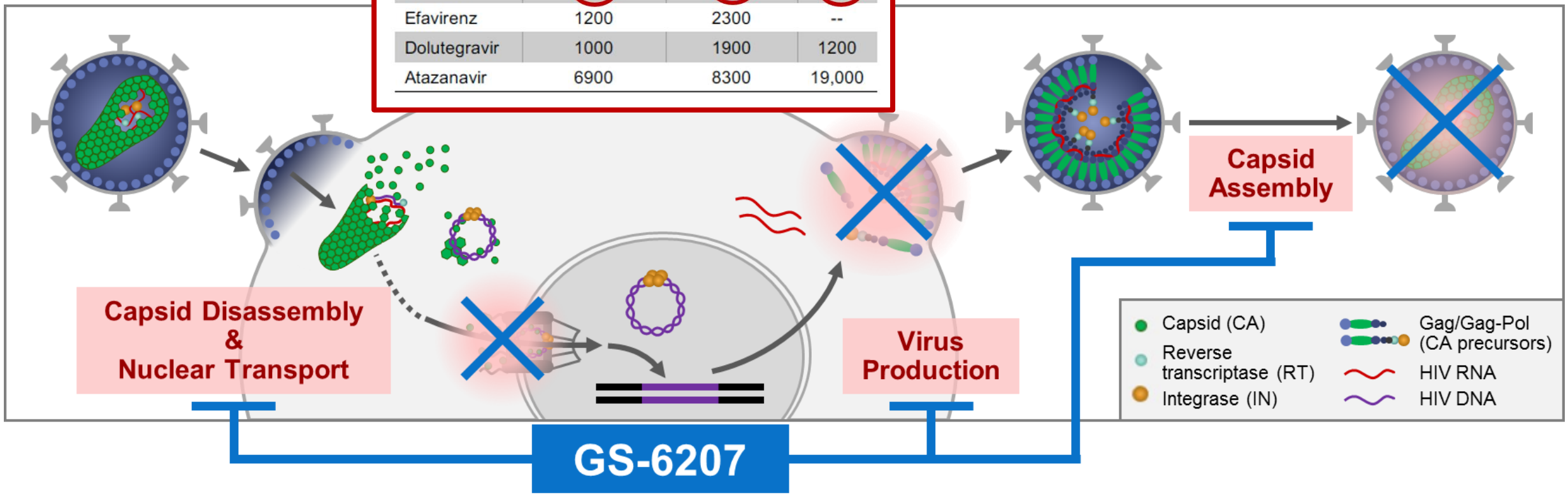
HIV capsid protein (CA; p24) is a product of HIV group-specific antigen (gag) processing by HIV protease, which plays a key role in the HIV life cycle

CA, capsid; MA, matrix; NC, nucleocapsid.

Yant S, et al. Bay Area Symposium on Viruses. June 2019. Berkeley, CA

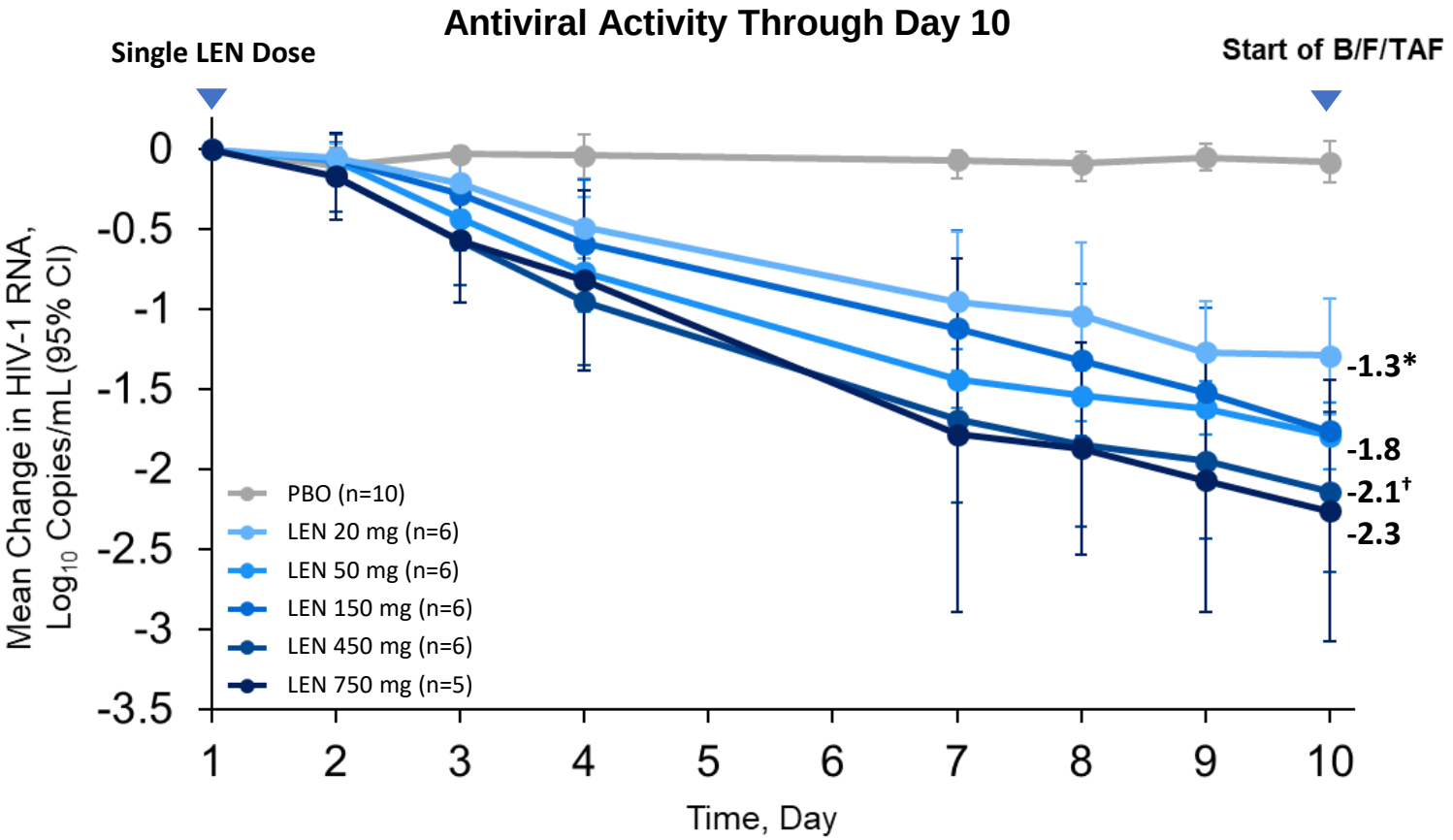
First-in-Class HIV Capsid Inhibitor: Mechanism of Action

	EC_{50} (pM)		
	CD4+ T Lymphocytes	Macrophages	Human PBMCs
GS-CA1	60	100	140
Efavirenz	1200	2300	--
Dolutegravir	1000	1900	1200
Atazanavir	6900	8300	19,000



LEN inhibits CA-mediated nuclear entry of viral DNA, HIV assembly, and proper capsid formation, functions essential for viral replication

Antiviral Activity of a Single Subcutaneous Dose



- Maximum mean HIV-1 declines for each group ranged from -1.4 to -2.3 $\log_{10}$ c/mL over 10 days

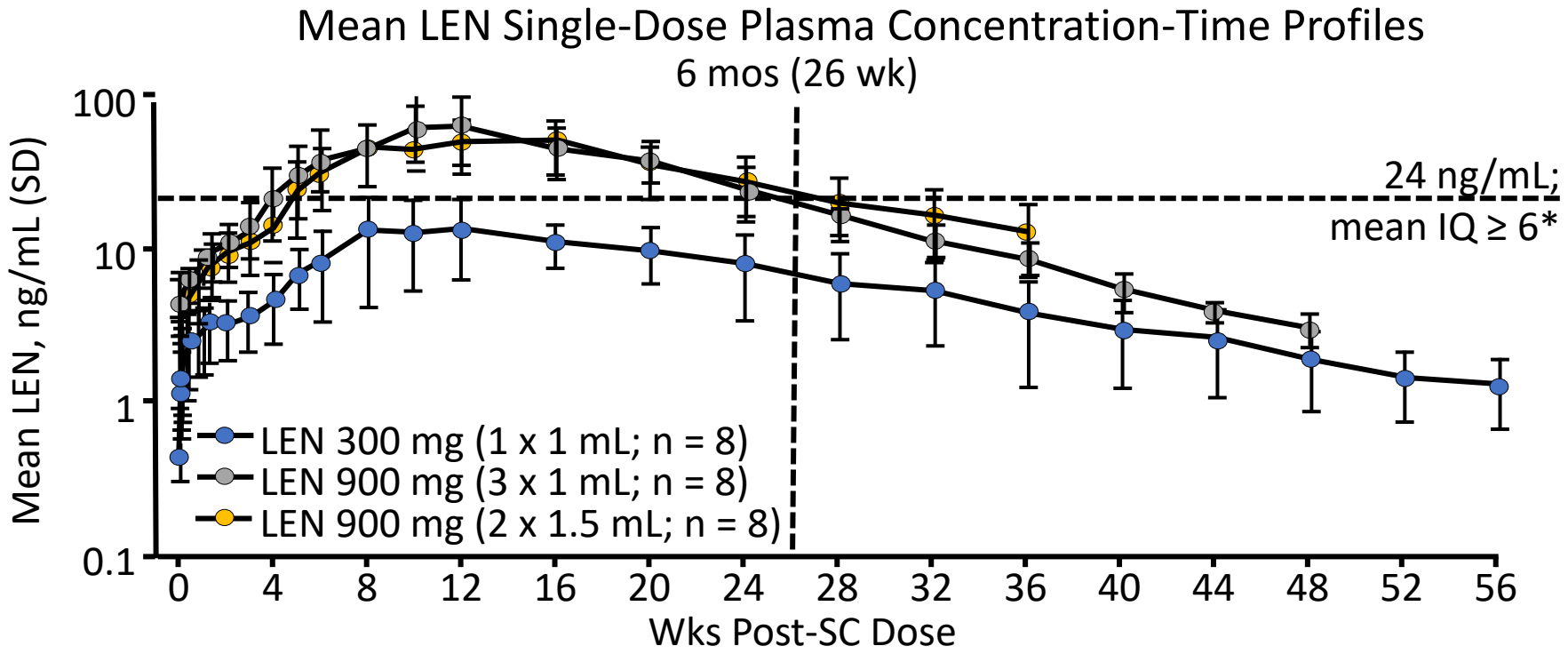
*Change (mean) on Day 10 in 20-mg cohort was -1.3 $\log_{10}$ copies/mL while maximal change (mean) through Day 10 was -1.4 $\log_{10}$ copies/mL †Change (mean) on Day 10 in 450-mg cohort was -2.1 $\log_{10}$ copies/mL while maximal change (mean) through Day 10 was -2.2 $\log_{10}$ copies/mL
CI, confidence interval; CV, coefficient of variation; LEN, lenacapavir

In this Phase 1 study, single SC doses of LEN resulted in potent antiviral activity over 10 days

Daar E, et al. CROI 2020. Boston, MA. #469
Margot N, et al. HIV Drug Therapy 2020. Glasgow. Oral #324

Lenacapavir Pharmacokinetic Profile

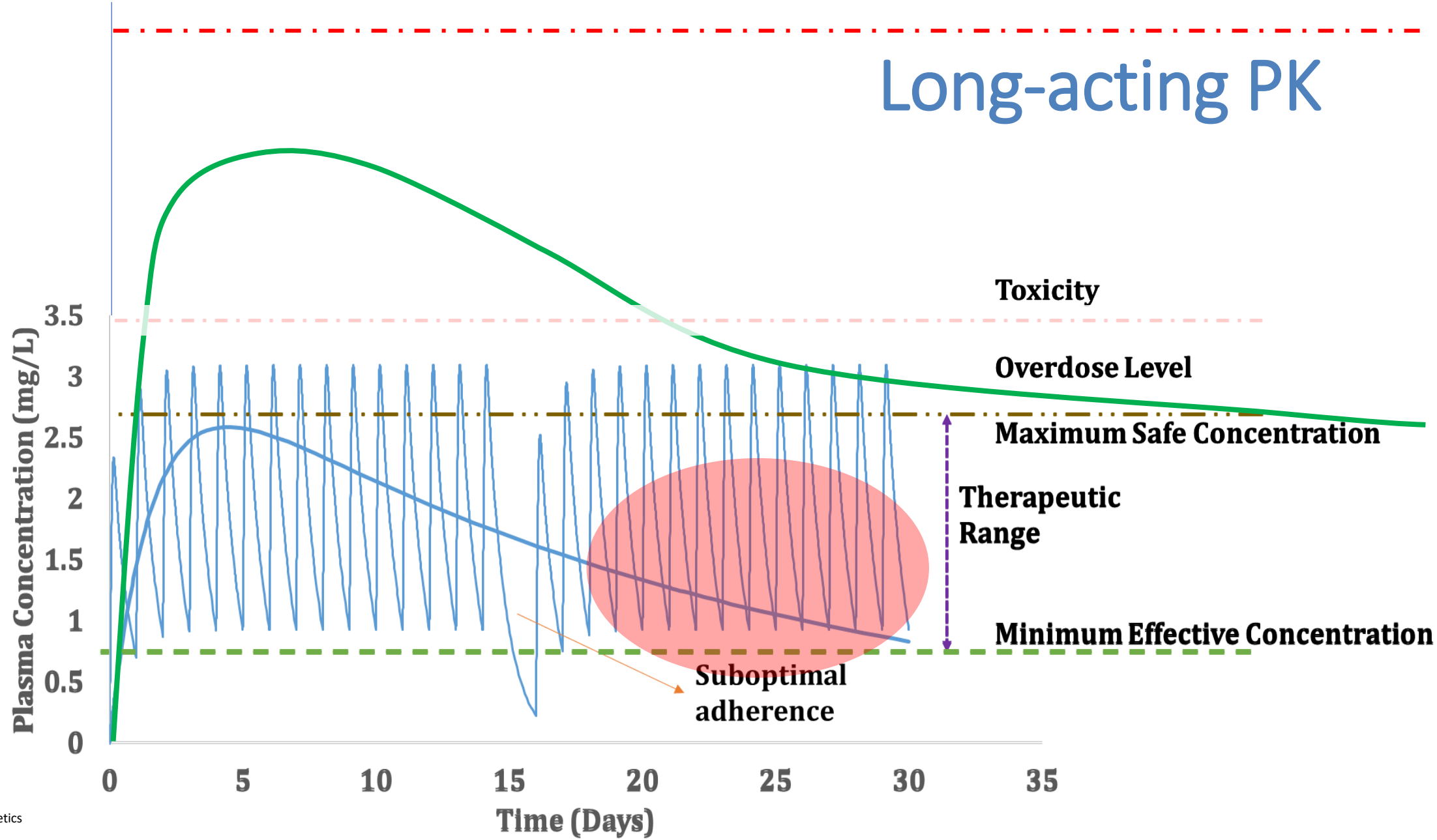
- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor with oral and SC long-acting formulations in development
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants (N = 30)



*Protein-adjusted EC_{95}: macrophages, 1.16 ng/mL; CD4+ cells, 2.32 ng/mL, MT-4 cells, 3.87 ng/mL.

Begley. AIDS 2020. Abstr PEB0265.

Long-acting PK



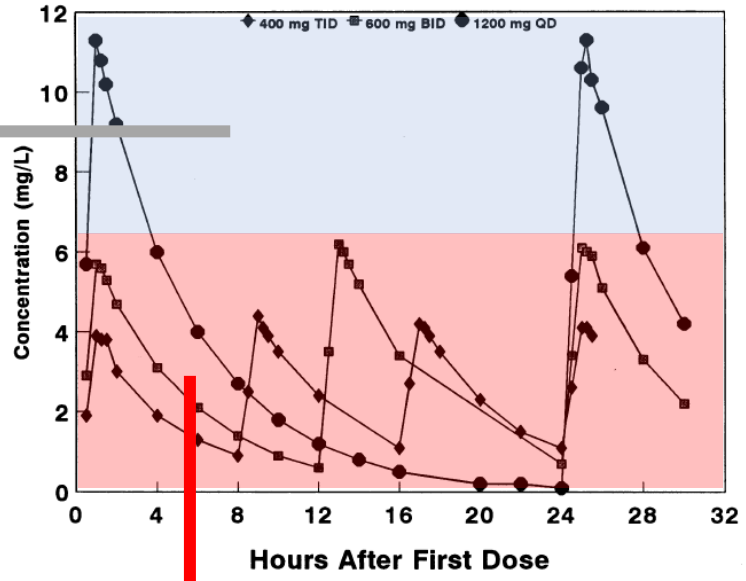
PK = pharmacokinetics

Dose Ranging and Fractionation of Intravenous Ciprofloxacin against *Pseudomonas aeruginosa* and *Staphylococcus aureus* in an In Vitro Model of Infection

Marchbanks CR, et al. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1993, p. 1756–1763

Organism and regimen	Peak/ MIC	T > MIC (0-8 h)	T > MIC (0-24 h)
P.aeruginosa			
400 mg TID	4.2	7.5	23
600 mg bid	6	8	20
1200 mg QD	11	8	13

The same total daily dose

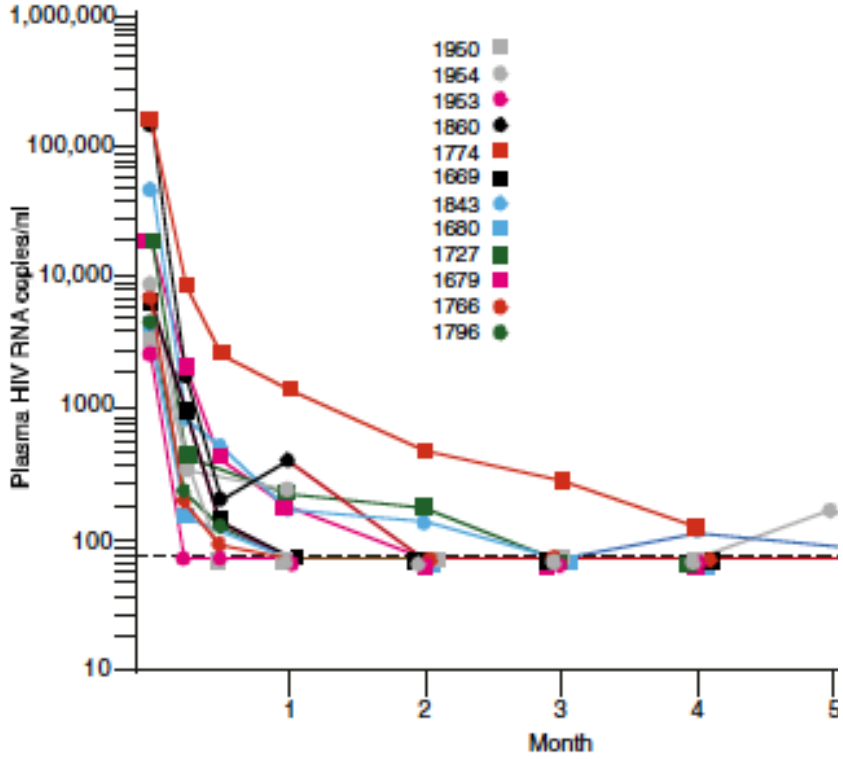


Regrowth without Resistance

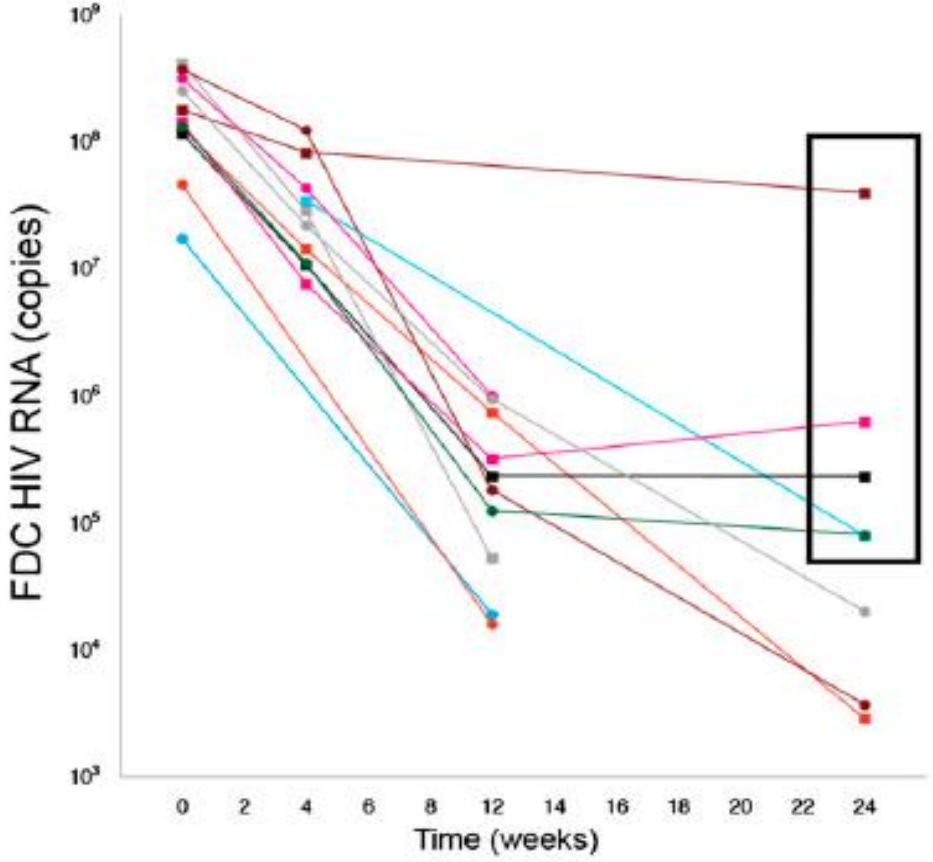
Regrowth with Resistance

Viral Replication in Plasma and Lymph Nodes during ART

Decay of Plasma HIV-RNA



Decay of Lymph Node FDCn copies of HIV RNA/gm

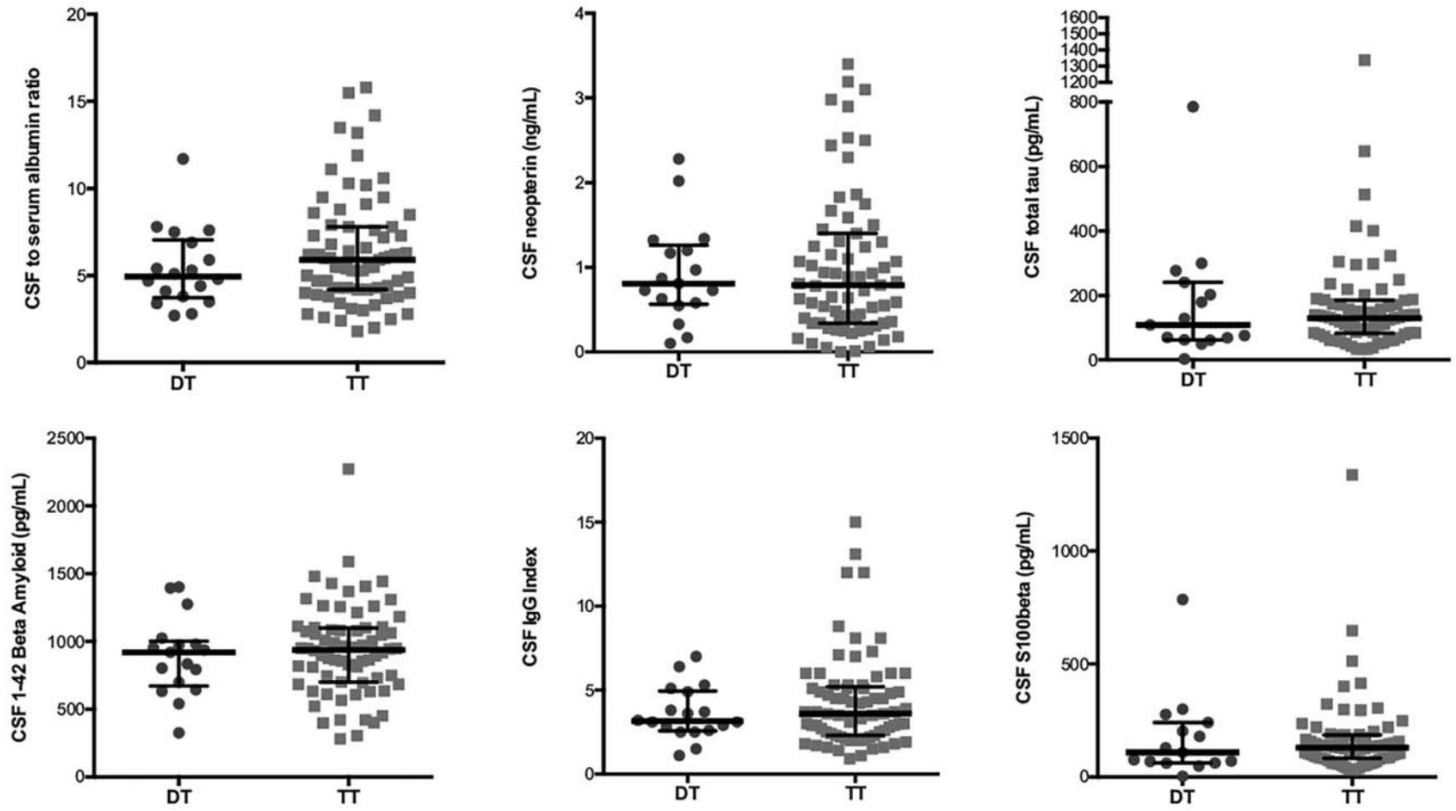


* Fletcher CV, et al. Proc Natl Acad Sci USA 2014; 111:2307-12.

Dual antiretroviral therapies are effective and safe regimens in the central nervous system of neurologically symptomatic people living with HIV

Mattia Trunfio[a], Walter Rugge[a], Lorenzo Mighetto[b], Daniela Vai[c], Cristiana Atzori[c], Marco Nigra[b], Simone Domini[c], Enrica Borgogno[a], Giulia Guastamacchia[c], Stefano Bonora[a], Giovanni Di Perri[a] and Andrea Calcagno[a]

AIDS. 2020 Nov 1;34(13):1899-1906.



Comparison of representative cerebrospinal fluid biomarkers in patients on dual vs. 2 nucleoside reverse transcriptase inhibitor-based three-drug regimens. The median cerebrospinal fluid concentrations of cerebrospinal fluid-serum albumin ratio, neopterin and total tau protein (top left, middle and right corner, respectively) did not significantly differ between dual therapy and triple therapy, as well as the median cerebrospinal fluid concentrations of amyloid b 1 – 42 fragment, IgG index and S100 b protein (lower left, middle and right corner, respectively). Data were analysed by Mann–Whitney test. CSF, cerebrospinal fluid; DT, dual therapies; TT, 2 nucleoside reverse transcriptase inhibitor-based three-drug therapies.

IMMUNE ACTIVATION / HYPERINFLAMMATION IN LESS DRUG REGIMENS: a (possible) new pharmacodynamic parameter

MONOTHERAPY (PI/r)

Merlini E, et al. *Antivir Ther.* (2018) 23:633–7.

Patients on monotherapy were more likely to display **increased T-cell apoptosis**

Torres B, et al. *J Int AIDS Soc.* (2014) 17:19246.

Patients on monotherapy display **higher levels** of monocyte activation—CD14+CD16-CD163+ cells and sCD14 levels.

Petrara MR, et al. *PLoS ONE.* (2017) 12:e0185128.

Significant increase of T- and B-cell activation in patients receiving one drug

DUAL THERAPY

Romero-Sánchez MC, et al. *Antiviral Res.* (2014) 111:26–32.

Belmonti S, et al. *J Antimicrob Chemother.* (2018) 73:1949–54.

Vallejo A, et al. *HIV Med.* (2019) 20:555–60.

No relevant changes in immune activation markers & a variety of soluble factors

Mussini C, et al. *BMC Med.* (2018) 16:79.

Higher CD8+ T-cell count in dual therapy

van Wyk J, et al. *J Acquir Immune Defic Syndr.* (2020) 85:325–30.

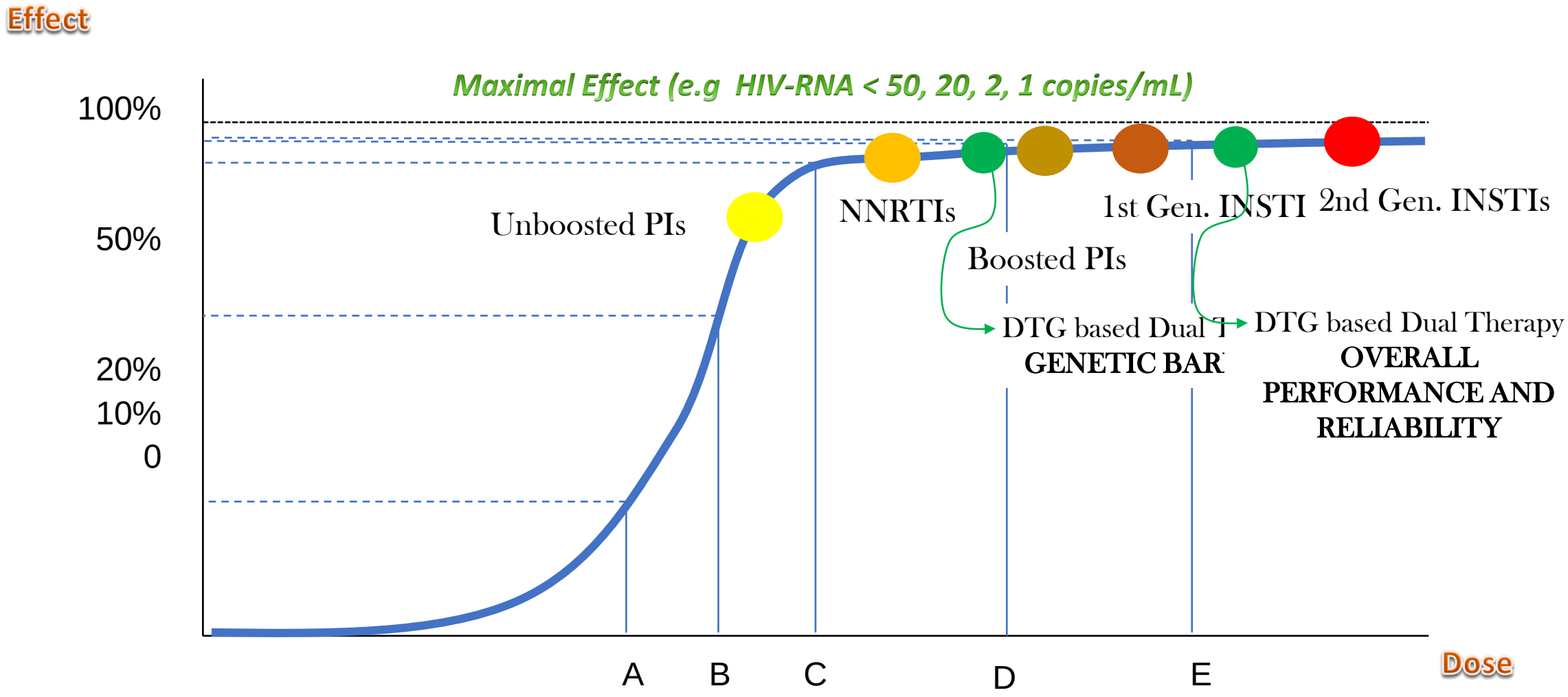
No consistent pattern of change from baseline to week 48 or differentiation between both groups in the following markers: IL-6, CRP, sCD14, sCD163, and D-dimer.

van Wyk J, et al. Clinical Infectious Diseases 2020; , 71 (8): 1920–1929.

Significantly **smaller decrease** in serum IL-6 levels in patients on dual therapy, but for sCD14 there was an exact **opposite trend.**

T-cell activation not tested

Emax Model



Coloured dots represent **my perception** of the overall ranking of antiretroviral options

CD

HIV-RNA

Doctors perceptions:

- Life habits
- Estimation of individual adherence

Individual Therapeutic History:

- Duration
- N. of regimens changed
- N. of Failures
- Resistance selection
- Associated disorders (e.g. CNS)
- Nadir CD4+/mL
- Zenit HIV/RNA
- Frequency of PCR “signals”
- Comorbidities

500 c./mL

200 / µL

0 / µL

0 c./mL

TI

2 drugs

3 drugs

? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ? ?

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