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AULA MAGNA POLO LITA

Ospedale Luigi Sacco
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Nuovi Paradigmi e Nuove Possibilità Terapeutiche: la Pipeline a Breve Termine

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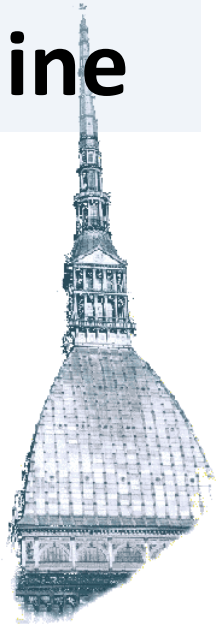

Ospedale Amedeo di Savoia

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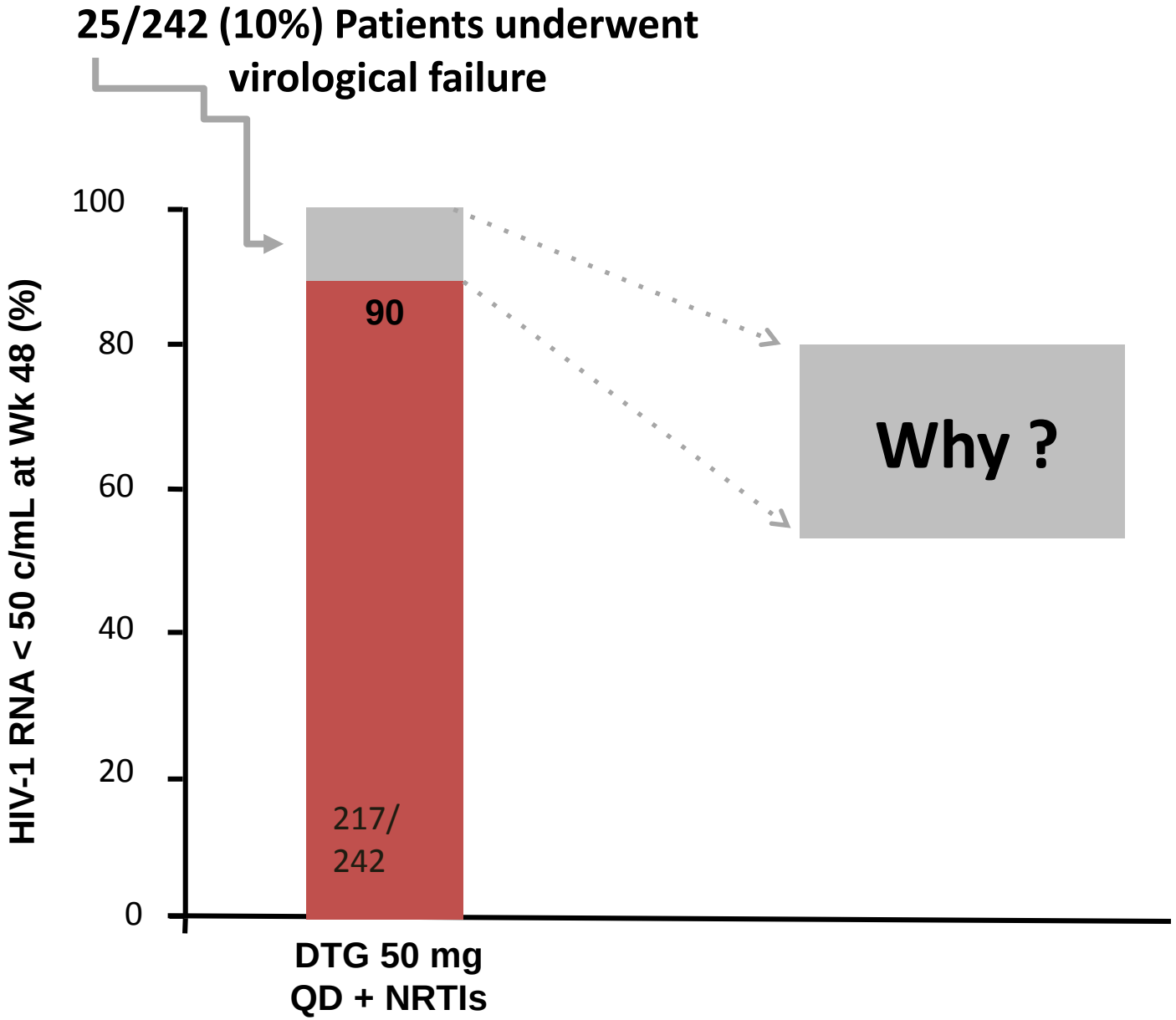


Feinberg J, et al. ICAAC 2013. Abstract H1464a.

1. In these patients (possibly with baseline unfavourable factors, e.g. very high VL, very low CD4+ cell counts) the potency of the regimen is insufficient;

Unlikely as sole factor

1. Incomplete drug/s absorption;

Rare, & drug potency usually compensates

2. Pre-existing drug-resistance;

Rare, easy to rule out

1. They stopped drug intake soon after enrollment (for whatever reason);

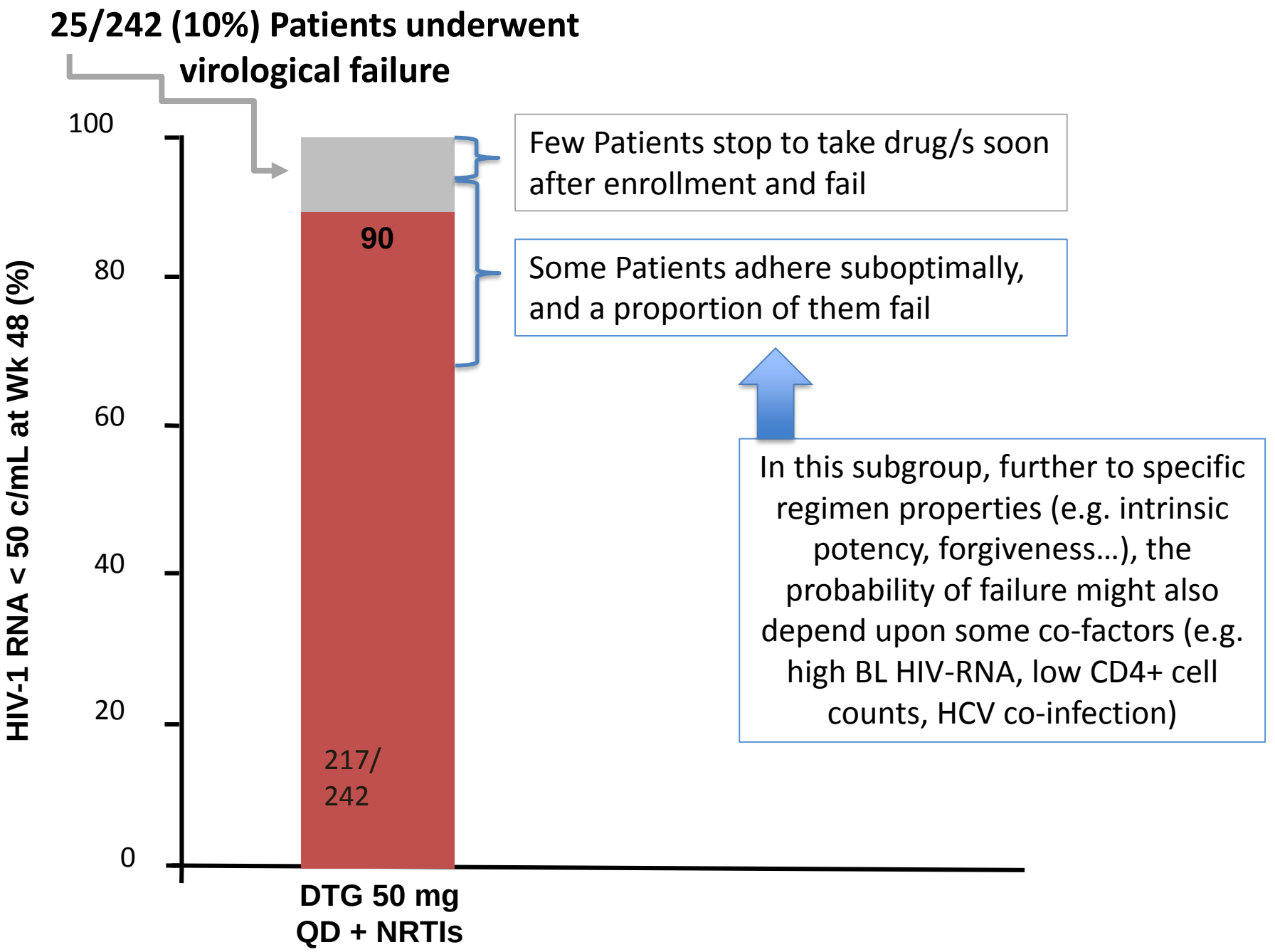
Yes, few Patients do so

2. They were not fully adherent (for whatever reason);

Yes, a sizeable % of Patients adhere subotimally

1. Other…..

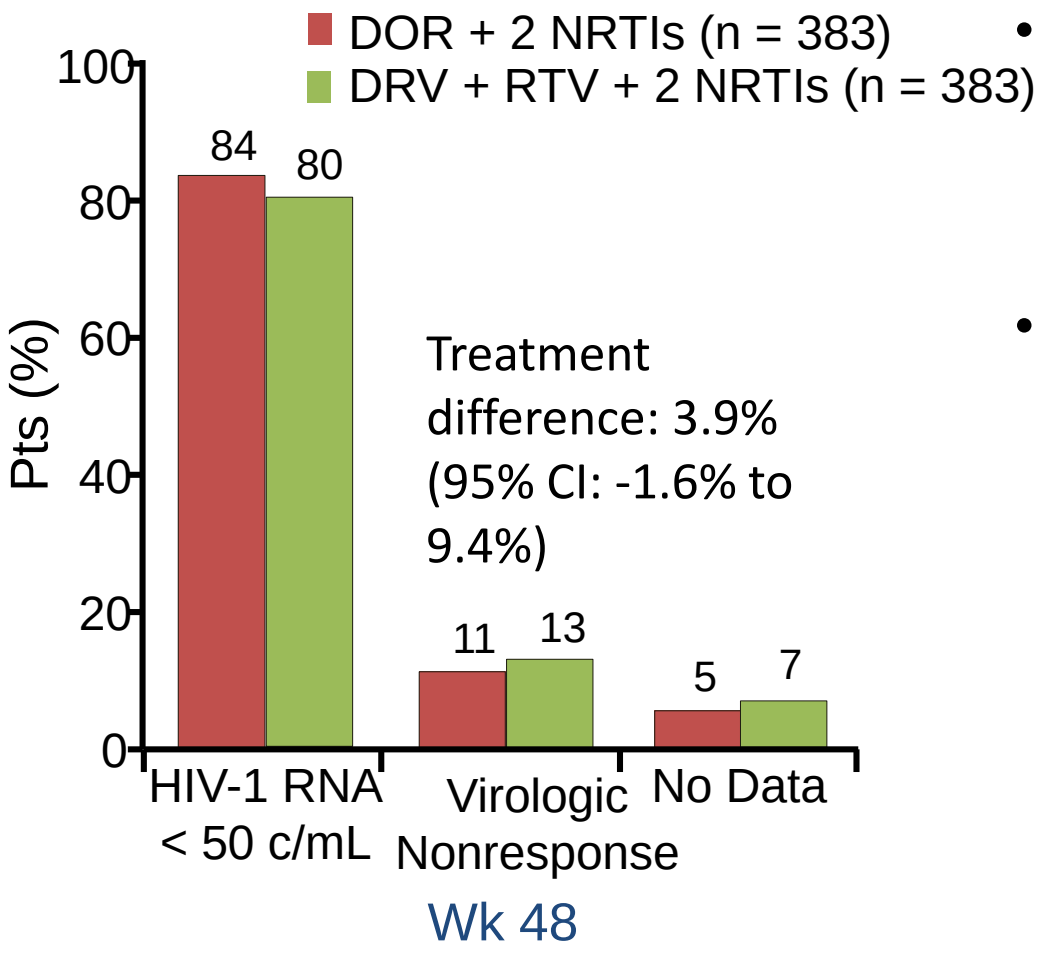
?



Feinberg J, et al. ICAAC 2013. Abstract H1464a.

New “coventional” options approaching…..

Doravirine Is Noninferior to DRV + RTV at Wk 48 (FDA Snapshot)



- Efficacy similar in both arms regardless of baseline HIV-1 RNA or CD4+ cell count
- No drug resistance detected in pts with PDVF through Wk 48 in either arm
  - n = 1 pt with noncompliance discontinued at Wk 24, developed DOR and FTC resistance

Molina JM, et al. CROI 2017. Abstract 45LB. Reproduced with permission.

DRIVE-AHEAD: Doravirine/3TC/TDF vs EFV/FTC/TDF for Treatment-Naive Pts

- **Doravirine:** …e, low drug–drug intera… noninferior to DRV/RTV + … phase III DRIVE-FOR…
- DRIVE-AHE… …e-controlled phase III tri…

ART-naive pts with H…
≥ 1000 copies/mL within 4…
no resistance to stu…
(N = 734)

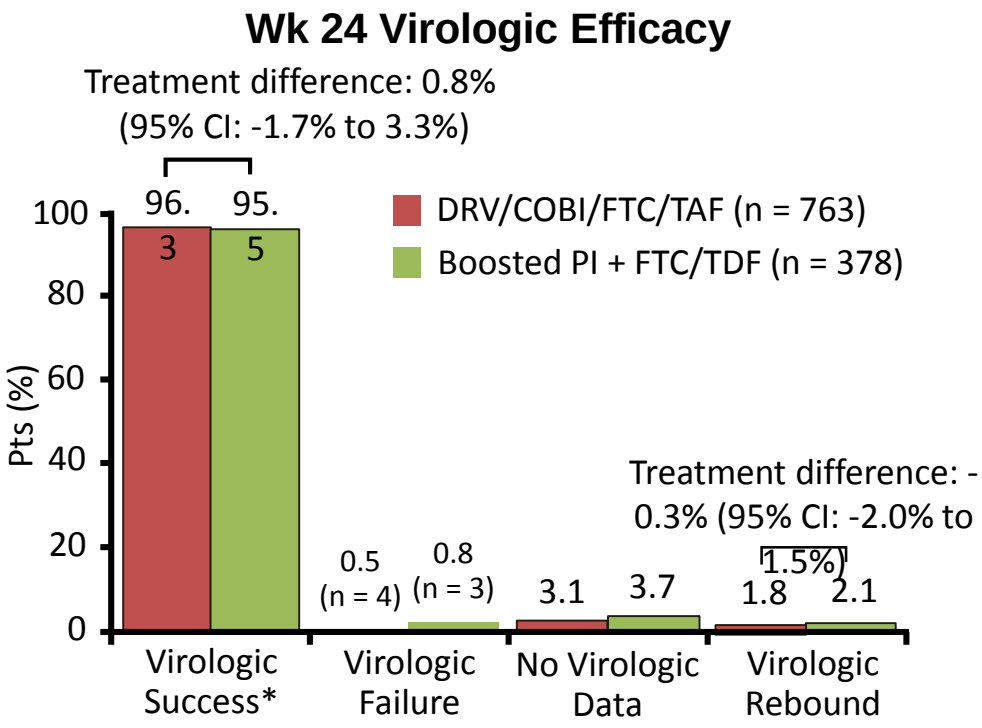
AEs at Wk 48,%[1]	DOR/3TC/TDF (n = 364)	EFV/FTC/TDF (n = 364)	Difference (95% CI)
Drug-related AE, %	31	63	-31.9 (-38.6, -24.8)
D/c for AEs, %	3	7	-3.6 (-6.9, -0.5)
Lipid Δ From BL at Wk 48, mg/dL	**DOR/3TC/TDF (n = 364)**	**EFV/FTC/TDF (n = 364)**	***P* Value**
LDL-C	-1.6	8.7	< .0001
Non–HDL-C	-3.8	13.3	< .0001
Cholesterol	-2.0	21.8	NR
Triglycerides	-12.4	22.0	NR
HDL-C	1.9	8.5	NR

- Baseline: male, 84% to 85%; mean CD4+ cell count, 416-435 cells/mm^3 (12% to 13% ≤ 200 cells/mm^3)

1. Molina JM, et al. CROI 2017. Abstract 45LB. 2. Squires KE, et al. IAS 2017. Abstract TUAB0104LB.

EMERALD: Switch From Boosted PI + FTC/TDF to DRV/COBI/FTC/TAF in Suppressed Pts

- Randomized, open-label, active-controlled phase III trial in which virologically suppressed pts **continued a boosted PI + FTC/TDF** regimen or switched to **DRV/COBI/FTC/TAF single-tablet regimen** (N = 1149)



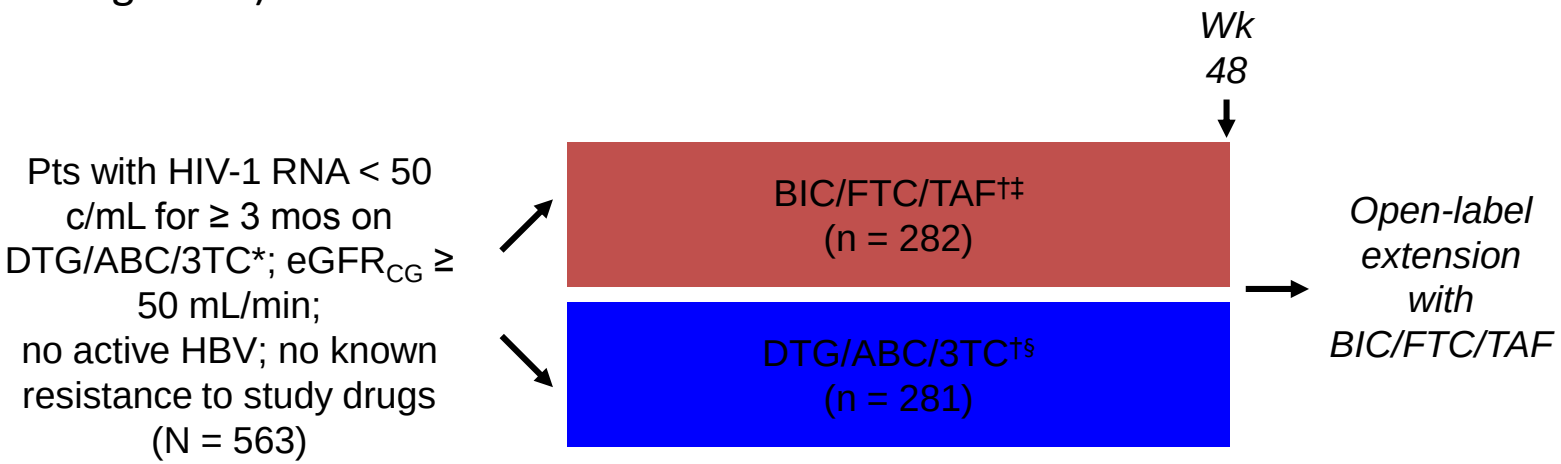
*HIV-1 RNA < 50 copies/mL.

- No PI or NRTI resistance associated mutations noted (n = 2 genotyped for each treatment group)
- Similar low rates of grade 3/4 AEs, d/c for AEs between treatment groups
- Significant improvements in hip/spine BMD for DRV/COBI/FTC/TAF vs control
- Similar eGFR by serum creatinine between groups (*P* = .118); increased eGFR by cystatin c with DRV/COBI/ FTC/TAF (*P* = .026)

Molina JM, et al. IAS 2017. Abstract TUAB0101.

Study 380-1844: Switch From Suppressive DTG/ABC/3TC to BIC/FTC/TAF

- Randomized, double-blind, international, active-controlled phase III trial
  - Primary endpoint: Wk 48 HIV-1 RNA ≥ 50 c/mL (FDA snapshot; noninferior. margin: 4%)



- Baseline: male sex, 88% to 90%; black race, 21% to 22%; median age, 45-47 yrs; median CD4+ cell count, 661-732 cells/mm^3; median eGFR$_{CG}$, 101 mL/min

*Could be STR or as separate components. †All pts also received placebo tablets for comparator regimen. ‡BIC/FTC/TAF 50/200/25 mg PO QD. §DTG/ABC/3TC 50/600/300 mg PO QD.

Switch From Suppressive DTG/ABC/3TC to BIC/FTC/TAF: Virologic Outcomes at Wk 48

Outcome at Wk 48, n (%)	Switch to BIC/FTC/TAF (n = 282)	Continued DTG/ABC/3TC (n = 281)	Treatment Difference, % (95.002% CI)	*P* Value
HIV-1 RNA ≥ 50 copies/mL	3 (1.1)	1 (0.4)	0.7 (-1.0 to 2.8)	.62
HIV-1 RNA < 50 copies/mL	264 (93.6)	267 (95)	NR	.59
No virologic data	15 (5.3)	13 (4.6)	NR	NR

- No treatment-emergent resistance detected in any pt

Molina J-M, et al. CROI 2018. Abstract O22.

Switch From Suppressive DTG/ABC/3TC to BIC/FTC/TAF: Safety Outcomes at Wk 48

Outcome, n (%)	BIC/FTC/TAF (n = 282)	DTG/ABC/3TC (n = 281)
Any TRAE	23 (8)*	44 (16)*
TRAE in ≥ 1% of pts		
▪ Headache	7 (3)	8 (3)
▪ Abnormal dreams	1 (< 1)	5 (2)
▪ Flatulence	0	5 (2)
▪ Nausea	0	5 (2)
▪ Diarrhea	2 (< 1)	4 (1)
▪ Fatigue	1 (< 1)	3 (1)
▪ Insomnia	0	3 (1)
Any gr 3/4 lab abnormality	47 (17)	32 (11)
Gr 3/4 lab abnormalities in ≥ 2% of pts		
▪ LDL elevation	14 (5)	13 (5)
▪ Increased amylase	7 (2)	0
▪ ALT elevation	6 (2)	0
▪ CK elevation	6 (2)	6 (2)
▪ Fasting hyperglycemia	6 (2)	2 (< 1)

- Median $eGFR_{CG}$ change from BL: BIC arm, 1.0 mL/min; DTG arm, -1.8 mL/min; $P < .001$
- No significance differences between arms in changes from BL for proteinuria levels, spine and hip BMD
- No significant differences in changes for fasting lipids, except triglycerides
  - Median change for triglycerides: BIC arm, -5 mg/DL; DTG arm, +3 mg/dL; $P = .028$

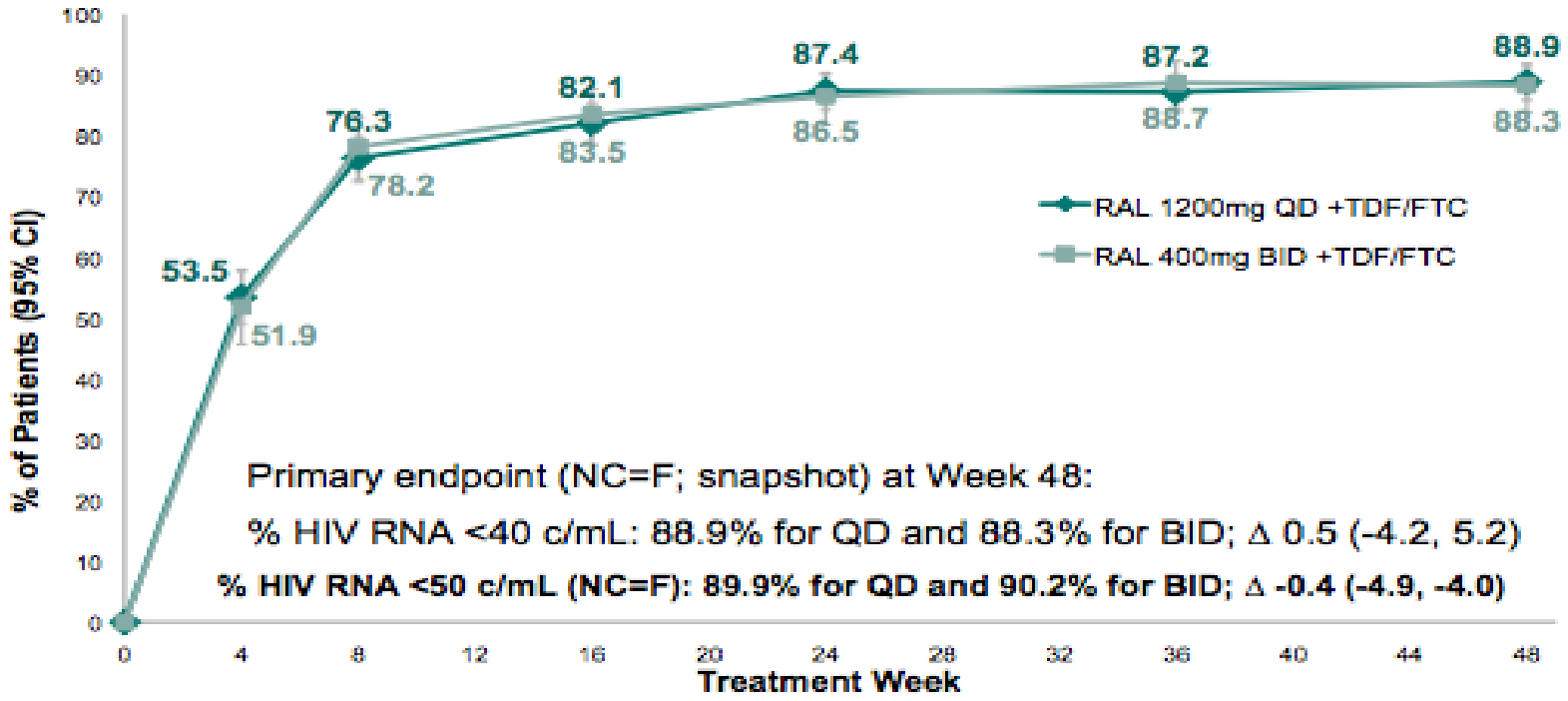
*Fischer exact test $P = .01$.

Molina J-M, et al. CROI 2018. Abstract O22.

ONCEMRK

- 802 pts randomized (2:1)
  - RAL 1200 mg QD + TDF/FTC
  - RAL 400 mg BID + TDF/FTC
- RAL QD non-inferior to RAL BID
  VL <40: 88.9% vs. 88.3%

Wk 48 VL<40 (Snapshot)

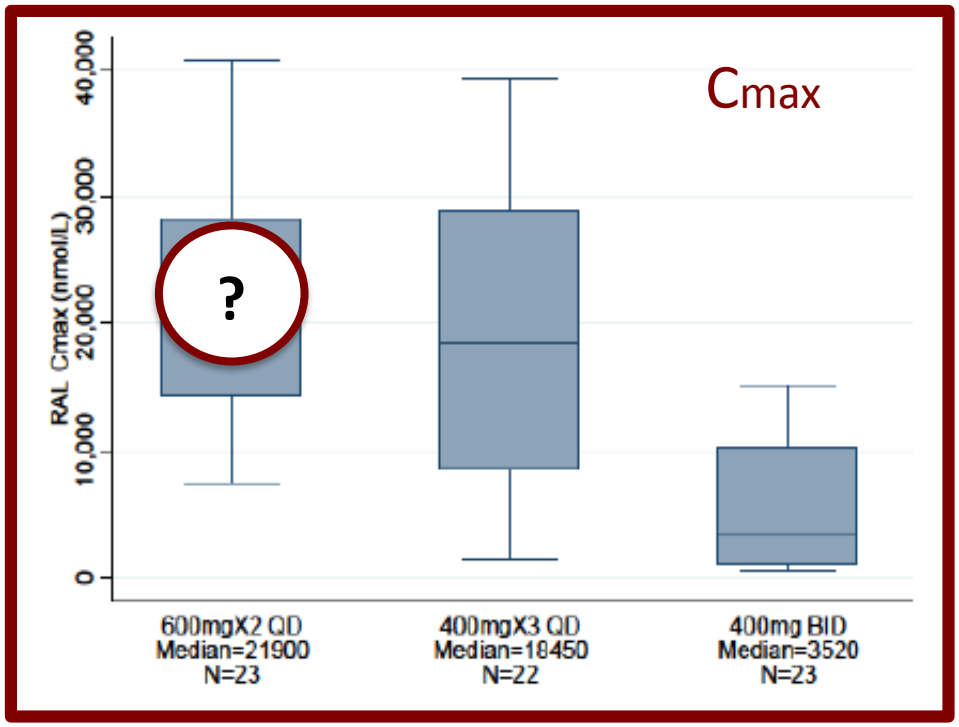


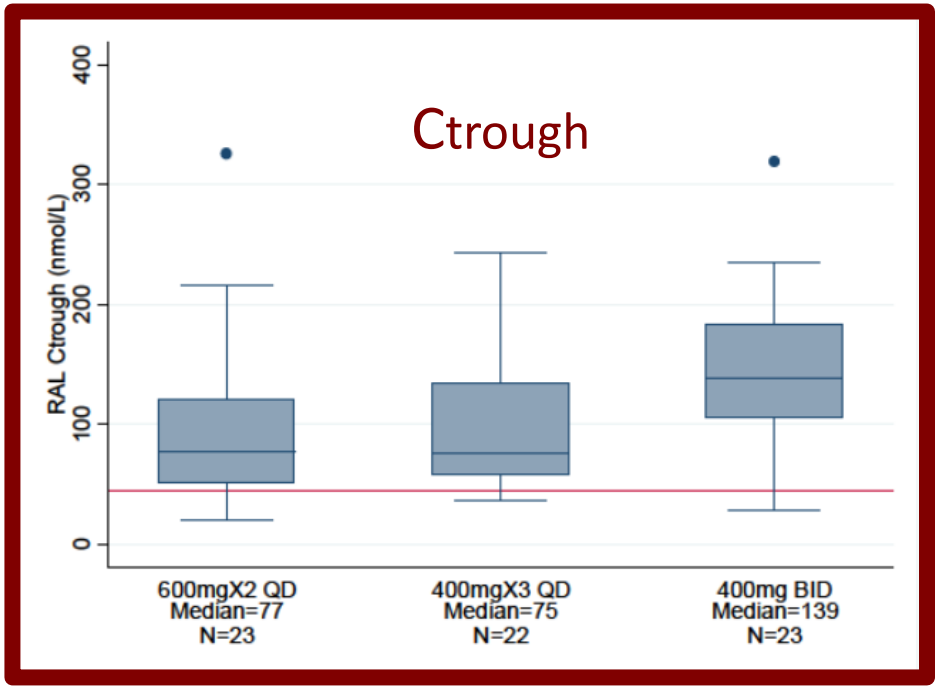
- **For subgroup with BL HIV RNA >100,000 c/mL:**
  % HIV RNA <40 c/mL (OF): 86.7% for QD and 83.8% for BID; Δ 2.9 (-6.5, 14.1)
- CD4 (cells/mm^3) increase (OF): 232 for QD and 234 for BID; Δ -2 (-31, 27)

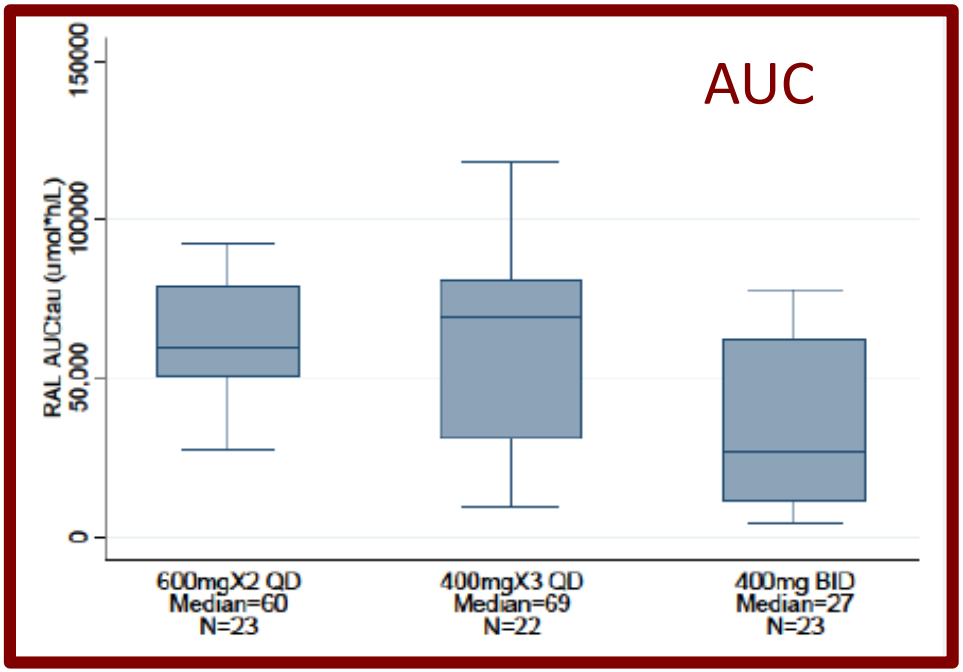
Cahn P et al, International AIDS Conference, 18-22 July 2016, Durban, South Africa. Abstract FRAB0103LB

Comparative PHARMACOKINETICS

Krishna R, et al. Clin Pharmacol Drug Dev 2018; 7: 196-206.



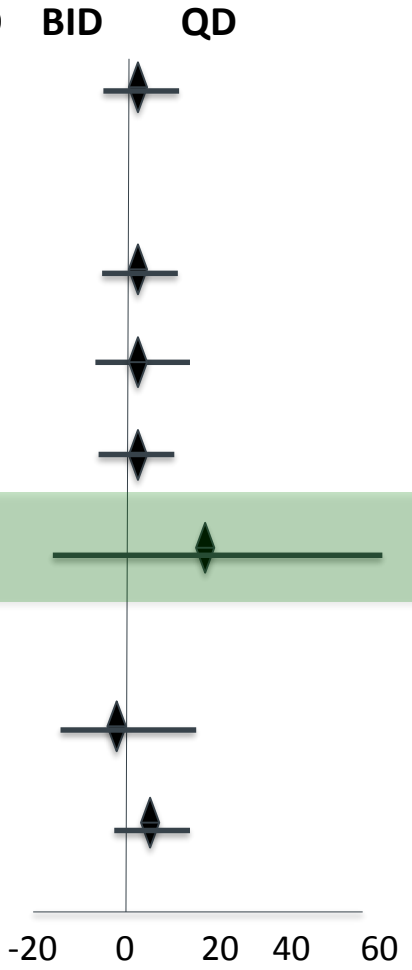




Subgroup Analyses from ONCEMRK, a Phase 3 Study of Raltegravir 1200 mg Once Daily vs RAL 400 mg Twice Daily, in Combination with Tenofovir/Emtricitabine, in Treatment-Naïve HIV-1 Infected Subjects: Results

HIV RNA < 40 c./mL

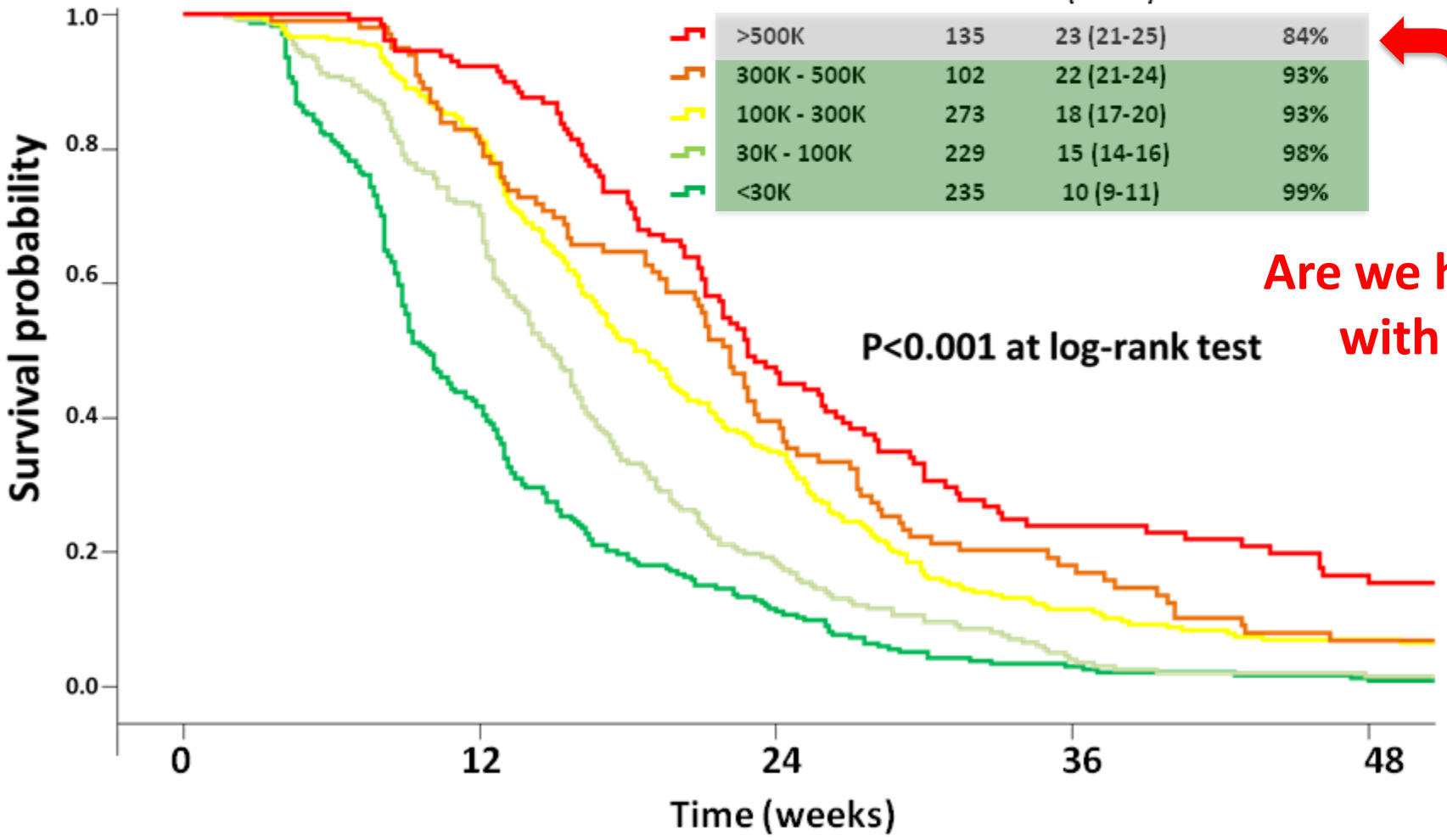
	% of Subjects (N)	
	400 mg BID	1200 mg QD
All subjects	93.6 (251)	94.2 (501)
Baseline HIV RNA		
≤ 100.000 c/mL	97.7 (177)	97.2 (358)
> 100.000 c/mL	83.8 (74)	86.7 (143)
≤ 500.000 c/mL	95.8 (237)	95.2 (479)
> 500.000 c/mL	57.1 (14)	72.7 (22)
Baseline CD4+ count		
< 200 cells/uL	87.9 (33)	85.1 (67)
> 200 cells/uL	94.5 (218)	95.6 (434)



Cahn P, et al. HIV Glasgow 2016. Abstr. N. 3514101

The time to achieve virological undectability and the rate of success at 48 weeks are pre-HAART viremia dependent

Pre-HAART viremia ranges (copies/mL)	No.	Median Time (95% CI) to achieve VS (weeks)	Probability of VS at 48 weeks
>500K	135	23 (21-25)	84%
300K - 500K	102	22 (21-24)	93%
100K - 300K	273	18 (17-20)	93%
30K - 100K	229	15 (14-16)	98%
<30K	235	10 (9-11)	99%



Are we happy with this ?

Santoro et al., Antivir ther 2013

Baseline patients' characteristics

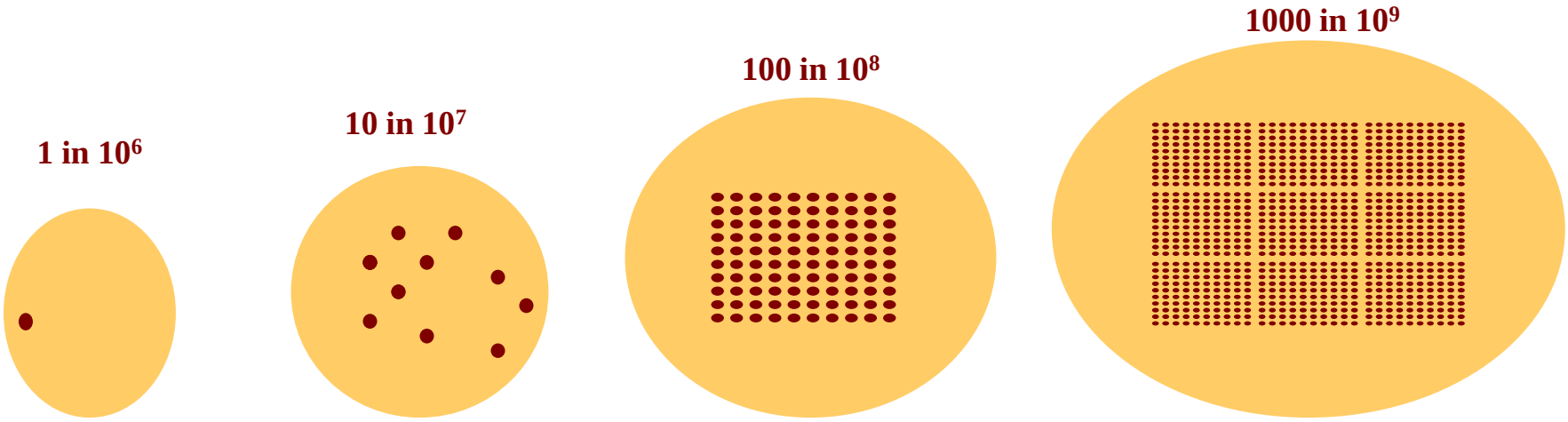
Variables	Overall (N=536)
Calendar year of cART start, median (IQR)	**2015 (2014-2017)**
Male, n (%)	469 (87.5)
Age, years, median (IQR)	**37 (29-45)**
Risk factor, n (%)	
Homosexual	263 (49.1)
Heterosexual	115 (21.5)
Drug abuser	32 (6.0)
Sexual	75 (14.0)
Other/unknown	51 (5.6)
Nationality	
Italian	**383 (71.5)**
Non-Italian	97 (18.1)
Unknown	**56 (10.4)**
Subtype, n (%)	
B	345 (64.4)
CRF02_AG	36 (6.7)
F	39 (7.3)
C	26 (4.8)
Other	90 (16.8)
Pre-cART viremia, copies/mL, n (%)	
<100,000	**243 (45.3)**
100,000-500,000	172 (32.1)
>500,000	**121 (22.6)**
Pre-cART CD4 cell count (cells/mm^3), n (%)	
<200	**145 (27.1)**
200-350	106 (19.8)
351-500	113 (21.1)
>500	172 (32.1)

cART: combined antiretroviral therapy; IQR: interquartile range.

Factors associated with virological response and resistance profile in HIV-1 infected patients starting first-line integrase inhibitors based regimen in clinical settings

Armenia D, et al. 16th European Meeting on HIV & Hepatitis 2018, abstract # 8

Infections with a high bacterial density at the initiation of antibiotic therapy may present a therapeutic problem, including a higher risk for the emergence of resistance due to the larger number of bacteria present and the **higher probability of having at least one resistant bacterial cell within a large initial inoculum** (CFUo)



A higher bacterial inoculum might correspond to a high BL viral load, and the sooner you get rid of it the lower is the chance of selecting resistant mutants…. So a quicker action does contribute to the genetic barrier…

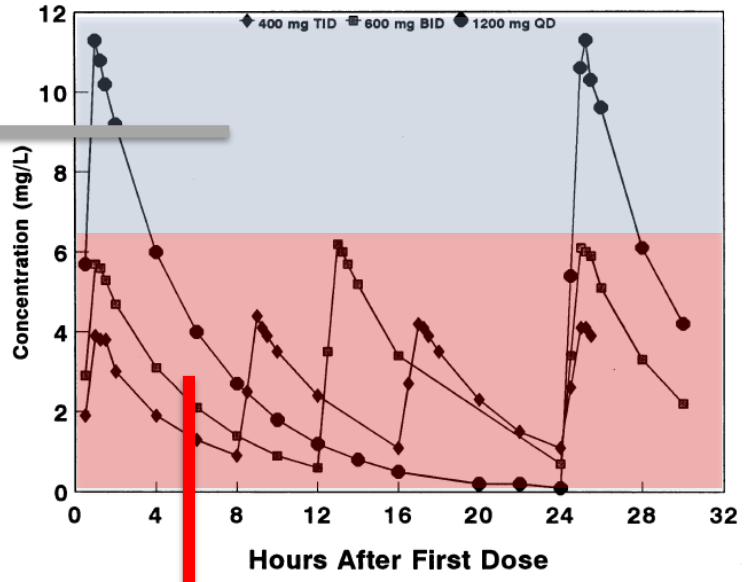
Johnson, C.C.,et al. J.AC 1995; 35:765-773.

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

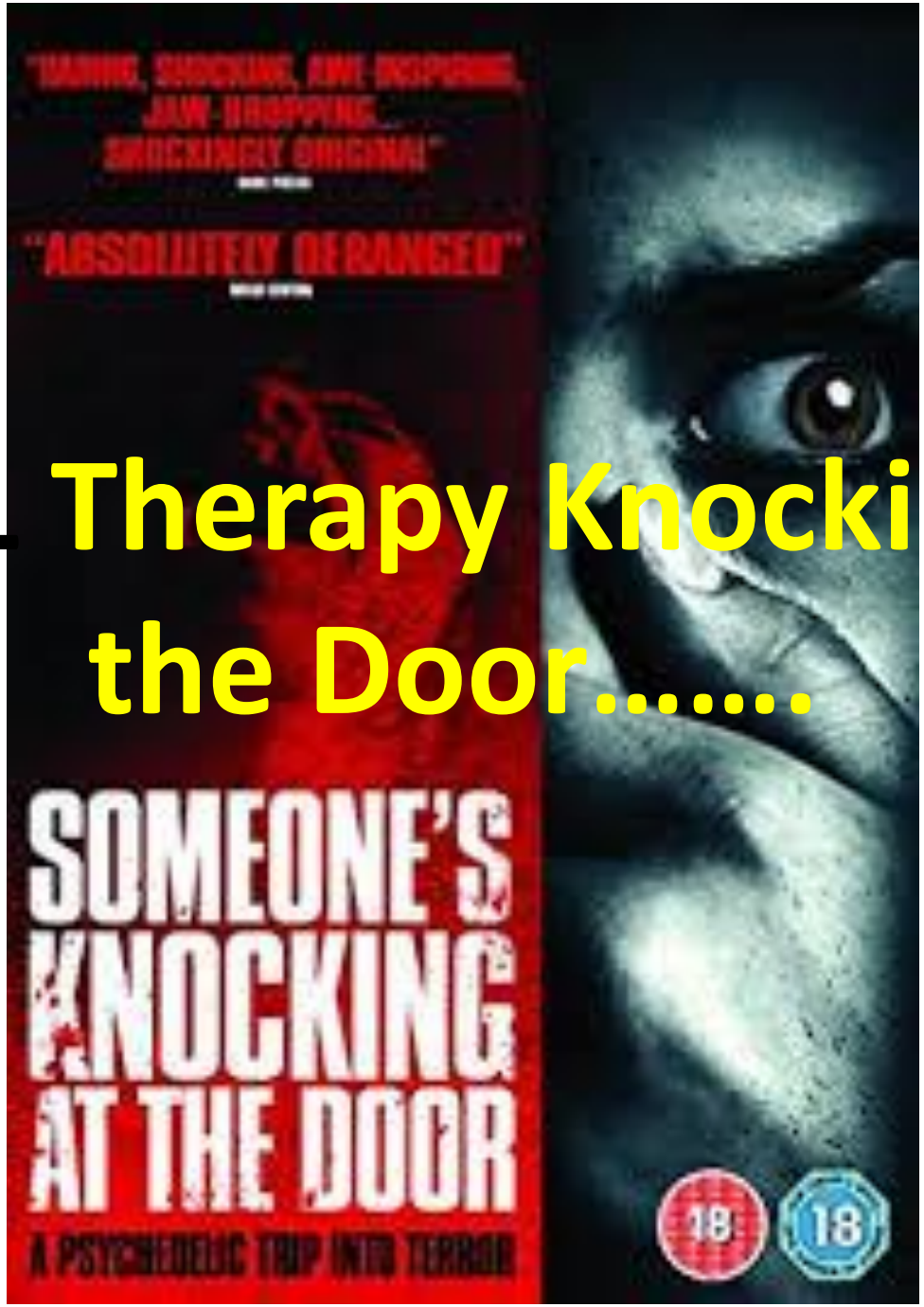
The same total daily dose



Regrowth without Resistance

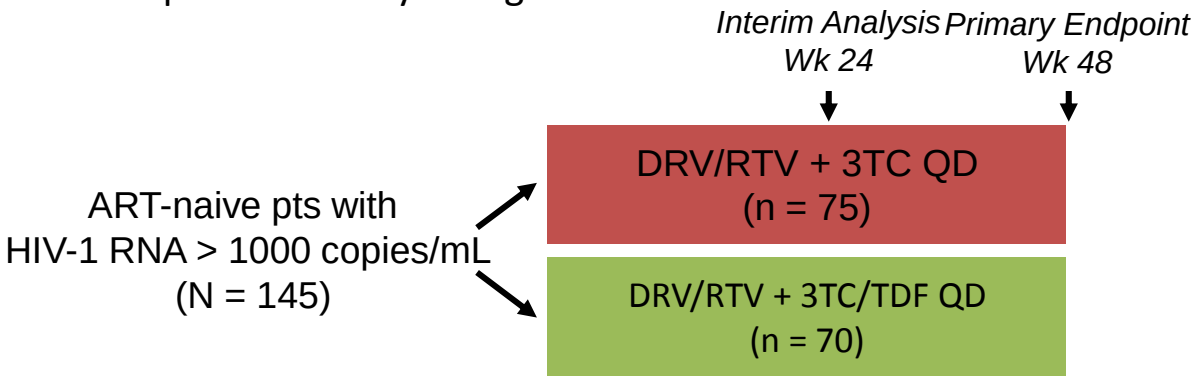
Regrowth with Resistance

DUAL Therapy Knocking at the Door…….



ANDES: DRV/RTV + 3TC vs DRV/RTV + 3TC/TDF for ART-Naive Pts

- Randomized, open-label phase IV study in Argentina



Dosing: DRV/RTV, 800/100 mg; 3TC, 300 mg; 3TC/TDF, 300/300 mg.

- Baseline: 24% HIV-1 RNA > 100,000 copies/mL

HIV-1 RNA < 400 c/mL (ITT) at Wk 24, n/N (%)	DRV/RTV + 3TC	DRV/RTV + 3TC/TDF
Overall	71/75 (95)	68/70 (97)
BL HIV-1 RNA > 100,000 copies/mL	20/20 (100)	15/15 (100)

- 1 virologic failure with DRV/RTV + 3TC/TDF

Sued O, et al. IAS 2017. Abstract MOAB0106LB.

ACTG A5353: DTG + 3TC for ART-Naive Pts

- Single-arm phase II study[1]

ART-naive pts with
HIV-1 RNA ≥ 1000 and < 500,000 copies/mL;
no RT, INSTI, major PI resistance mutations
(N = 120)

→ DTG 50 mg + 3TC 300 mg

Primary Endpoint Wk 24

- Baseline: 31% HIV-1 RNA > 100,000 c/mL

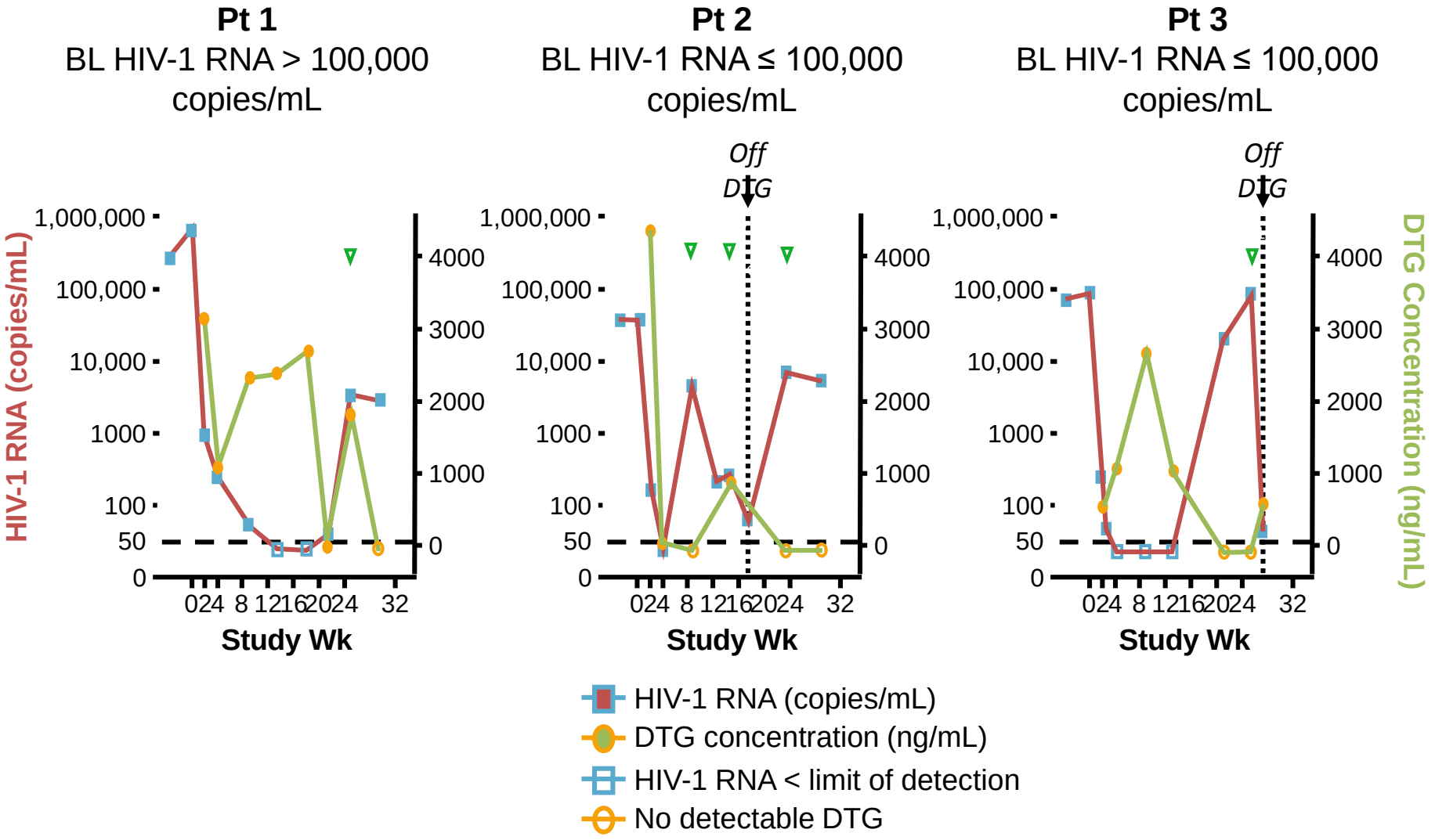
Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
  - All 3 pts had DTG levels reflective of suboptimal adherence
- GEMINI 1/2 randomized phase III trials of DTG + 3TC ongoing[2,3]

1. Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB.
2. ClinicalTrials.gov. NCT02831673. 3. ClinicalTrials.gov. NCT02831764.

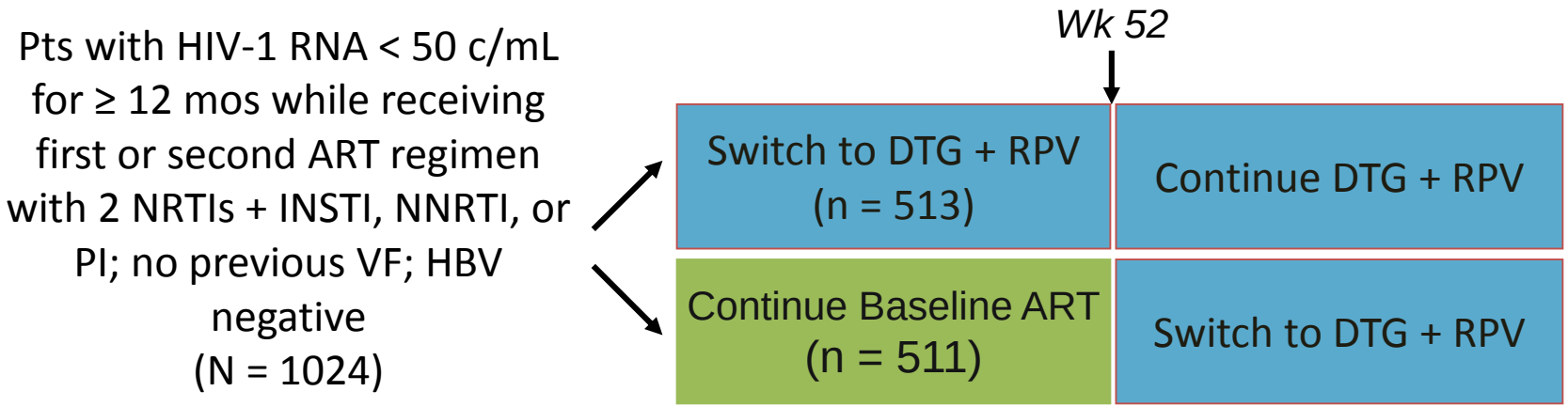
ACTG A5353: HIV-1 RNA Levels and DTG Concentration in Pts Experiencing PDVF



Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB. Reproduced with permission.

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

- Randomized, open-label, multicenter phase III trials
- HIV-1 RNA < 50 c/mL at Wk 48 (primary endpoint; ITT-E snapshot)
  - 95% in both arms; **Wk 48 treatment difference showed noninferiority of switch: -0.2% (95% CI: -3.0% to 2.5%)**

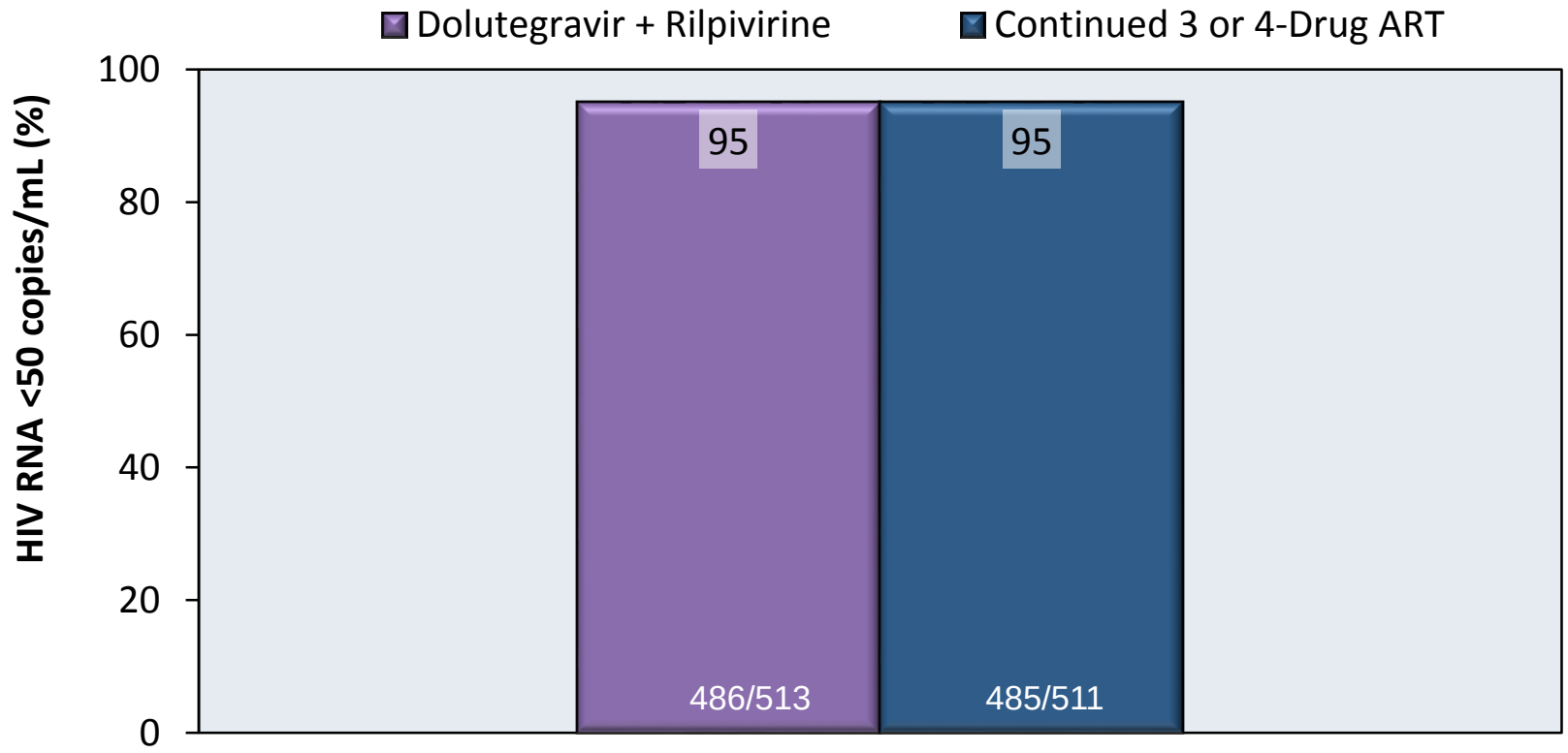


- Significantly greater improvement in bone turnover markers from baseline to Wk 48 in switch arm

Walmsley S, et al. IDWeek 2017. Abstract 1382. Llibre JM, et al. CROI 2017. Abstract 44LB.

Dolutegravir plus Rilpivirine as Maintenance Dual Therapy
SWORD-1 and SWORD-2: Pooled Results at Week 48

Week 48 Virologic Response (by FDA Snapshot Analysis)



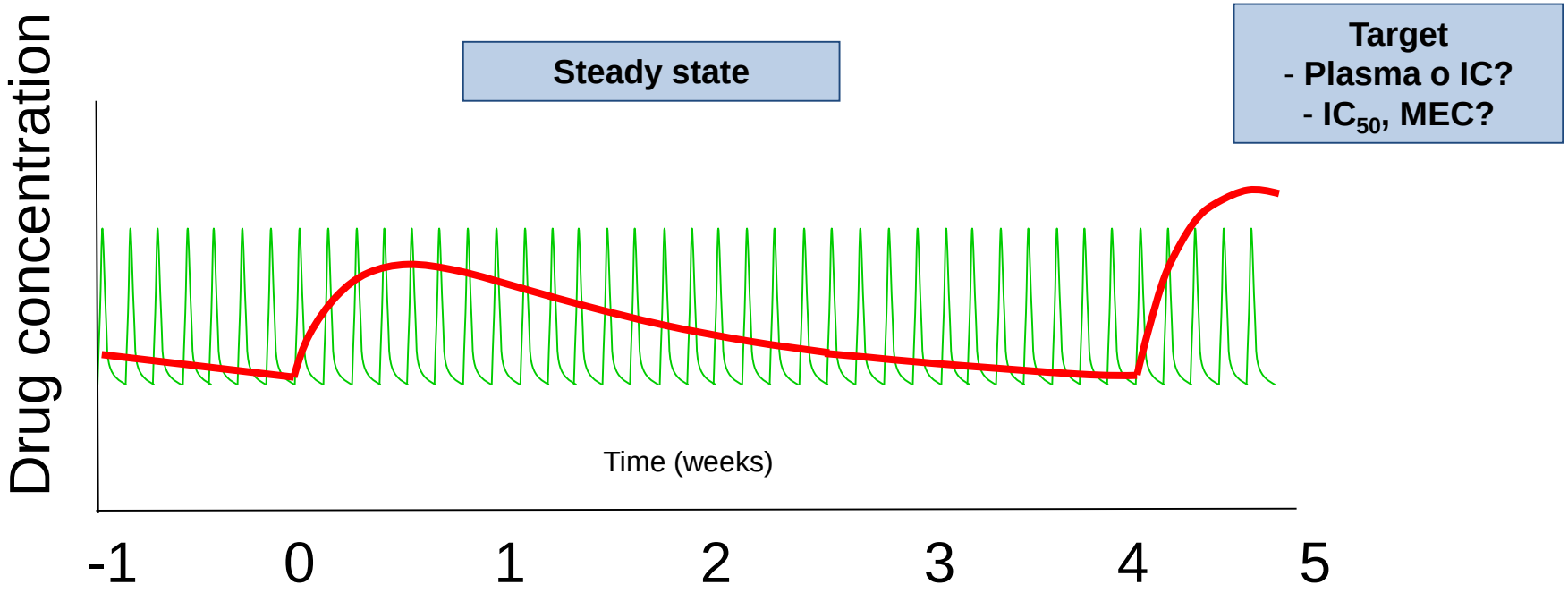
Confirmed virologic withdrawal: 2 (<1%) in each arm
One NNRTI resistance mutation (K101K/E) detected in DTG + RPV arm
No integrase resistance occurred

Source: Llibre JM et al. Abstract 44LB. CROI 2017. Seattle, WA.

LONG – ACTING AGENTS

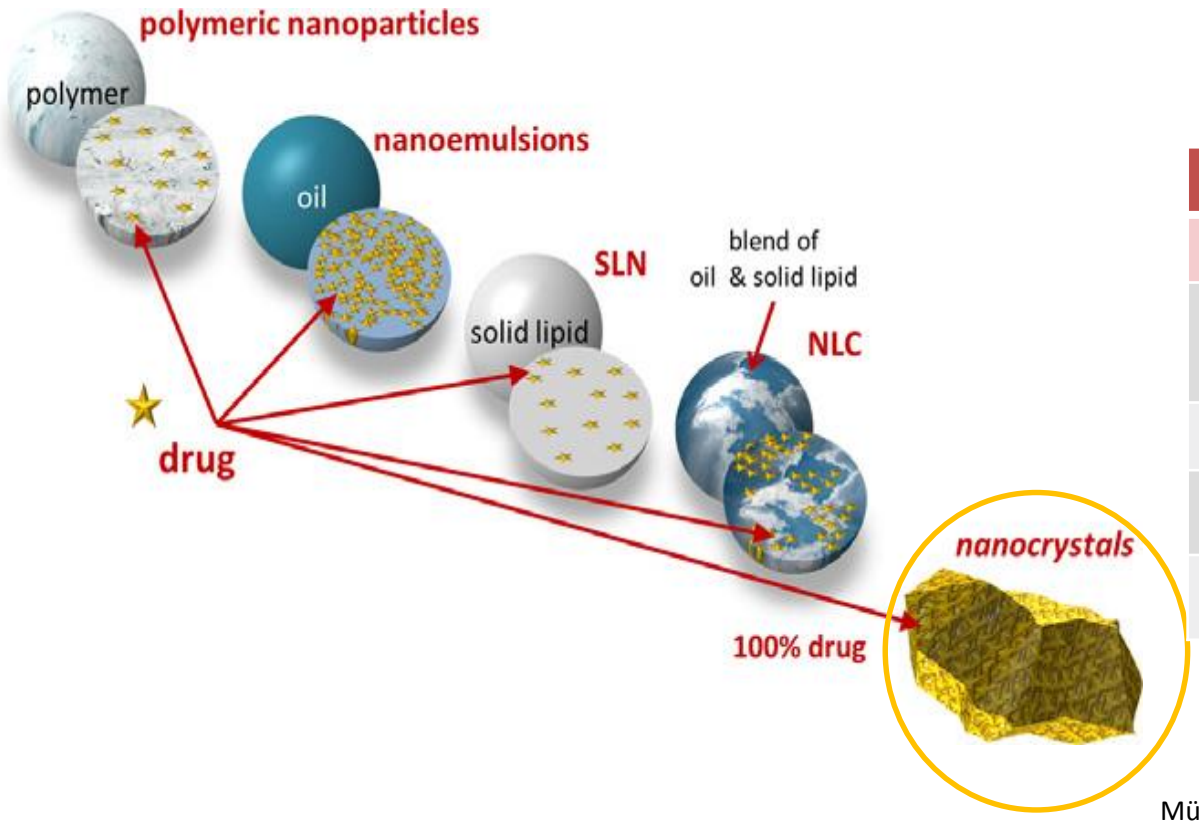
Simulation of drug concentration profiles following multiple dosing of immediate release vs. extended release: higher versus lower dose?

- Are high C_{max} values only potentially toxic in case of drugs with a Time-dependent pharmacodynamics?
- Should this be the case, LA formulations of ARVs are going to fit optimally from a clinical-pharmacological standpoint
- In case of β-lactam antibiotics, however, peak levels proportionally correlate with the chance of avoiding the outgrowth of resistant mutants, while, at the same time, these drugs work according to a time-dependent pattern



Cabotegravir nanocrystals

- **Drug nanocrystals are particles made from 100% drug**; typically, they are stabilized by surfactants or polymeric steric stabilizers.
- The high loading makes them very efficient in transporting drug to or **into cells**, reaching a sufficiently high therapeutic concentration for the pharmacological effect.
- Higher drug loading versus matrix approaches for **lower injection volume**

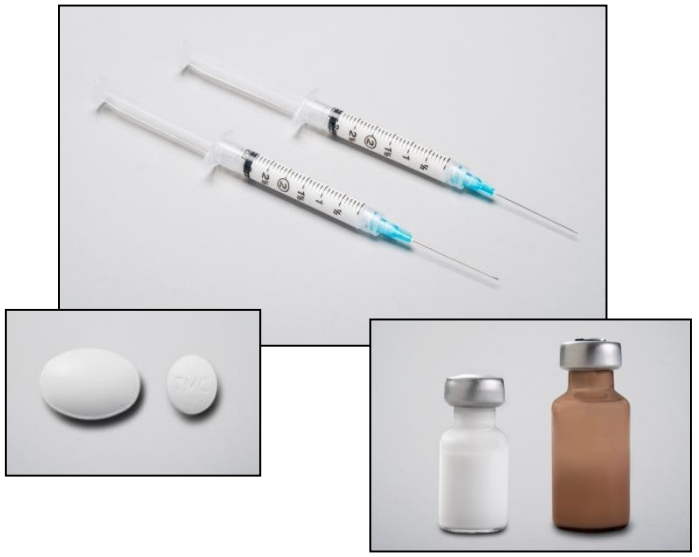


CAB LA 200 mg/mL	
Component	**Function**
Cabotegravir free acid (d50 ~200 nm)	Active drug
Mannitol	Tonicity agent
Surfactant system	Wetting agent/stabiliser
Water for injection	Solvent

Müller RH *et al. Eur J Pharm Biopharm* 2011:78;1–9

LATTE Study: Background

- CAB is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet ($t_{½}$, ~40 hours)
  - LA nanosuspension 200 mg/mL ($t_{½}$, ~20-40 days)
- RPV is an HIV-1 NNRTI
  - Oral 25 mg tablet ($t_{½}$, ~50 hours)
  - LA nanosuspension 300 mg/mL ($t_{½}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1



Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial

Margolis DA, et al
Lancet Infect Dis 2015; 15: 1145–55

All treatments here are oral

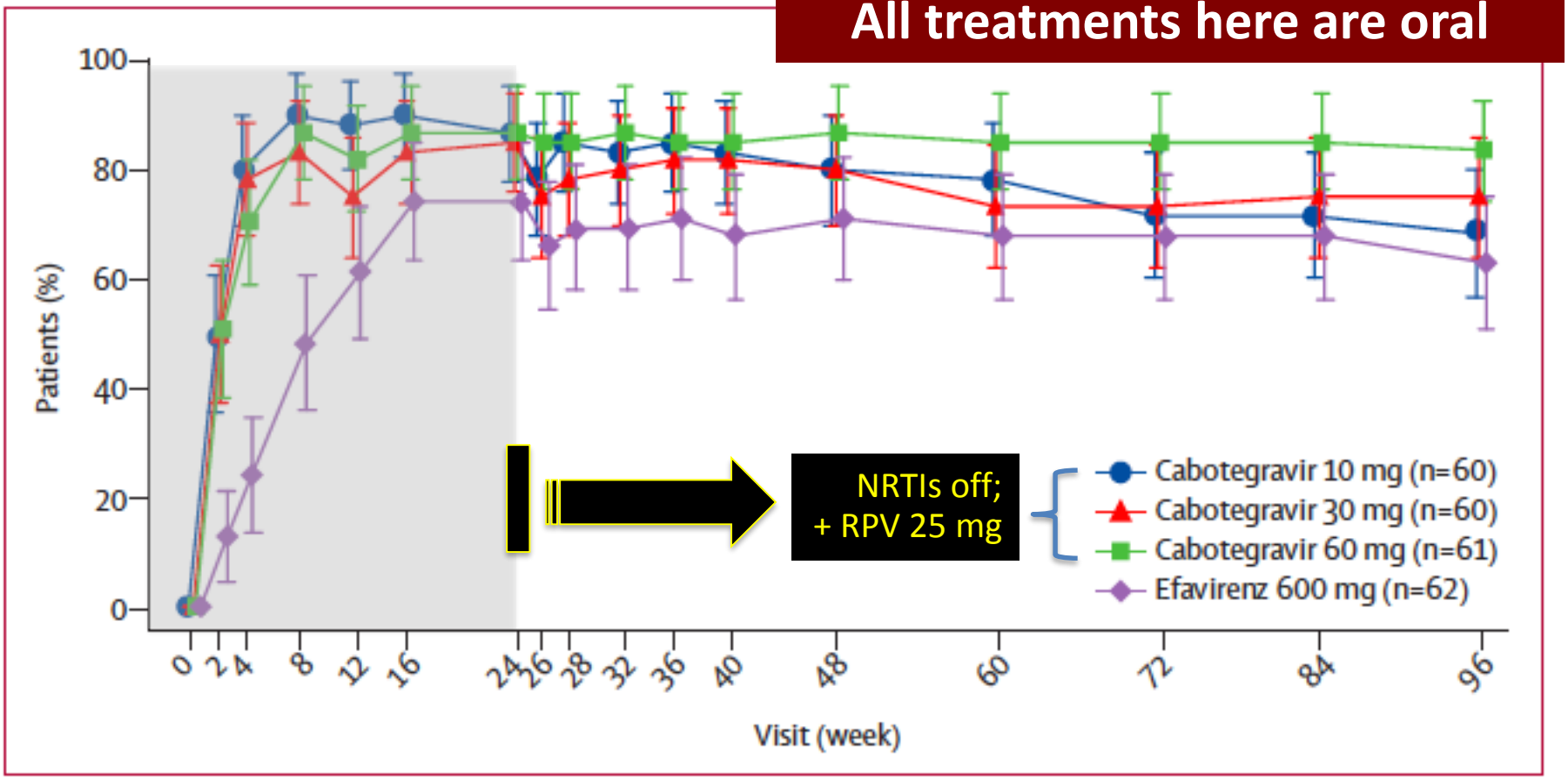
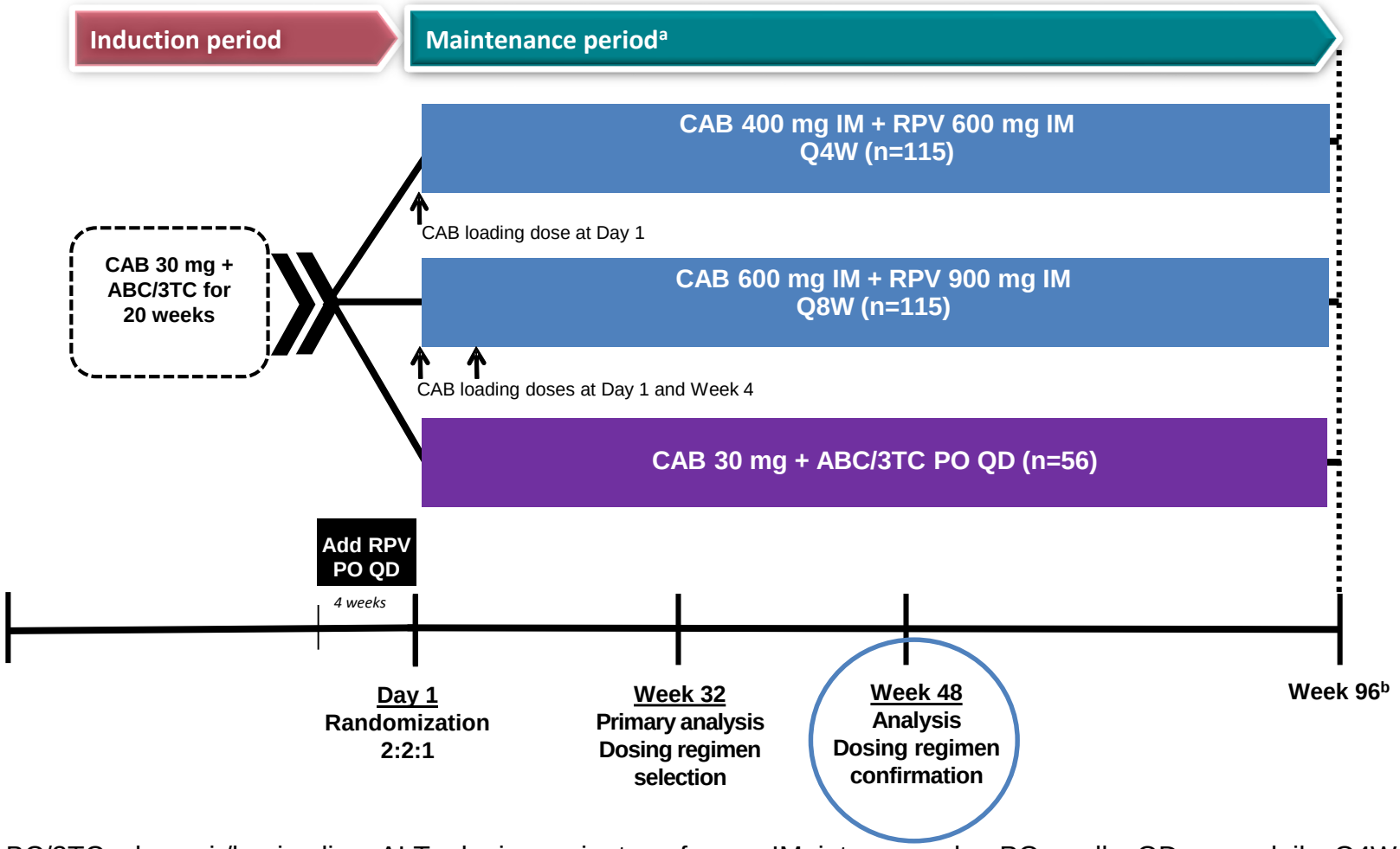


***Figure 2*: Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population**
Error bars indicate 95% CI.

LATTE-2 Study Design

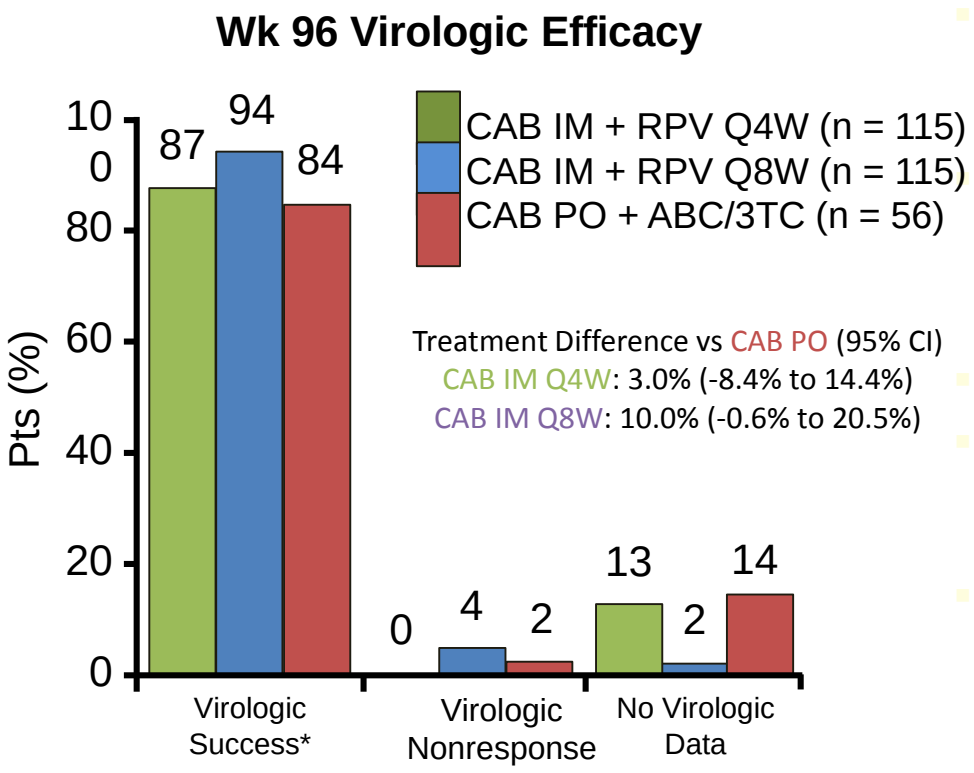


ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART

- **Cabotegravir:** INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to **CAB 400 mg IM + RPV 600 mg Q4W, CAB 600 mg IM + RPV 900 mg Q8W**, or **CAB 30 mg PO + ABC/3TC 600/300 mg QD** after induction/ virologic suppression with oral CAB + ABC/3TC (N = 309)[1,2]



*HIV-1 RNA < 50 copies/mL.

- At 96 wks, ~ 30% of pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving CAB IM very satisfied to continue present treatment at Wk 96 vs 43% receiving CAB PO
- Phase III maintenance trials (ATLAS and FLAIR) moving forward with Q4W dose[3,4]

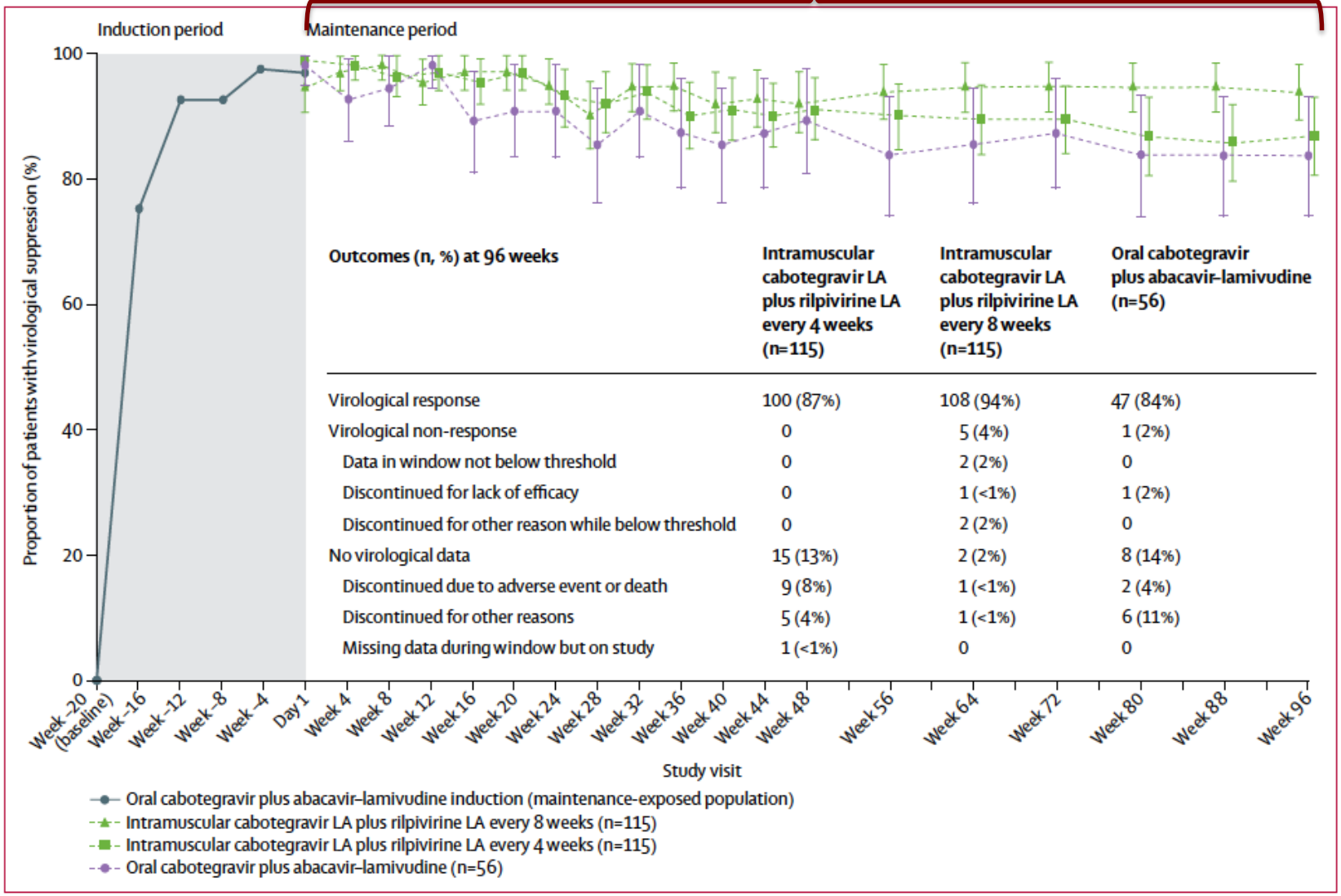
1. Eron J, et al. IAS 2017. Abstract MOAX0205LB.
2. Margolis DA, et al. Lancet. 2017;[Epub ahead of print].
2. ClinicalTrials.gov. NCT02951052.
3. ClinicalTrials.gov. NCT02938520.

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 !!



Outcomes (n, %) at 96 weeks	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

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 Lancet 2017; 390: 1499–510

At week 96:

4-week arm
CAB 400 mg + RPV 600 mg Qmonth

0 virological non-response

8-week arm
CAB 600 mg + RPV 900 mg Q2months

5 virological non-response

2 protocol-defined virologic failures

Controls
CAB 30 mg + ABV/3TC QD

1 virological non -response

1 protocol-defined virologic failure

Virological non-response = HIV-RNA > 50 c./mL
Protocol-defined virological failure = HIV-RNA > 200 c./mL

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

At week **48**:

4-week arm
CAB 400 mg + RPV 600 mg Qmonth

8-week arm
CAB 600 mg + RPV 900 mg Q2months

Controls
CAB 30 mg + ABV/3TC QD

All had RPV [c] in the lowest 25th quartile

1 virological non-response

8 virological non-response

1 virological non -response

4 patients were resuppressed (HIV-RNA < 50 c./mL) at week 96 without any change in 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

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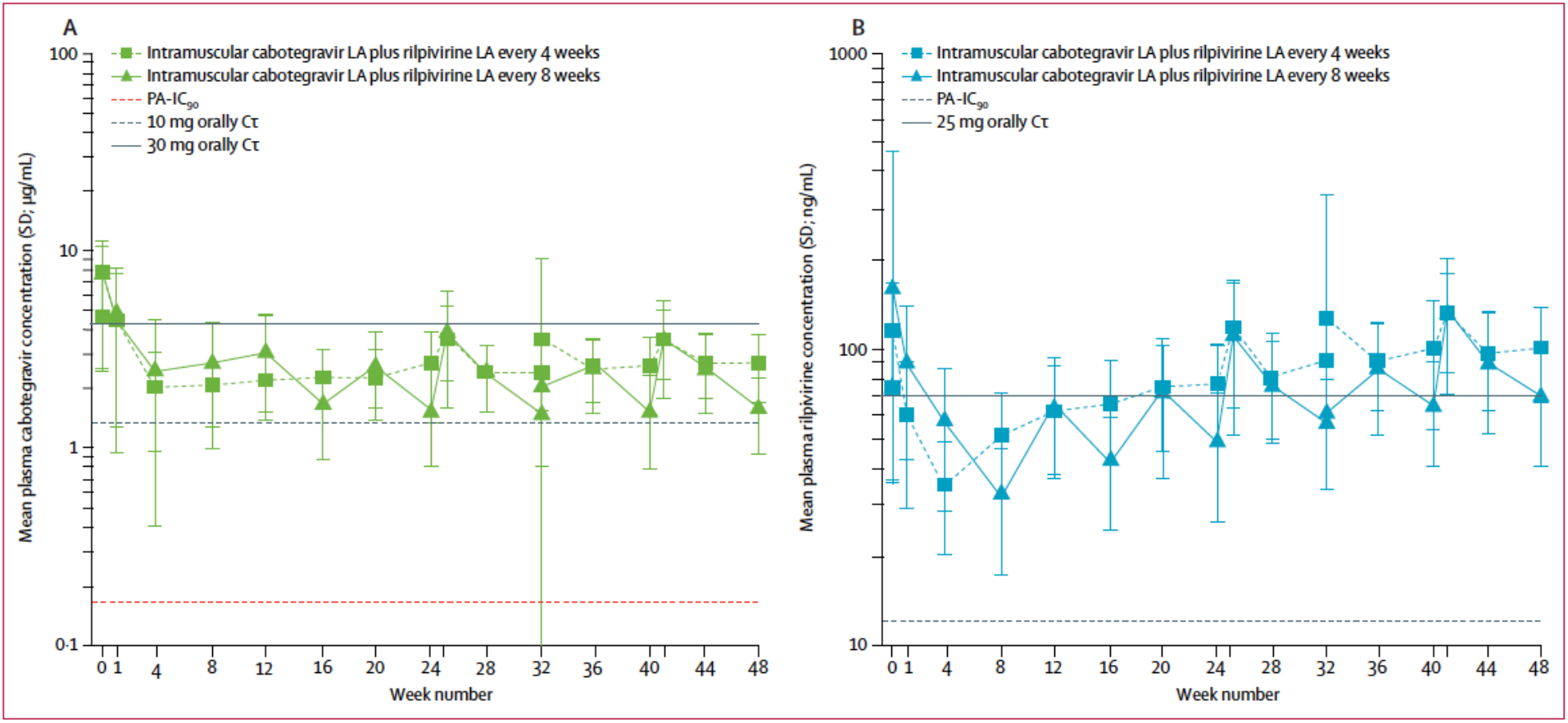

***Figure 3*: Arithmetic mean (SD) plasma concentration–time profiles following every 4 weeks and every 8 weeks administration of (A) cabotegravir LA and (B) rilpivirine LA through week 48**

Cτ=concentration at the end of dosing interval. LA=long-acting. PA-IC_{90}=protein-adjusted 90% inhibitory concentration.

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

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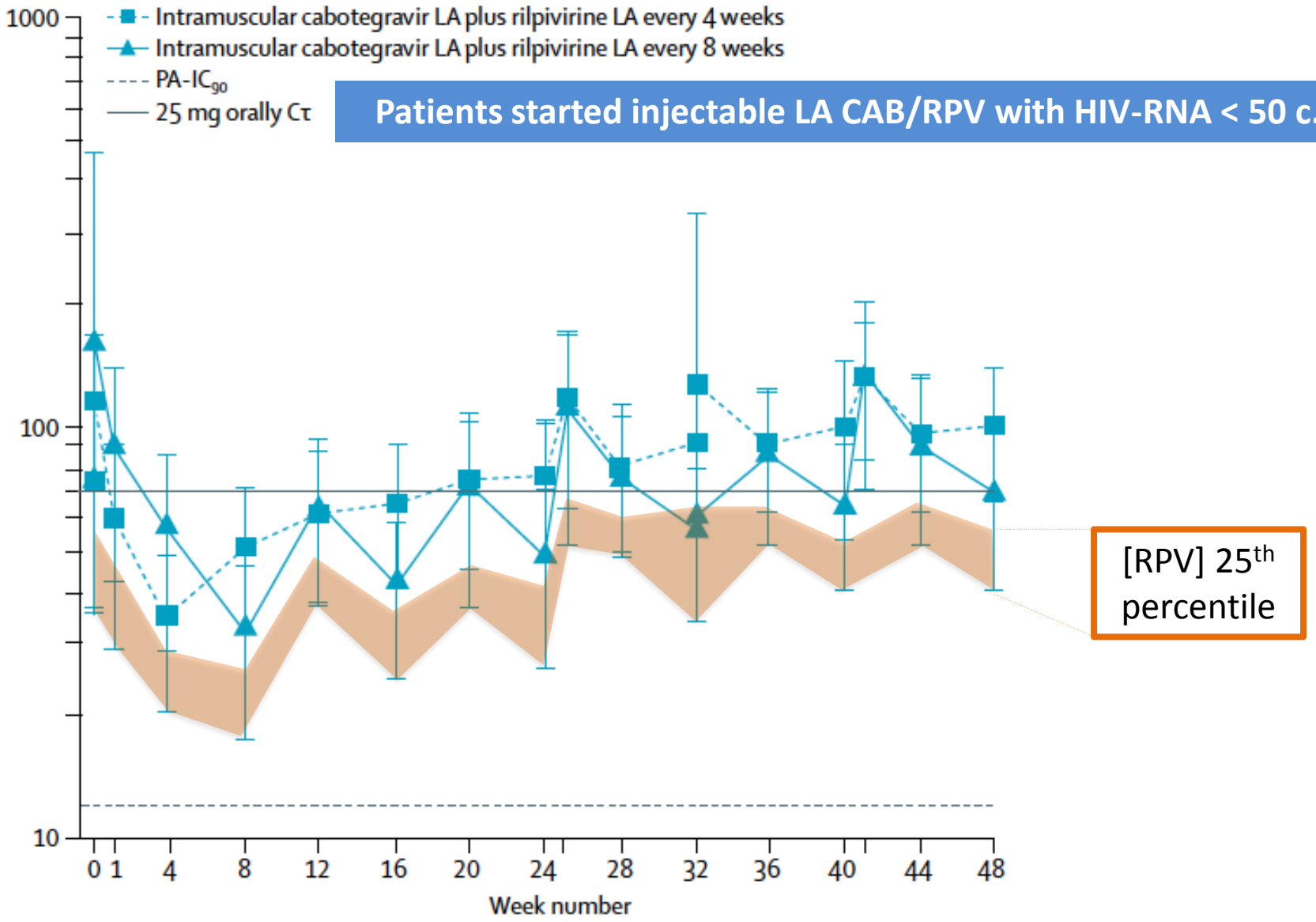


LONG – ACTING AGENTS
(in development)

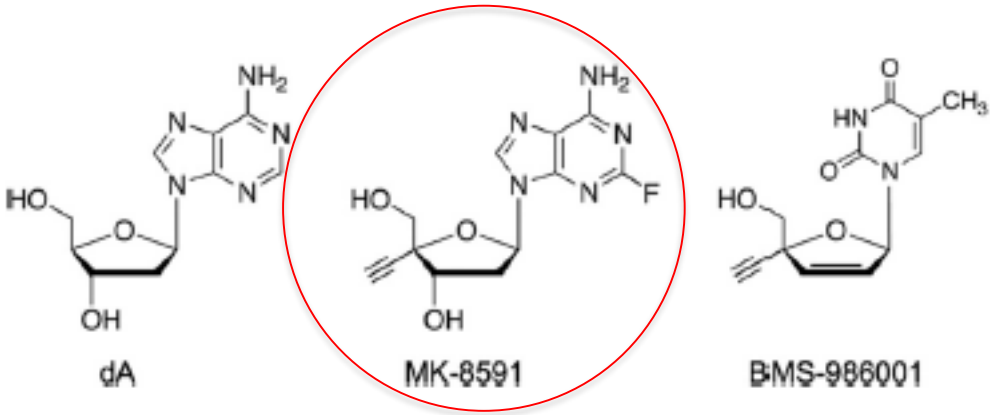
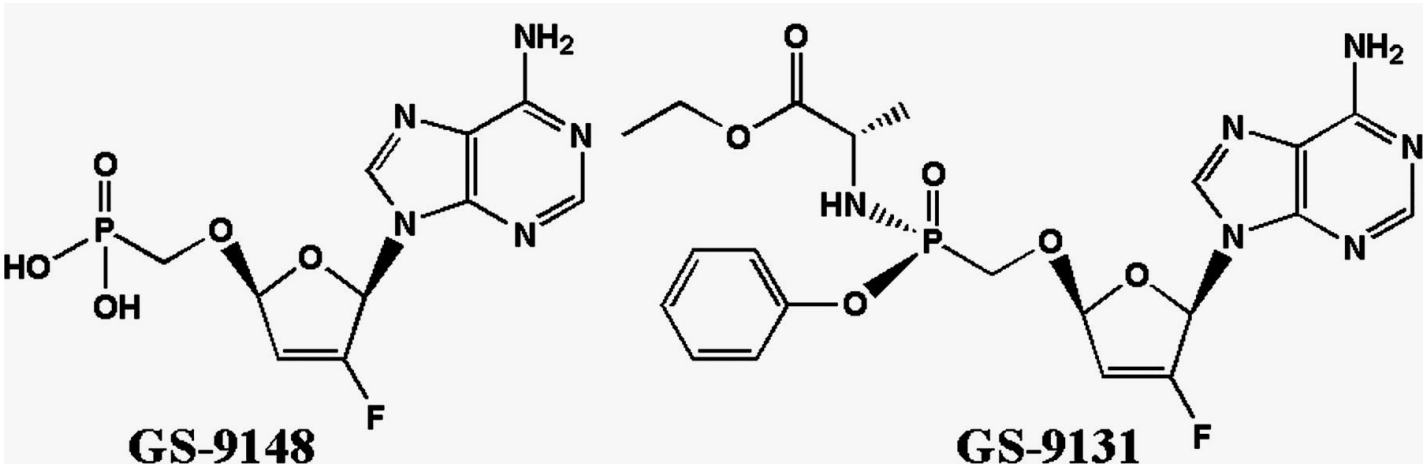


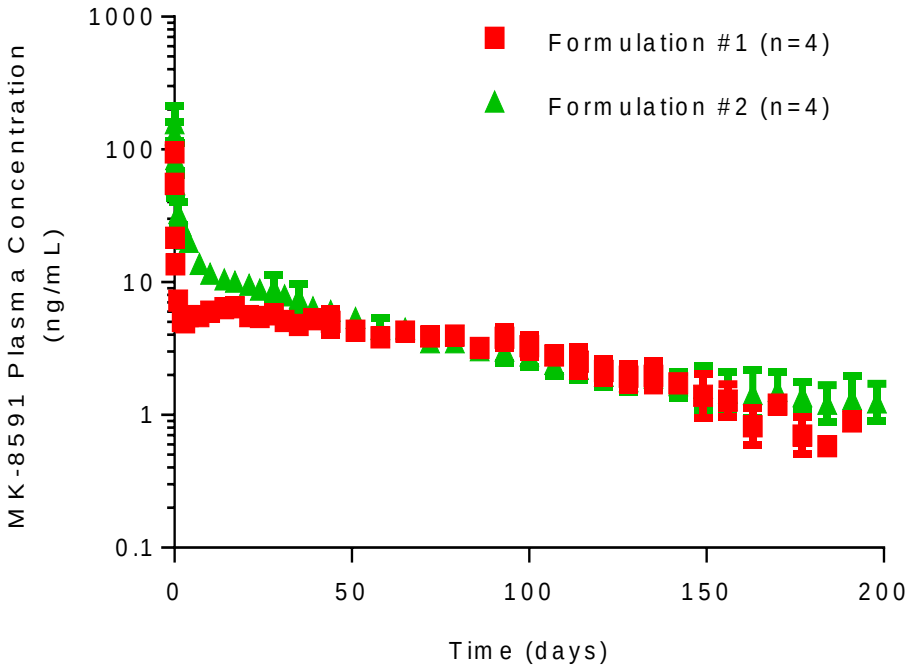
FIG 1 Chemical structures of 2′-deoxyadenosine (dA), MK-8591 (4′-ethynyl-2-fluoro-2′-deoxyadenosine [EFdA]), and BMS-986001 (2′,3′-didehydro-3′-deoxy-4′-ethynyl-thymidine; also known as festinavir, censavudine, 4′-ethynyl stavudine, 4′-ethynyl-d4T, and OBP-601).

GS-9131 is a monoamidate prodrug of the nucleotide analog GS-9148 (phosphonomethoxy-2'-fluoro-2',3'-dideoxydidehydroadenosine). GS-9131 undergoes conversion in lymphocytes to GS-9148 diphosphate, a potent inhibitor of HIV-1 RT.



MK-8591 (EFdA) Implant Formulations Release Effective Drug Levels for >180 days

- Open-label study (n=6)
  - Treatment-naïve males
  - CD4 >500 cells/mm^3
- MK-8591 (NRTI)
  - Single, 10-mg oral dose
- Intracellular MK-8591-TP in PBMC
  - T1/2 (geometric mean): 103 hours
- No evidence of resistance out to day 10
- HIV RNA reduction (log_{10} copies/mL)
  - Day 7: 1.67
  - Day 10: 1.78
- Generally well tolerated



- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

- Grobler JA et al. CROI, 2/22-2/25, 2016, Boston, MA

LA ARV Implants – Tenofovir Alafenamide

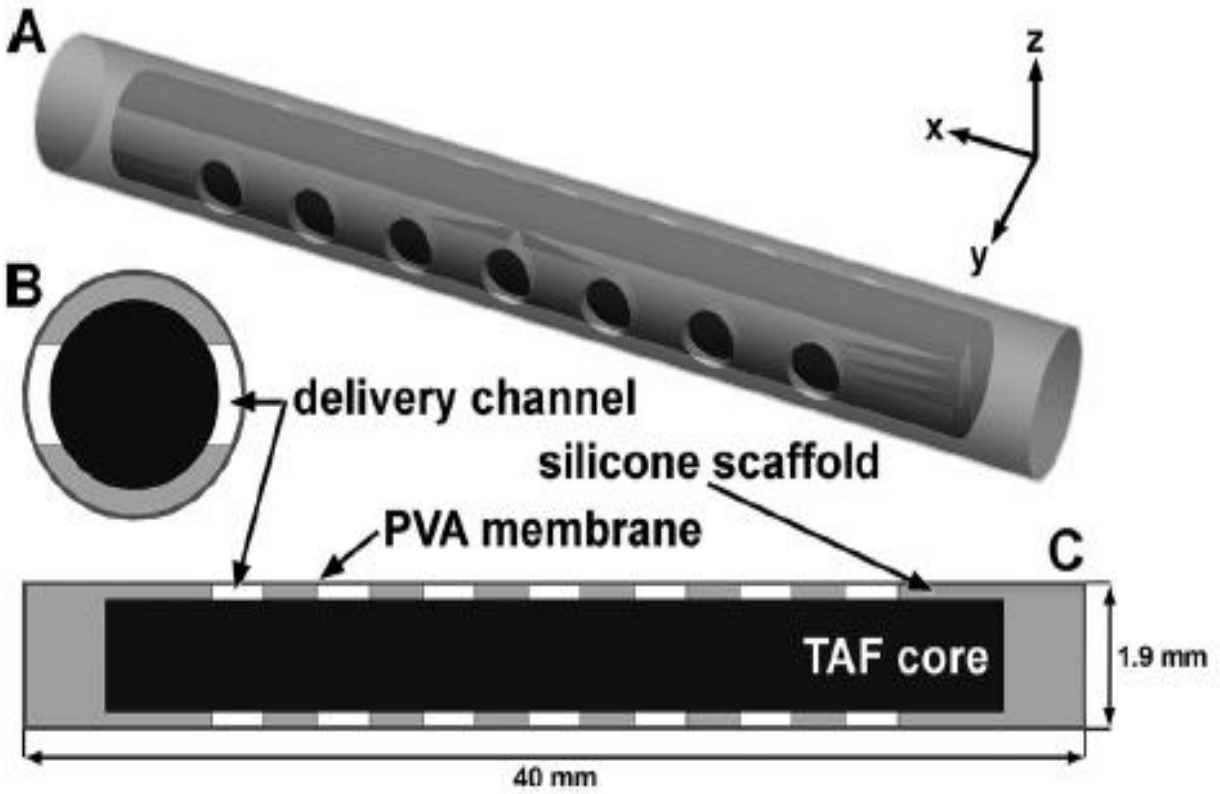
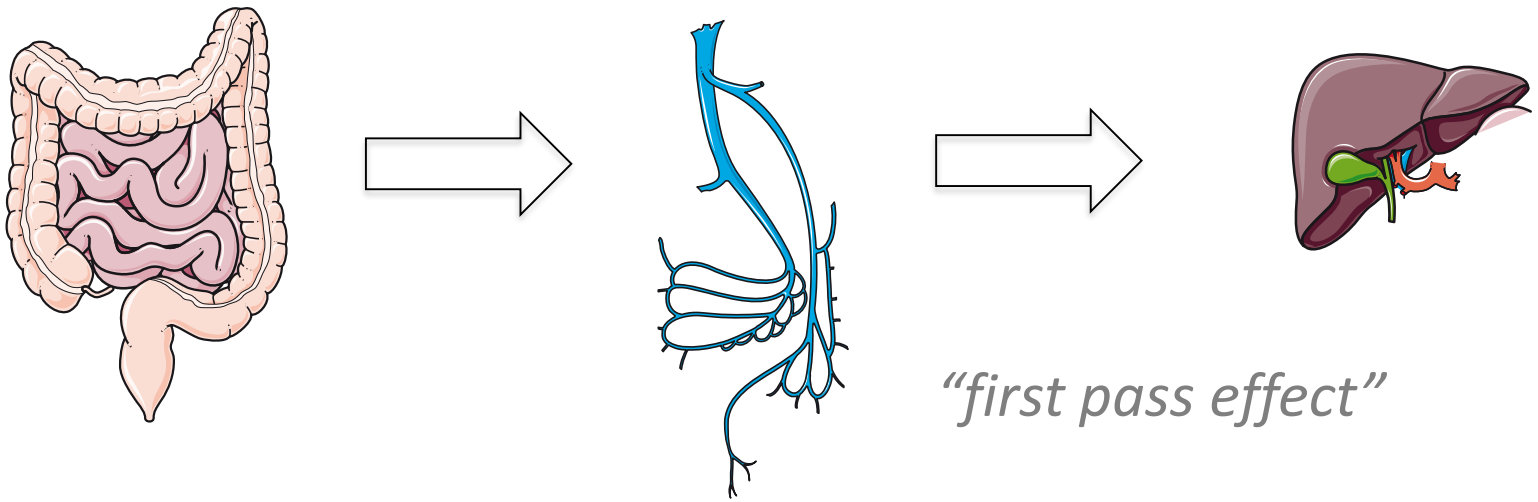


FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the *y-z* (B) and *x-y* planes (C).

M Gunawardana et al., *Antimicrob Agents Chemother* 2015; 59: 3913



“first pass effect”

Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation

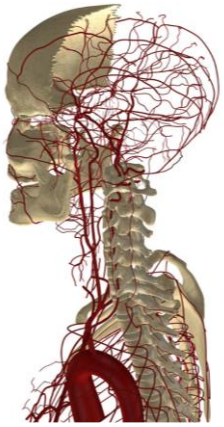
Blood flow distribution in an anatomically detailed arterial network model: criteria and algorithms

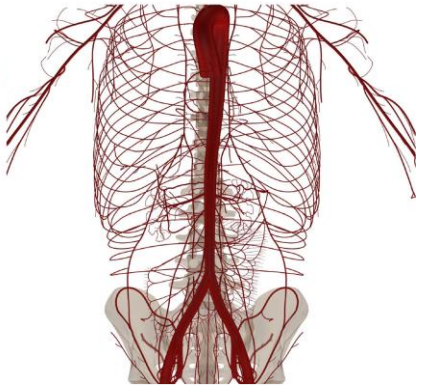
Pablo J. Blanco · Sansuke M. Watanabe · Enzo A. Dari
Marco Aurélio R. F. Passos · Raúl A. Feijóo

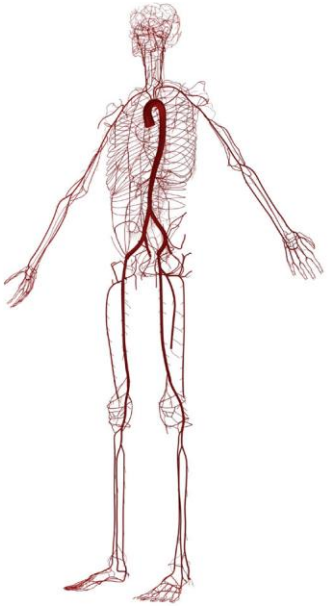
Biomech Model Mechanobiol (2014) 13:1303–1330

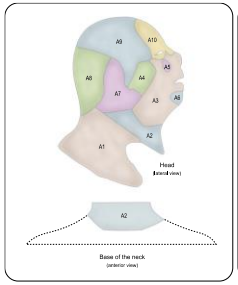
Table 5 Description of specific organs and their blood supply

Code	Organ	BFF (%)	DT
O1	Heart	4	PD
O2	Encephalon	12	PD
O3/O4	Eye (×2)	0.014286	PD
O5/O6	Ear (×2)	0.000014	PD
O7	Nose	0.000089	MD
O8	Tongue	0.3	MD
O9	Teeth	0.0012	VD
O10	Thyroid	1.5	PD
O11	Hypophysis	0.009429	MD
O12	Liver	6.5	PD
O13	Gallbladder	0.004286	MD
O14/O15	Kidney (×2)	9.5	PD
O16/17	Suprarenal (×2)	0.15	PD
O18	Stomach	1	PD
O19	Pancreas	1	PD
O20	Spleen	3	PD
O21	Small intestine	10	PD
O22	Large intestine	3.25	PD
O23	Bladder	0.06	PD
O24	Penis	0.893140	VD
O25/O26	Testicle (×2)	0.028750	MD
O27	Rectum	0.75	PD
O28	Diaphragm	1.058718	LD
	Total	64.712962	

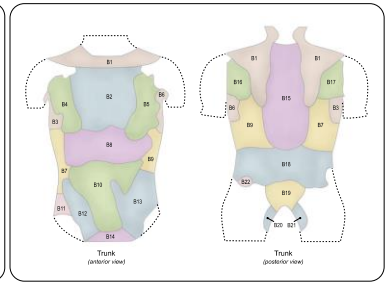




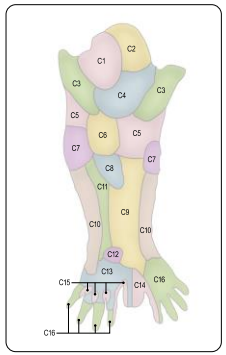




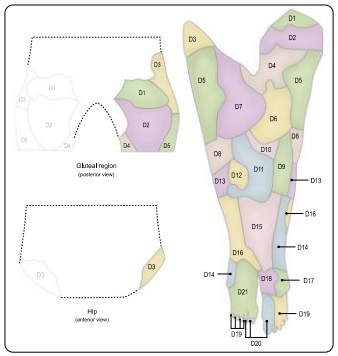
(a) Head and neck



(b) Trunk

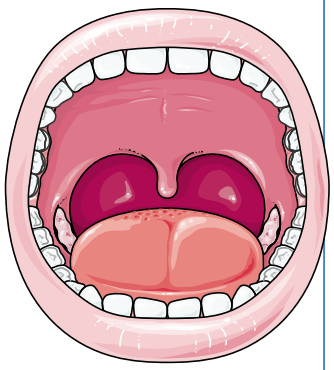


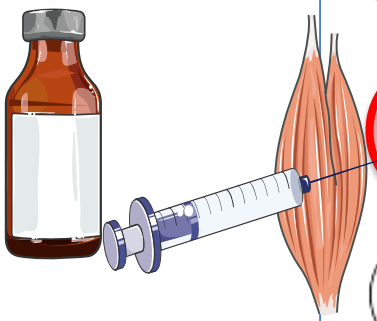
(c) Upper limb



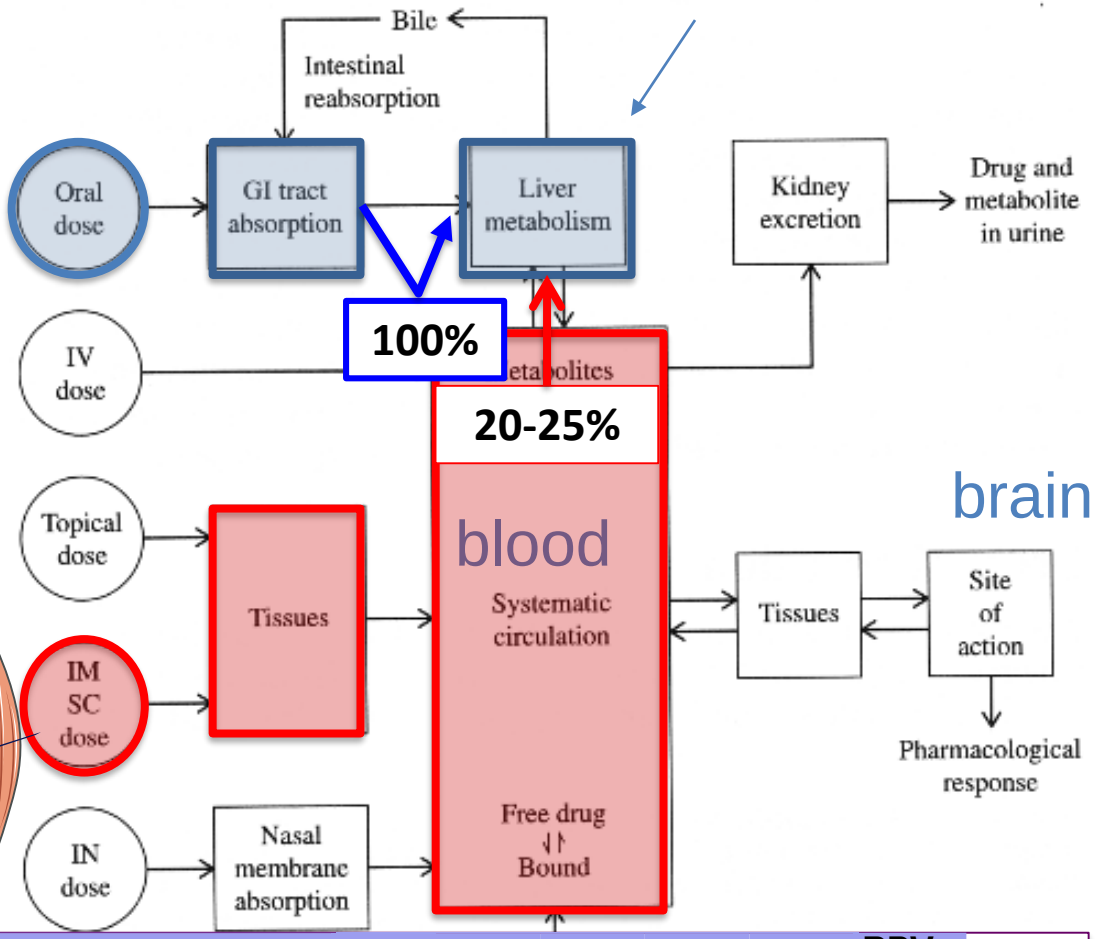
(d) Lower limb

Estrogens	Ethinylestradiol
	Estradiol
Progestins	Desogestrel
	Drospirenone
	Dydrogesterone
	Etonogestrel
	Gestodene
	Levonorgestrel
	Medroxy-progesterone (IM)
	Medroxy-progesterone (oral)
	Norelgestromin
	Norethisterone (Norethindrone)
	Norgestimate
	Norgestrel
Other	Levonorgestrel (EC)
	Mifepristone
	Ulipristal





first pass metabolism



	DLV	EFV	ETV	NVP	RPV	RPV + F/TAF
Medroxyprogesterone (IM depot injection)	♦	♦	♦	♦	♦	♦
Medroxyprogesterone (oral)	■	■	■	■	♦	♦

●/○	These drugs should not be coadministered
■/□	Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
◆/◇	No clinically significant interaction expected
✦/✧	There are no clear data, actual or theoretical, to indicate whether an interaction will occur

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