16th Residential Course on Clinical Pharmacology of Antiretrovirals

www.fcarvturin.it

January 13-15, 2021

Clinical Pharmacology of Two-Drug Regimens

Gianni Di Perri

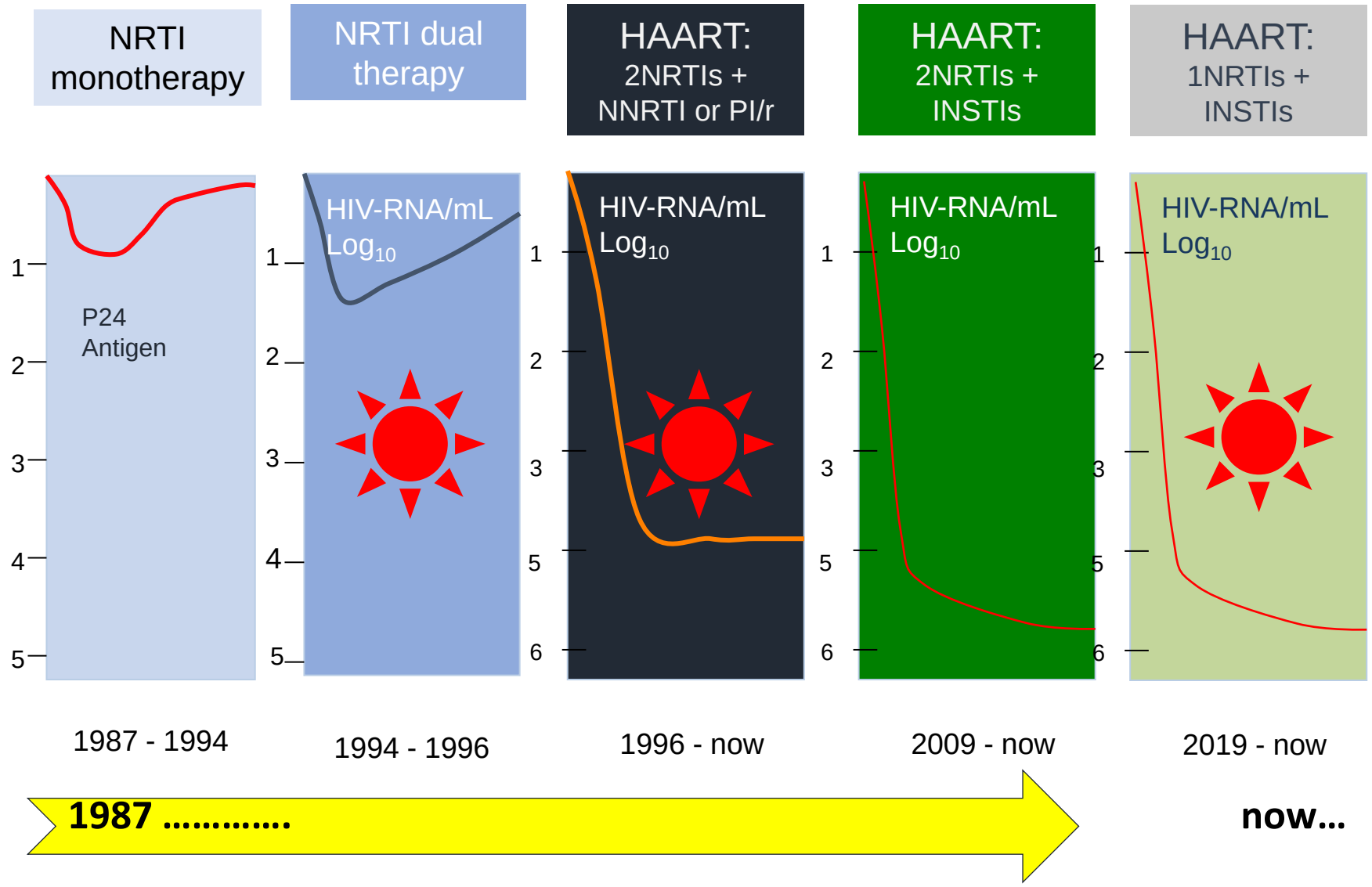
Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia

Financial Disclosures

Speaker fees, consultancies, research grants from:

- Abbvie
- BMS
- GS
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea
- Zambon
- Correvio
- Angelini

ANTIRETROVIRAL REGIMENS and their Antiviral Performance in the HIV Treatment History



The short but important story of the (first) dual therapy:

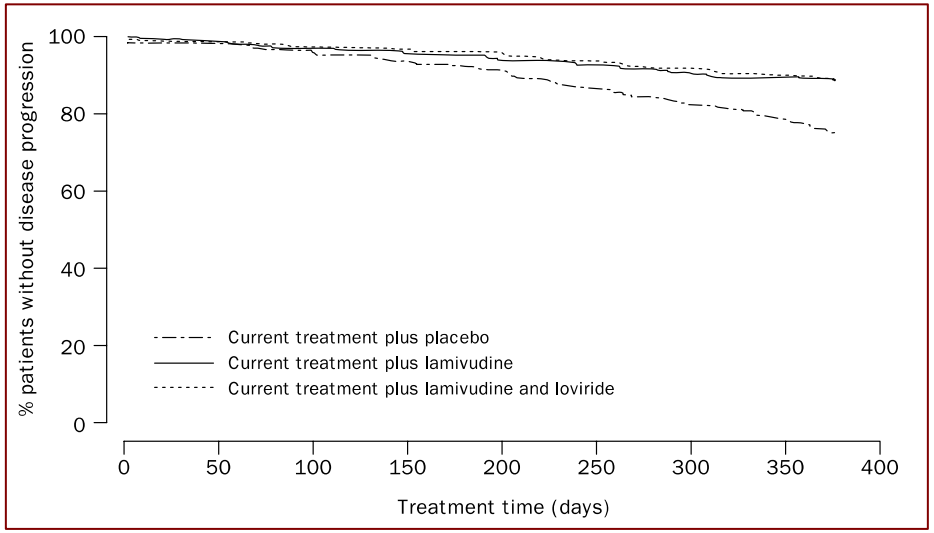
first signs that the pathway to multidrug regimens was the right one

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**

Methods Eligible patients receiving zidovudine monotherapy or zidovudine plus zalcitabine or didanosine combination therapy were assigned 52 weeks of treatment with the addition of placebo, lamivudine (150 mg twice a day), or lamivudine (150 mg twice a day) plus loviride (100 mg three times a day). Patients were unaware of type of treatment allocated. The primary endpoint was progression to a new protocol-defined AIDS event or death.



AZT
AZT + ddI or ddC

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

Primary endpoints:
Death
Progression to AIDS

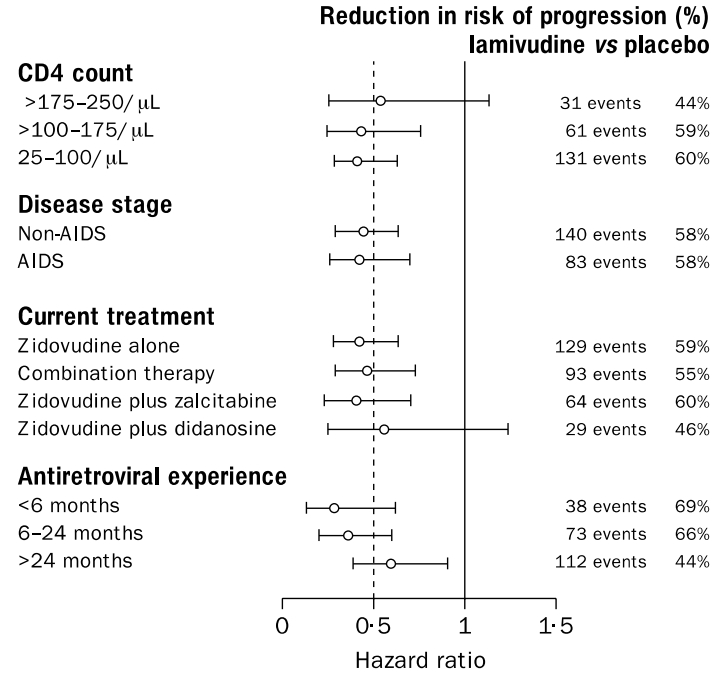


Figure 3: **Relative hazards and 95% CIs for subgroup analyses**

The NEW ENGLAND JOURNAL of MEDICINE Volume 341:1865-1873December 16, 1999

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.***

- The patients received open-label **efavirenz** (600 mg daily) plus **indinavir** (1000 mg every eight hours),
- Efavirenz (600 mg daily) plus zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily),
- Indinavir (800 mg every eight hours) plus zidovudine (300 mg twice daily) and lamivudine (150 mg twice daily).

- **The higher dose of indinavir compensates for its increased catabolism in the presence of efavirenz.**

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

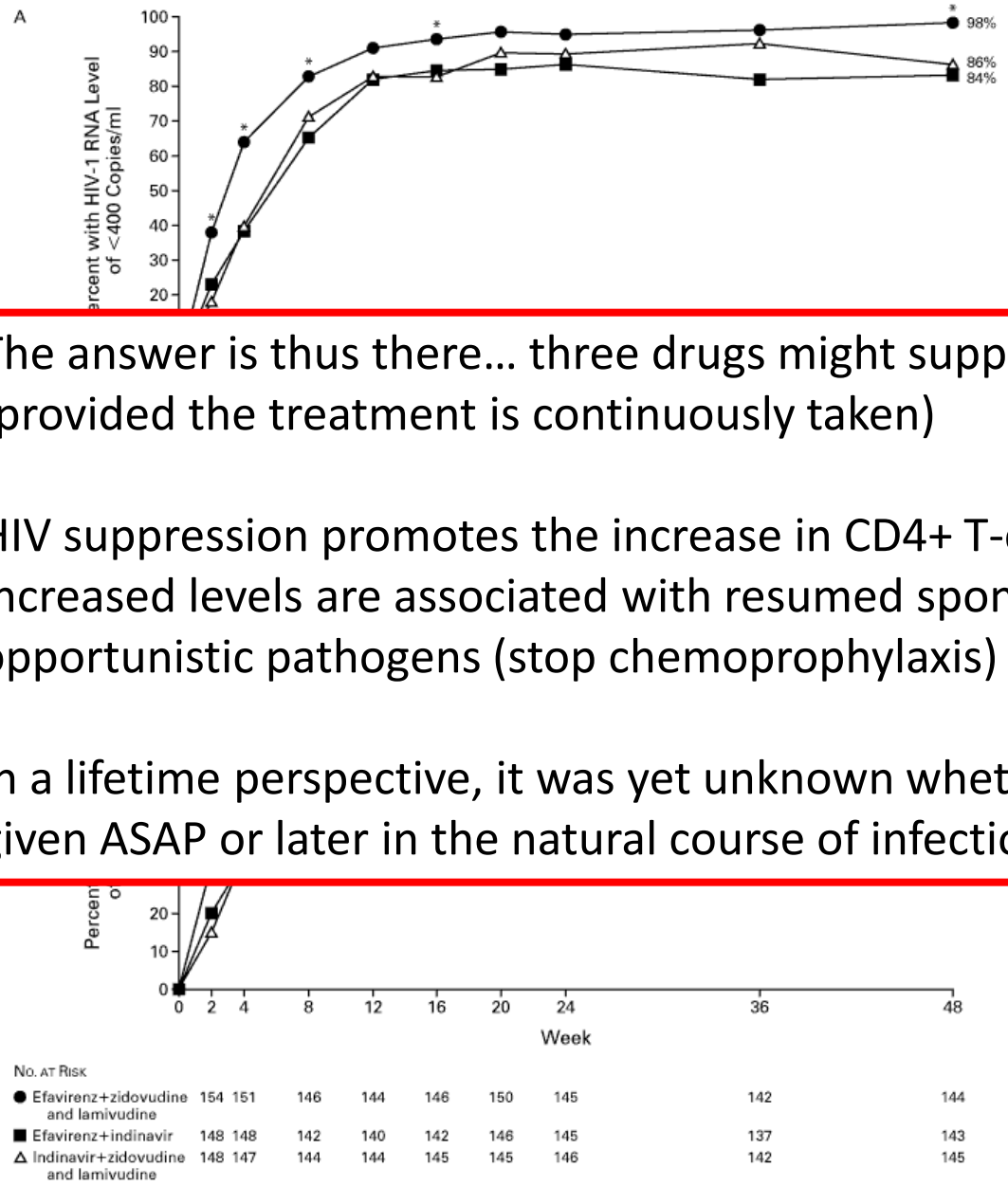


Figure 1. Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than

indinavir plus zidovudine and lamivudine

The answer is thus there… three drugs might suppress HIV permanently (provided the treatment is continuously taken)

HIV suppression promotes the increase in CD4+ T-cell count and such increased levels are associated with resumed spontaneous control of opportunistic pathogens (stop chemoprophylaxis)

In a lifetime perspective, it was yet unknown whether treatment should be given ASAP or later in the natural course of infection

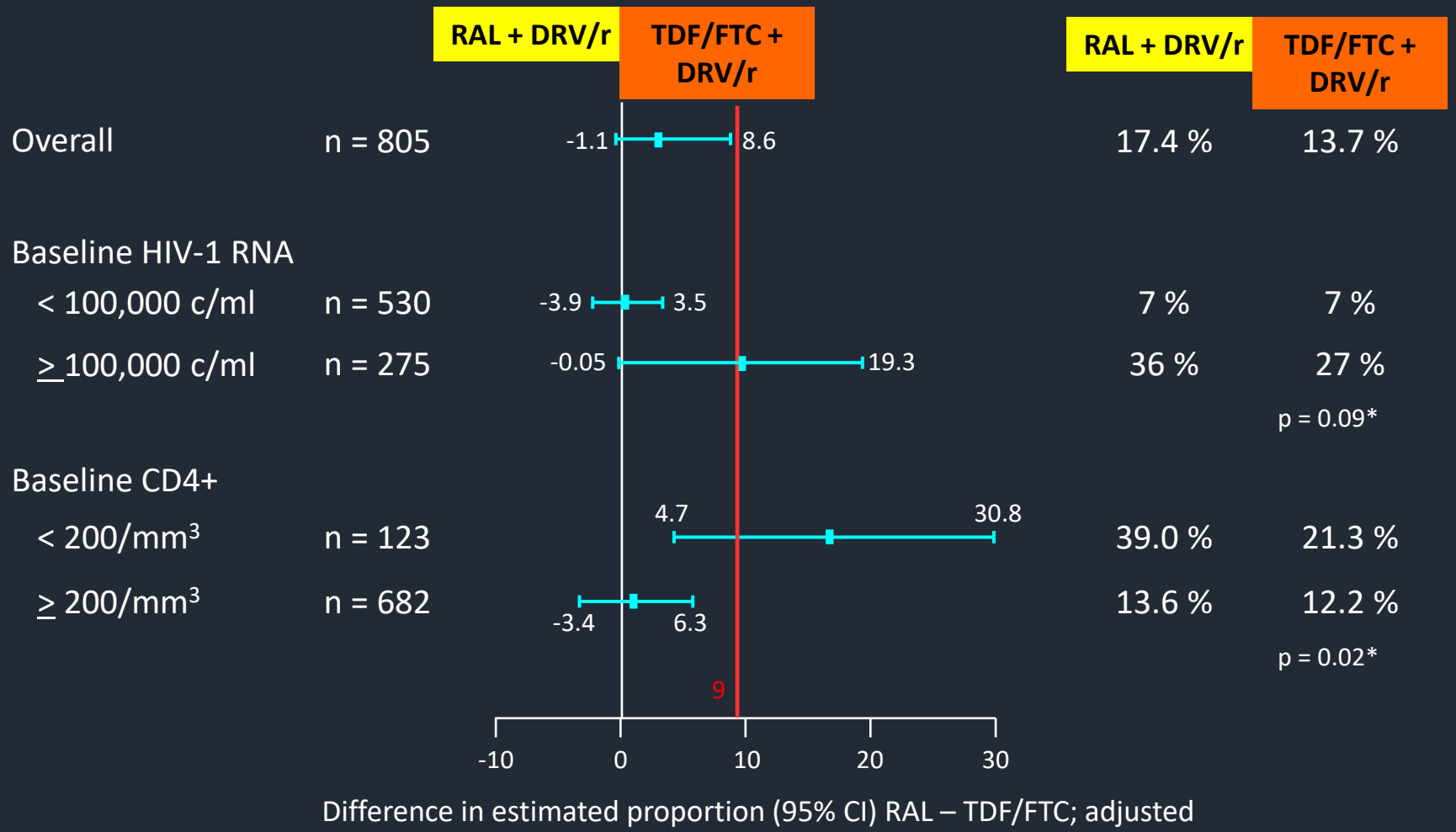
2DR Studies - overview

	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

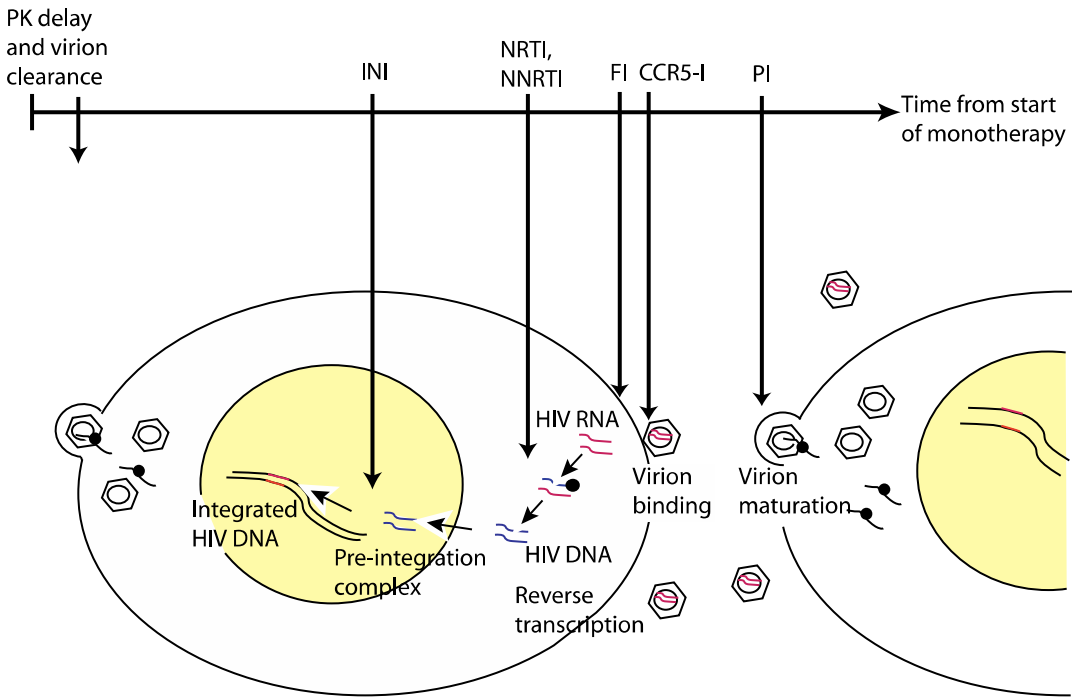


FIG. 1. The positions in the HIV life cycle affected by each drug class and their relative timing in terms of when they impact HIV RNA levels in blood.

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

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

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

EACS European AIDS Clinical Society

Version 10.0
November 2019

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INST (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

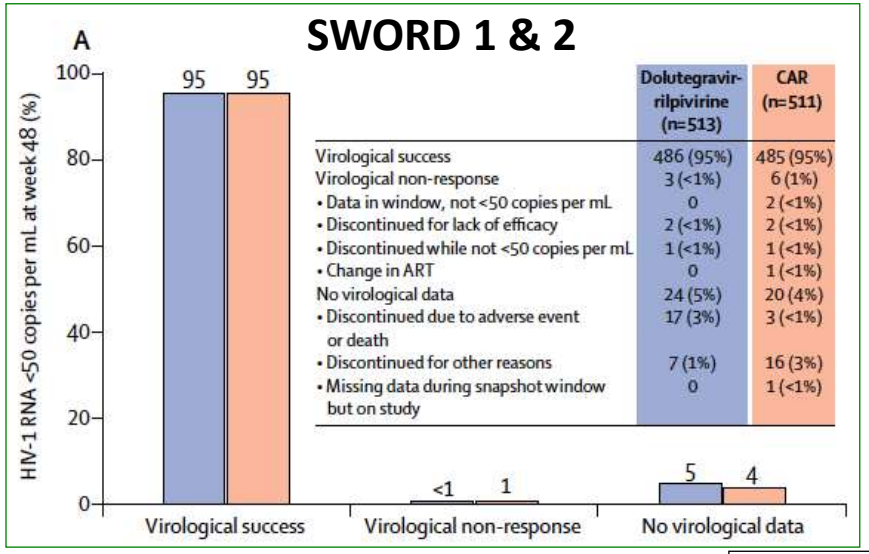
Dual therapies supported by large randomized clinical trials or meta-analyses

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

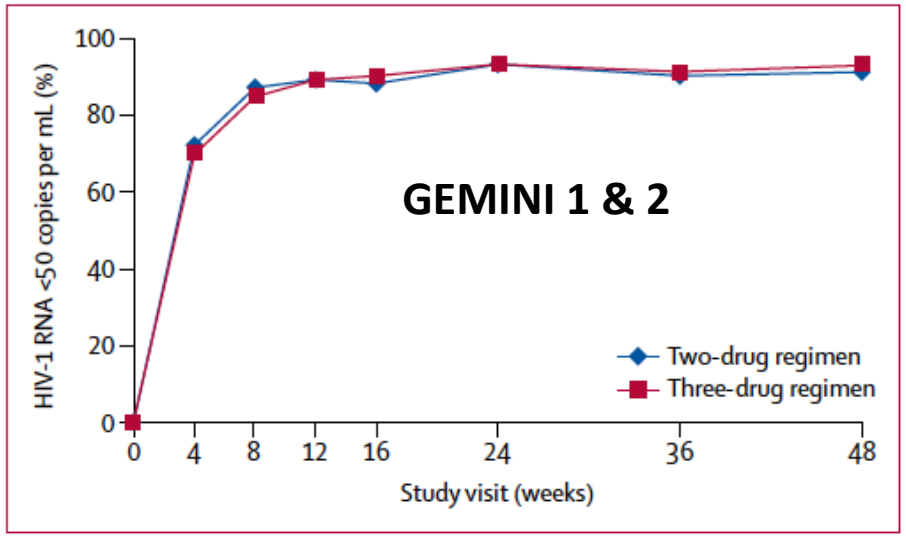
2

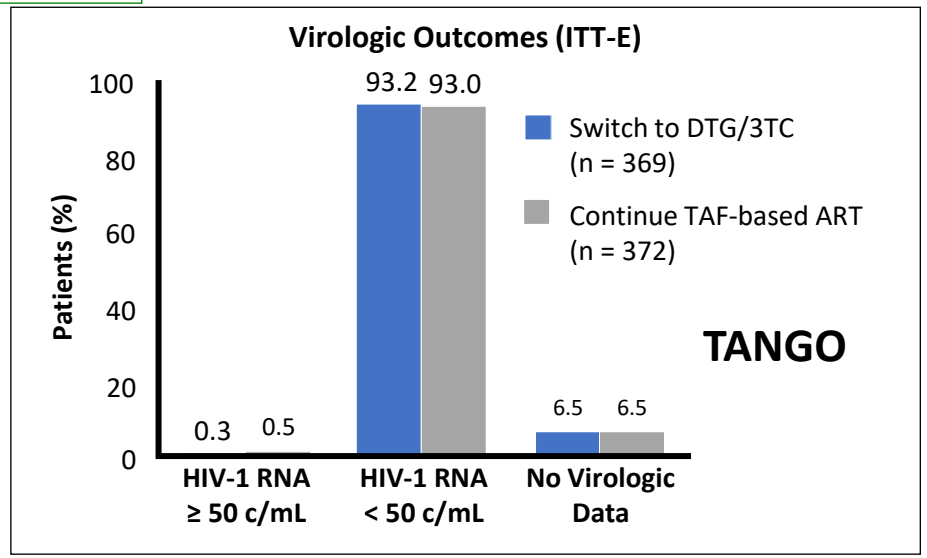
In HIV infection, until 2019 the recognized successful paradigm has been the use of 3 drugs, although the introduction of more potent drugs has improved the Pk/PD performance of antiretroviral therapy

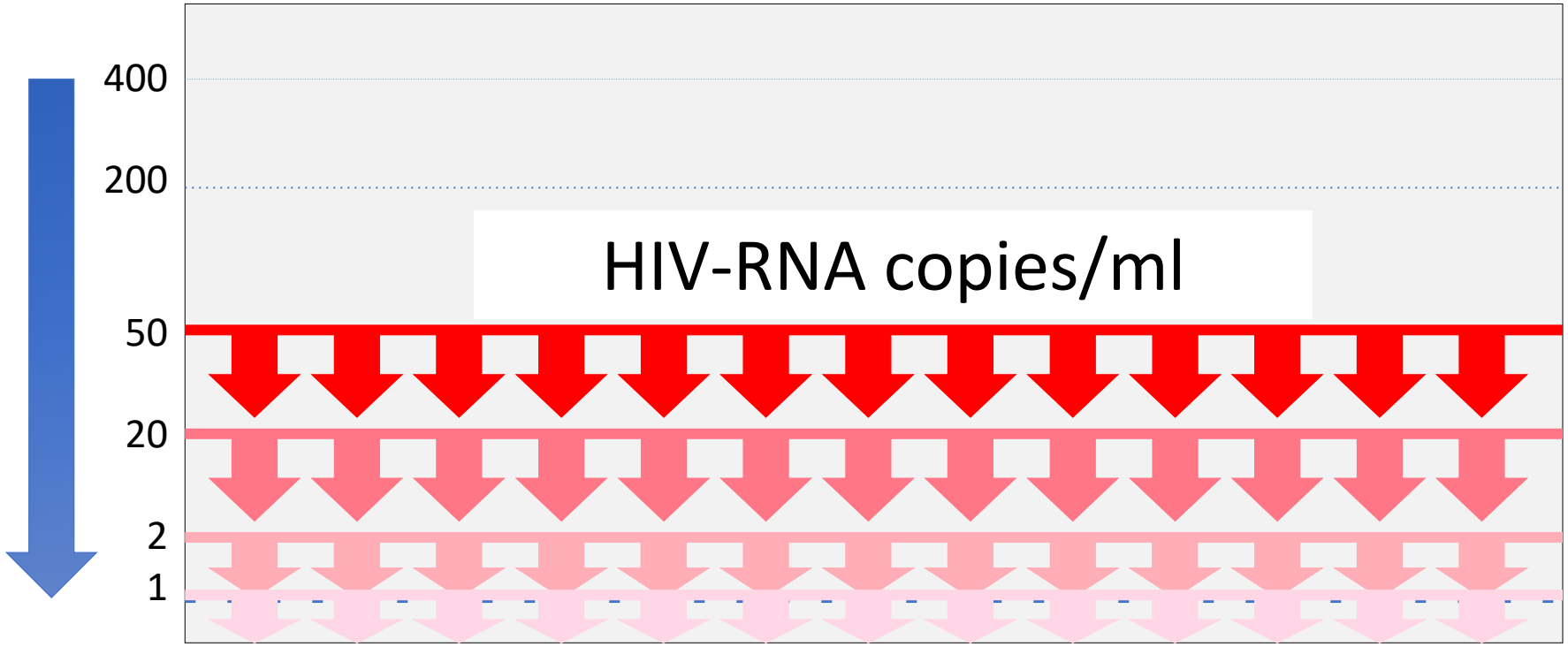
In 2019, following the release of data on comparative, controlled, registration-sized clinical trials, regimens consisting of 2 drugs rather than 3 have been approved for clinical use, both in naïve and experienced patients with HIV infection



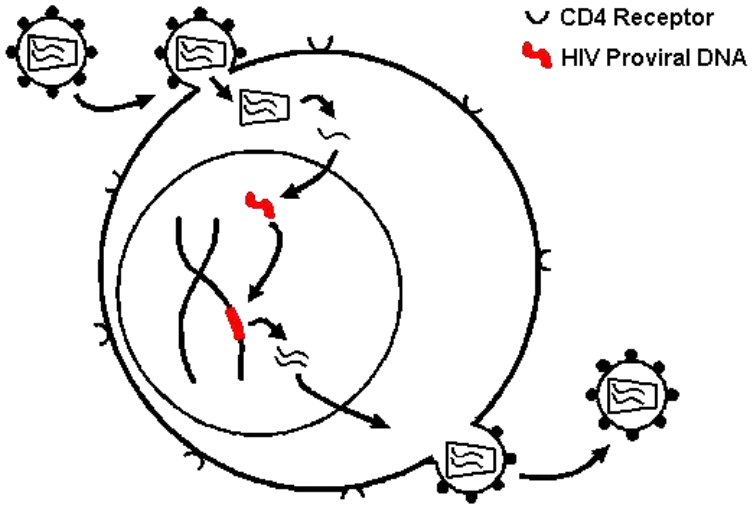
	Dolutegravir-rilpivirine (n=513)	CAR (n=511)
Virological success	486 (95%)	485 (95%)
Virological non-response	3 (<1%)	6 (1%)
• Data in window, not <50 copies per mL	0	2 (<1%)
• Discontinued for lack of efficacy	2 (<1%)	2 (<1%)
• Discontinued while not <50 copies per mL	1 (<1%)	1 (<1%)
• Change in ART	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%)



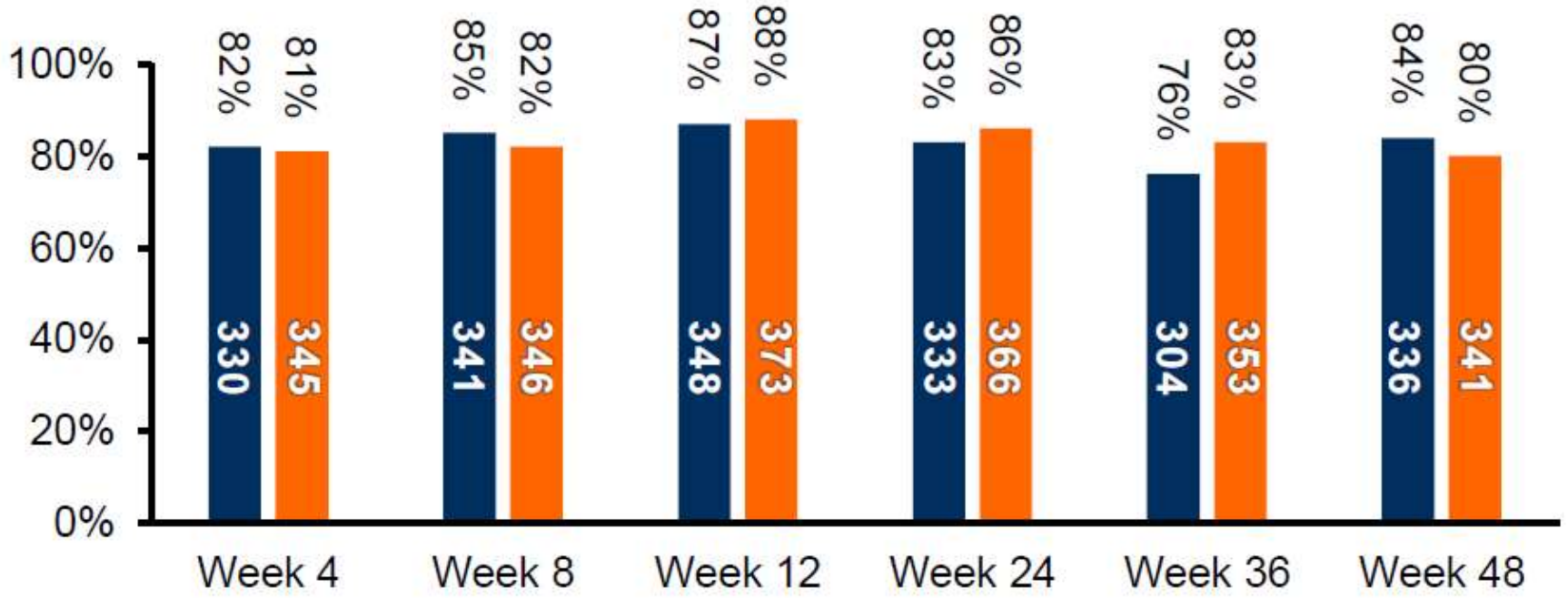




PROVIRAL HIV-DNA MEASUREMENT as a clinical tool to quantify HIV reservoir



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

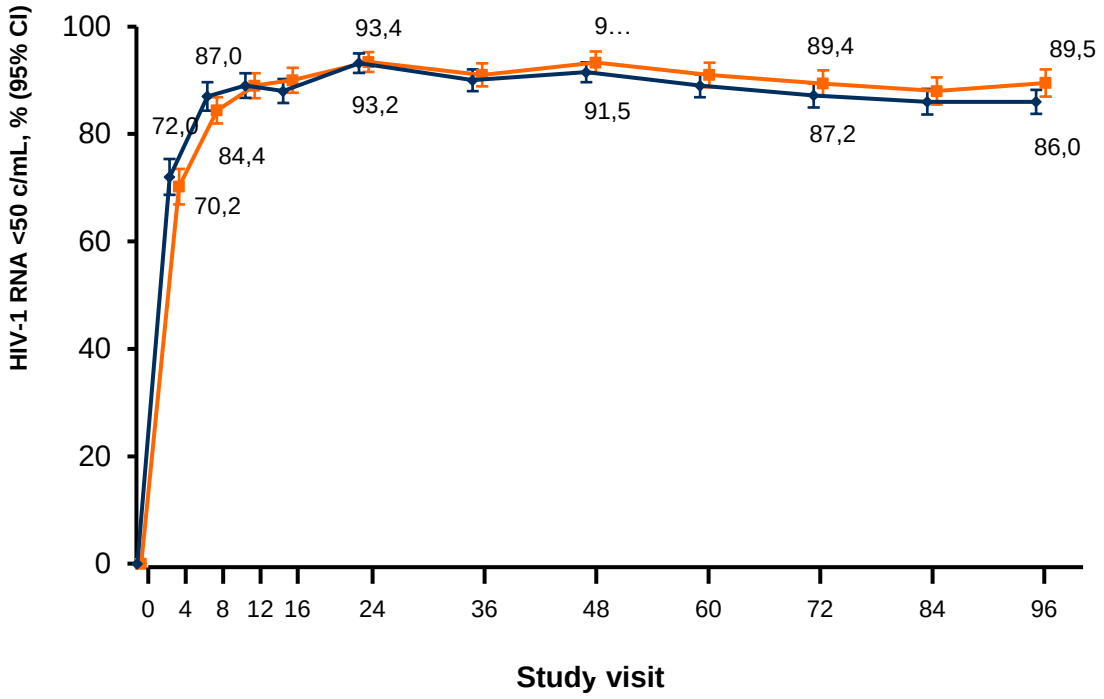
DTG + RPV

Current Antiretroviral Regimen (CAR)

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

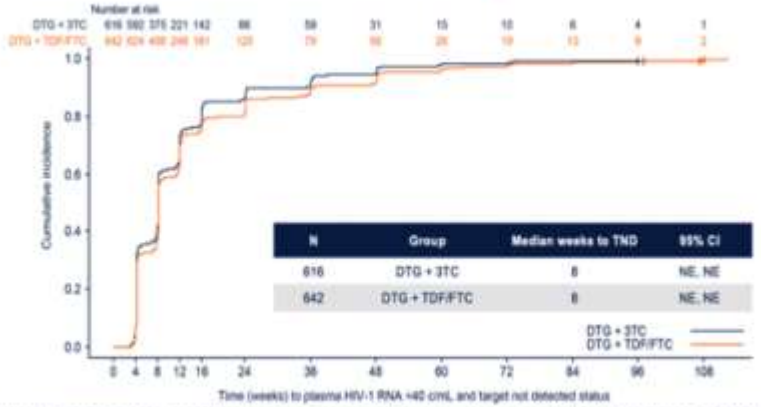
ASSESSMENTS OF VERY-LOW-LEVEL HIV REPLICATION FOR DOLUTEGRAVIR + LAMIVUDINE (DTG + 3TC) VS DOLUTEGRAVIR + TENOFOVIR DISOPROXIL/EMTRICITABINE (DTG + TDF/FTC) IN THE GEMINI-1&-2 STUDIES THROUGH WEEK 96

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)	

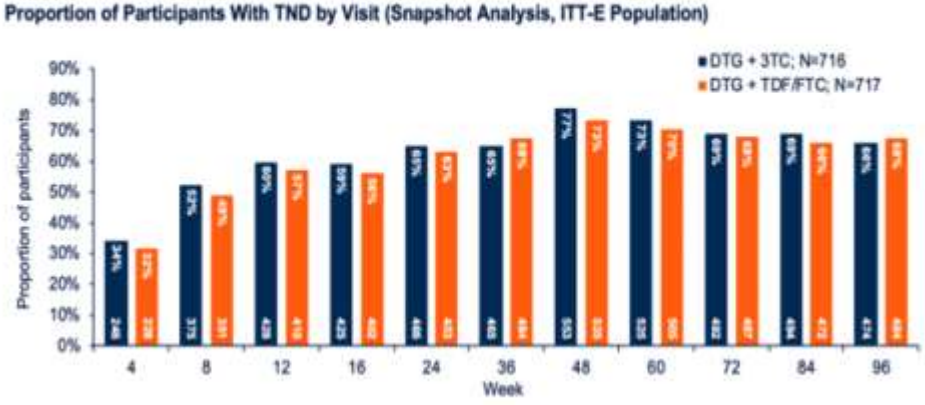
Similar Median Weeks to TND Across Groups in Observed Analysis



- 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

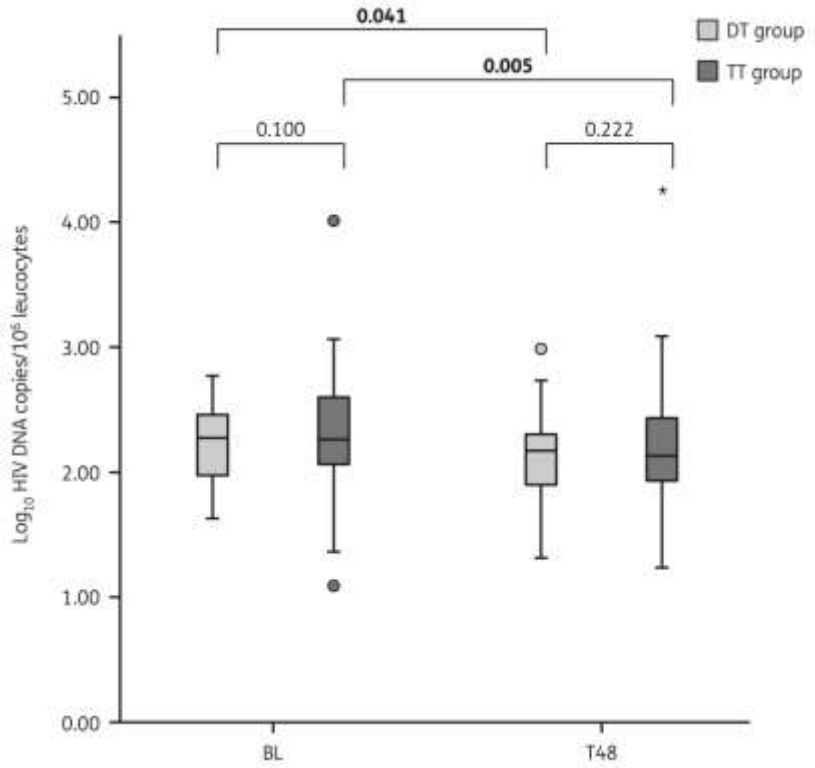


Number at base of bars is number of participants reaching TND at week visit

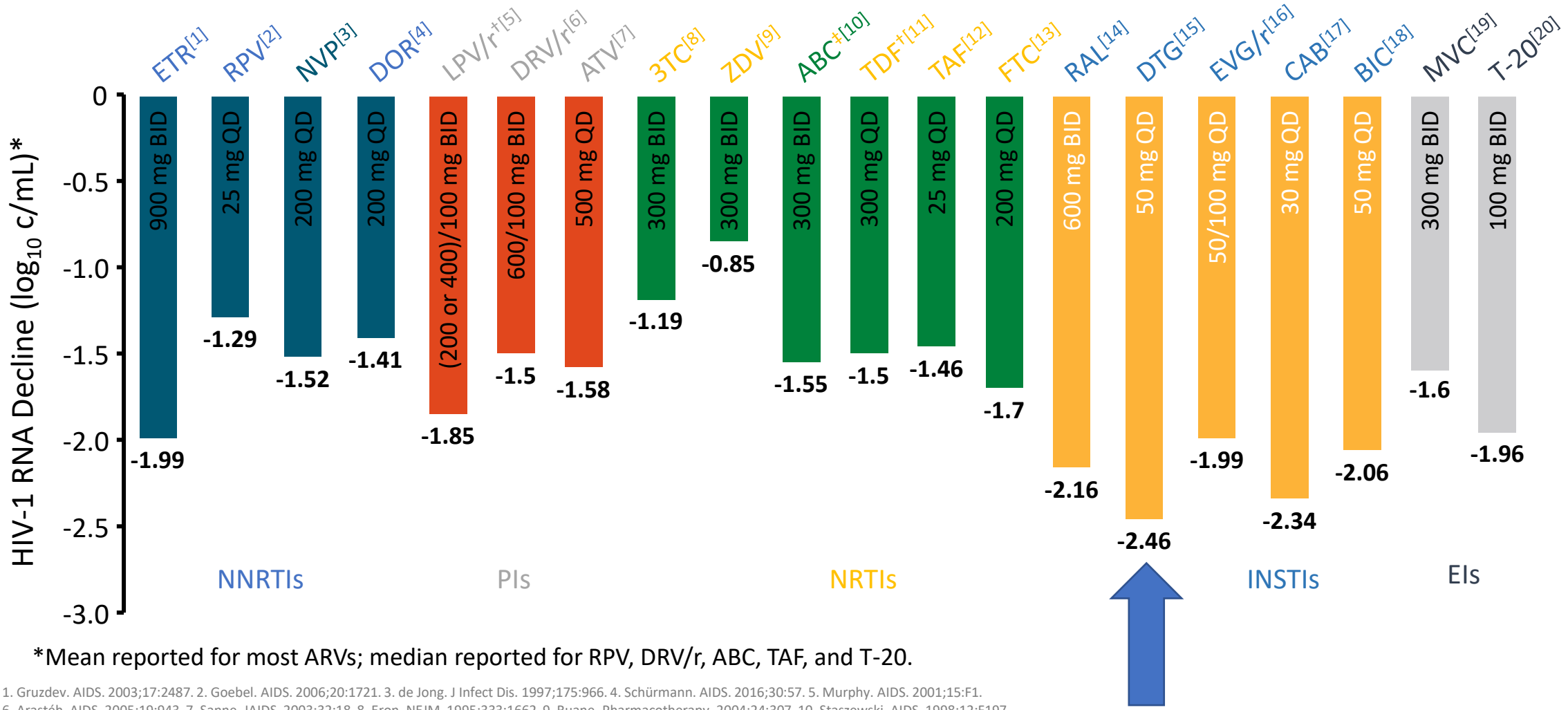
Evolution of cellular HIV DNA levels in virologically suppressed patients switching to dolutegravir/lamivudine versus maintaining a triple regimen: a prospective, longitudinal, matched, controlled study

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.



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.

NMA study

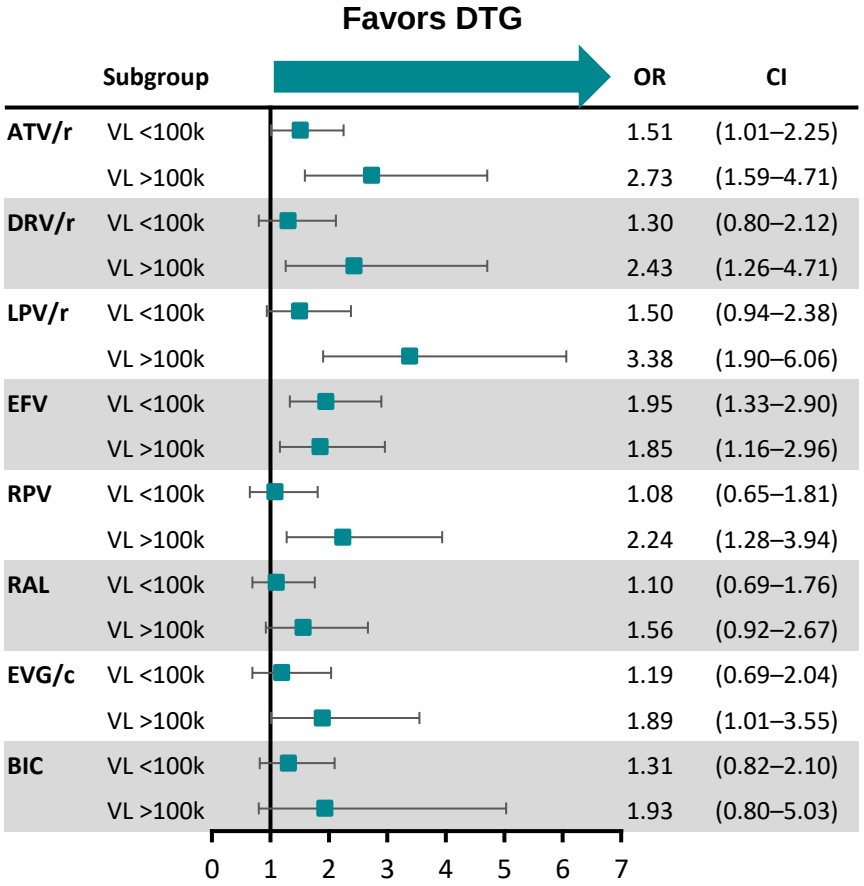
Network…… Meta…….. Analysis

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



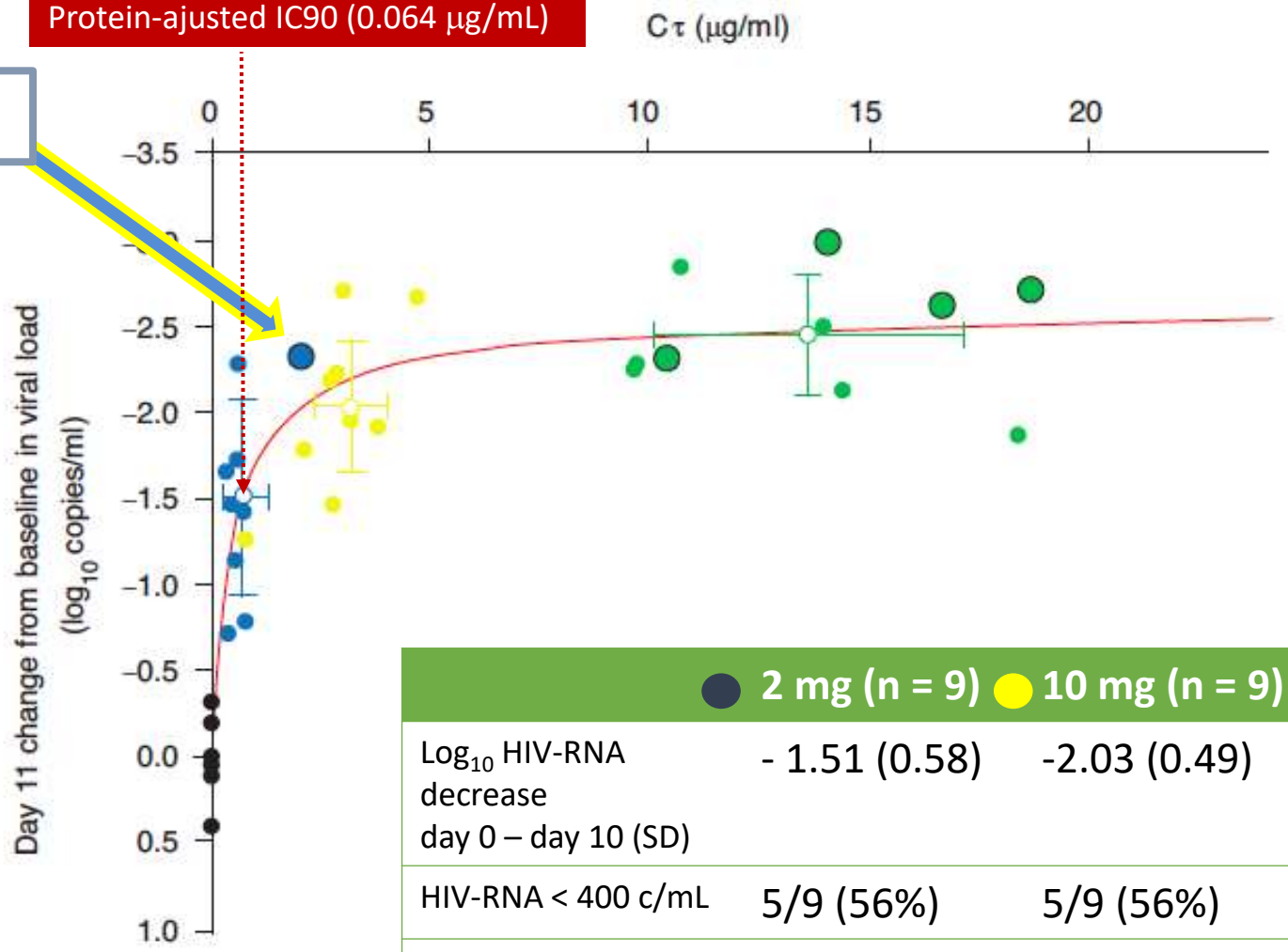
- ATV, atazanavir; BIC, bictegravir; c, cobicistat; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; LPV, lopinavir; OR, odds ratio; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; VL, viral load.

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

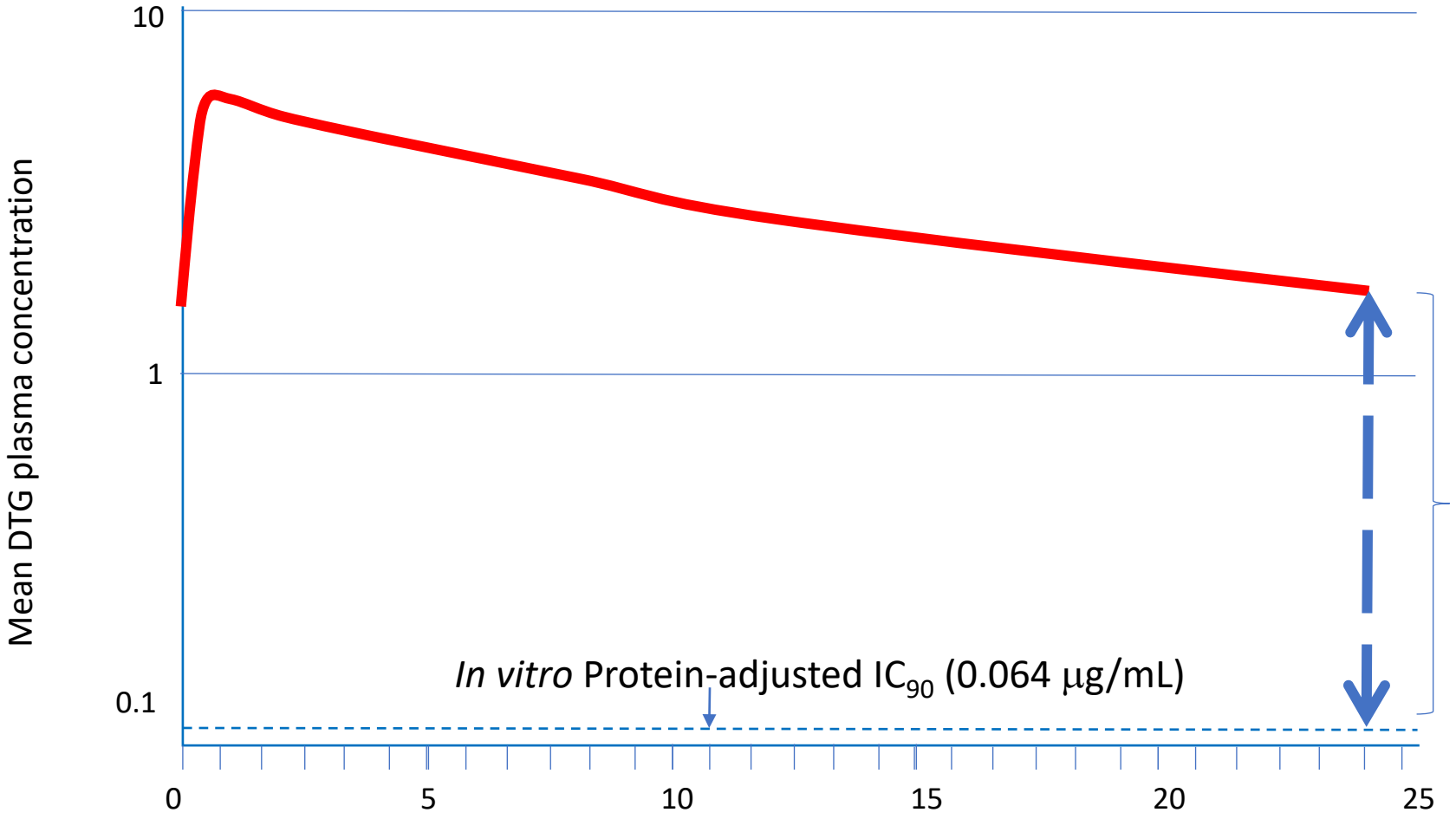
Min S, et al.
AIDS 2011, 25:1737–1745

Protein-ajusted IC90 (0.064 µg/mL)

2 mg dose

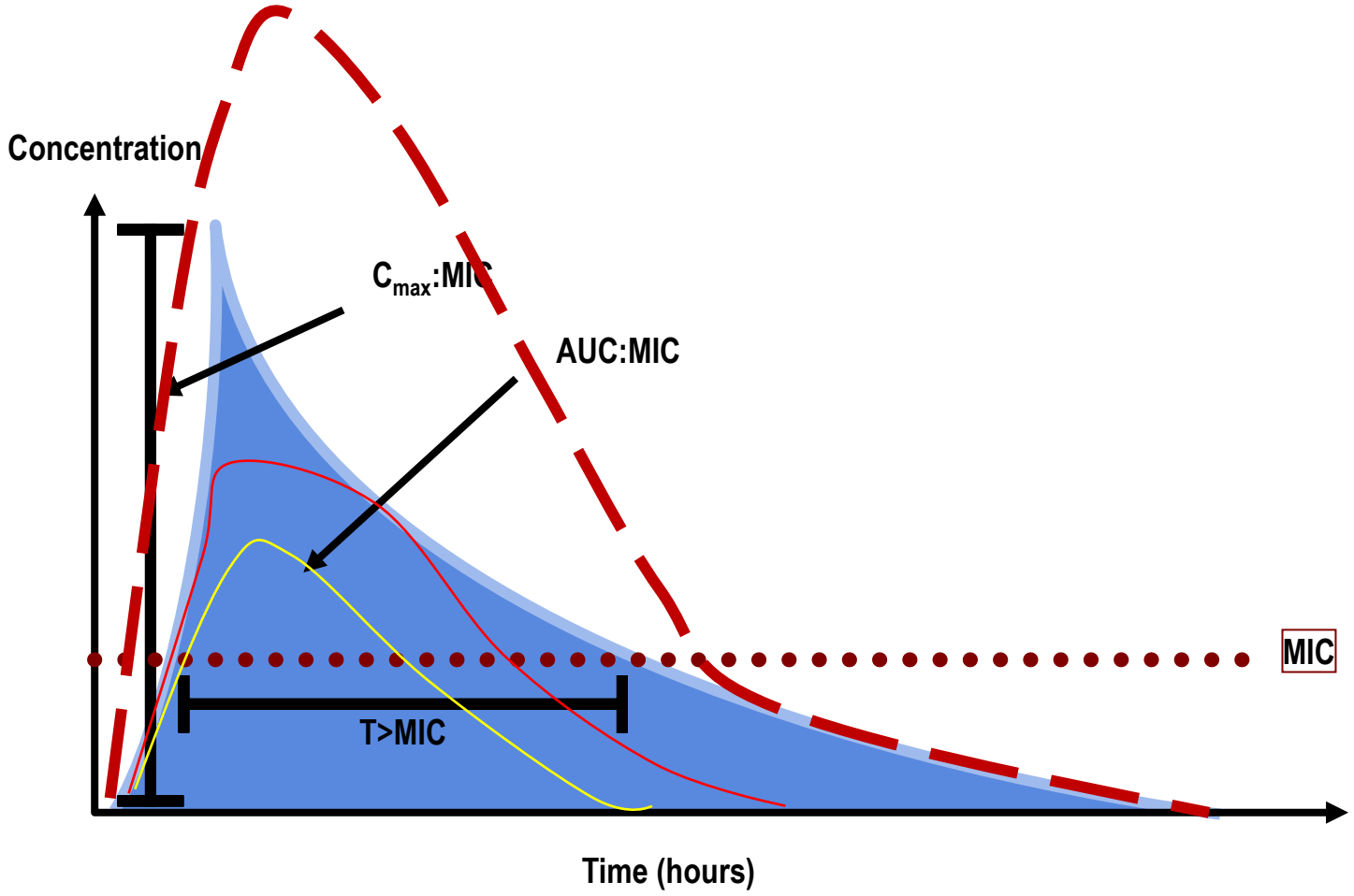


	2 mg (n = 9)	10 mg (n = 9)	50 mg (n = 10)
Log_{10} HIV-RNA decrease day 0 – day 10 (SD)	- 1.51 (0.58)	-2.03 (0.49)	-2.46 (0.35)
HIV-RNA < 400 c/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
HIV-RNA < 50 c/mL	1/9 (11%)	0	7/10 (70%)


Mean DTG plasma concentration
10
1
0.1
0
5
10
15
20
25
In vitro Protein-adjusted IC_{90} (0.064 μg/mL)

IQ

Although antiretrovirals are thought to act in a **time-dependent manner**, with last-generation drugs the **overall pK exposure is significantly increased**, and as a consequence not only the **C_{trough}** is higher, but also **C_{max} is far higher than commonly seen with prior antiretrovirals**….

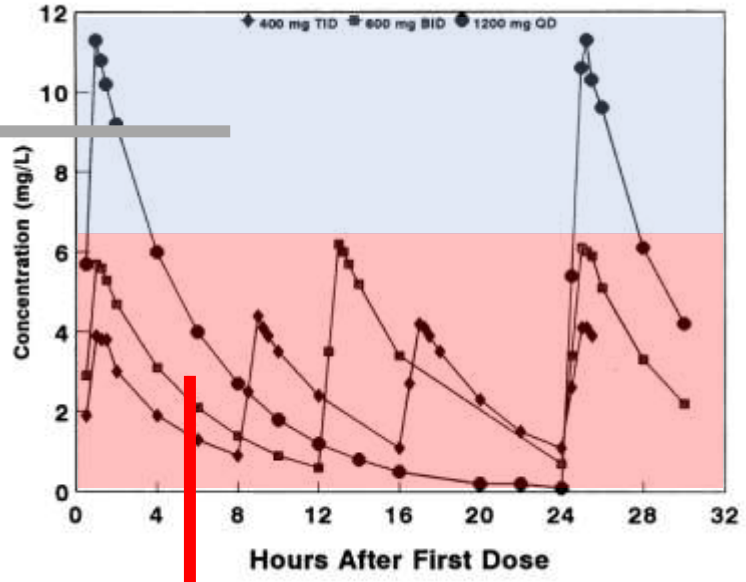


Dose Ranging and Fractionation of Intravenous Ciprofloxacin against *Pseudomonas aeruginosa* and *Staphylococcus aureus* in an In Vitro Model of Infection

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

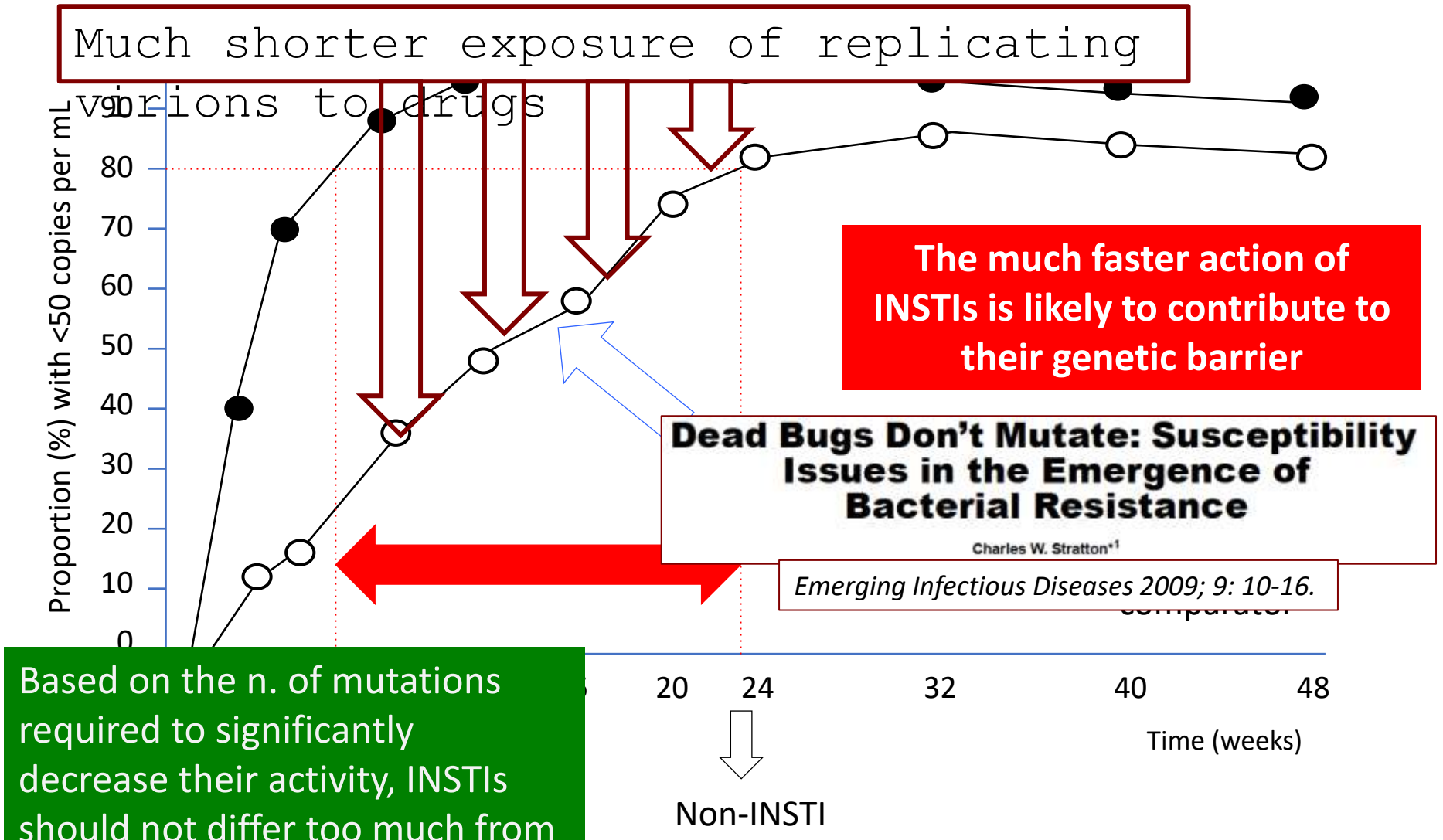
Organism and regimen	Peak/ MIC	T > MIC (0-8 h)	T > MIC (0-24 h)
P.aeruginosa			
400 mg TID	4.2	7.5	23
600 mg bid	6	8	20
1200 mg QD	11	8	13

The same total daily dose



Regrowth without Resistance

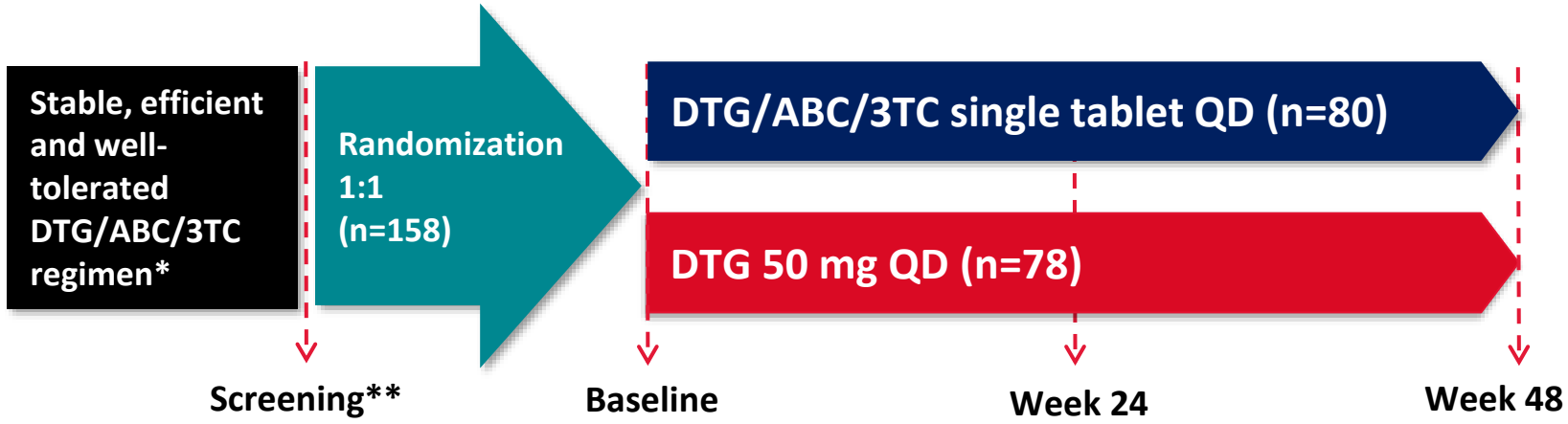
Regrowth with Resistance



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

Study design

Open-label, randomized, controlled trial in 9 reference centers in France



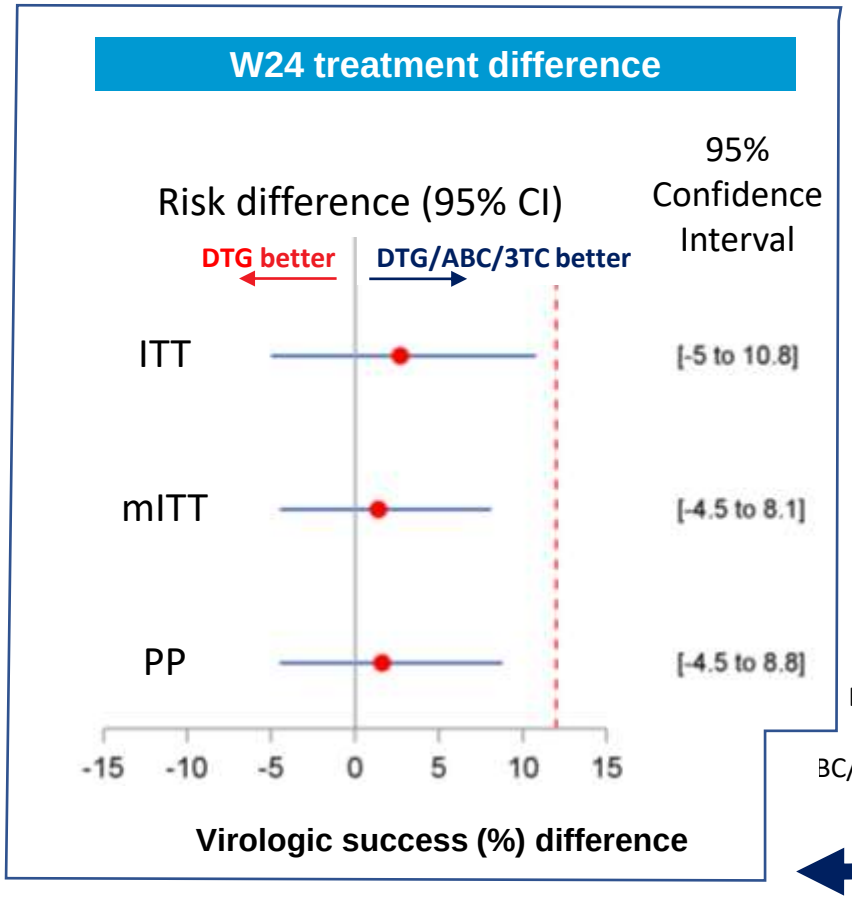
* HIV-RNA (pVL) <50 c/mL for >12 months, no AIDS event (except past tuberculosis), nadir CD4 >100/mm^3, no mutation to or failure on any INSTI-based regimen

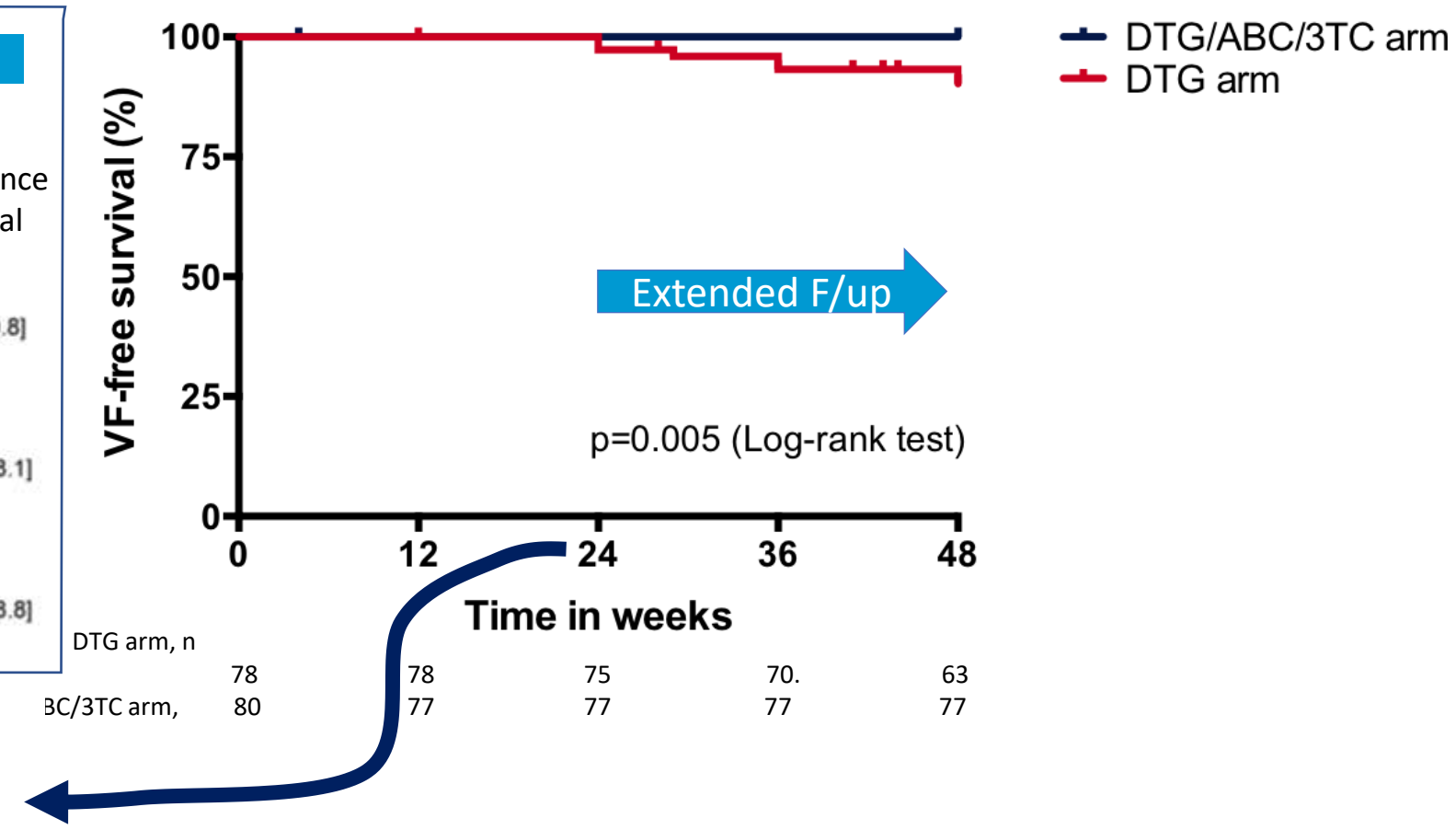
** pVL < local threshold (20 to 40 c/mL)

Primary endpoint:
proportion with pVL <50 c/mL in ITT, mITT and PP analyses (with a pre-planned non-inferiority margin of 12%);
virologic failure (VF) = 2 consecutive pVL >50 c/mL;
ITT, missing or switch = failure (M=F)

Secondary endpoints:
changes in CD4 count,
CD4:CD8 ratio, eGFR, lipids;
HIV-DNA and genital sub-studies

VF incidence after W24





Following a DSMB held on Dec. 21st 2017, the sponsor decided to **stop the monotherapy arm, according to DSMB recommendations**. All patients in the DTG-arm who had not completed the W48-visit (n=8) were re-intensified.

Summary of VF in the DTG-arm

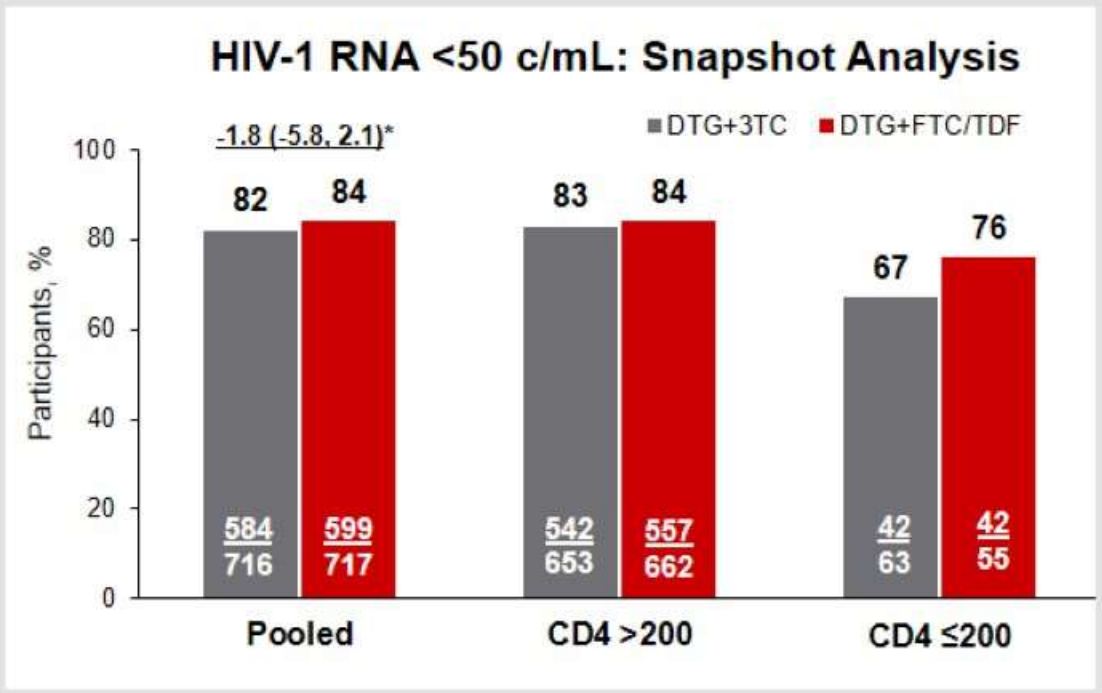
Patient	Wk	CD4 nadir	cART before DTG mono	Self-reported adherence at W4	Peak pVL, c/mL	Integrase sequencing at failure
02-023	24	231	11 years	100%	84	No mutation
08-007	24	163	10 years	100%	55	No mutation
01-034	29	197	5 years	95%	604	No mutation
02-016	36	252	19 years	100%	**46300**	**S147G, N155H***
06-006	36	200	2 years	95%	110	No mutation
02-033	48	119	21 years	95%	**2230**	**R263K***
07-003	48	118	4 years	100%	626	No mutation

* Likely emerging mutations (as wild-type virus was found at baseline in HIV-DNA)

Patients who experienced VF (as compared with those who did not) were more likely to have:
A low nadir CD4 (p=0.004)
A low CD4 count at screening (p=0.027)
A « PCR signal* » at pVL screening (p=0.026)

* i.e. a detectable but not quantifiable plasma HIV-RNA

Open Label Phase: Virologic Outcomes at Week 144



Resistance

- 1 DTG+3TC participant with reported non-adherence and BL VL 93,515 c/mL & CD4 393 cells/mm^3 developed RT resistance which evolved to 2-class resistance despite maintaining VL <200 c/mL
  - Suppressed <50 c/mL from W4 to W120 with viral rebound to 61,927 c/mL at W132 and resuppressed to <200 c/mL

W132	**RT:**	**M184V**	**VL 61,927 c/mL**
W144	**IN:**	**R263R/K**	**VL 135 c/mL**

  - Not a confirmed virologic withdrawal since did not meet criteria of consecutive VL ≥200 c/mL where only 1st sample would have been tested for resistance†

At W144 DTG+3TC maintained non-inferior efficacy but showed numerically lower viral suppression rates in participants with baseline CD4 ≤200 cells/mm^3

2-class treatment emergent resistance observed in one DTG+3TC participant

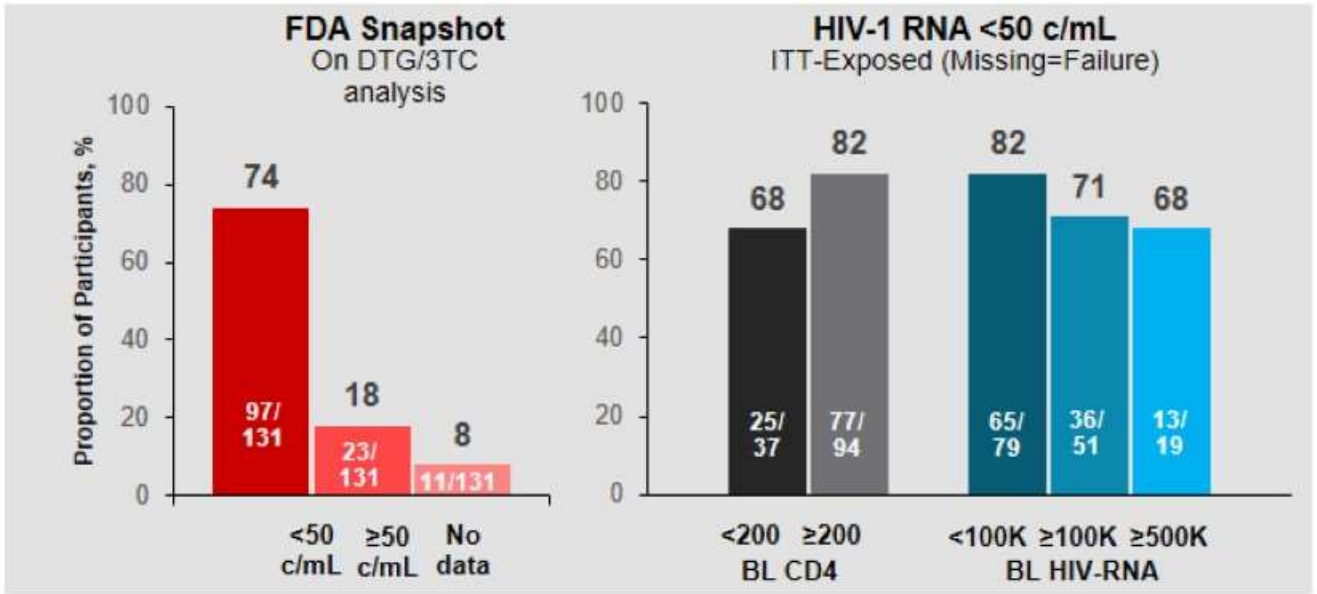
CI, confidence interval; IQR, interquartile range; VL, viral load (HIV-1 RNA)
*Adjusted treatment difference (95% CI)
†Protocol required discontinuation if VL decrease <1log10 by W12 (except if <200 c/mL by W12), confirmed rebound ≥200 c/mL at/after W24 with first initial suspected VL sample used for resistance testing

Cahn P, et al. HIV Drug Therapy 2020. Glasgow. Poster #018

DTG/3TC as a First-Line Regimen: Test and Treat (within 14 Days) Strategy

Evaluation of efficacy and safety of DTG/3TC initiated within 14 days of diagnosis in ART-naïve adults where baseline laboratory results are not available (N=131)

Efficacy at Week 24



- 87% (97/111) achieved HIV-1 RNA <50 c/mL in the observed analysis
- No treatment-emergent resistance detected

Safety

- Grade 2-5 drug-related AEs (2%) and serious AEs (2%)
- 8 (6%) participants switched from DTG/3TC
  - 5 HBV, 1 M184V, 1 adverse event (rash), 1 withdrew
  - 7/8 switched to 3-drug regimen
- 15 (11%) participants discontinued the study
  - 9% loss to follow-up or withdrew consent
  - 2% investigator decision
- Absolute median increase in weight: +4.6 kg

DTG/3TC in a test and treat setting showed numerically lower viral suppression rates in participants with baseline CD4 <200 cells/mm^3 and VL ≥100,000 c/mL

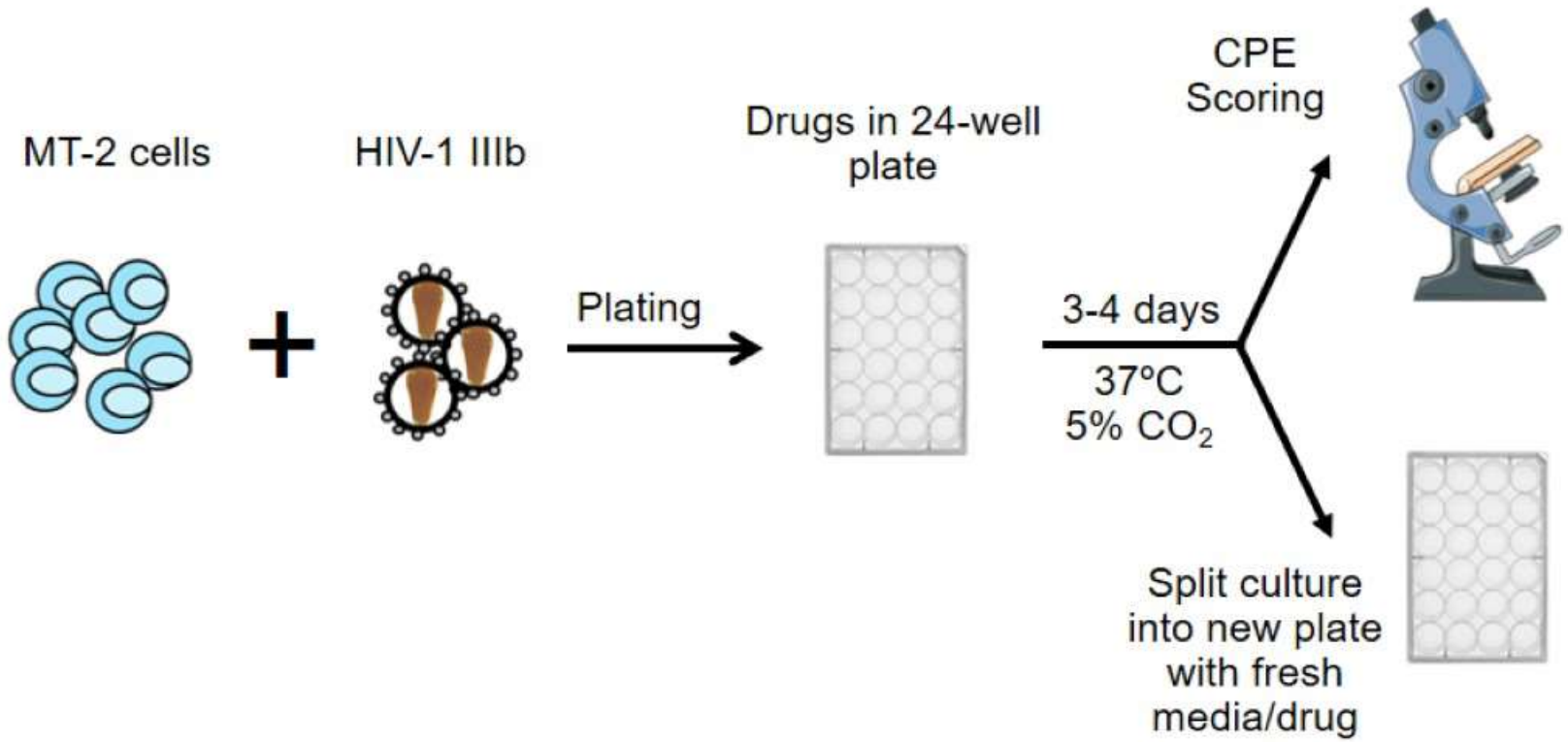
Treatment modifications were necessary as a result of baseline HBV coinfection and NRTI resistance

Rolle CP, et al. HIV Drug Therapy 2020. Glasgow. P020

AE, adverse event; BL, baseline; ITT, intention to treat

Assessing Barrier to Resistance: *In Vitro* Methodology

Drug Combinations: BIC+FTC+TAF or DTG+3TC

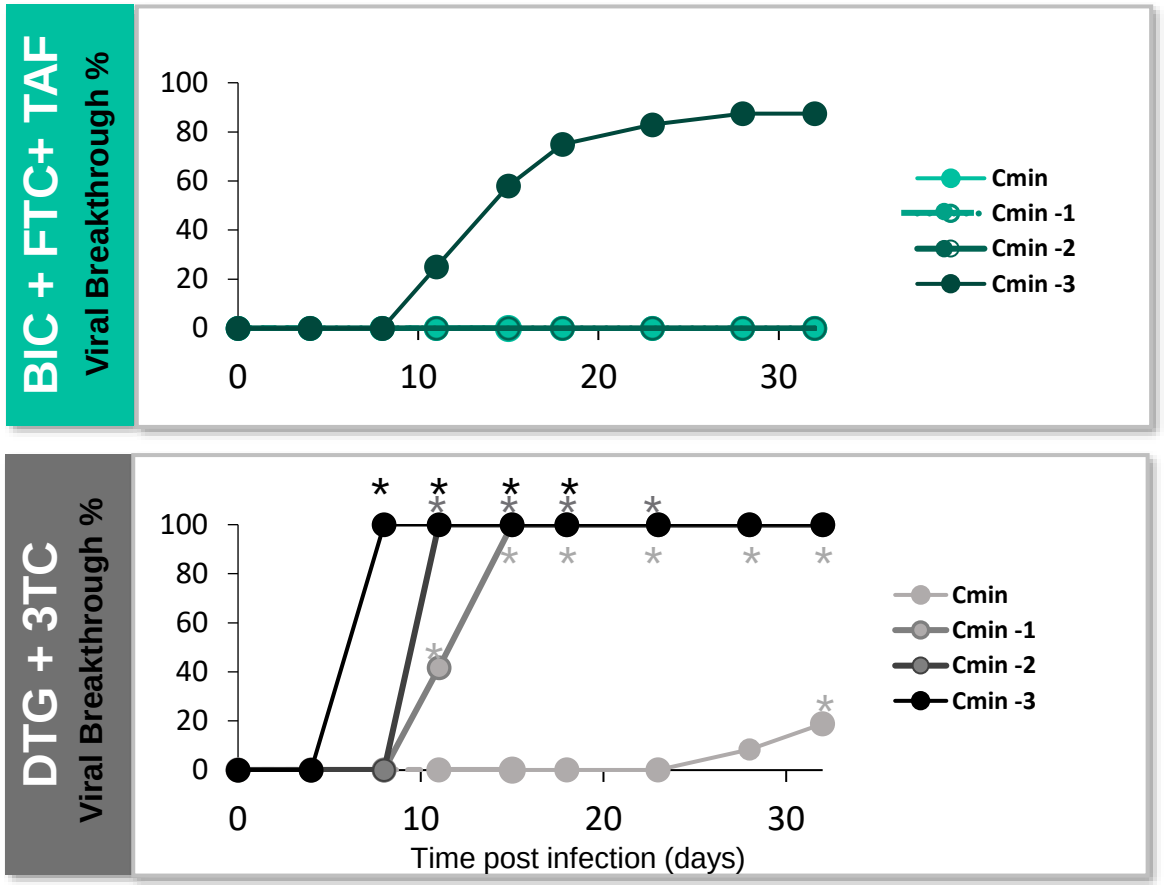


- Maintain culture for 5 weeks
- Deep sequence supernatant virus at time of breakthrough

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

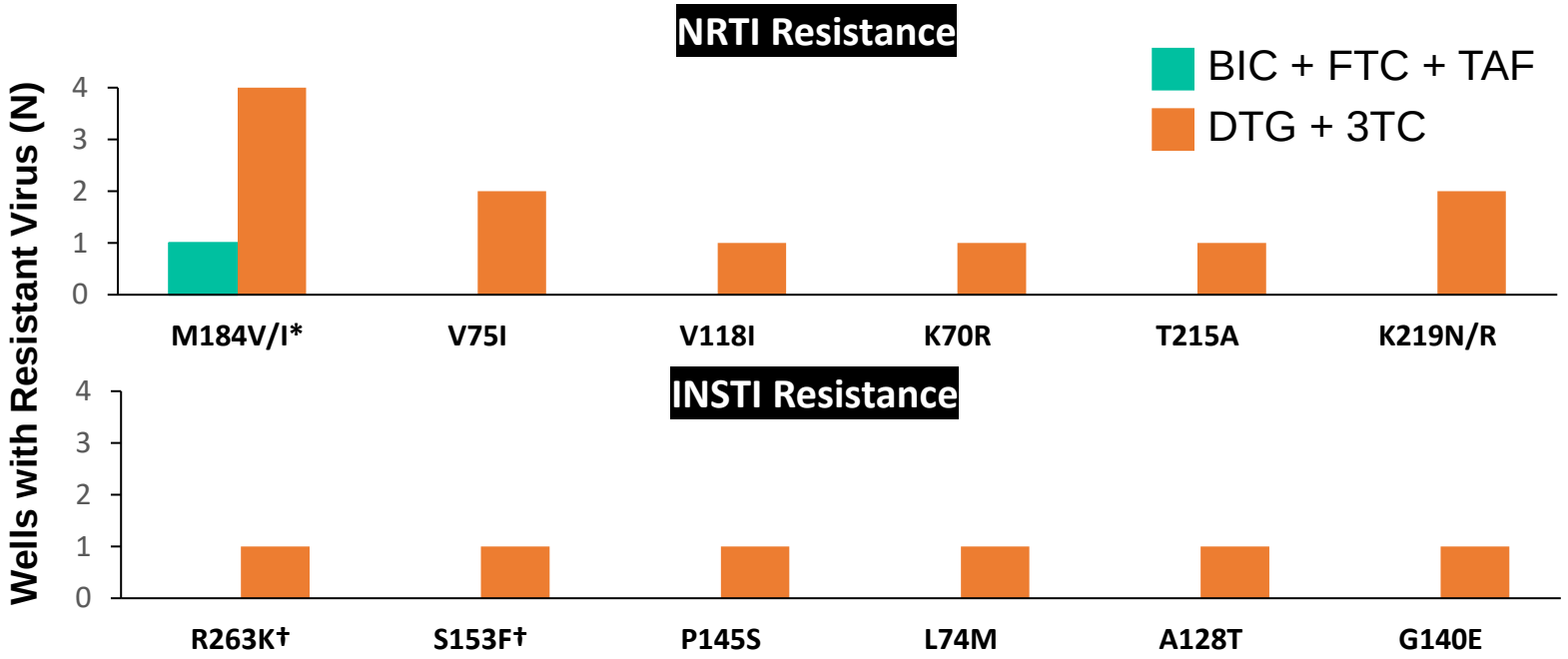
There was a lower threshold for viral breakthrough with missed doses for DTG + 3TC compared to BIC + FTC + TAF *in vitro* with wild-type HIV

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



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

Resistance Emergence in BIC + FTC + TAF wells

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

Resistance Emergence in DTG + 3TC wells

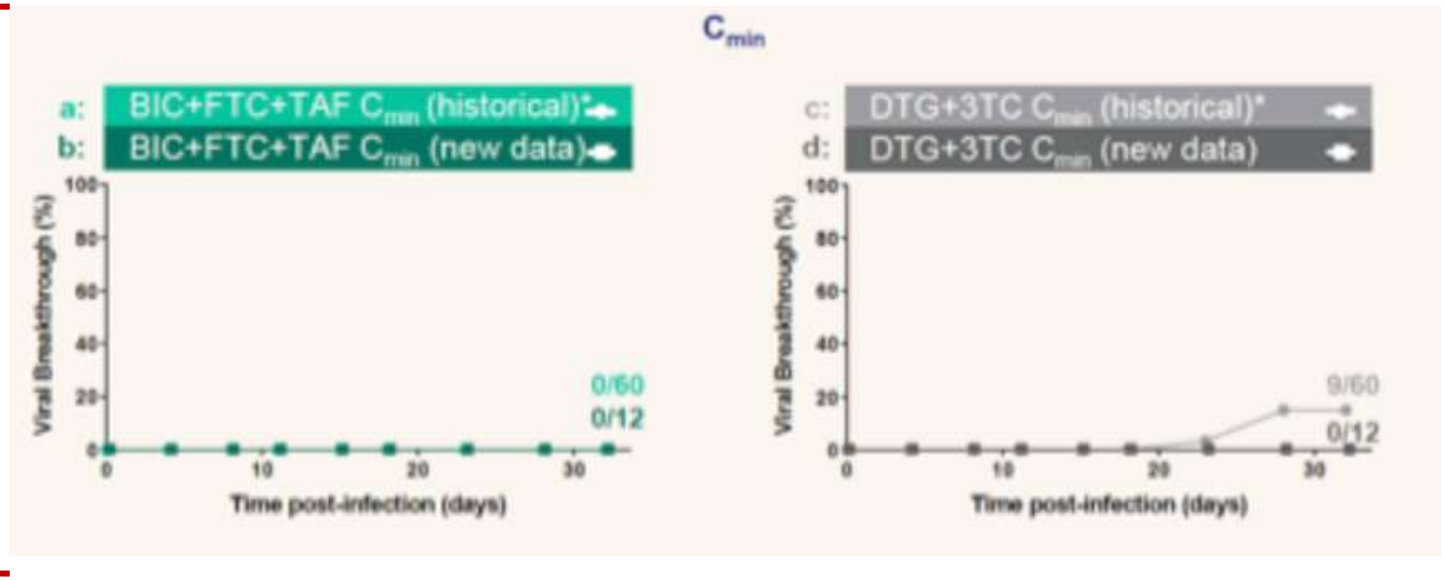
More resistance emergence with DTG+3TC (15/144) from Cmin to Cmin-2

Emergence of both INSTI and NRTI resistance

* 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

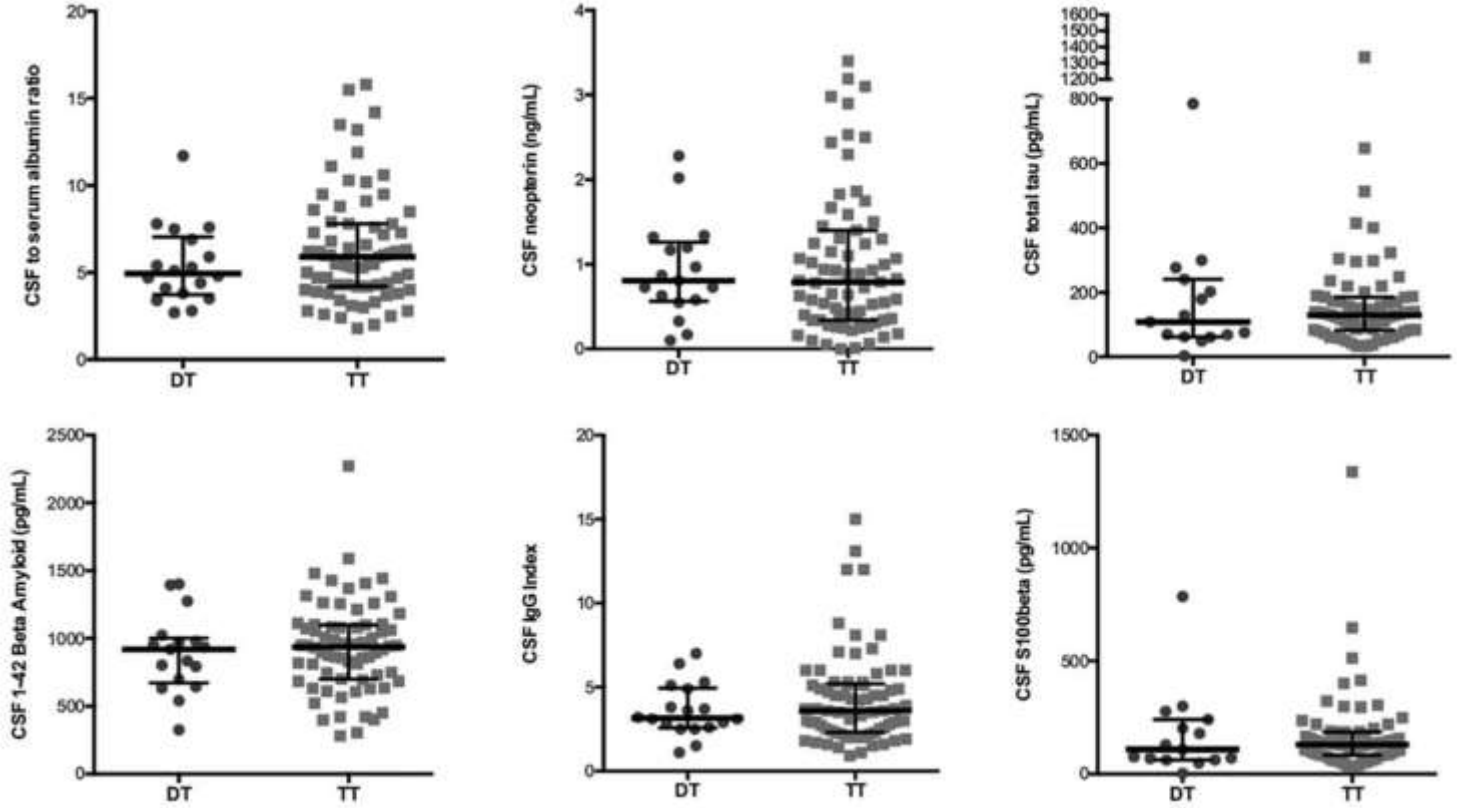
- The “in vitro” simulation of decreasing adherence might not include the complete interplay of “in vivo” factors
- The dynamic environment of ”in vivo” situation might compensate for decreased drug exposure of the target (e.g. dissociation time)
- The effect of lont-term HIV suppression cannot be easily 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”



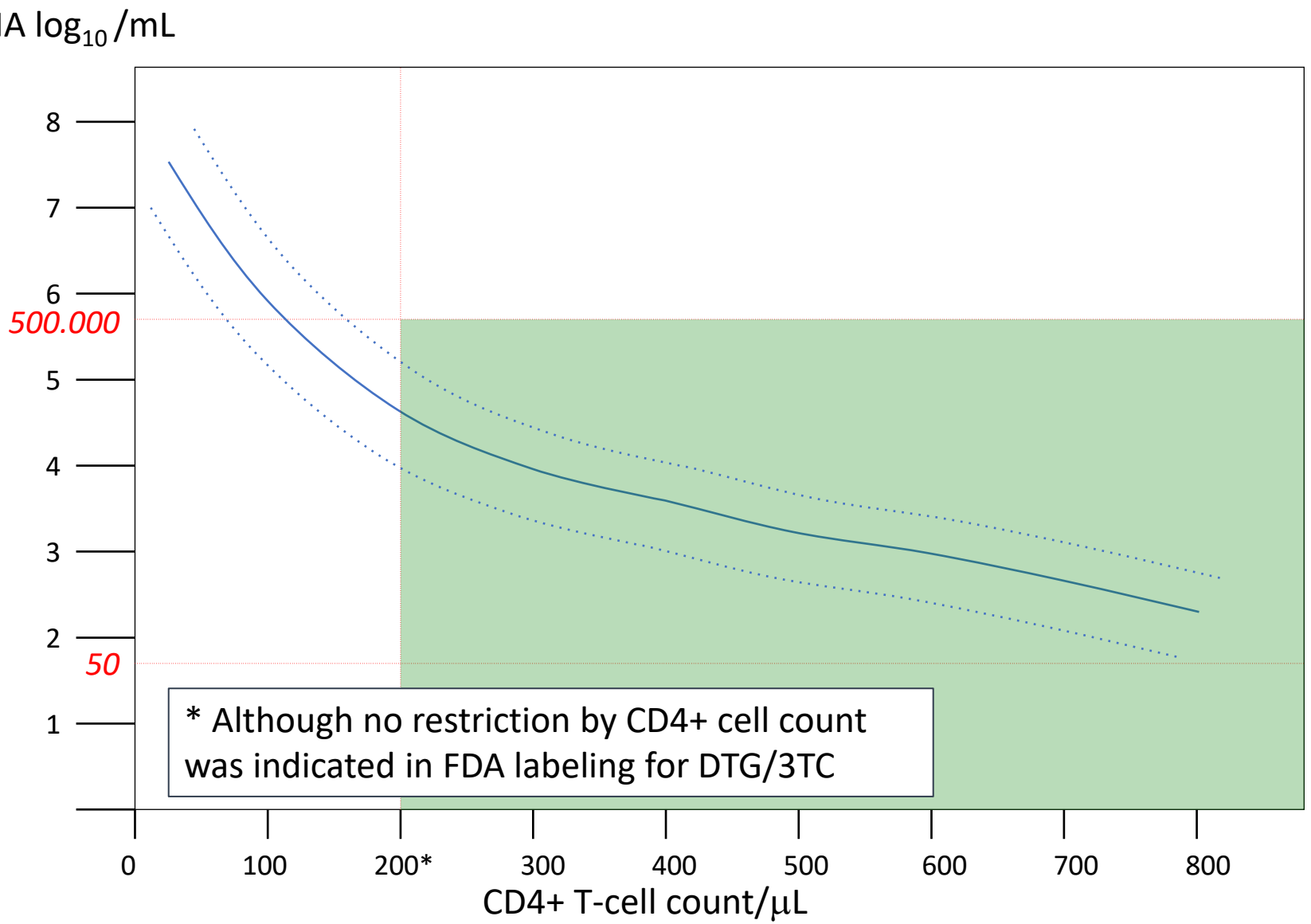
Dual antiretroviral therapies are effective and safe regimens in the central nervous system of neurologically symptomatic people living with HIV

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]



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.

GEMINI 1&2 – derived baseline immunovirologial cut-off defining the suitable treatment-naïve patients with chronic HIV infection who are candidate for successful DTG/3TC dual therapy

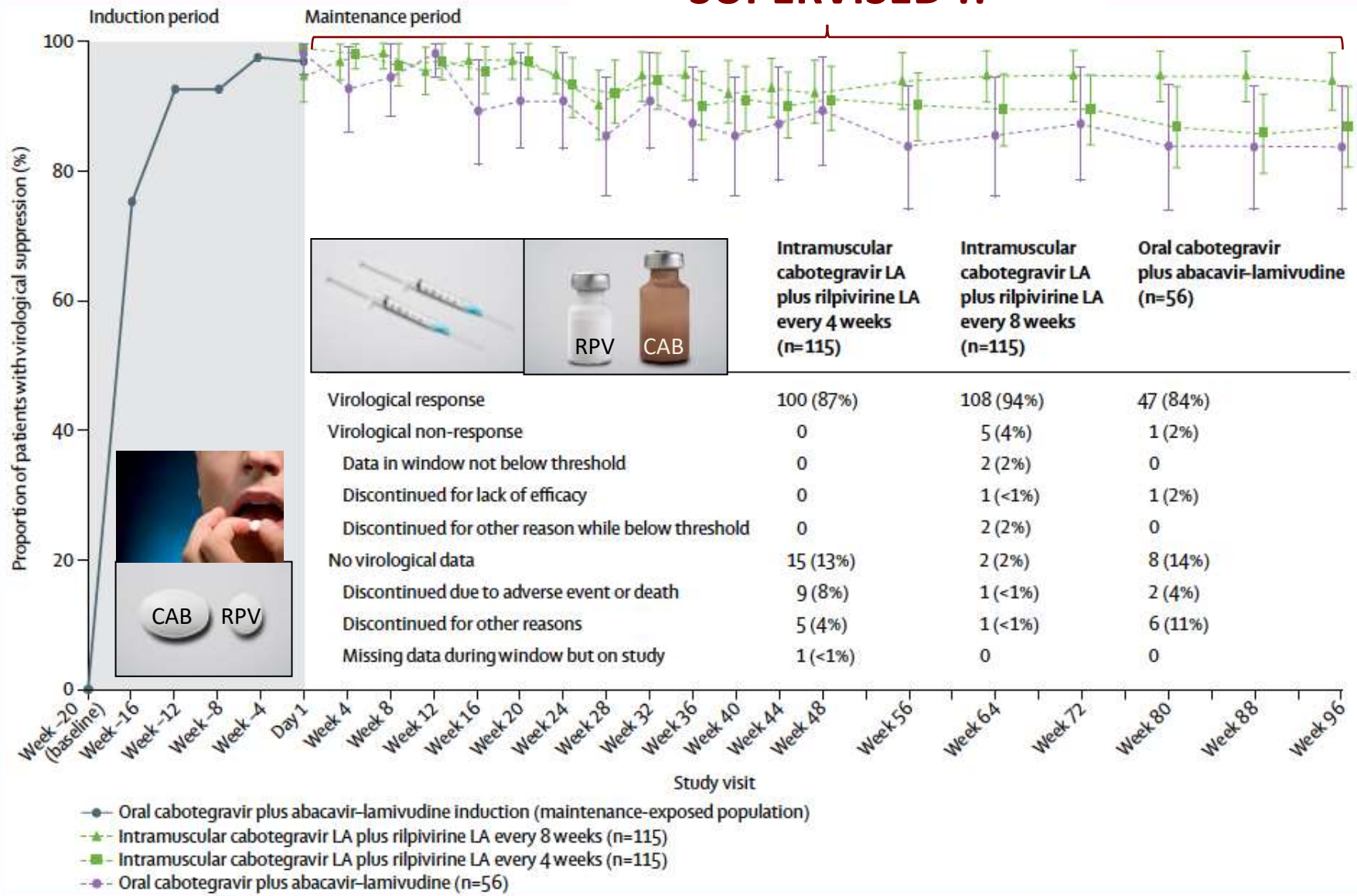


Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al

Lancet 2017; 390: 1499–510

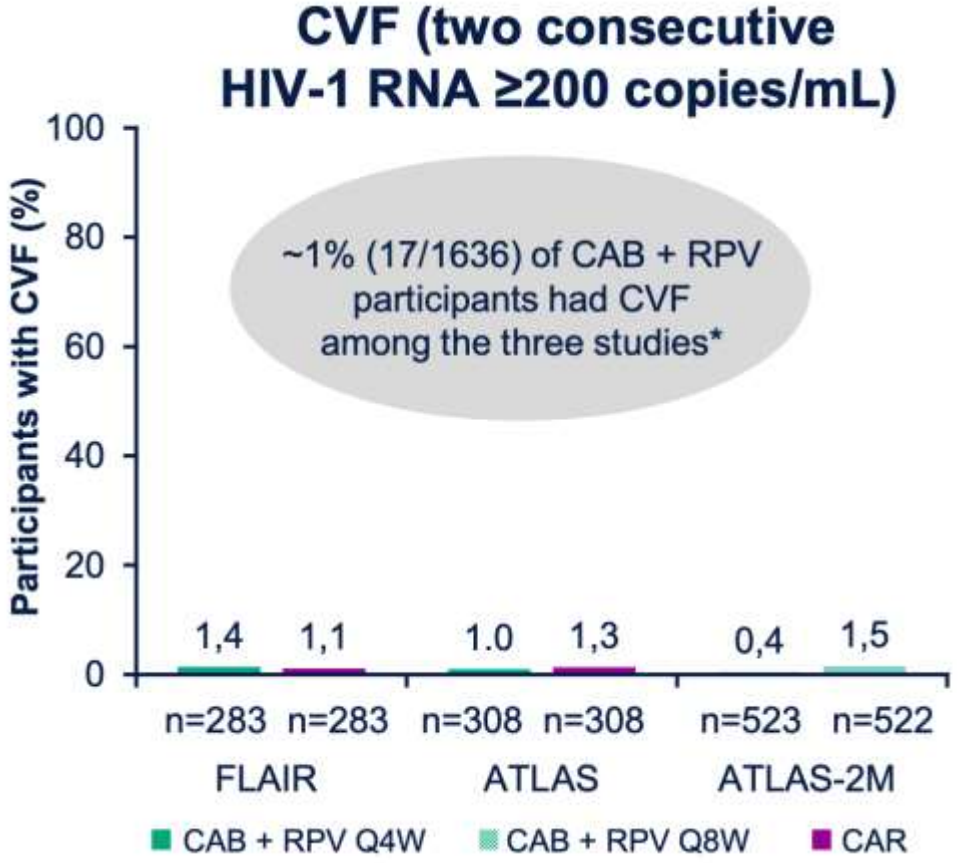
SUPERVISED !!



	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

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.



Factors explored in the MVA:

- CAB and RPV PK (i.e. initial trough concentrations at Week 8) and pre-existing † resistance mutations, adjusting fort he following covariates:
- Sex at birth
- BMI
- HIV-1 subtype
- Q4W and Q8W regimen

***13 of 17 participants who met the CVF criterion were CAB + RPV naive at study entry and received at least one LA injection were included in the multivariable analysis; three participants with CVF were excluded as they rolled over from ATLAS. An additional participant in FLAIR was excluded because CVF occurred prior to receiving LA injection (withdrawn due to false-positive pregnancy test).**

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							√			

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.

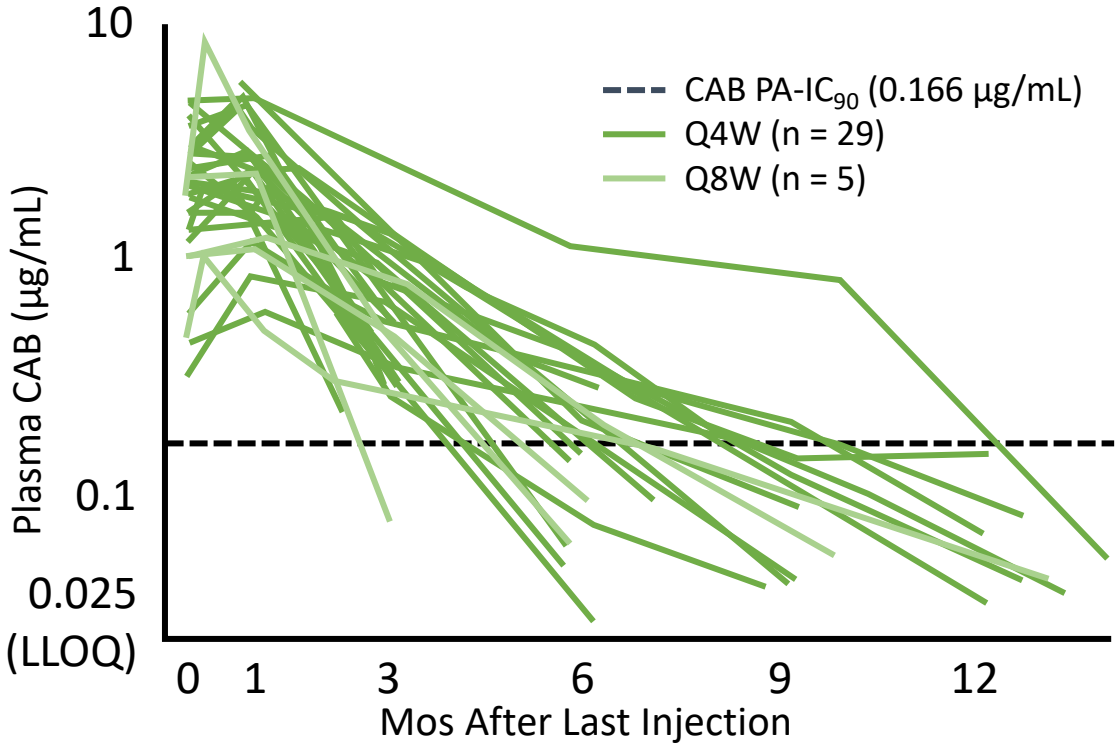
Multivariable Analysis: A Combination of Baseline RPV RAMs*, Subtype A6/A1 or BMI ≥30 Modestly Increased the Risk of Virologic Failure

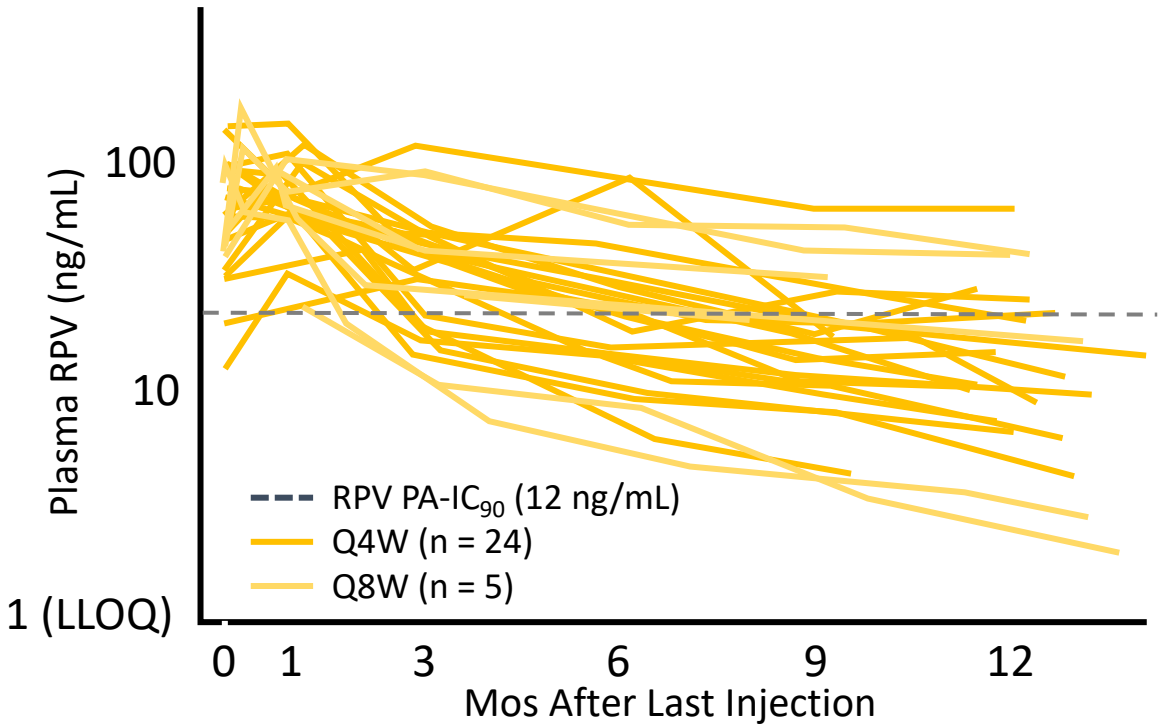
Factor	CVF, n (%)	HIV-1 RNA <50 copies/mL, n (%)
No baseline factors	3/732 (0.41)	694/732 (95)
Any one baseline factor	1/272 (0.37)	261/272 (96)
Two or more baseline factors	**9/35 (26)**	**25/35 (71)**
TOTAL [95% CI]	13/1039 (1.3) [0.67–2.13]	980/1039 (94) [92.74–95.65]

- CAB + RPV Q4W and Q8W regimens provide comparable, high rates of efficacy
- 94% of participants in this large pooled dataset maintained viral suppression over 48 weeks
- CVF is an infrequent multifactorial event (~1%)
- **CVF influenced by the presence of at least 2 baseline factors: RPV RAMs, BMI ≥30, HIV-1 subtype A6/A1**
- **Week 48 CVF rate was <0.5% when 0 or 1 baseline factor was present**
- While low RPV trough concentrations were observed in some CVFs, this rarely occurred without other predictive factors
- These findings should be contextualized with the high overall success rates and participants' preference for CAB + RPV LA, and may inform prescribers when considering this novel LA regimen

LATTE-2/ATLAS: Pharmacokinetics After Long-Acting CAB + RPV Discontinuation

- After d/c, LA CAB + RPV may be detectable in plasma for ≥ 1 yr
- No DDIs expected between residual LA CAB + RPV after d/c and newly begun ARVs, even CYP3A/UGT1A1 inducers or inhibitors



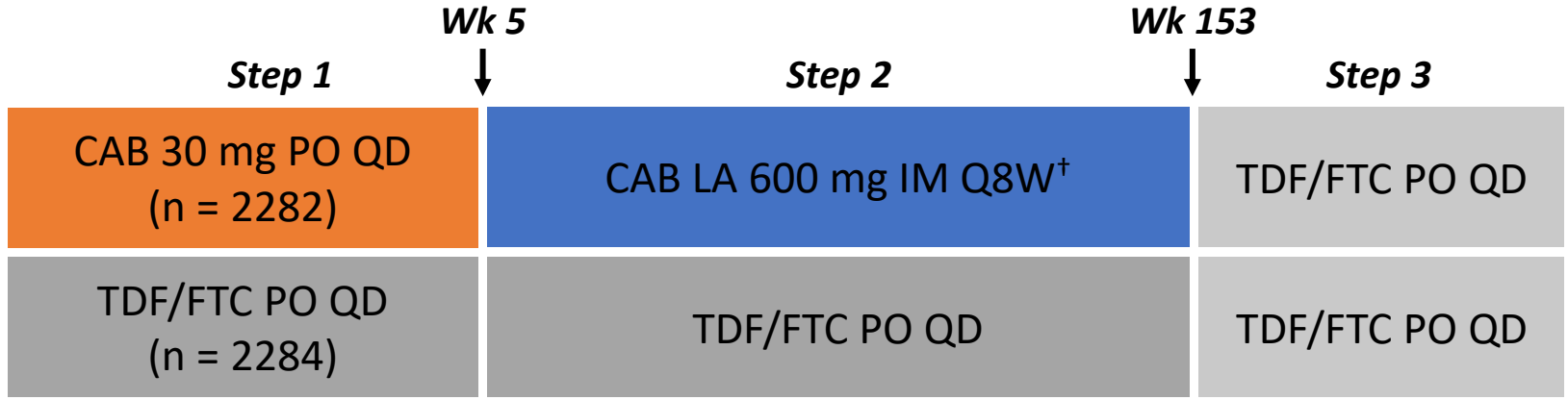


Ford. CROI 2020. Abstr 466.

HPTN 083: Efficacy and Safety of LA Injectable CAB vs Daily Oral TDF/FTC for PrEP in MSM and TGW

- International, randomized, double-blind phase IIb/III study

HIV-uninfected MSM and TGW ≥ 18 yrs of age at high risk of HIV infection*; no HBV/HCV infection, contraindication to gluteal injection, seizures, or gluteal tattoos/skin conditions (N = 4566)



In Steps 1/2, all participants received matching placebo. At interim analysis on May 14, 2020 with 25% of endpoints accrued, DSMB recommended termination of blinded study due to crossing of pre-specified O'Brien-Fleming stopping bound.

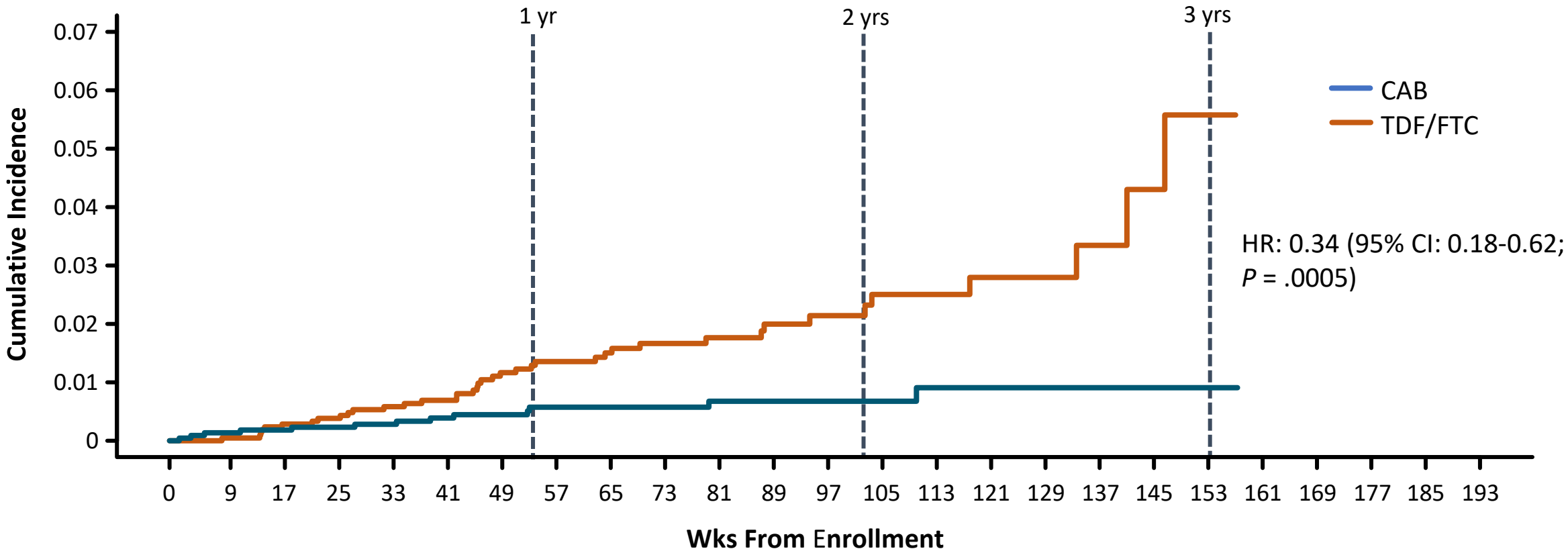
*Any non-condom receptive anal intercourse, > 5 partners, stimulant drug use, incident rectal or urethral STI (or incident syphilis) in past 6 mos; or SexPro Score ≤ 16 (US only).

†First 2 doses given 4 wks apart then every 8 wks thereafter.

Primary endpoints: incident HIV infections in Steps 1/2, grade ≥ 2 AEs

Landovitz. AIDS 2020. Abstr OAXLB0101. NCT02720094.

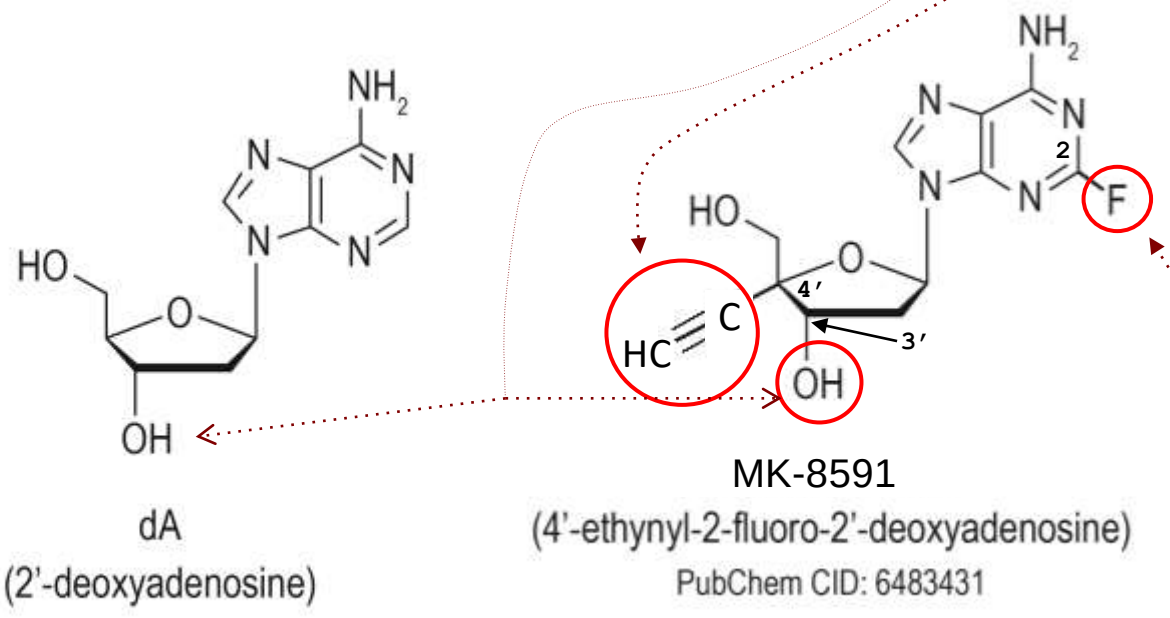
HPTN 083: HIV Incidence (ITT) With LA Injectable CAB vs Daily Oral TDF/FTC PrEP



Landovitz. AIDS 2020. Abstr OAXLB0101. Reproduced with permission.

- **4’-Ethynyl-2-Fluoro-2’-deoxyadenosine**
- **MK-8591**
- **EFdA**
- **Islatravir**

Molecular Structure



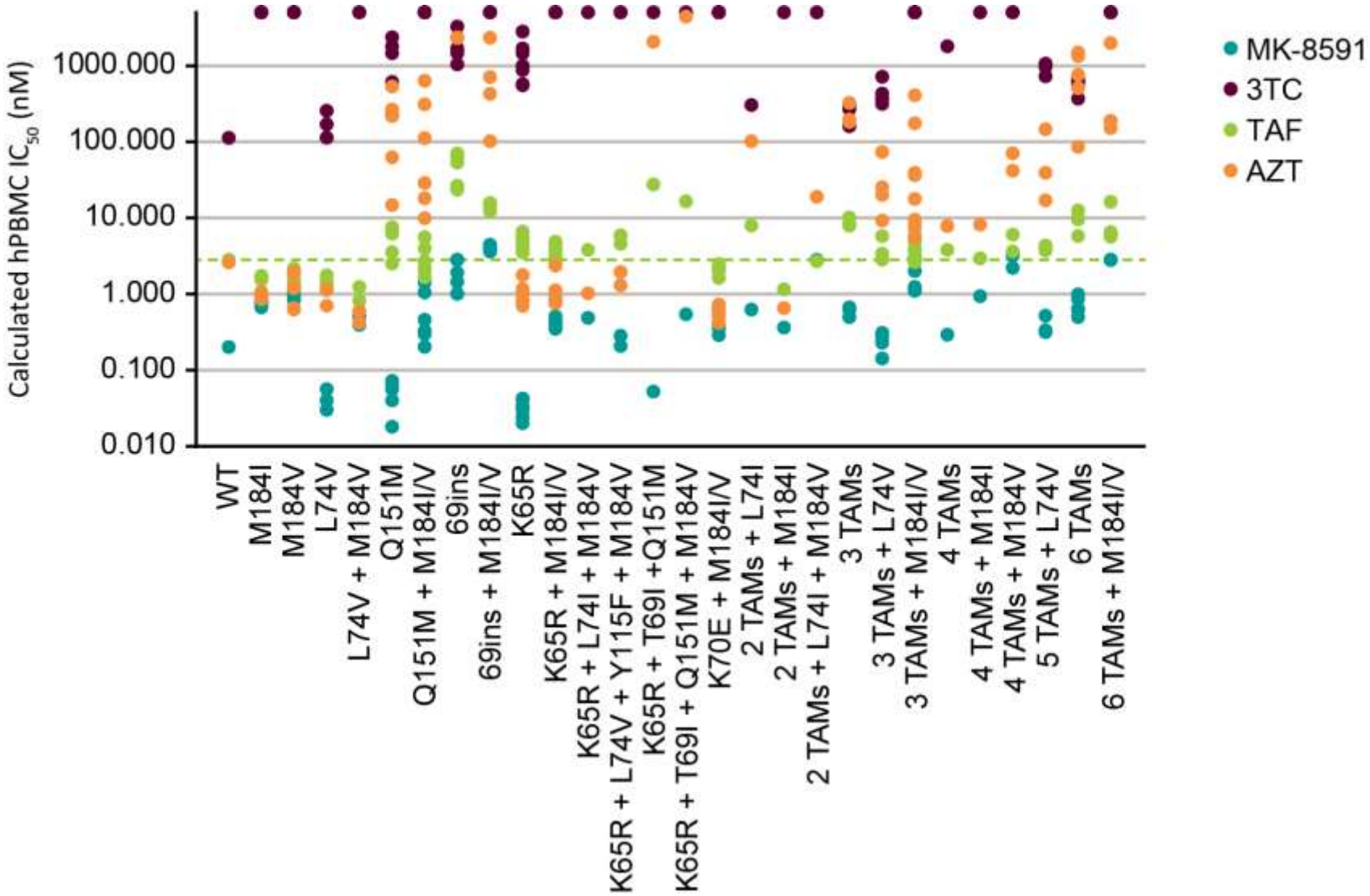
Michailidis E et al. *J Biol Chem.* 2014;289(35):24533-24548.

- MK-8591 has a **3’-OH,** which mimics the structure of natural dNTPs. This property enhances phosphorylation of nucleoside reverse-transcriptase inhibitors by cellular kinases, thereby increasing antiviral efficacy

- MK-8591 also contains a **4’-ethynyl group** that establishes hydrophobic interactions with conserved amino acid residues in a hydrophobic pocket in the RT active site. The strength of these interactions causes immediate chain termination by preventing translocation of the RT. If the RT translocate and a new nucleotide is added to the DNA chain, steric crowding by the 4’-ethynyl group prevents further additions of new nucleotides, leading to delayed inhibition of DNA synthesis

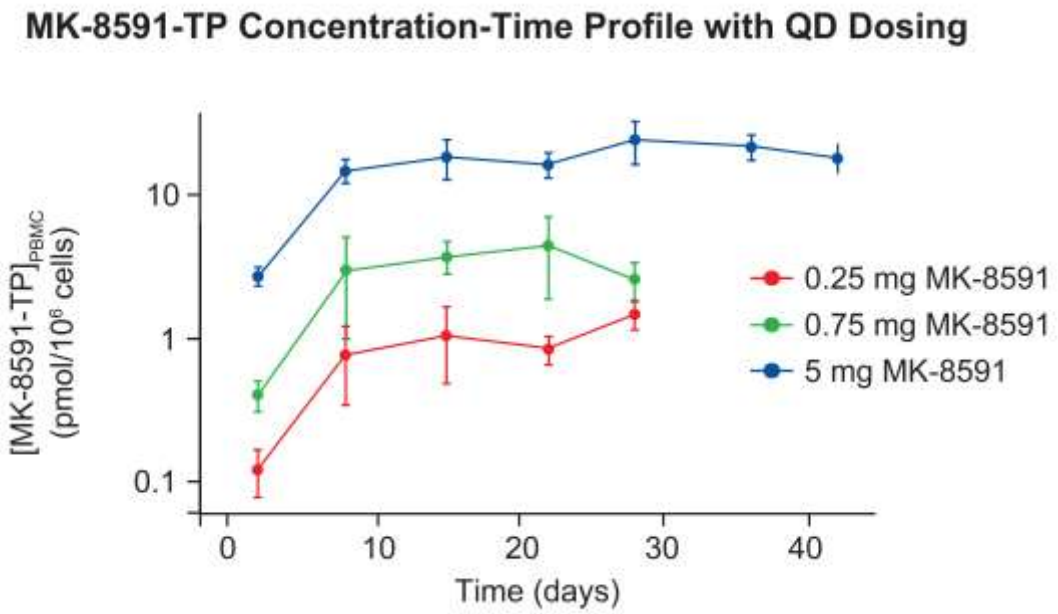
- The **2-fluoro group** alters the electronic distribution in the MK-8591 adenine ring, which makes it resistant to degradation by adenosine deaminase. The net result is a longer intracellular half-life of MK-8591

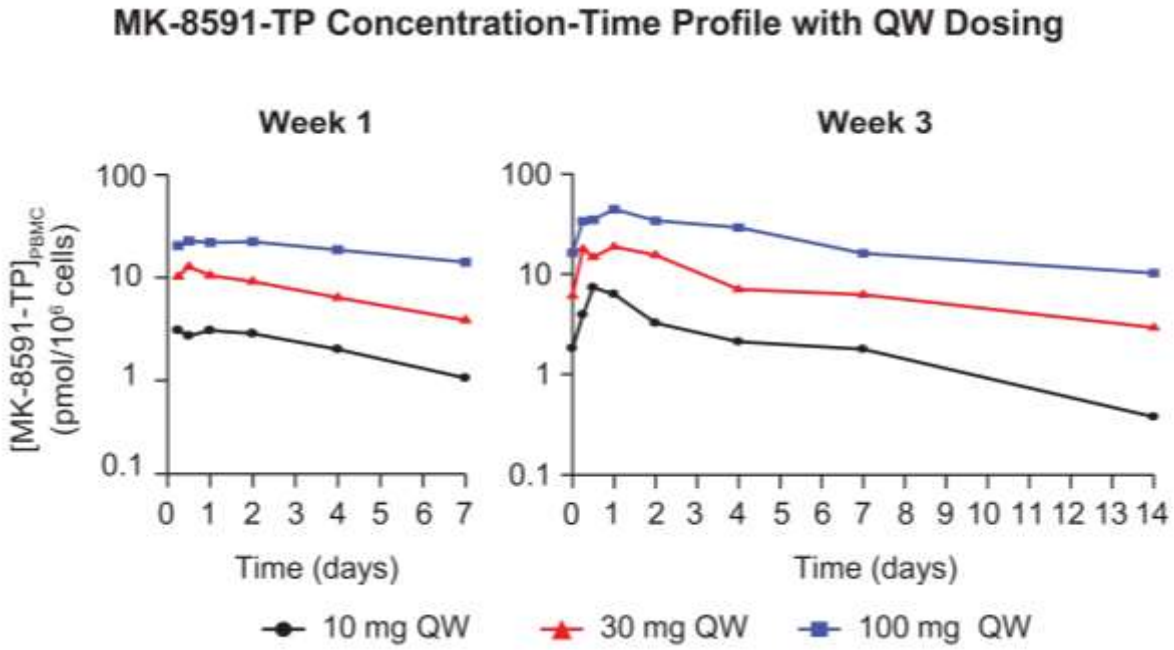
MK-8591 is More Potent Against Most Resistant Mutants Than Approved NRTIs



GROBLER, MK-8591 PK STUDY, CROI 2019

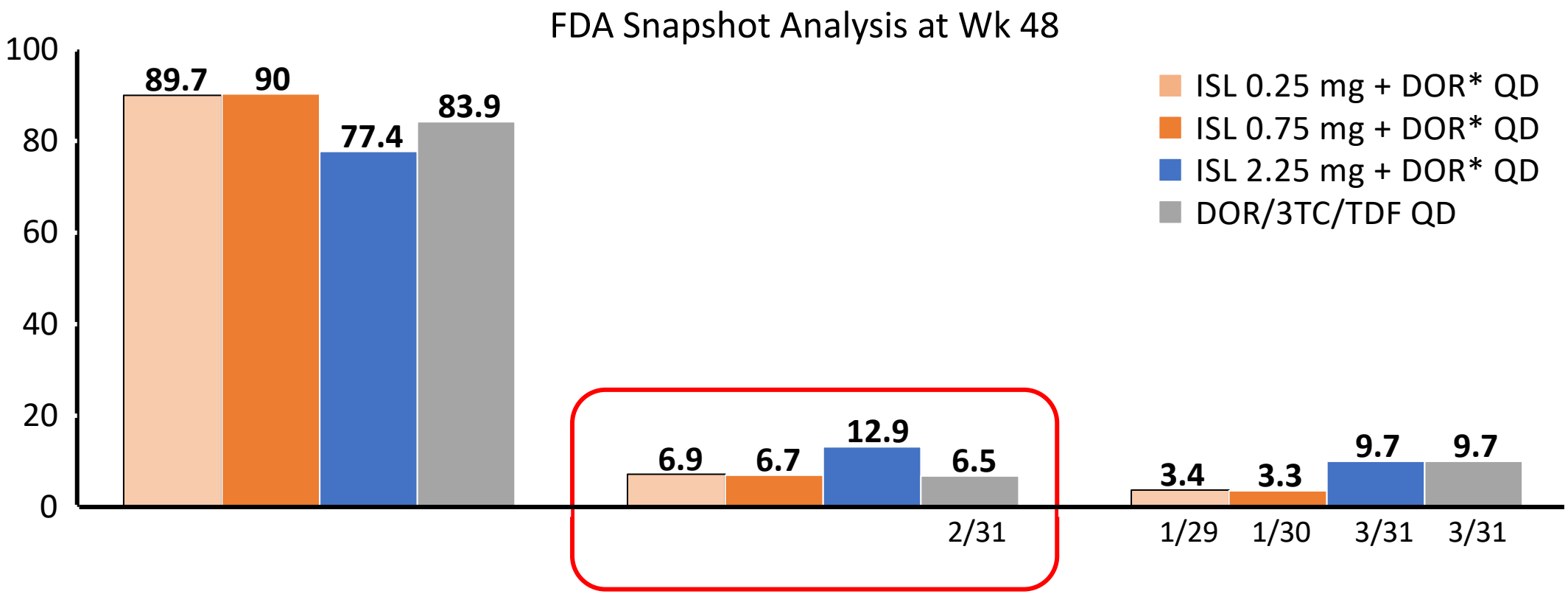
MK-8591-TP Accumulates to High Levels at Low Doses in Humans and Exhibits a Long Intracellular $t_{1/2}$ [1/2]





Matthews, CROI 2018
Grobler et al, CROI 2016

P011 Study: ISL + DOR vs DOR/3TC/TDF in Treatment-Naive Adults



*Participants initially received ISL + DOR + 3TC and switched to ISL + DOR during the Wk 24-48 period of the study.

Orkin. AIDS 2020. Abstr OAB0302. Reproduced with permission.

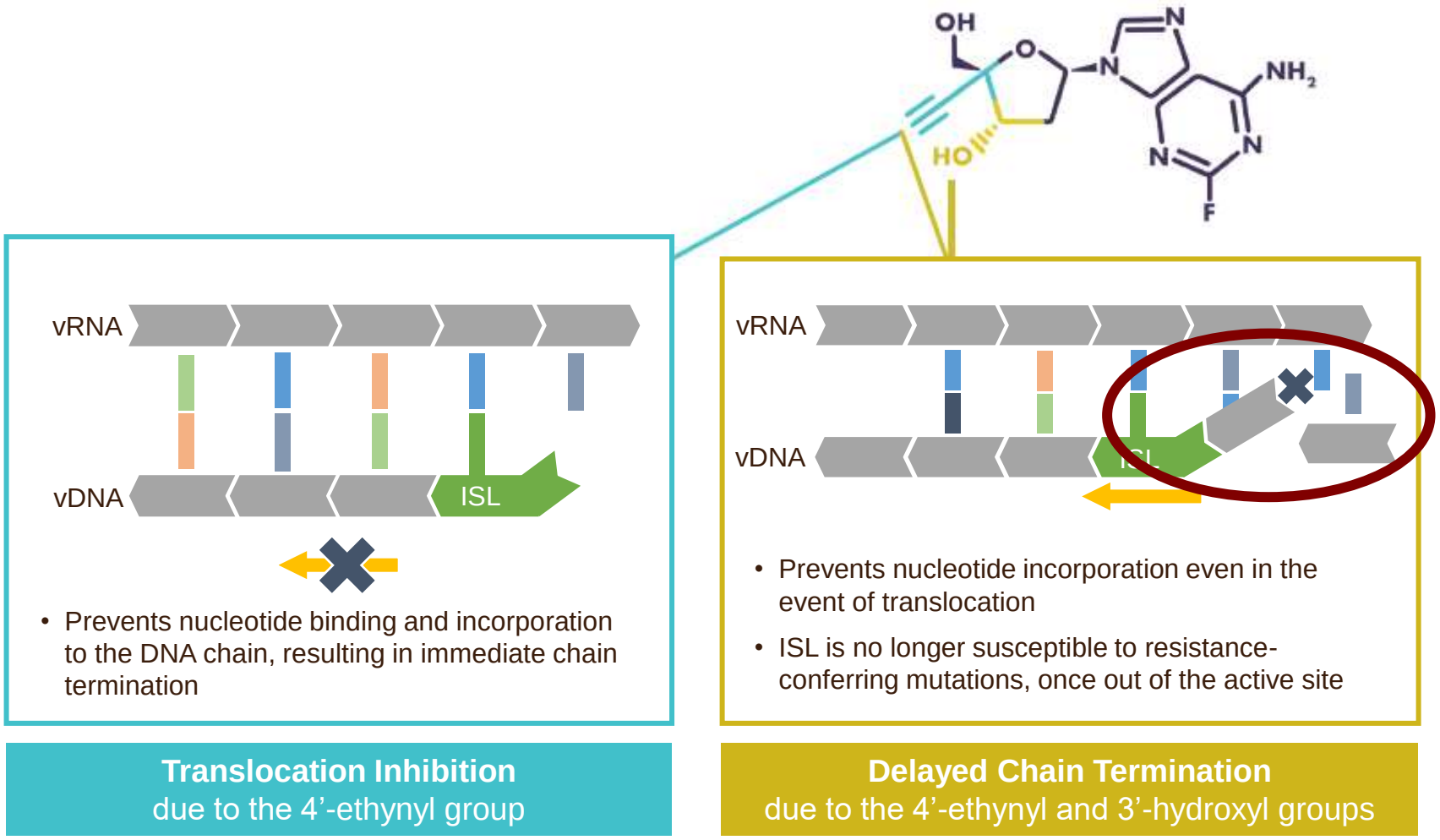
P011: Protocol Defined Virologic Failure at Wk 48

- HIV-1 RNA levels at second assessment were < 80 copies/mL in all patients with PDVF; no patient met criteria for resistance testing (HIV-1 RNA > 400 copies/mL)
- **No evidence that PDVF was associated with drug pharmacokinetics**

Outcome at Wk 48	ISL 0.25 mg + DOR QD (n = 29)	ISL 0.75 mg + DOR QD (n = 30)	ISL 2.25 mg + DOR QD (n = 31)	DOR/3TC/TDF QD (n = 31)
PDVF, n (%)				
▪ Nonresponse	0 (0)	0 (0)	1 (3.2)	0 (0)
▪ Rebound with HIV-1 RNA > 50 c/mL	2 (6.9)	2 (6.7)	0 (0)	1 (3.2)
▪ Rebound with HIV-1 RNA > 200 c/mL	0 (0)	0 (0)	0 (0)	0 (0)
HIV-1 RNA ≥ 50 c/mL not classified as PDVF, n (%)				
Early d/c	0 (0)	0 (0)	3 (9.7)	1 (3.2)
Reason for early d/c	--	--	2 LTFU; 1 withdrawal	1 protocol violation

Orkin. AIDS 2020. Abstr OAB0302.

Islatravir (MK-8591): First-in-class NRTTI with Multiple Mechanisms of Action



- Prevents nucleotide binding and incorporation to the DNA chain, resulting in immediate chain termination

Translocation Inhibition
due to the 4'-ethynyl group

- Prevents nucleotide incorporation even in the event of translocation
- ISL is no longer susceptible to resistance-conferring mutations, once out of the active site

Delayed Chain Termination
due to the 4'-ethynyl and 3'-hydroxyl groups

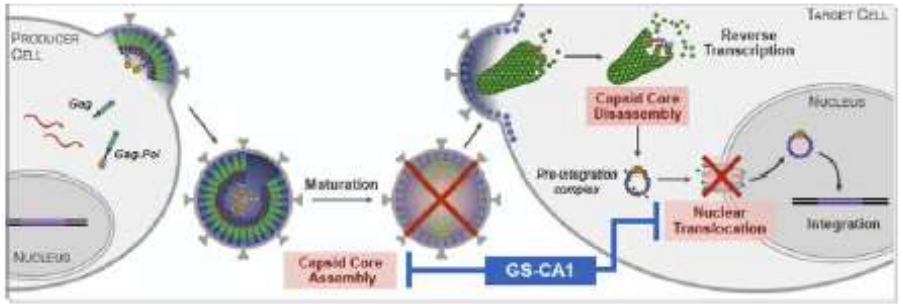
Multiple mechanisms contribute to the high potency of ISL against HIV-1 and drug-resistant variants as well as its high barrier to resistance

Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB and Poster #LBPED46.

GS-CA1 HIV Capsid Inhibitor: More Potent Than Any Approved Antiretroviral

- Inhibits multiple steps in the HIV replication cycle
  - Capsid core assembly
  - Capsid core disassembly
  - Nuclear translocation
- Highly active against major HIV-1 mutants selected by clinical PIs, NRTIs, NNRTIs, and INSTIs
- No measurable cytotoxicity in target and non-target primary cells
- Single sc injection maintains plasma concentrations 9 times the plasma adjusted EC_{95} for >10 weeks – in rats
- Currently in Phase 1 studies in humans

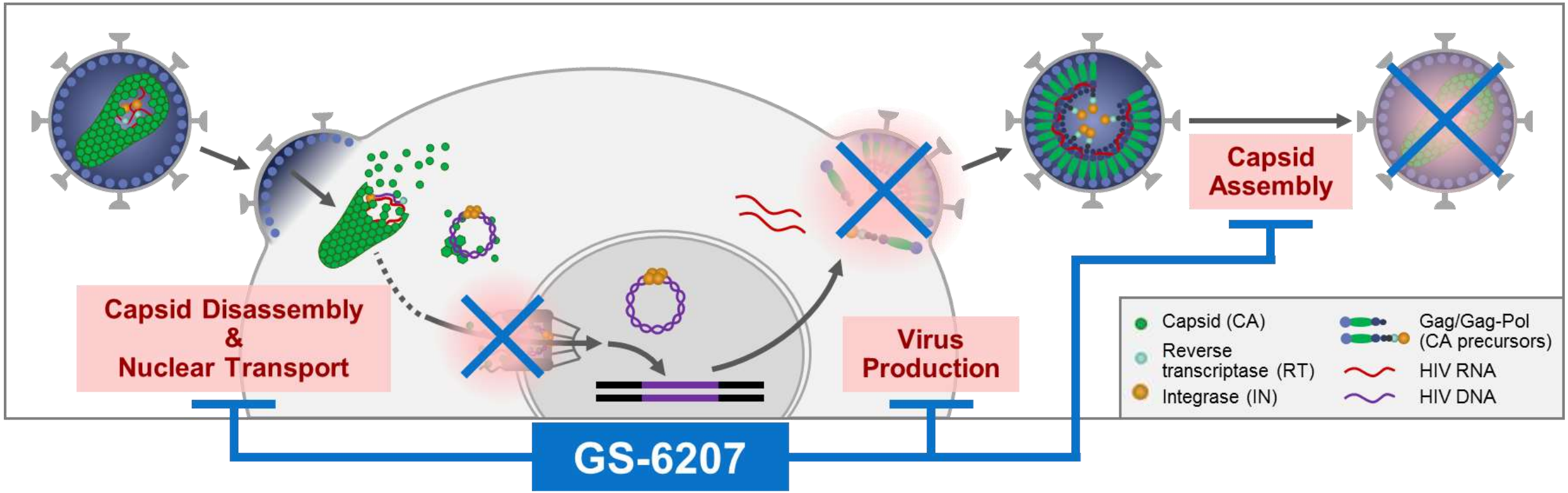
GS-CA1: Multiple Sites of Action



	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

Tse WC, et al. 24th CROI. Seattle, 2017 Abstract 38.

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

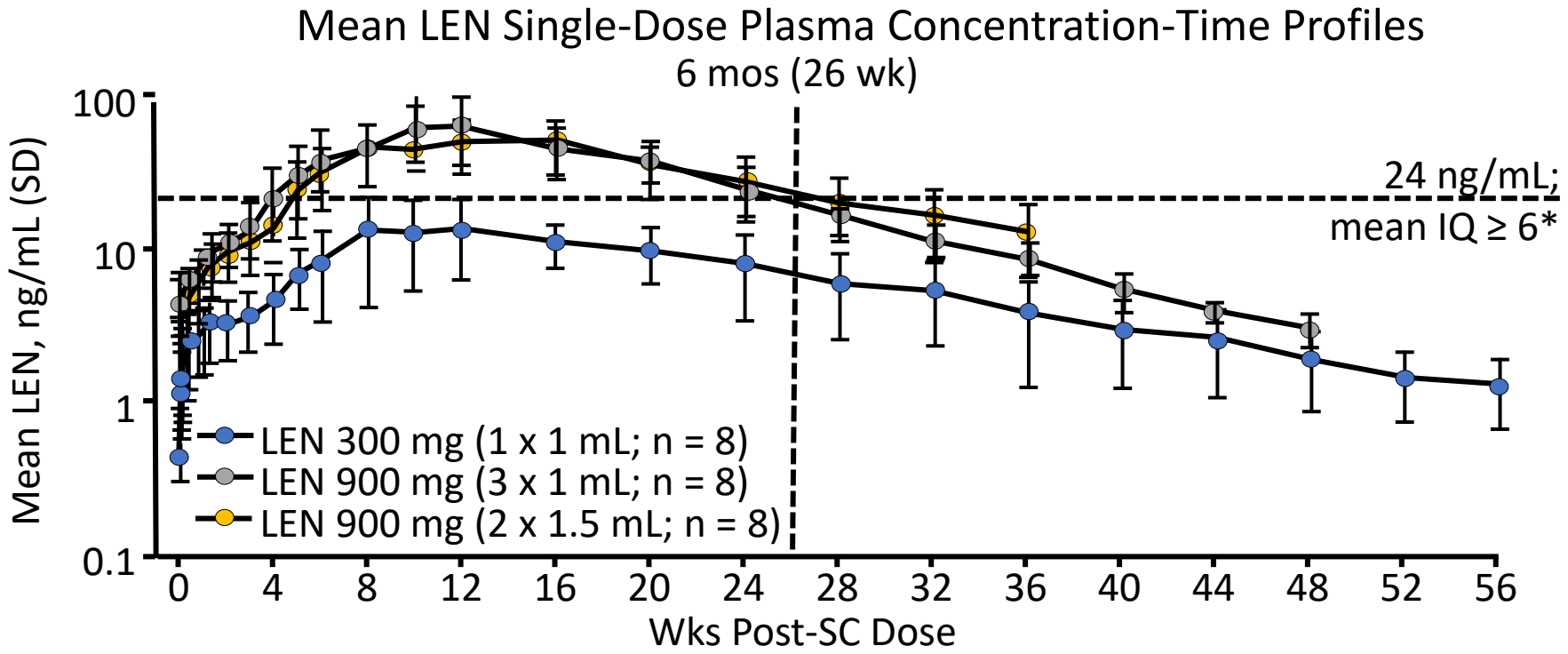


LEN inhibits CA-mediated nuclear entry of viral DNA, HIV assembly, and proper capsid formation, functions essential for viral replication

Margot N, et al. HIV Drug Therapy 2020. Glasgow. Oral #324

Lenacapavir Pharmacokinetic Profile

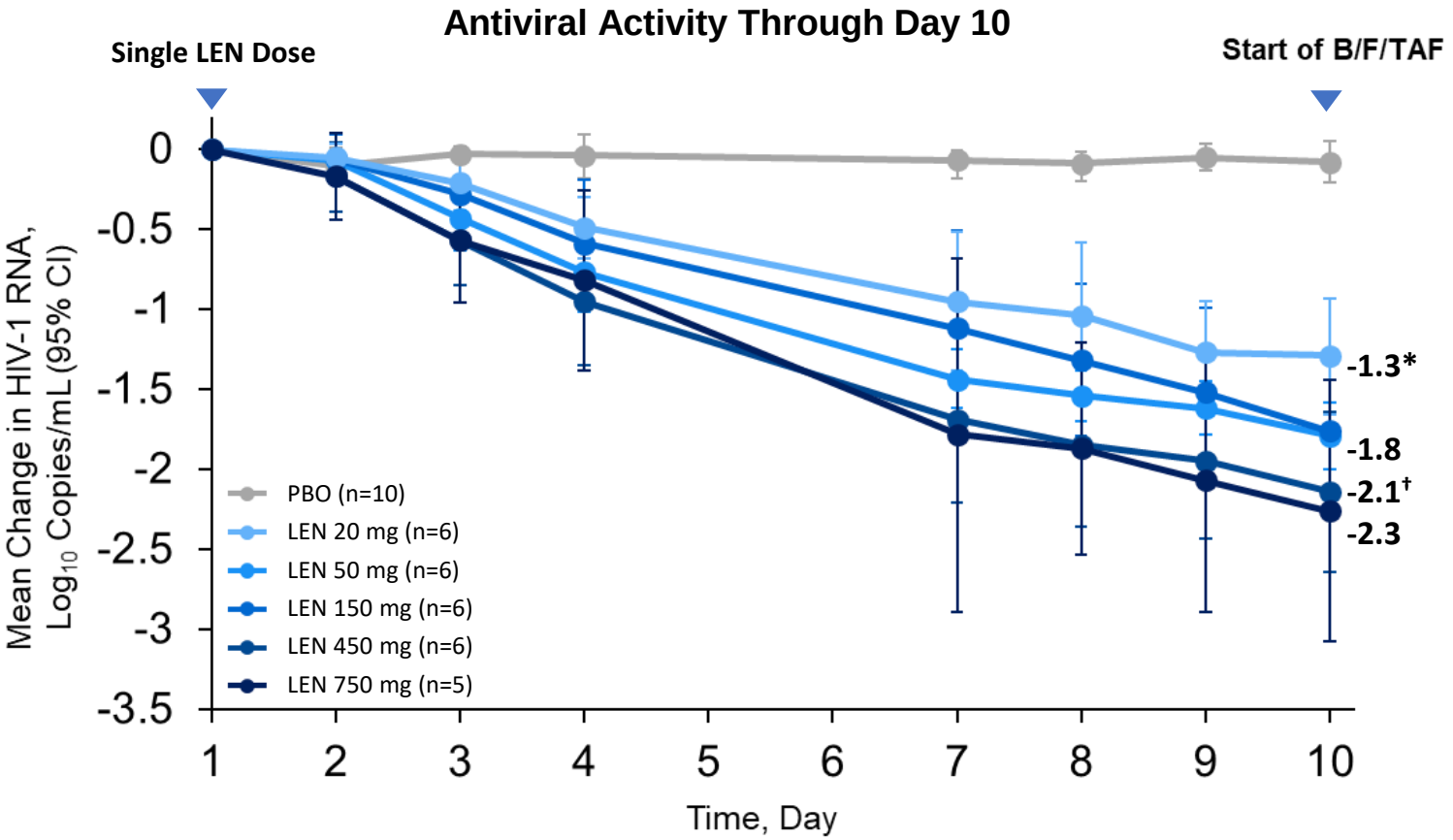
- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor with oral and SC long-acting formulations in development
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants (N = 30)



*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.

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

GS-US-200-4072: LEN Safety & Antiviral Activity following Single Subcutaneous Dose

Capsid Resistance Analyses

- Performed for all participants:
  - Genotyping/phenotyping (BL and D10, Monogram)
  - Genotyping (D10, Seq-IT)

- Pre-treatment analyses:
  - No resistance mutations to LEN
  - WT phenotypic susceptibility to LEN

LEN SC dose	Number of Participants with Emerging CA Resistance at Day 10	RAMs Detected	
		Monogram Biosciences (NGS >10%)	Seq-IT (NGS >2%)
20 mg (n=6)	1	Q67Q/H	Q67Q/H
50 mg (n=6)	1	-	Q67H
150 mg (n=6)	0	-	-
450 mg (n=6)	0	-	-
750 mg (n=5)	0	-	-

- Low-level resistance mutation Q67H in 2 participants at lowest LEN doses (20 mg and 50 mg)
- No other substitutions observed in CA protein

Rare low-level resistance to LEN via a single mutation (Q67H) emerged only at LEN exposures below the expected exposure in Ph2/3 studies

LEN, lenacapavir

Margot N, et al. HIV Drug Therapy 2020. Glasgow. Oral #324

TORINO:

Stefano Bonora

Francesco G. De Rosa

Andrea Calcagno

Antonio D'Avolio

Mauro Sciandra

Marco Siccardi

Cristina Tettoni

Sabrina Audagnotto

Letizia Marinaro

Jessica Cusato

Laura Trentini

Marco Simiele

Amedeo De Nicolò

Anna Lucchini

Filippo Lipani

Roberto Bertucci

Chiara Montrucchio

Chiara Alcantarini

Marino Bonasso

Ilaria De Benedetto

Stefano Biffi

Paolo Tiralongo

Micol Ferrara

Alice Trentalange

Lucio Boglione

Pino Cariti

Ilaria Motta

Silvia Corcione

Ambra Barco

Tommaso Lupia

Simone Mornese Pinna

Enrica Borgogno

Silvia Scabini

Giancarlo Orofino

Valeria Ghisetti

Valeria Avataneo

Alessandra Manca

Ilaria Zedda

Alice Ianniello

Elisa De Vivo

Luca Paglietti

Miriam Antonucci

Mattia Trunfio

Elena Salvador

Walter Rugge

Acknowledgments

THE UNIVERSITY *of* LIVERPOOL

LIVERPOOL:

David Back

Saye Khoo

Andy Owen

Marco Siccardi

SSAT ST STEPHEN'S AIDS TRUST

LONDON:

Marta Boffito

Margherita Bracchi

Nicole Pagani

ROMA:

Andrea Antinori

Adriana Ammassari

Giuseppe Ippolito