14th Residential Course on Clinical Pharmacology of Antiretrovirals

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Two-drug regimen in HIV infection

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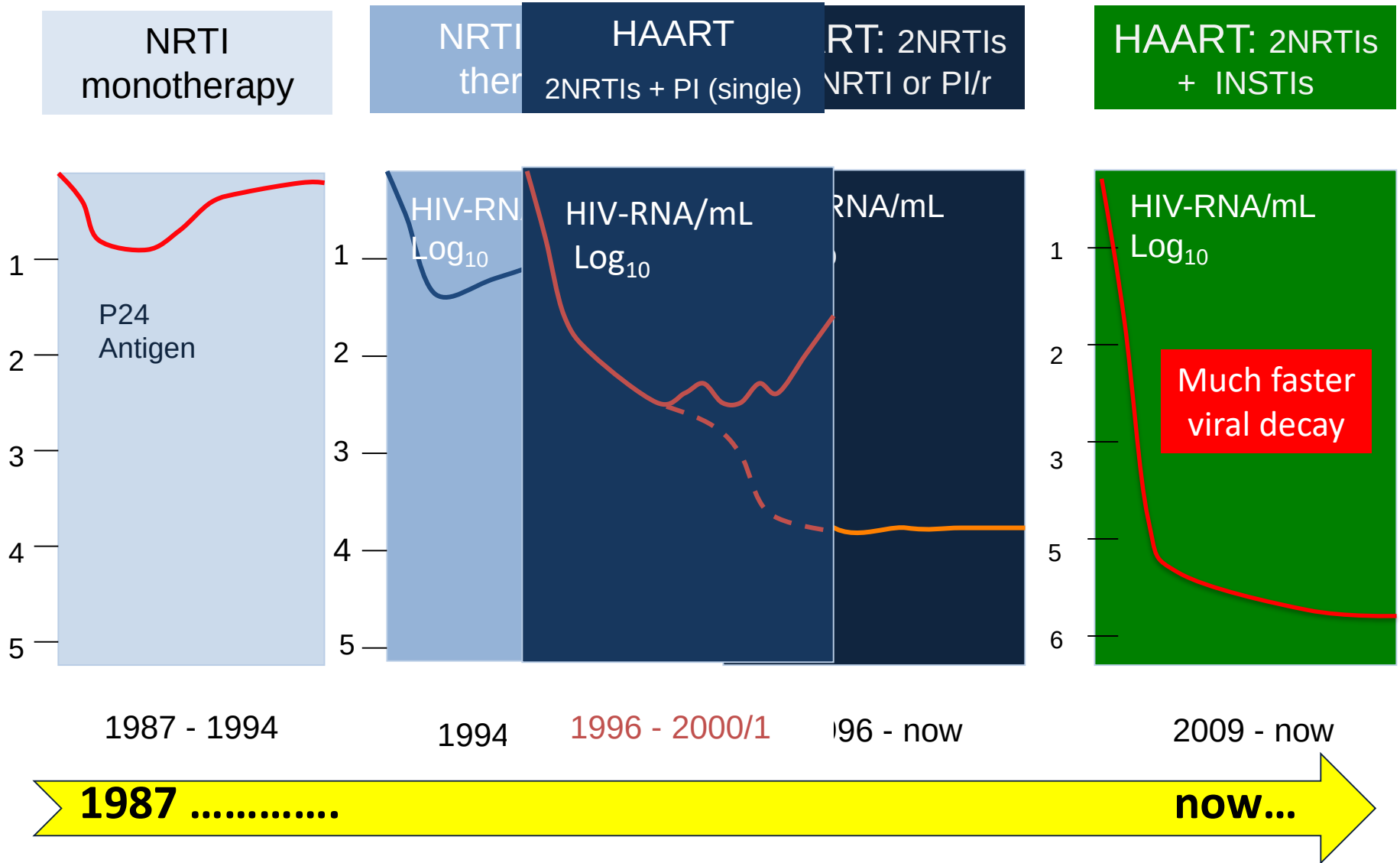
- Novartis
- Astellas
- Basilea

ANTIRETROVIRAL REGIMENS and their Antiviral Performance in the HIV Treatment History



Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients.

Baril JG,et al. PLOS ONE 2016; 11(2): e0148231. https://doi.org/10.1371/journal.pone.0148231

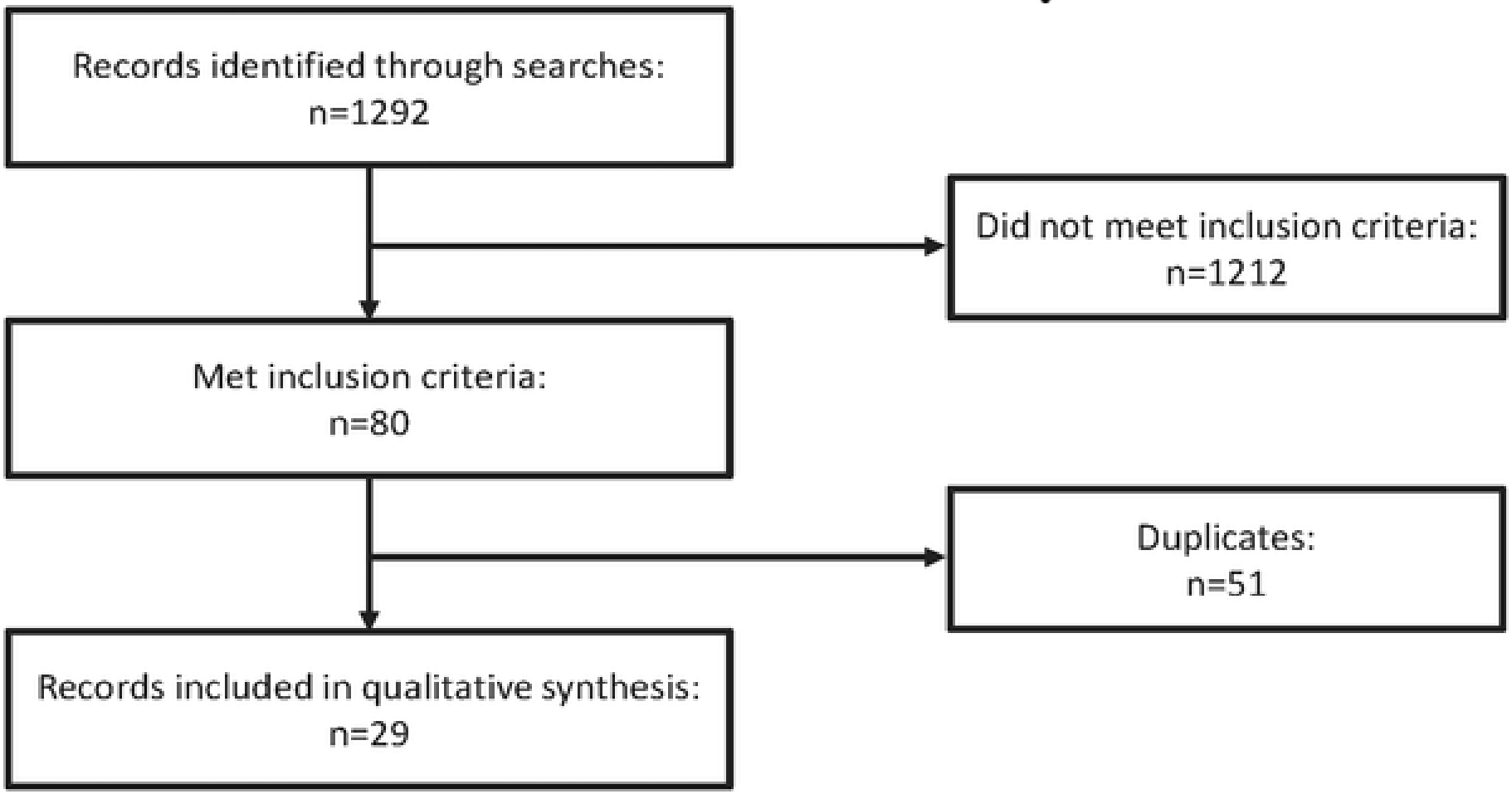


Fig 1. Flow diagram of literature search for systematic review.

Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients.

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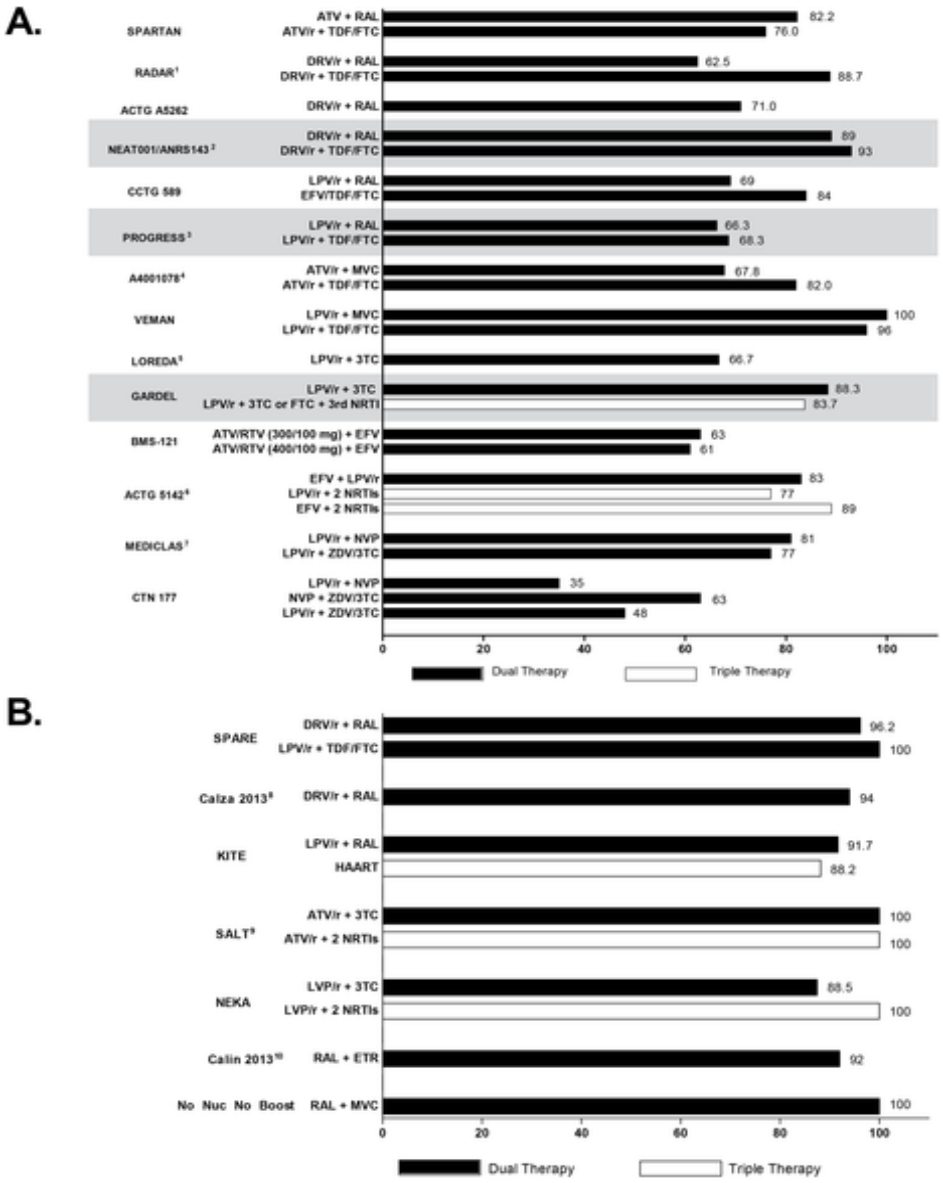


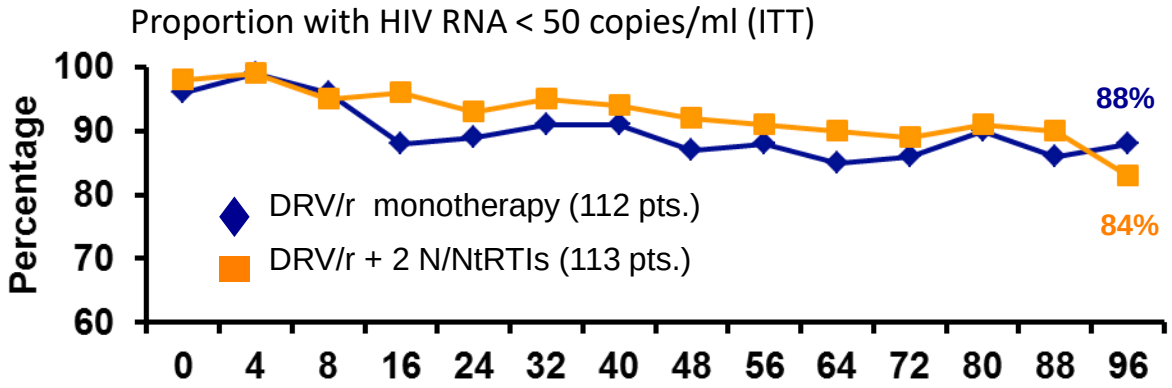
Fig 2. Efficacy of therapy by regimen in A) in ARV-naive, and B) ARV-experienced, virologically suppressed patients.

Dual Therapy: Potential Boosted PI Regimens for Initial/Maintenance Therapy

Study	Treatment Setting	N	Regimen	Results
NEAT001[1]	Initial	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts
GARDEL[2]	Initial	426	LPV/RTV + 3TC	Similar efficacy as LPV/RTV + 2 NRTIs
MODERN[3]	Initial	813	DRV/RTV + MVC	Inferior efficacy vs DRV/RTV + FTC/TDF
SPARTAN[4]	Initial	94	ATV + RAL	Similar virologic suppression, higher VF and hyperbilirubinemia rates vs ATV/RTV + FTC/TDF
OLE[5]	Switch	250	LPV/RTV + 3TC	Similar efficacy as continued standard ART
KITE[6]	Switch	60	LPV/RTV + RAL	Small study; encouraging efficacy
SALT[7]	Switch	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M[8]	Switch	266	ATV/RTV + 3TC	Improved efficacy vs ATV/RTV + 2 NRTIs
DUAL-GESIDA[9]	Switch	257	DRV/RTV + 3TC	Similar efficacy as DRV/RTV + 2 NRTIs

1. Raffi F, et al. Lancet. 2014;384:1942-1951.
2. Cahn P, et al. EACS 2015. Abstract 961.
3. Stellbrink H-J, et al. AIDS 2014. Abstract TUAB0101.
4. Kozal MJ, et al. HIV Clin Trials. 2012;13:119-130.
5. Arribas JR, et al. Lancet Infect Dis. 2015;15:785-792.
6. Ofotokun I, et al. AIDS Res Hum Retroviruses. 2012;28:1196-1206.
7. Perez-Molina JA, et al. Lancet Infect Dis. 2015;15:775-784.
8. Di Giambenedetto S, et al. EACS 2015. Abstract 867.
9. Pulido F, et al. HIV Glasgow 2016. Abstract O331.

MONOI: Switch to DRV/r ± NRTIs

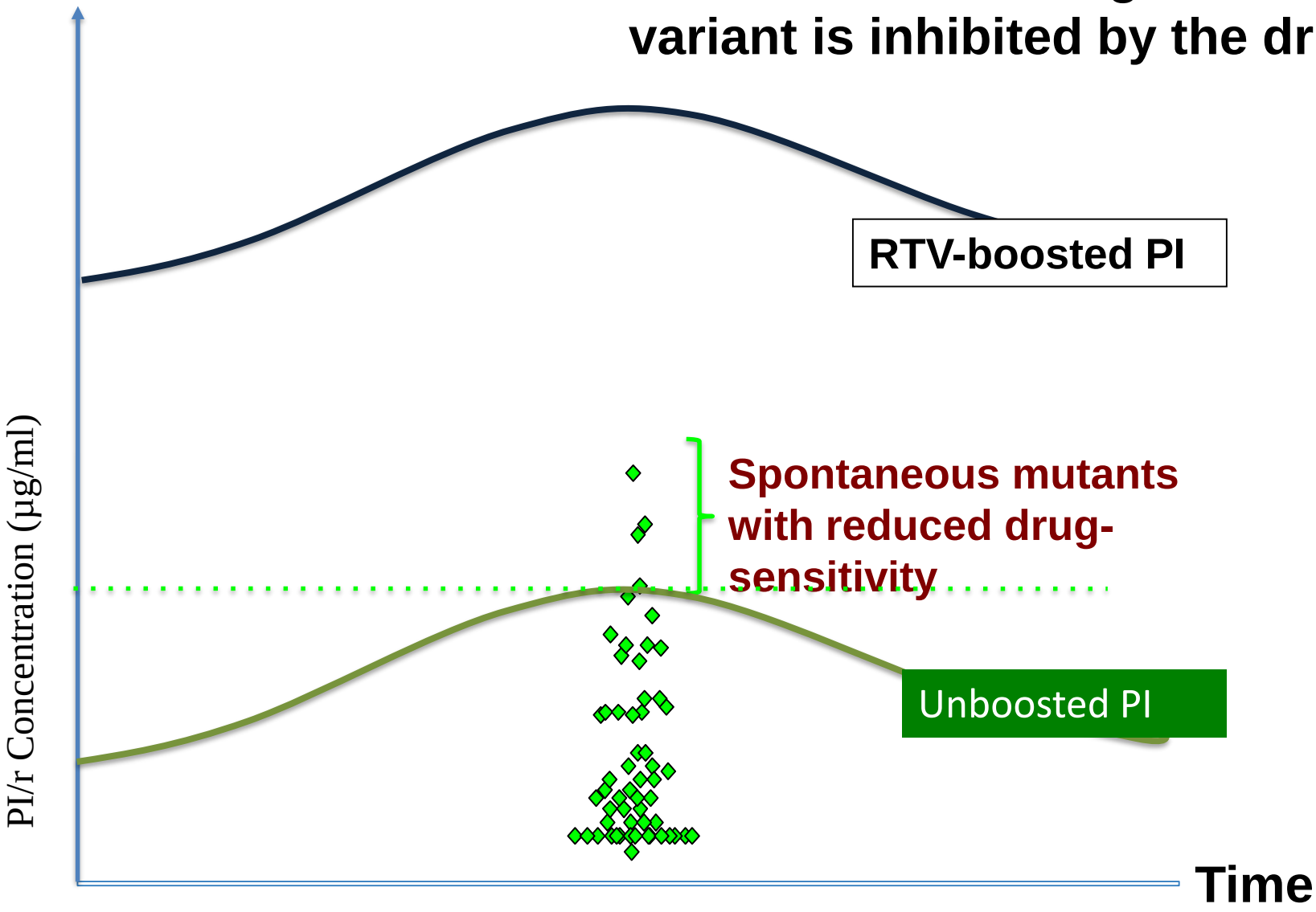


Response Predictors:

	Univariate analysis		Multivariate analysis	
Variables associated with rebound at week 96	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Duration of prior ART (per 5 year decrease)	1.74 (1.11, 2.73)	0.013	2.11 (1.23, 3.8)	0.009
Difficulty in Adherence (<100% vs 100%)	2.36 (0.94, 5.92)	0.07	3.84 (1.29, 12.49)	0.02
HIV-1 DNA at D0 (per 1 log10 copies/106 cells increase)	2.45 (1.07, 5.61)	0.03	2.66 (1.11, 7.48)	0.04

Valantin M-A, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 534.

In case of a WT HIV viral population Pk exposure of boosted-PIs is such that even the least drug-sensitive variant is inhibited by the drug

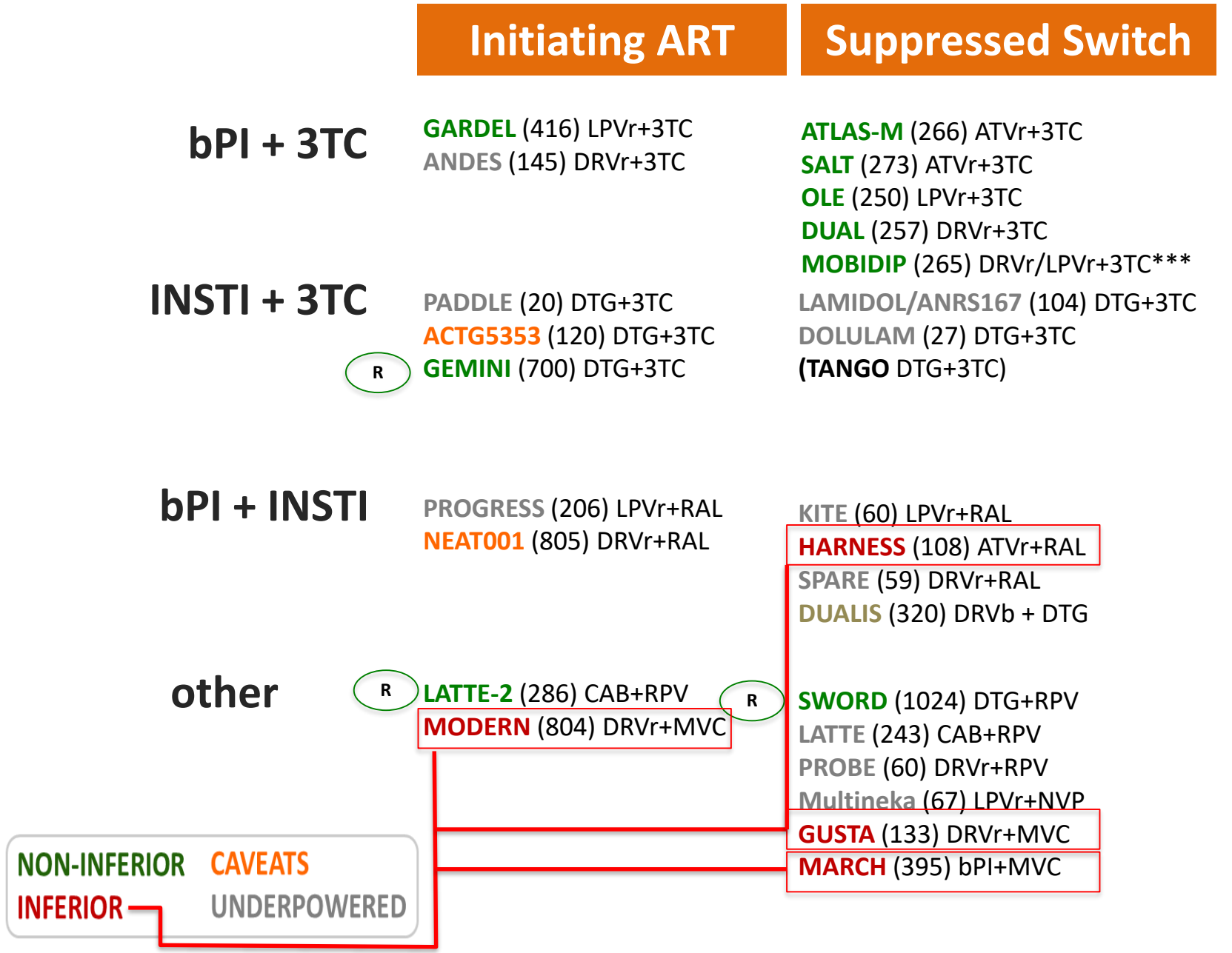


- Until the development of 2nd generation INSTIs, boosted – PIs have been considered as the pillars of the vast majority of LDR antiretroviral therapeutic attempts because of their strong genetic barrier and the extremely low frequency of resistance selection upon virological failure.

- In carefully selected patients, this was also proven in case of monotherapy

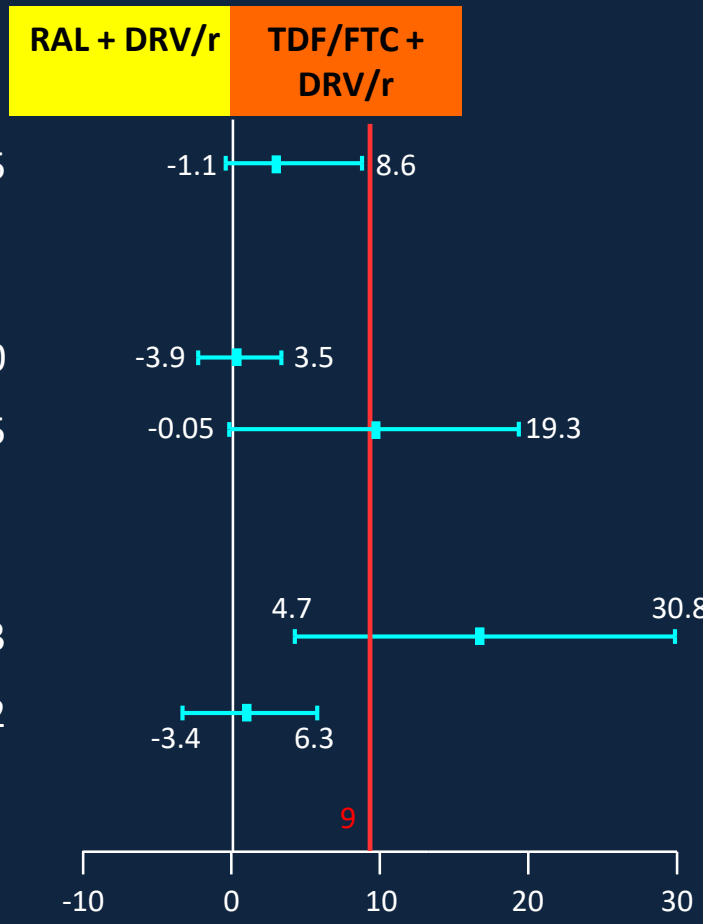
- However, the importance of including a **Reverse Transcriptase inhibitor** in two-drug regimens was noted in many clinical trials well before the current successful scenario of DTG-based dual treatments.

2DR Studies - overview



Primary endpoint at W96 by baseline characteristics

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



		RAL + DRV/r	TDF/FTC + DRV/r
Overall	n = 805	17.4 %	13.7 %
Baseline HIV-1 RNA			
< 100,000 c/ml	n = 530	7 %	7 %
≥ 100,000 c/ml	n = 275	36 %	27 %
			p = 0.09*
Baseline CD4+			
< 200/mm^3	n = 123	39.0 %	21.3 %
≥ 200/mm^3	n = 682	13.6 %	12.2 %
			p = 0.02*

Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* 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

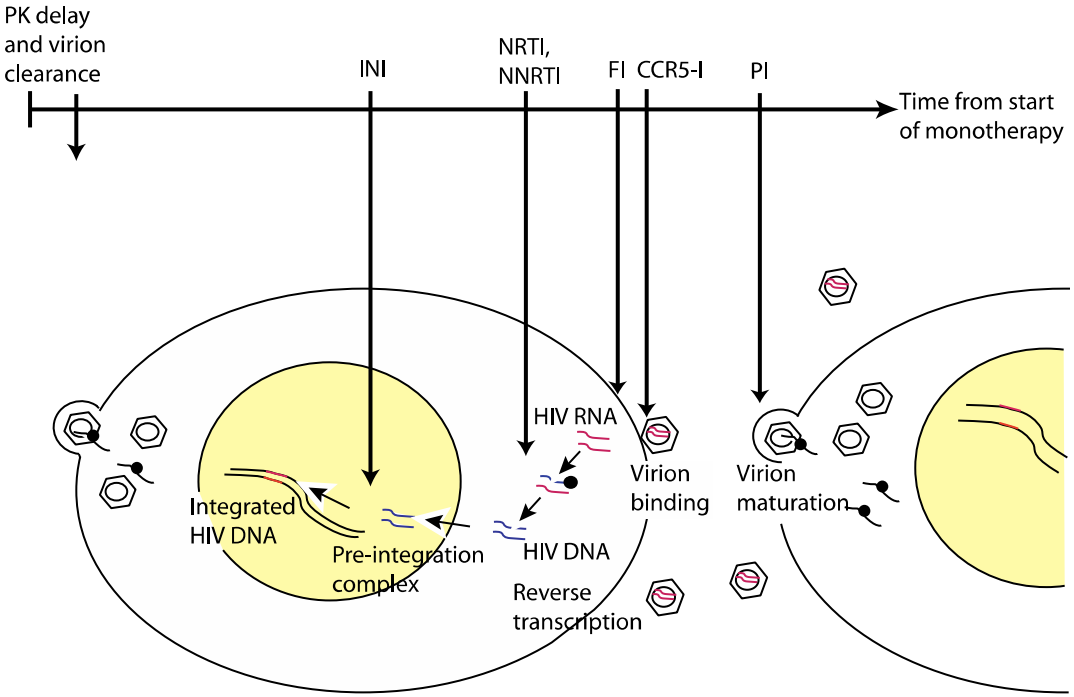


FIG. 1. The positions in the HIV life cycle affected by each drug class and their relative timing in terms of when they impact HIV RNA levels in blood.

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

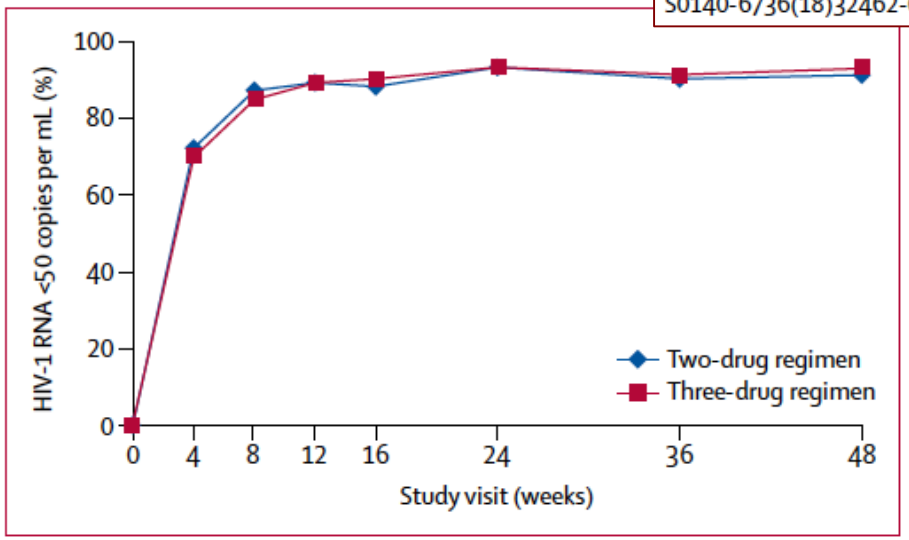
Most of this time is taken by reverse transcription (RT, 33 h)

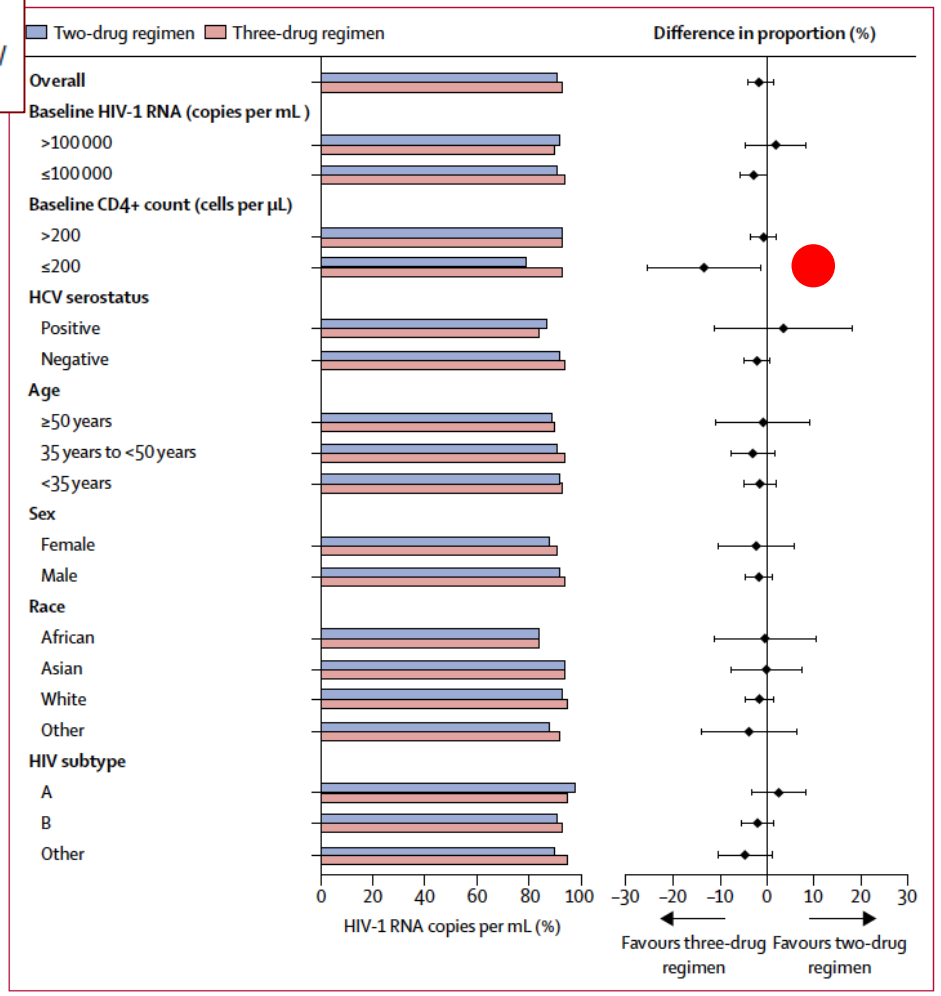
Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials

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.





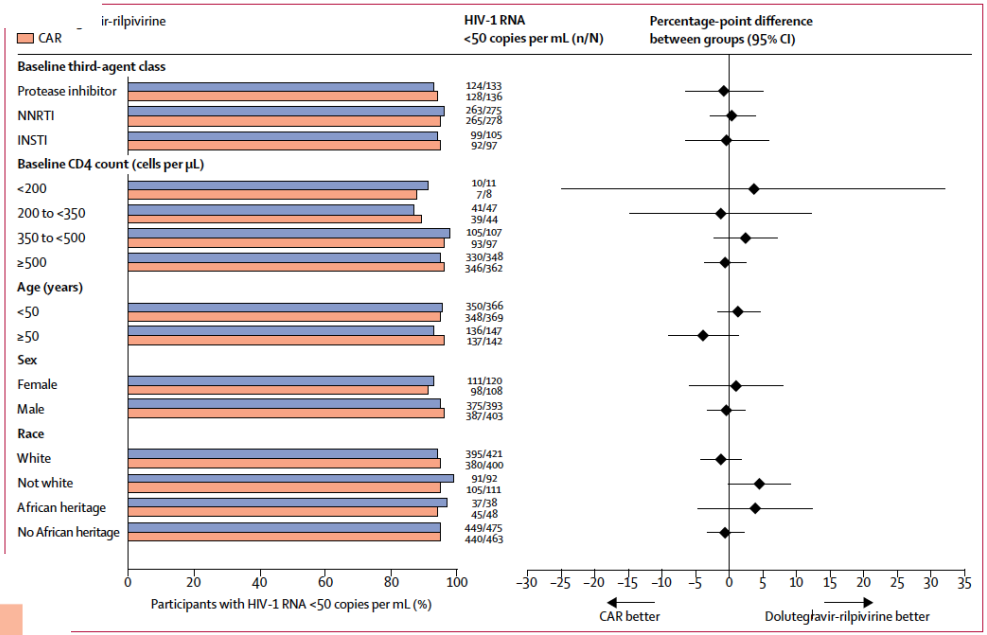
The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a guidelinerecommended three-drug regimen at 48 weeks in ART-naive adults supports its use as initial therapy for patients with HIV-1 infection.

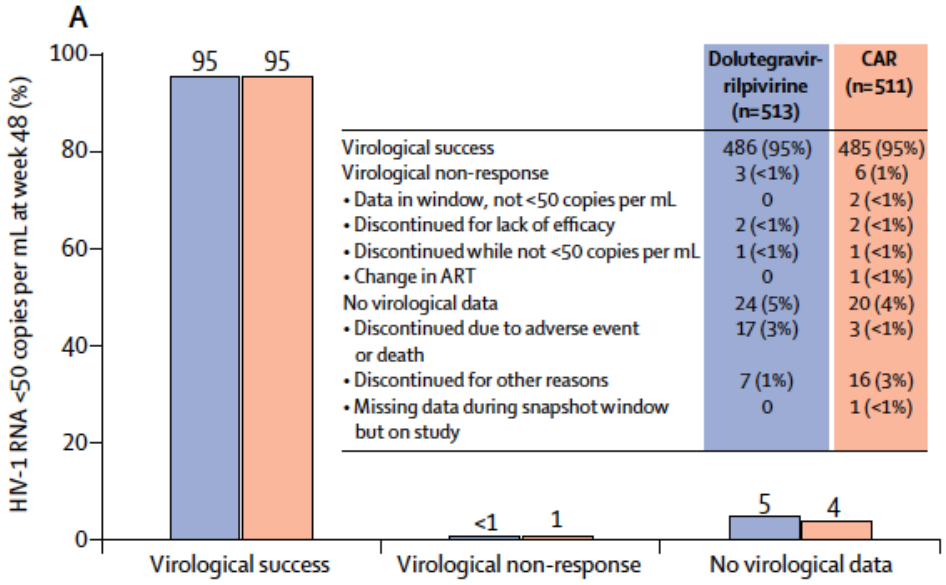
Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies

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%)

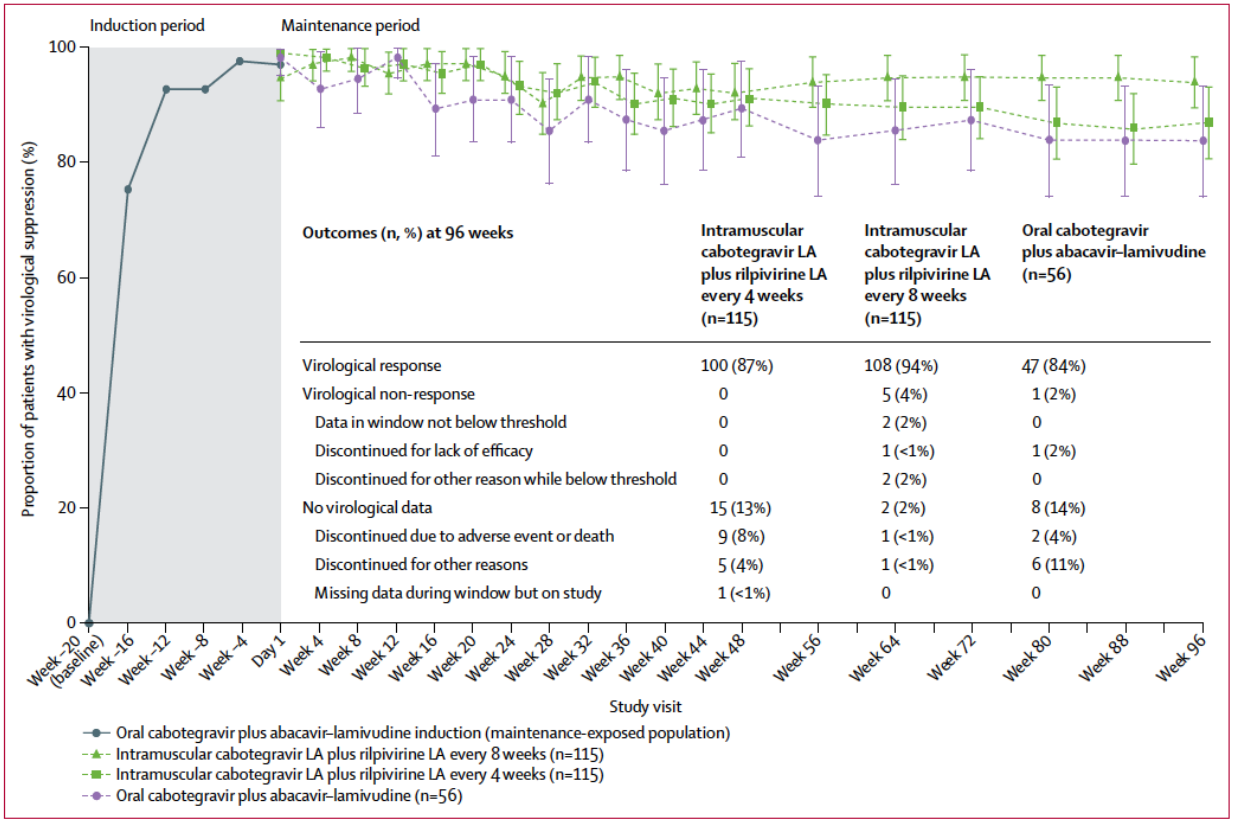
Dolutegravir-rilpivirine was non-inferior to CAR over 48 weeks in participants with HIV suppression and showed a safety profile consistent with its components. Results support the use of this two-drug regimen to maintain HIV suppression.

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

Lancet 2017; 390: 1499–510

David A Margolis, Juan Gonzalez-Garcia, Hans-Jürgen Stellbrink, Joseph J Eron, Yazdan Yazdanpanah, Daniel Podzamczer, Thomas Lutz, Jonathan B Angel, Gary J Richmond, Bonaventura Clotet, Felix Gutierrez, Louis Sloan*, Marty St Clair, Miranda Murray, Susan L Ford, Joseph Mrus, Parul Patel, Herta Crauwels, Sandy K Griffith, Kenneth C Sutton, David Dorey, Kimberly Y Smith, Peter E Williams, William R Spreen

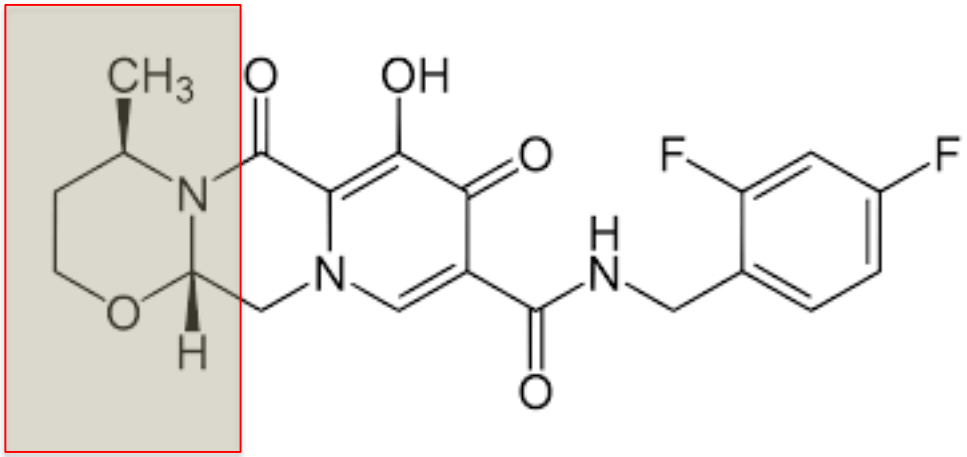
After a 20-week induction period on oral cabotegravir plus abacavir–lamivudine, patients with viral suppression (plasma HIV-1 RNA <50 copies per mL) were randomly assigned (2:2:1) to intramuscular long-acting cabotegravir plus rilpivirine at 4-week intervals (long-acting cabotegravir 400 mg plus rilpivirine 600 mg; two 2 mL injections) or 8-week intervals (long-acting cabotegravir 600 mg plus rilpivirine 900 mg; two 3 mL injections) or continued oral cabotegravir plus abacavir–lamivudine.



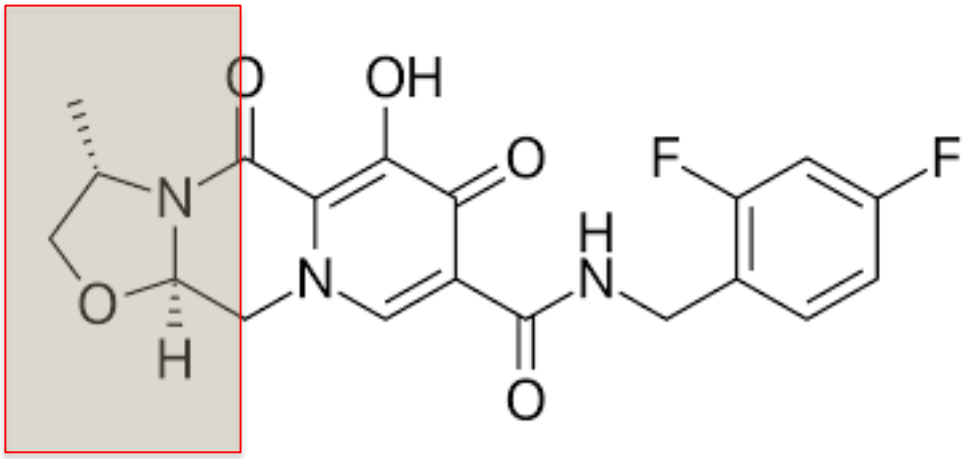
Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (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

The two-drug combination of all-injectable, long-acting cabotegravir plus rilpivirine every 4 weeks or every 8 weeks was as effective as daily three-drug oral therapy at maintaining HIV-1 viral suppression through 96 weeks and was well accepted and tolerated.

By all means the current era of two-drug regimens gravitates around the 2nd generation INSTIs:



Dolutegravir

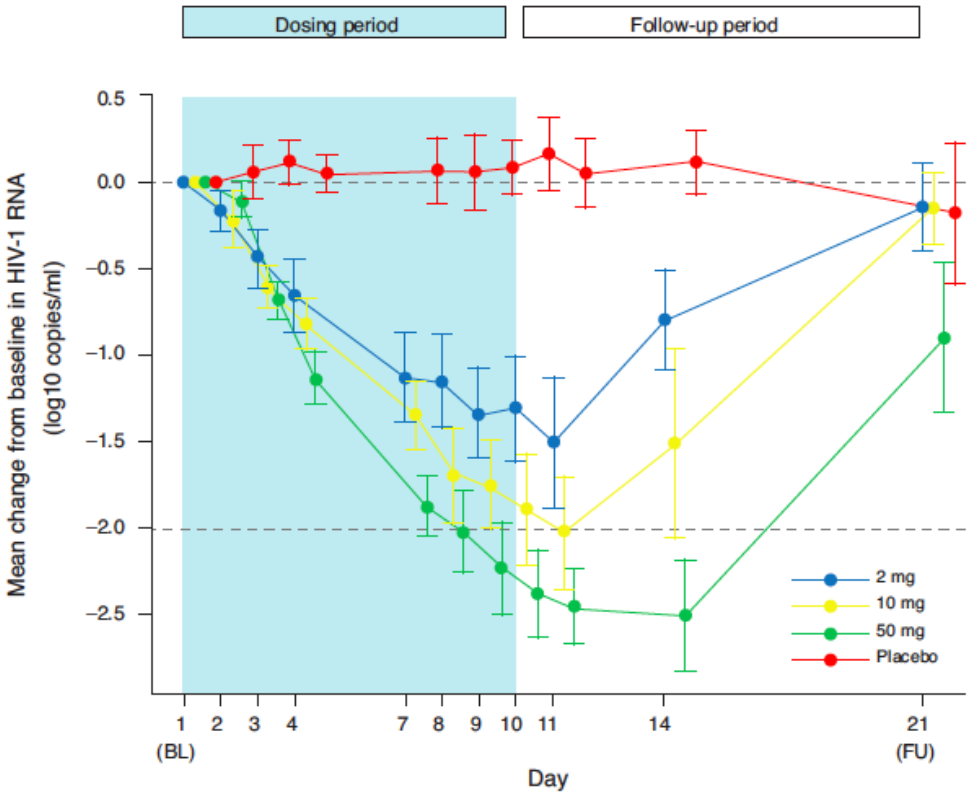


Cabotegravir

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

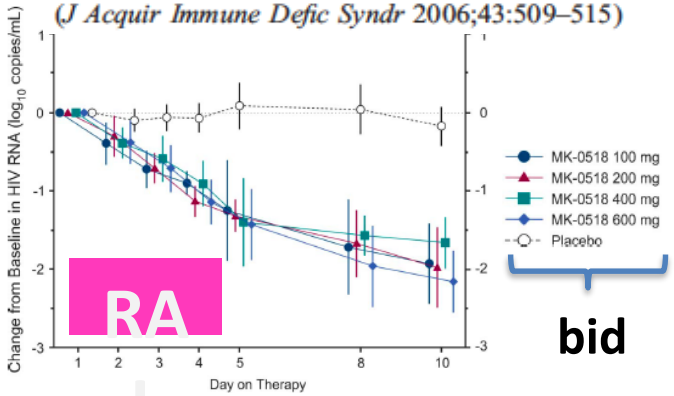
Min S, et al.

AIDS 2011, 25:1737–1745



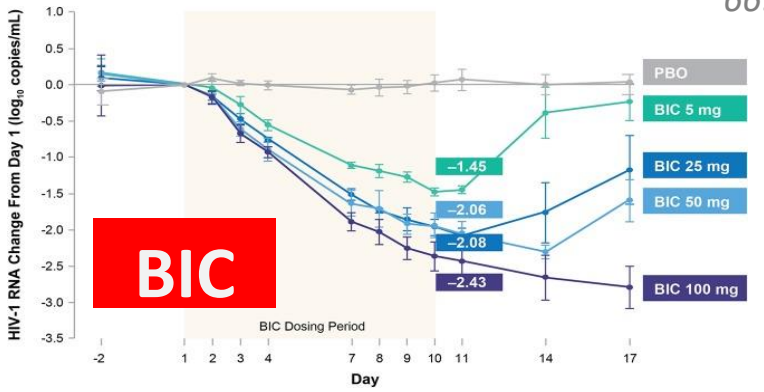
Markowitz M, et al.

(J Acquir Immune Defic Syndr 2006;43:509–515)



Gallant JE, et al.

J Acquir Immune Defic Syndr. 2017 May 1; 75(1): 61–66.



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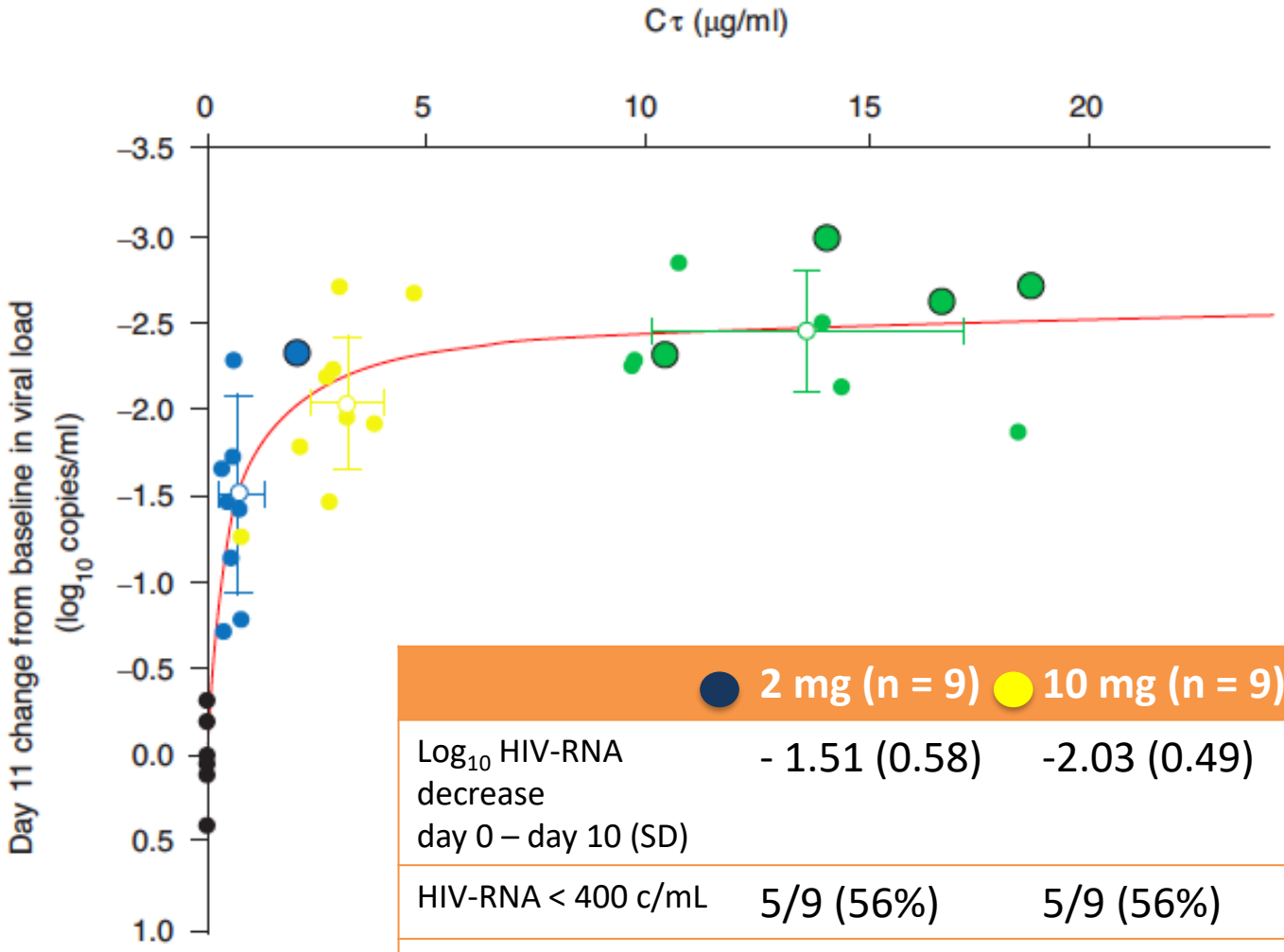


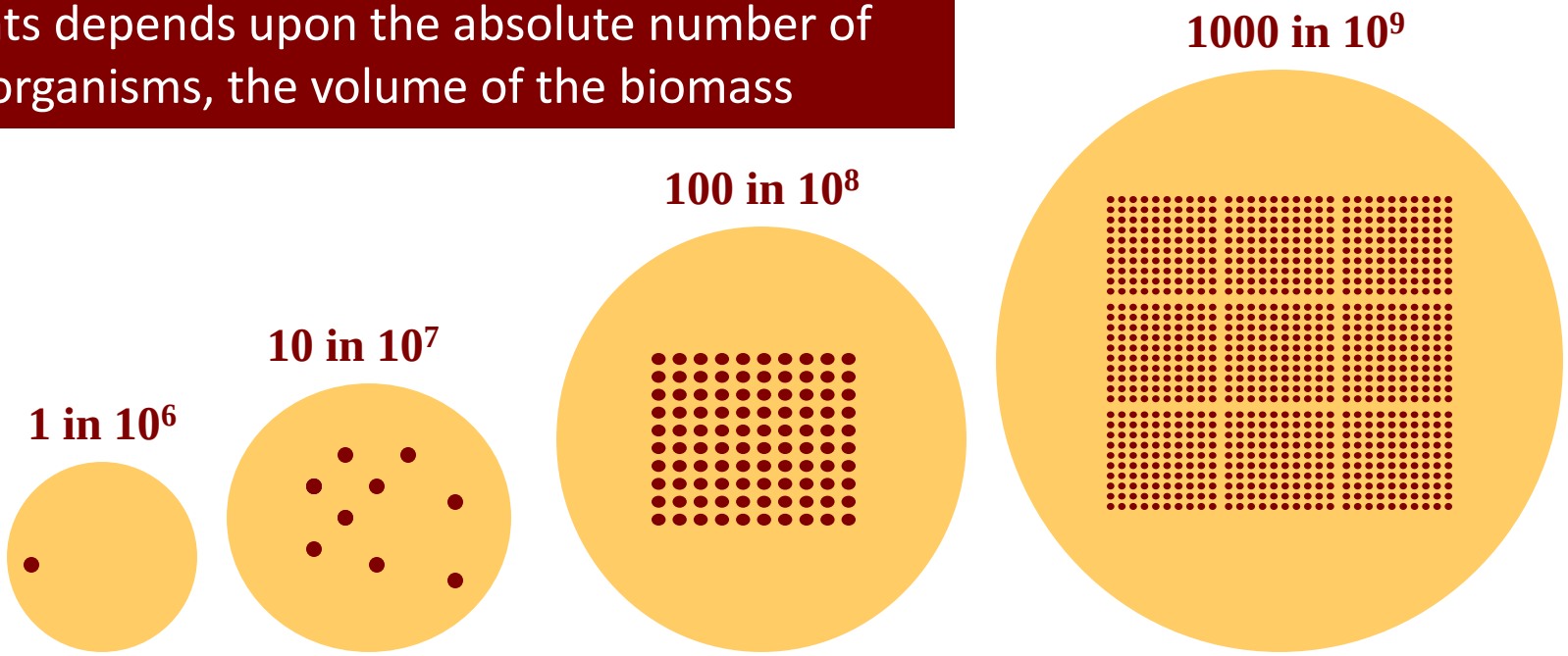
	2 mg (n = 9)	10 mg (n = 9)	50 mg (n = 10)
Log_{10} HIV-RNA decrease day 0 – day 10 (SD)	- 1.51 (0.58)	-2.03 (0.49)	-2.46 (0.35)
HIV-RNA < 400 c/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
HIV-RNA < 50 c/mL	1/9 (11%)	0	7/10 (70%)

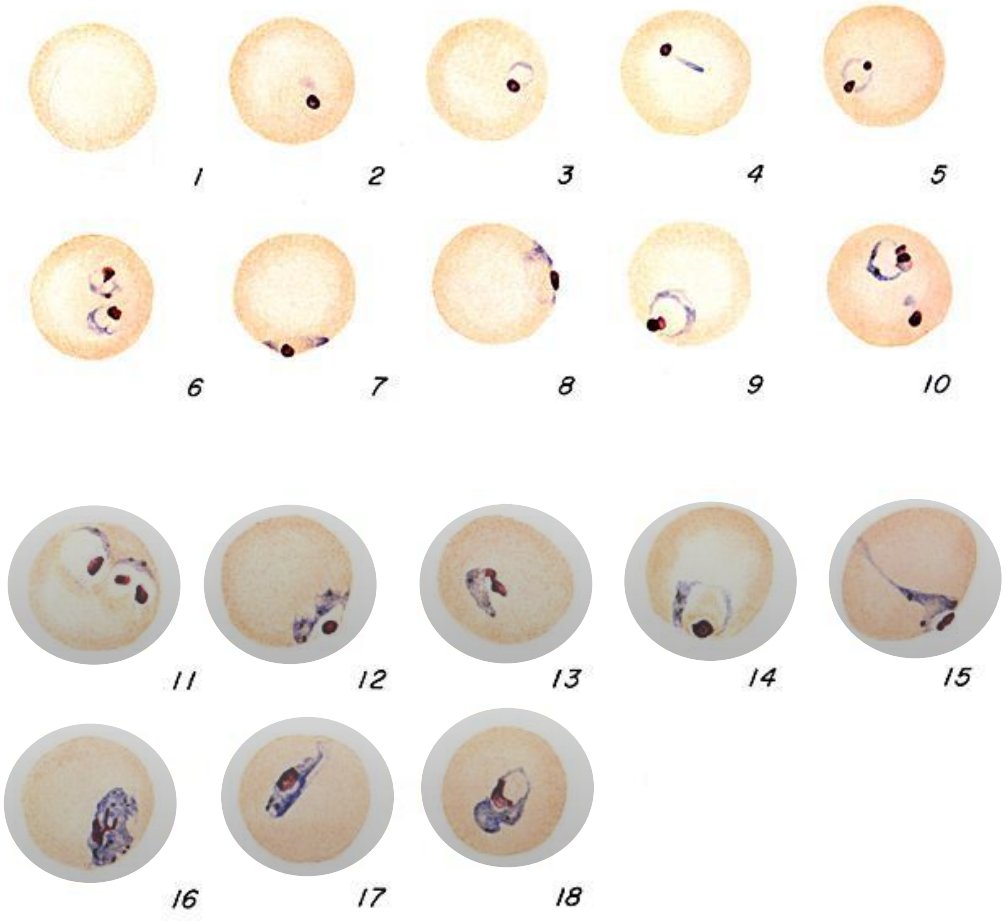
The Inoculum concept

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)

Johnson, C. C., et al. J. Antimicrob. Chemother 1995, 35:765-773.

Given a certain spontaneous frequency of **drug-resistant mutants**, the absolute number of such mutants depends upon the absolute number of microorganisms, the volume of the biomass



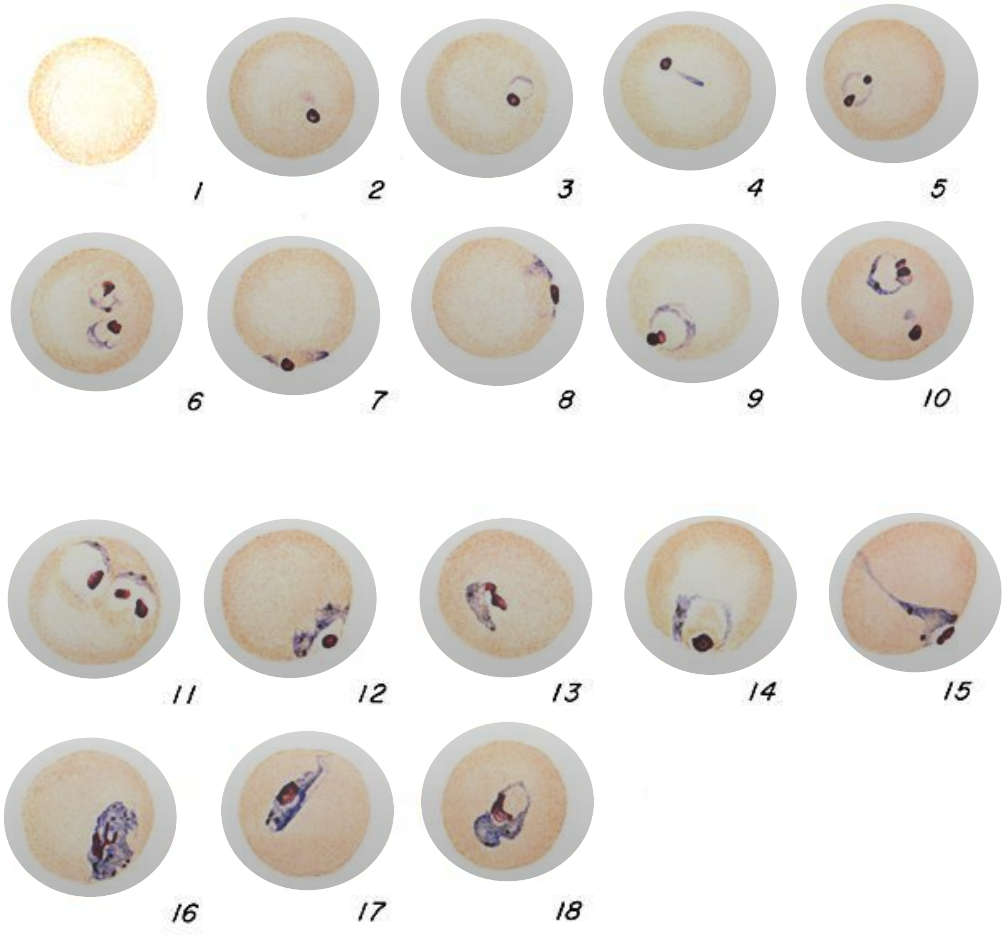


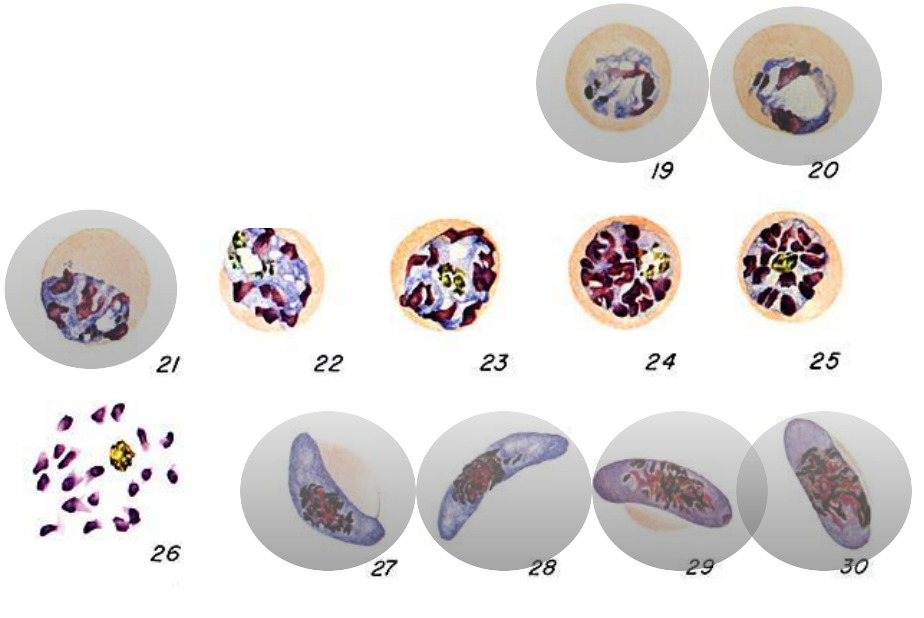
Differentiation and asexual multiplication of *Plasmodium falciparum*

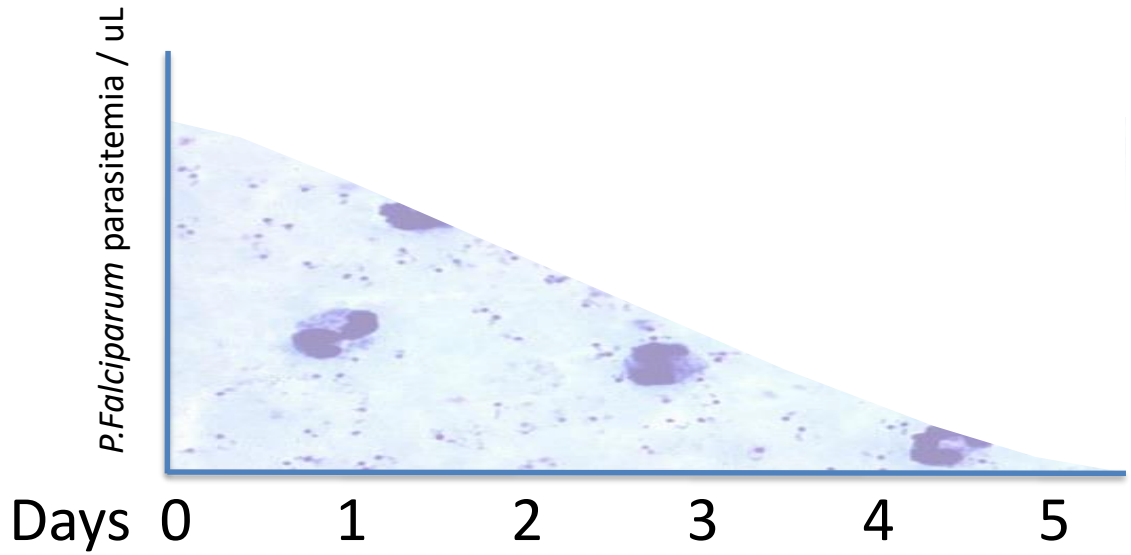
In the *P.falciparum* life cycle these are the forms whose growth is inhibited by DHFR inhibitors, quinine, quinidine and mefloquine

Differentiation and asexual multiplication of *Plasmodium falciparum*

.. while these are the developmental stages inhibted by artemisinine derivatives….

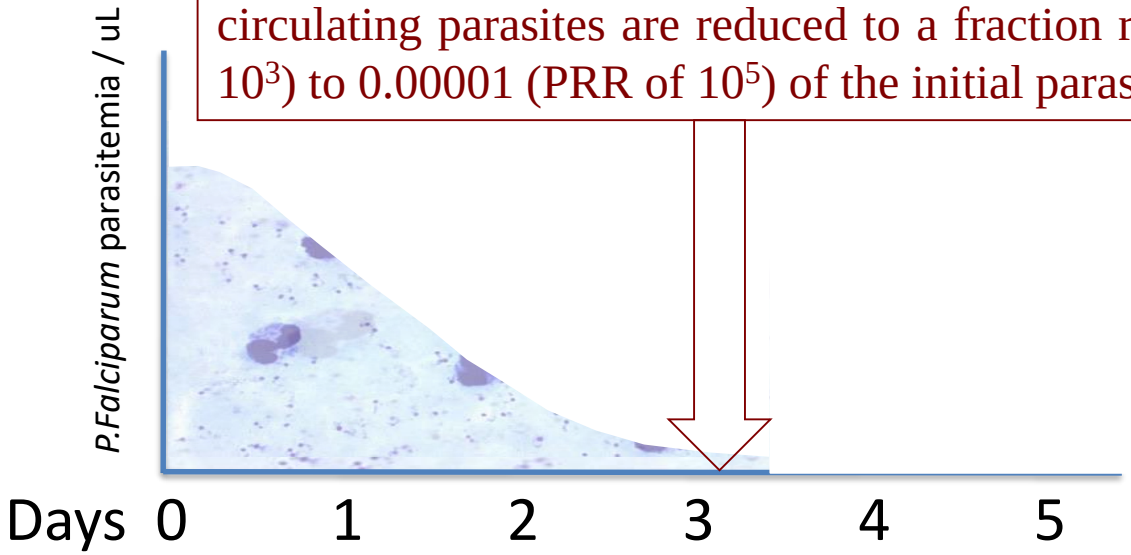






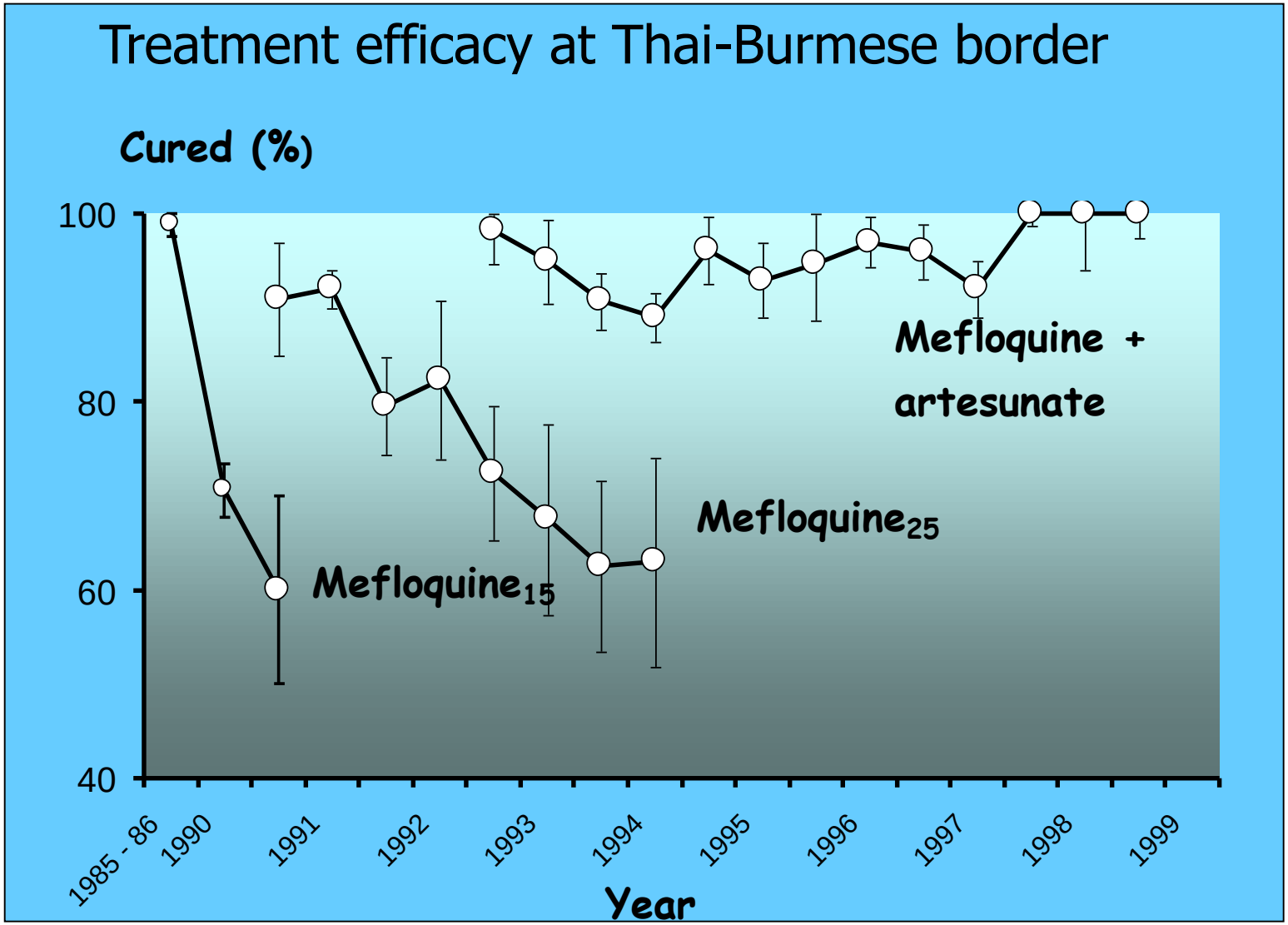
Mefloquine

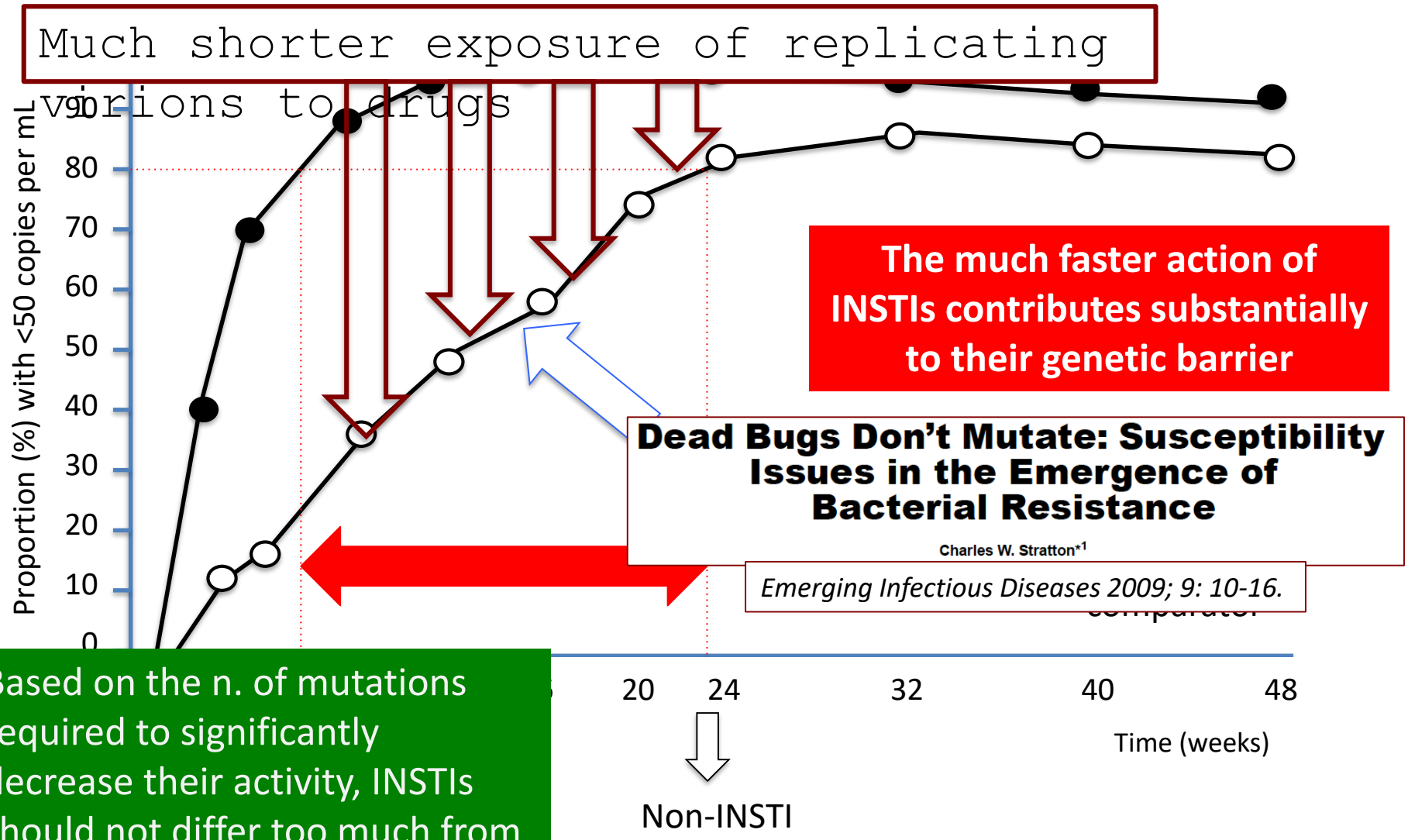
When *Mefloquine* will remain the only antimalarial still present, the circulating parasites are reduced to a fraction ranging from 0.001 (PRR of 10^3) to 0.00001 (PRR of 10^5) of the initial parasitaemia by *Artemisinin der.*



Artesunate + Mefloquine

First demonstration project in Thailand





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

Therapeutic barrier of INSTI

Overall low rate of resistance emergence at W48 in ARV-naive trials:

- **RAL 400 mg** 1 tablet bid : **0% to 1.4%**

SPRING-2 [2], STARTMRK [8], ONCEMRK [9]

- **RAL 600 mg** 2 tablets qd : **0.8%**

ONCEMRK [9]

- **DTG** : **0% to 0.2%**

ARIA [1], SPRING-2 [2], SINGLE [3], FLAMINGO [4]

- **EVG/c** : **0 % to 2%**

ARIA [1], WAVES [5], Study 102 [6], Study 103 [7]

1. Orrell C. Lancet HIV, July 17 (epub ahead of print) ; 2. *Raffi F. Lancet 2013;381:735-43* ; 3. *Walmsley S. NEJM 2013;369:1807-18 ; 4. Clotet B. Lancet 2014;383;2222-31 ; 5. Squires K. Lancet HIV 2016; 3(9):e410-e420 ; 6. Sax PE. Lancet 2012;379:2439-48 ; 7. DeJesus E. Lancet 2012;379:2429-38 ; 8.* Lennox JL. Lancet 2009;374:796-806 ; 9. Cahn P. Lancet HIV

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

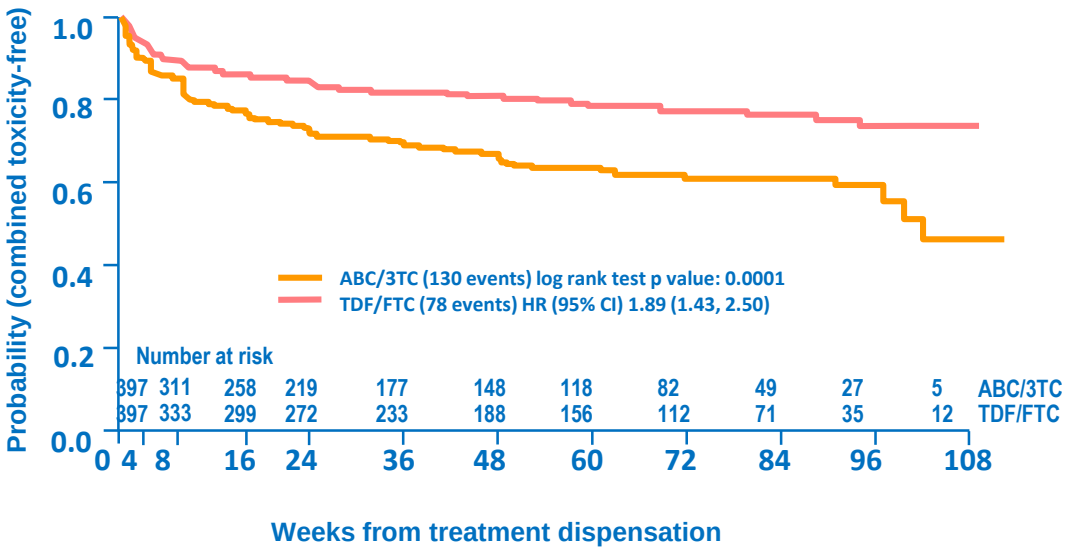
Variable, n (%)	GEMINI 1		GEMINI 2		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

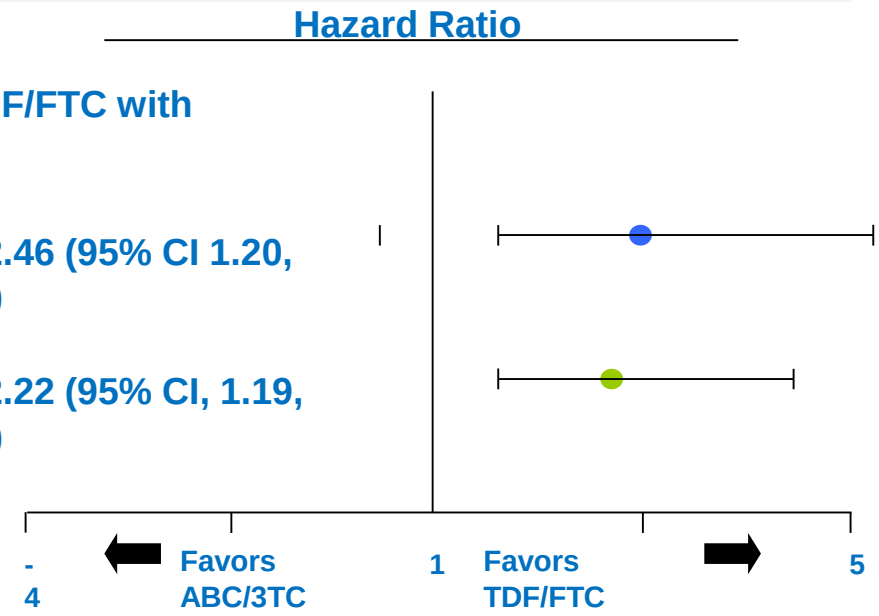
As-treated analysis of patients receiving first NRTI backbone



ACTG 5202 interim results: time to first safety event (High viral load stratum at DSMB action)

Sax et al. NEJM 2009;361:2230

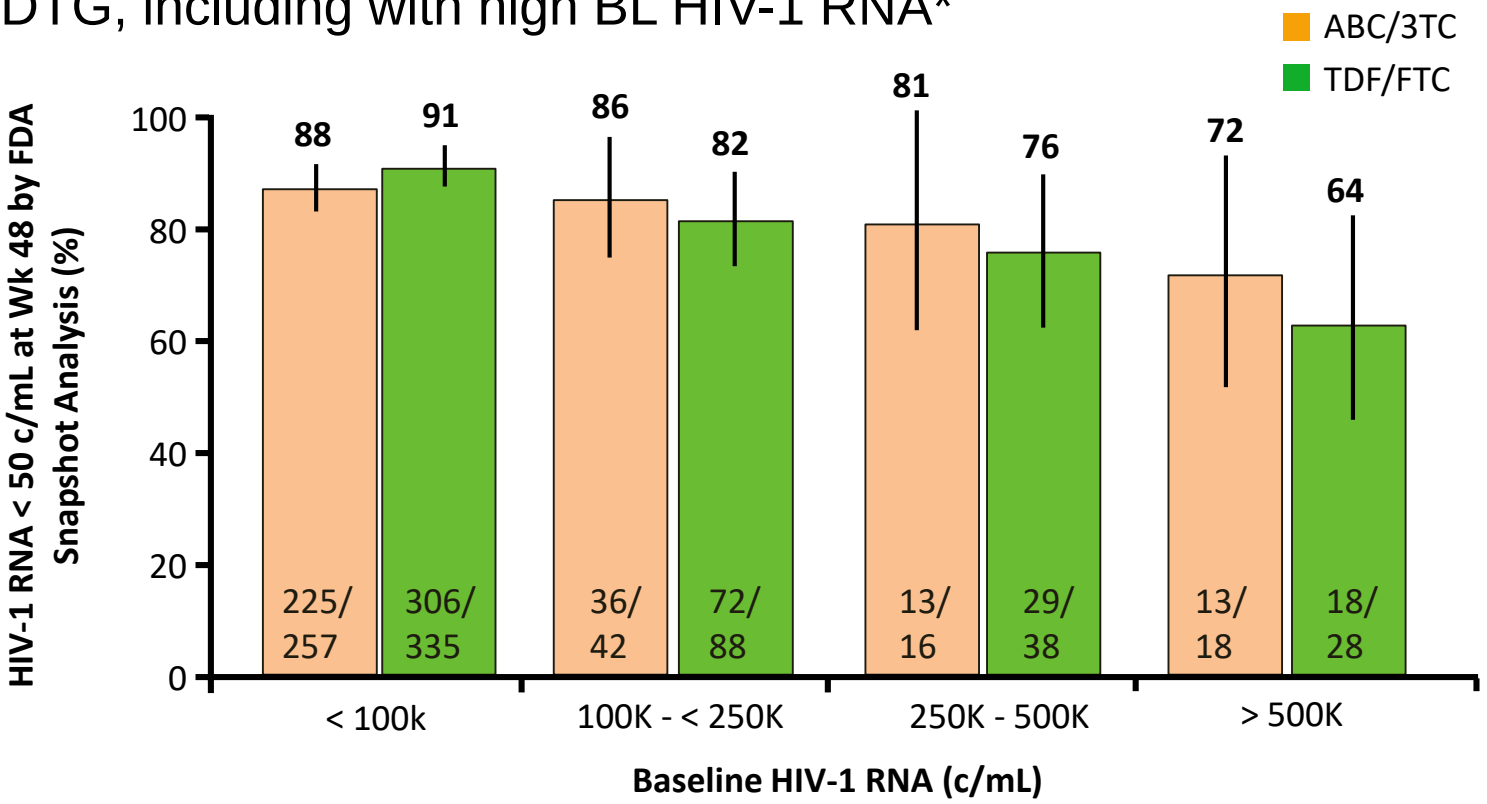
ABC/3TC vs. TDF/FTC: primary virologic endpoint (High viral load stratum at DSMB action)



Darr, E. et al. 17th *CROI*, San Francisco, CA, 2010, presentation 59LB.

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even for High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA*



*Pooled data from both INSTIs.

Eron J, et al. Glasgow 2012. Abstract P204.

Virological Efficacy at W24
Proportion of patients with HIV RNA <50 cp/mL

MonoDTG

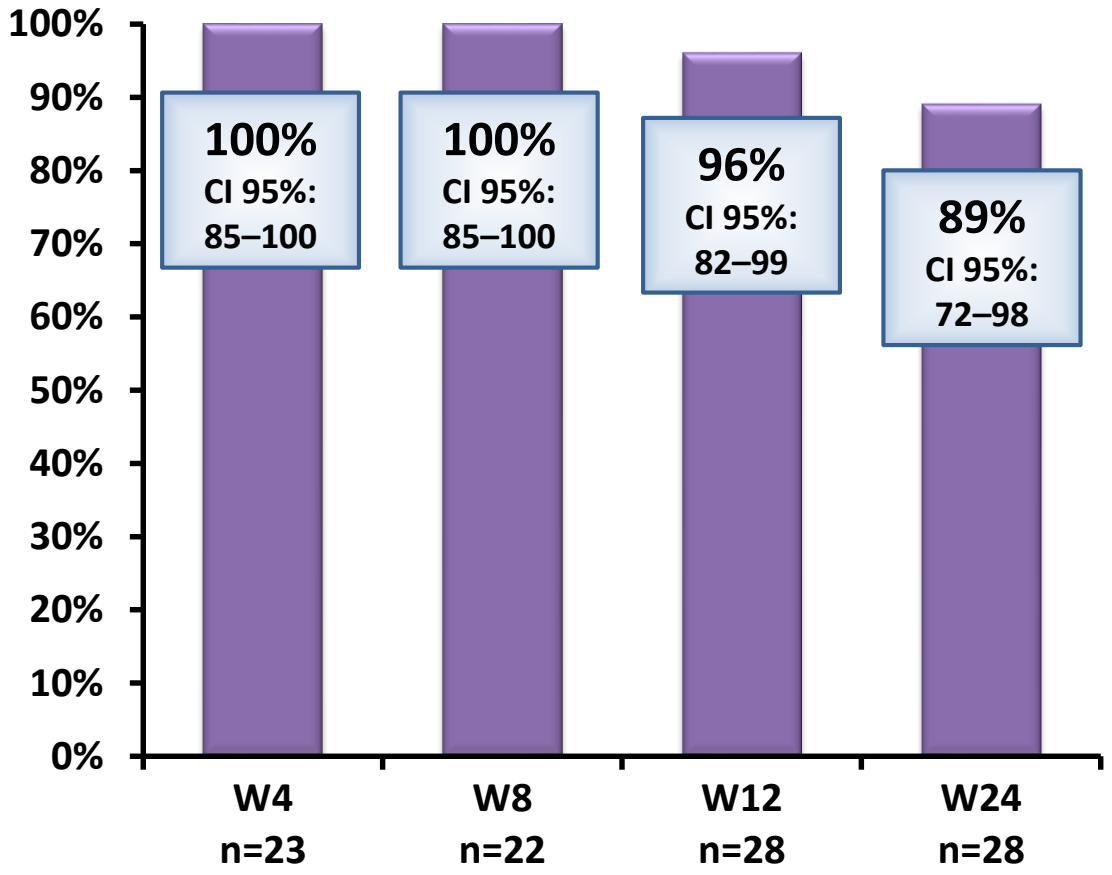
28 pts

25/28 VL <50 cp/mL

- All <50 cp/mL
- All <20 cp/ml except 37 cp/mL (1)
- 1 blip W4 (52 cp/mL)

3 virological failures

- W12: 1 pt
  - VL 138/469 cp/mL
- W24: 2 pts
  - VL: 2220 cp/mL
  - VL: 291 cp/mL



Dolutegravir-Lamivudine as initial therapy
in HIV-infected ARV naïve patients
First results of the PADDLE trial
ClinicalTrials.gov : # NCT02211482

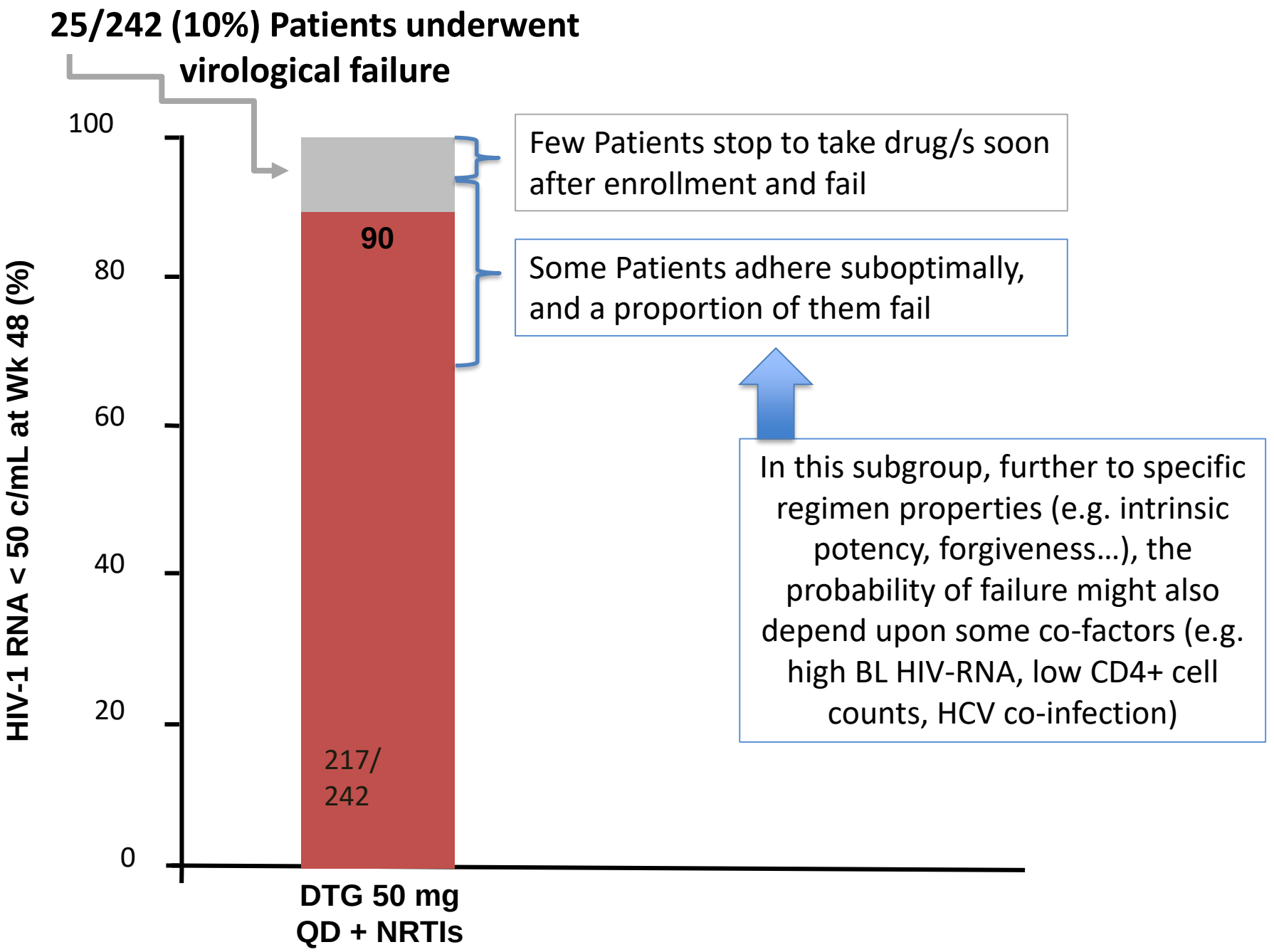
Viral suppression at week 24

#	SCR	BSL	DAY 2	DAY 4	DAY 7	DAY 10	W.2	W.3	W.4	W.6	W.8	W.12	W.24
1	5.584	10.909	3.701	383	101	71	< 50	< 50	< 50	< 50	< 50	< 50	< 50
2	8.887	10.233	5.671	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
3	67.335	151.569	37.604	1.565	1.178	266	97	53	< 50	< 50	< 50	< 50	< 50
4	99.291	148.370	11.797	3.303	432	179	178	55	< 50	< 50	< 50	< 50	< 50
5	34.362	20.544	4.680	1.292	570	168	107	< 50	< 50	< 50	< 50	< 50	< 50
6	16.024	14.499	3.754	1.634	162	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
7	37.604	18.597	2.948	819	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
8	25.071	24.368	6.264	1.377	Not done	268	105	< 50	< 50	< 50	< 50	< 50	< 50
9	14.707	10.832	Not done	516	202	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
10	10.679	7.978	5.671	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
11	50.089	273.676	160.974	68.129	3.880	2.247	784	290	288	147	< 50	< 50	< 50
12	13.508	64.103	3.496	3.296	135	351	351	84	67	< 50	< 50	< 50	< 50
13	28.093	33.829	37.350	26.343	539	268	61	< 50	< 50	< 50	< 50	< 50	< 50
14	15.348	15.151	3.994	791	198	98	< 50	61	64	< 50	< 50	< 50	< 50
15	23.185	23.500	15.830	4.217	192	69	< 50	< 50	< 50	Not done	< 50	< 50	< 50
16	11.377	3.910	370	97	143	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
17	39.100	25.828	11.879	1.970	460	147	52	< 50	< 50	< 50	< 50	< 50	< 50
18	60.771	73.069	31.170	2.174	692	358	156	< 50	< 50	< 50	< 50	< 50	< 50
19	82.803	106.320	35.517	2.902	897	352	168	76	< 50	< 50	< 50	< 50	< 50
20	5.190	7.368	3.433	147	56	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50

From week 8 onwards all patients had pVL <50 copies/mL

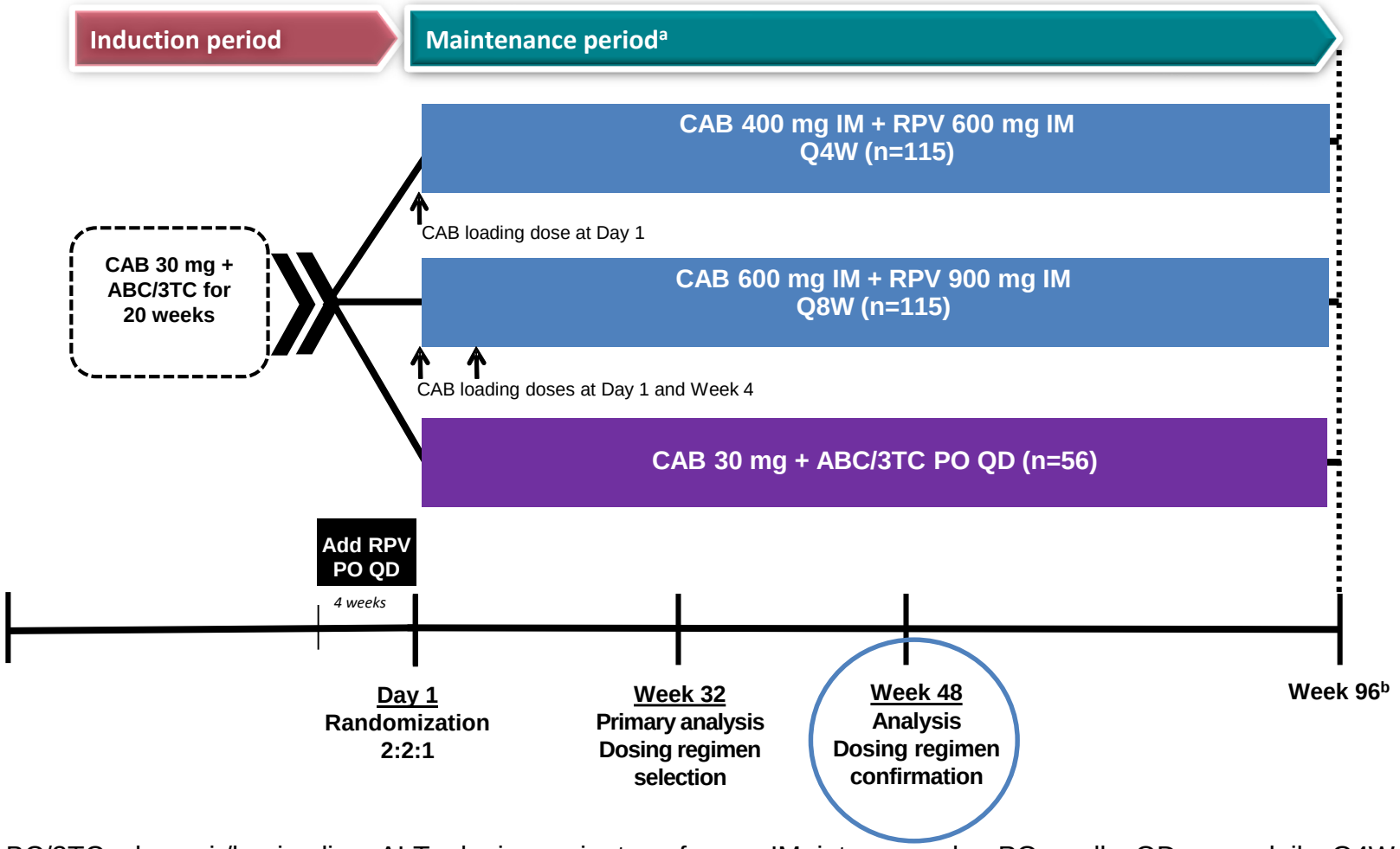
So…. regimens with two drugs including a 2nd generation INSTI are ok, provided both drugs are there…

The unique lesson from the Latte-2 Study



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

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.

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

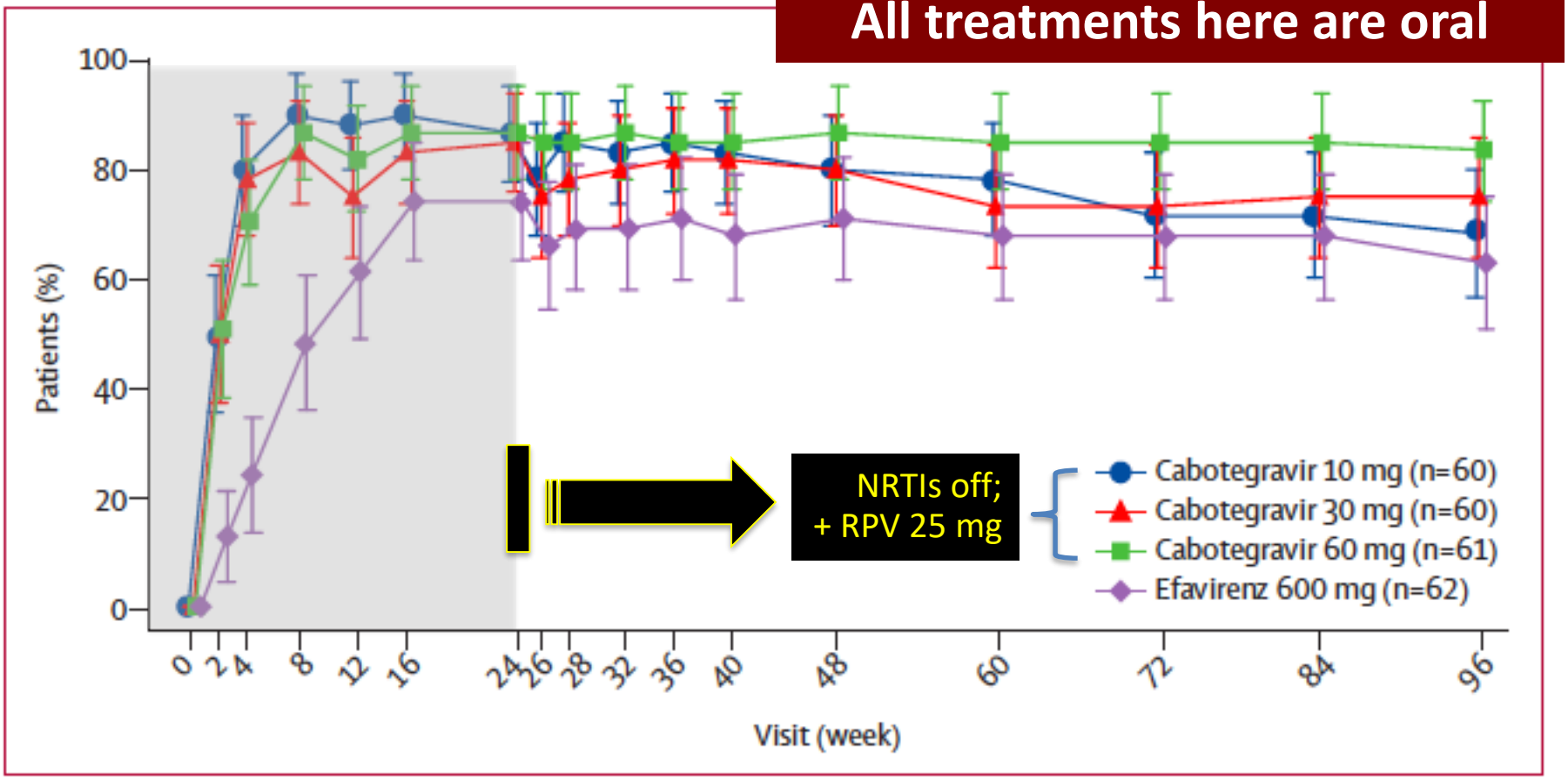


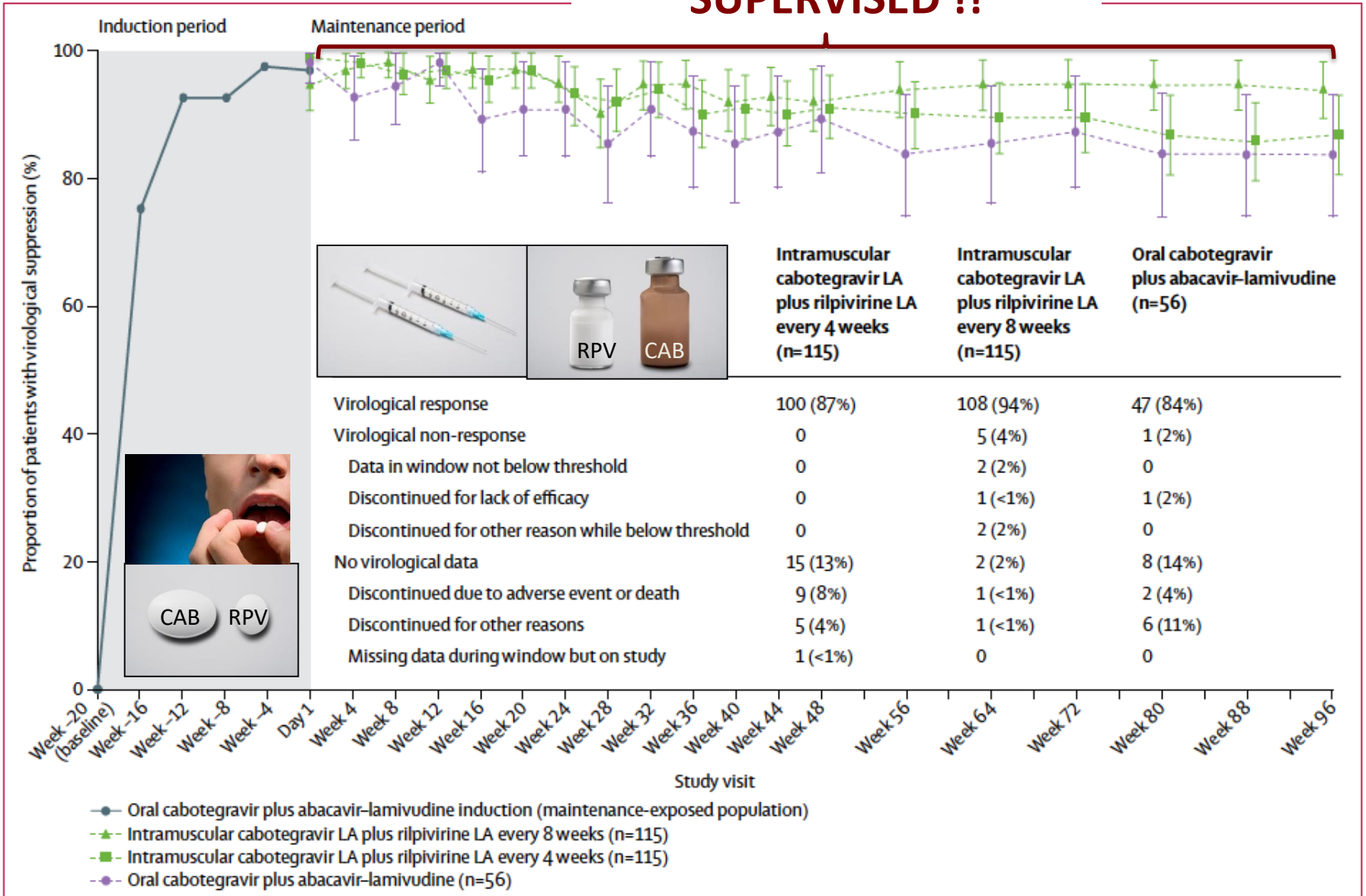
***Figure 2*: Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population**
Error bars indicate 95% CI.

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

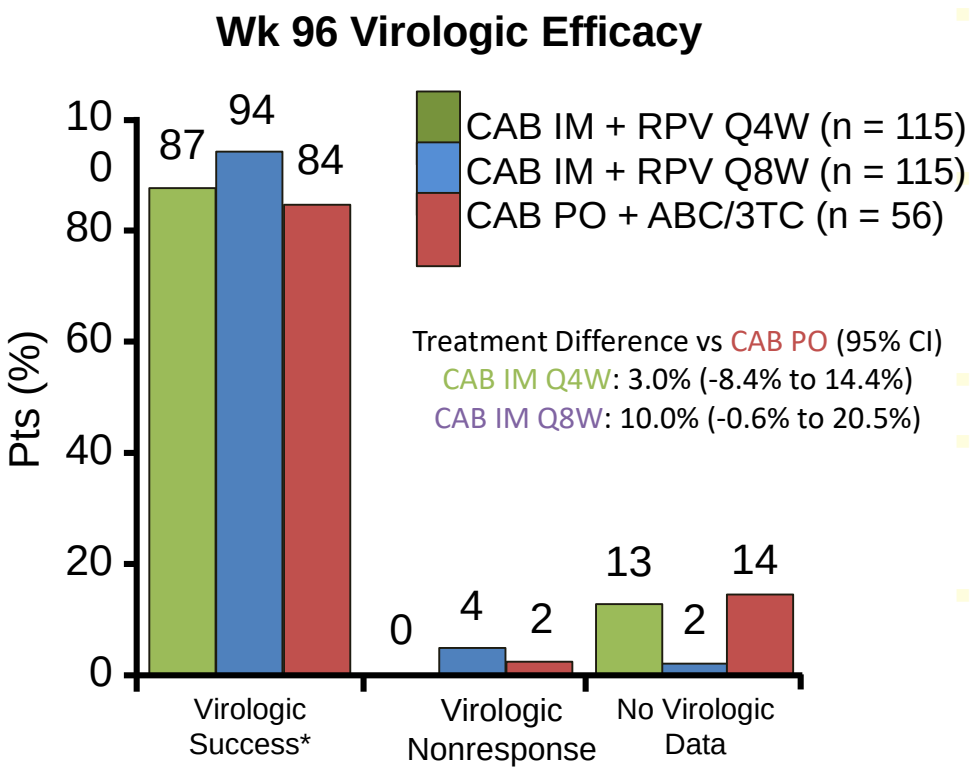
SUPERVISED !!



	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

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 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 (50< HIV-RNA <200 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

Lancet 2017; 390: 1499–510

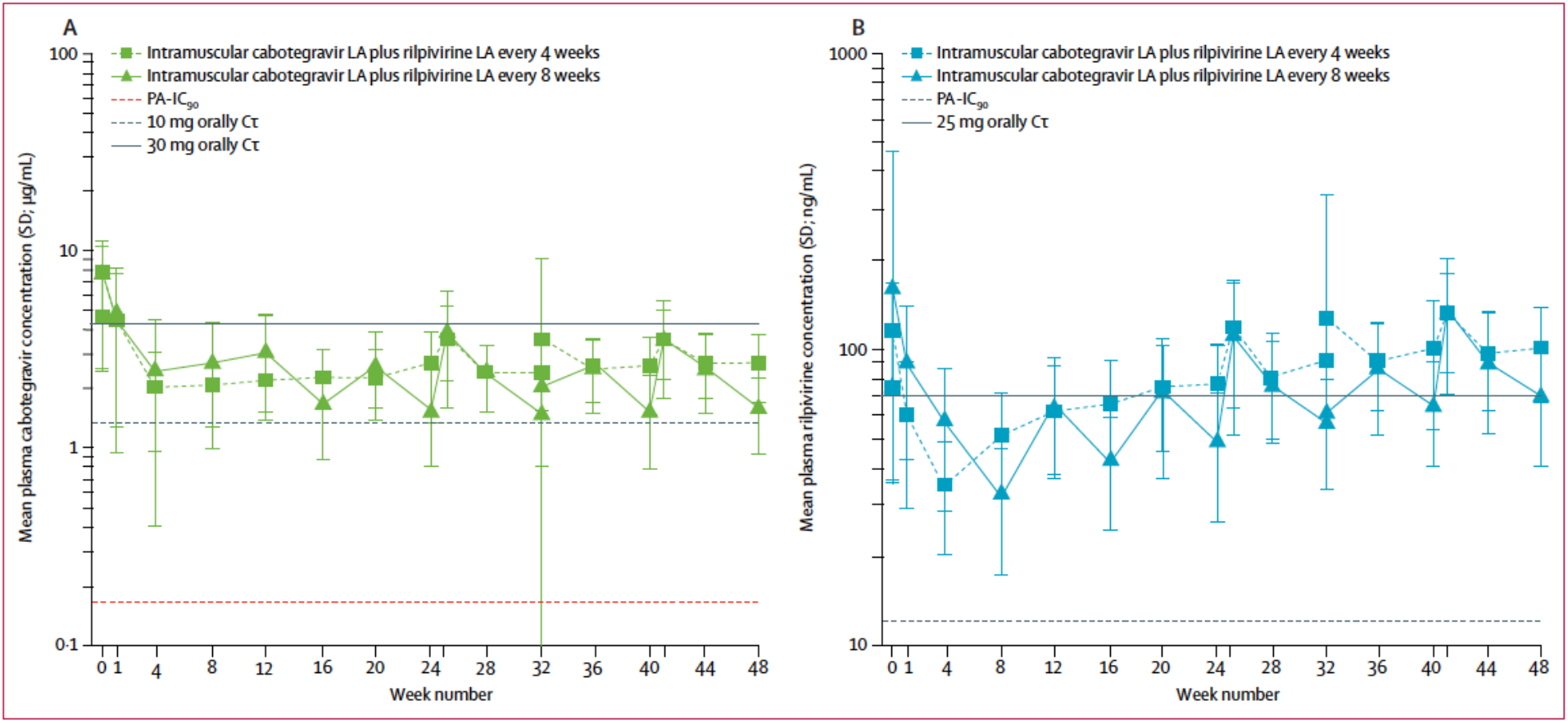


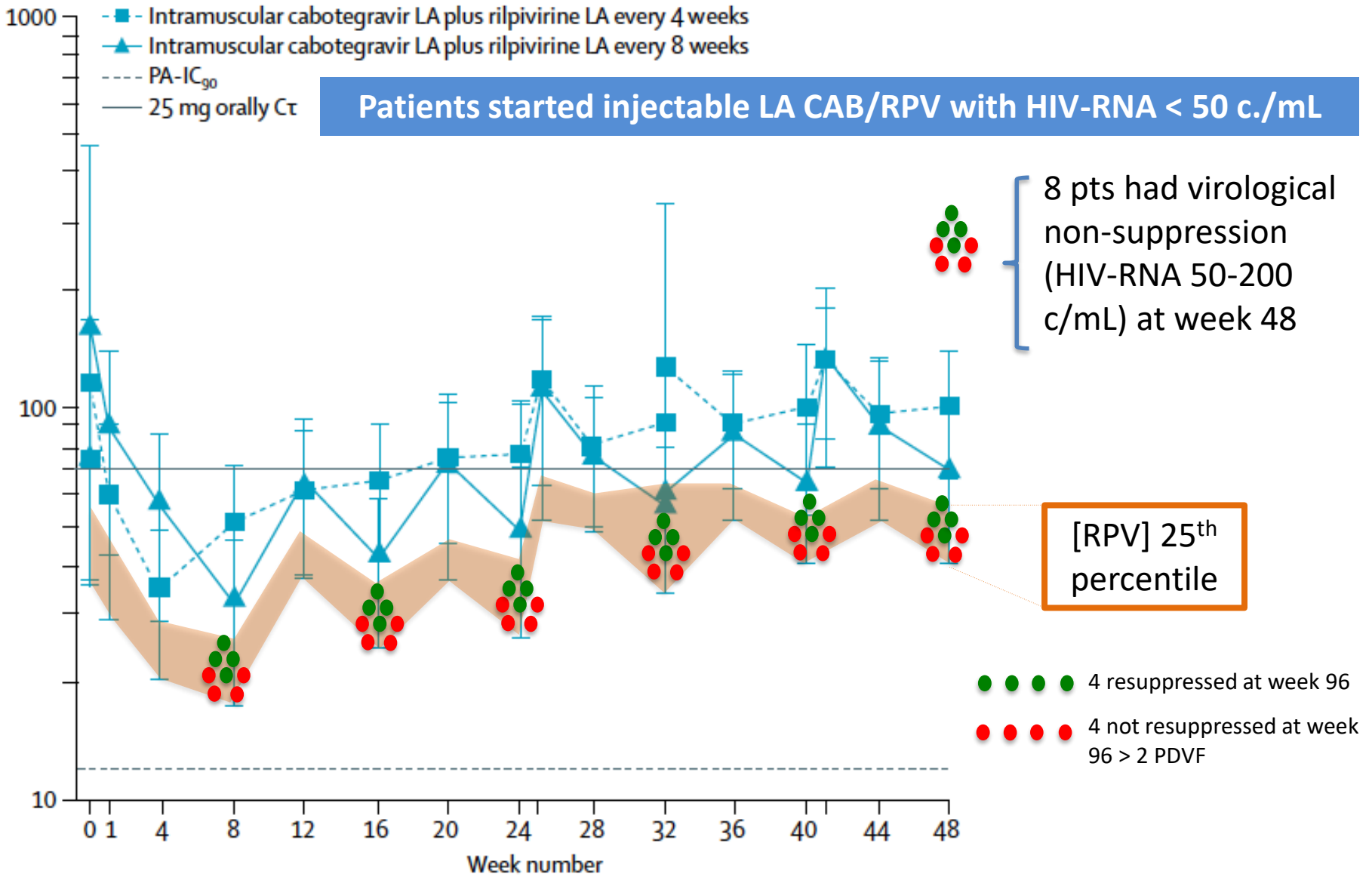
***Figure 3*: Arithmetic mean (SD) plasma concentration–time profiles following every 4 weeks and every 8 weeks administration of (A) cabotegravir LA and (B) rilpivirine LA through week 48**

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

Margolis DA, et al

Lancet 2017; 390: 1499–510

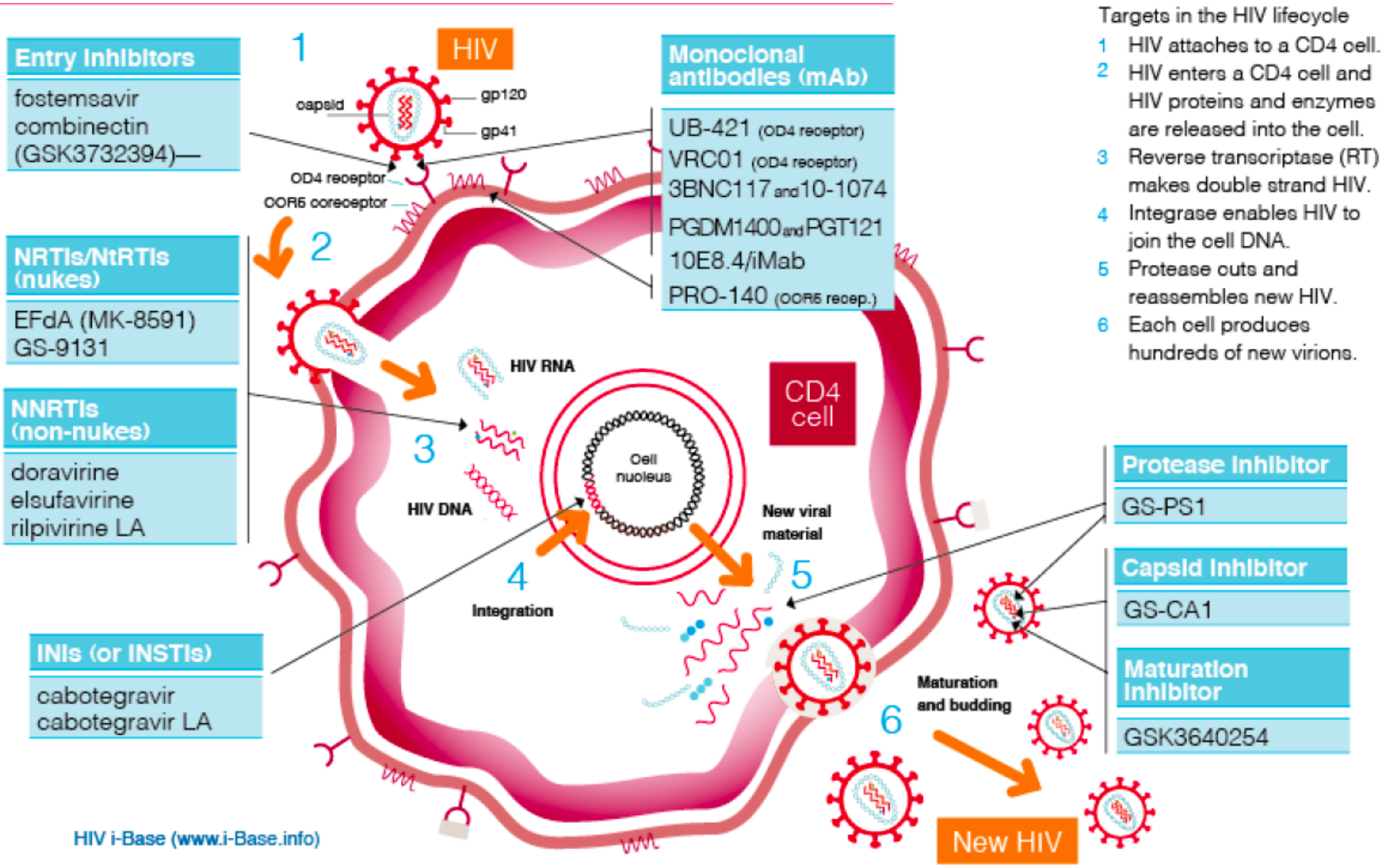


Two limitations are still present for 2nd gen.INSTI - based2DR (characterized for DTG/3TC):

1. **Patients with > 500.000 copies of HIV-RNA at baseline (among the inclusion criteria of GEMINI)**

2. **Patients with nadir CD4+ T-cell count < 200/uL**

A possible future solution might be to reinforce the 2nd component of the regimen, such as the RT inhibitor



Targets in the HIV lifecycle

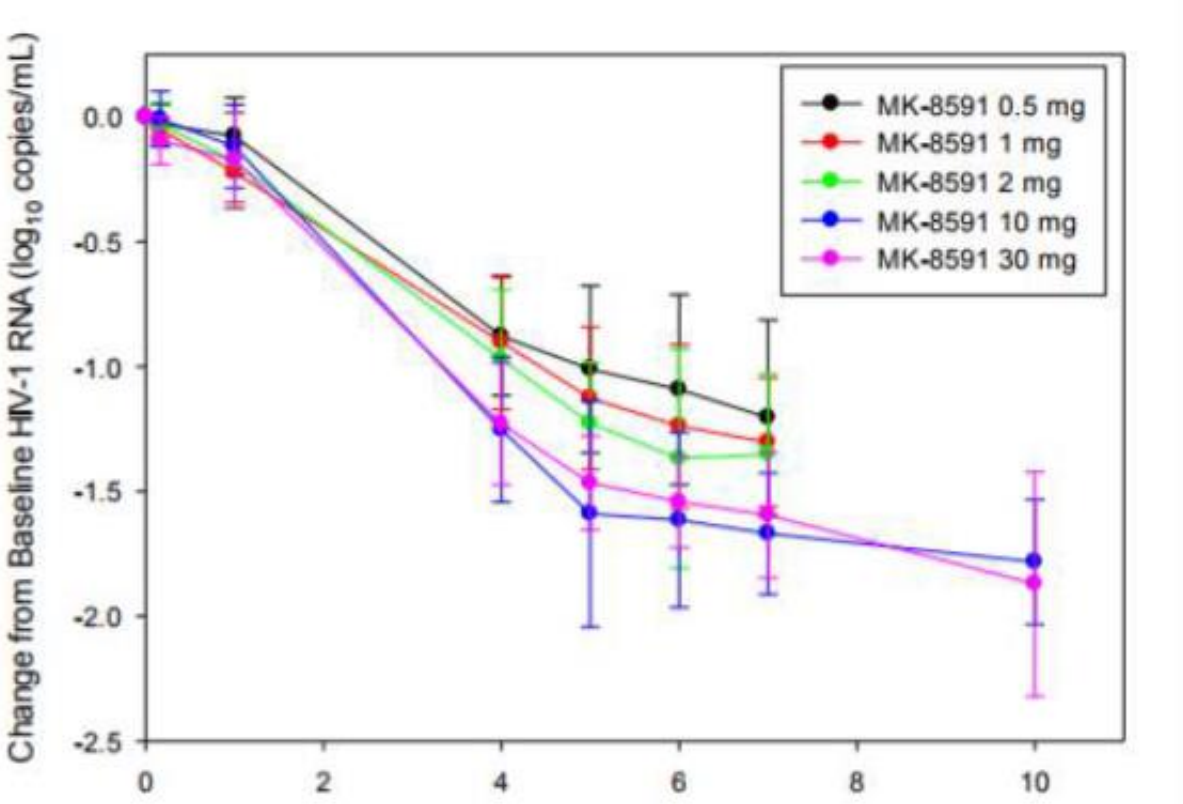
1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and reassembles new HIV.
6. Each cell produces hundreds of new virions.

4’-Ethynyl-2-fluoro-2’-deoxyadenosine (EFdA)

Unique properties

- Exceedingly potent (possible dose in humans of <5 mg/day)
- Lack of cross-resistance with most NRTI’s
- Minor impact of M184V
- More active against HIV-2 than other NRTI’s
- Long half-life of intracellular TP (>72 hours) in rhesus macaques
- Possibility of once-weekly oral dosing
- Possibility of implant formulation with dosing interval of ≥one year

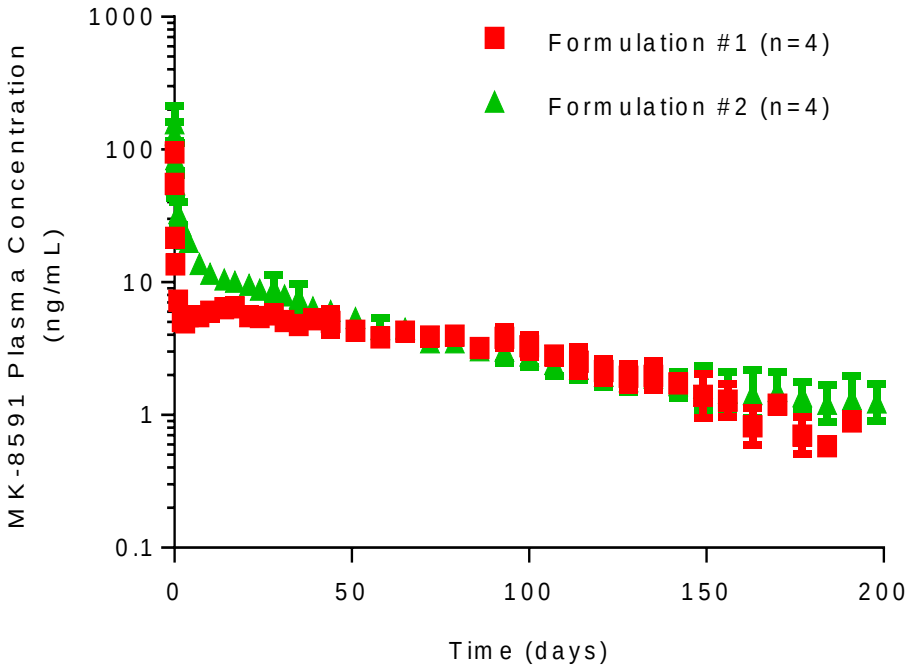
MK-8591: Single-dose (!) Pharmacodynamic Study



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

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



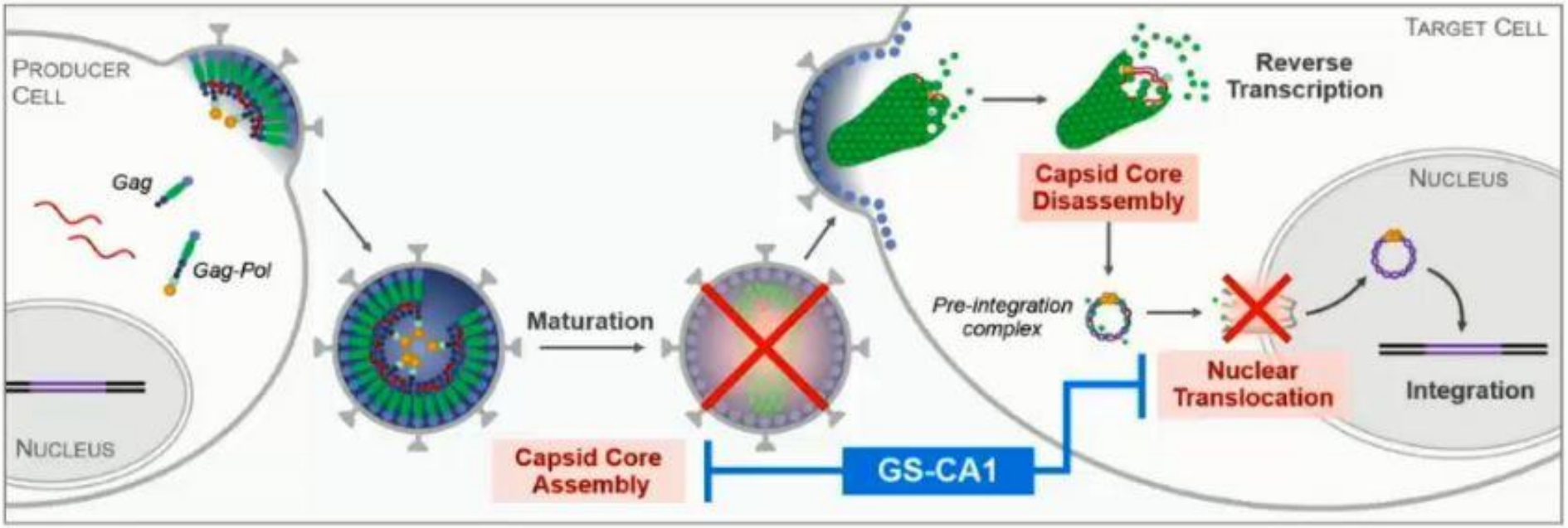
- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

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

Capsid is the cone-shaped structural core within the virion that protects HIV RNA and related enzymes. As part of a dynamic process, the capsid protein (p24) first breaks down to release viral contents into the CD4 cell to enable reverse transcription and also needs to reassemble inside new virions as part of the maturation process at the end of the lifecycle.

GS-CA1 acts in both the early and late stages by binding at a site that blocks both disassembly and assembly leading to defective new virions that are non-infectious.

GS-CA1 Mode of Action Summary



Results

IDWeek
October 3 -7, 2018
San Francisco, CA

GS-6207: A Novel, Potent and Selective First-In-Class Inhibitor of HIV 1 Capsid Function Displays Nonclinical Pharmacokinetics Supporting Long Acting Potential in Humans

Table 1. Antiviral Activity of GS-6207 vs. Currently Marketed ARVs

	MT-4 Cell Line ± Infection with HIV-1 (IIIb strain)						
	Antiviral EC_{50} (nM)[a]	Cytotoxicity CC_{50} (μM)[a]	Selectivity Index (SI)	Hill Slope[a]	Antiviral EC_{95} (nM)[b]	Human Serum Shift	Antiviral $paEC_{95}$ (nM)[b]
GS-6207	0.10 ± 0.01	26.6 ± 14.2	140,740	3.51	0.23 ± 0.02	17.4	4.0 ± 0.4
EFV	0.79 ± 0.06	20.6 ± 4.6	14,940	3.25	2.0 ± 0.2	22.4	44 ± 3
RPV	0.57 ± 0.03	6.8 ± 1.5	11,890	3.17	1.4 ± 0.7	32.2	45 ± 2
DTG	1.34 ± 0.14	15.3 ± 5.0	7,980	2.14	5.3 ± 0.6	29.5	156 ± 16
ATV	7.23 ± 0.50	50.5 ± 8.1	4,720	3.13	18.5 ± 1.3	8.1	150 ± 11

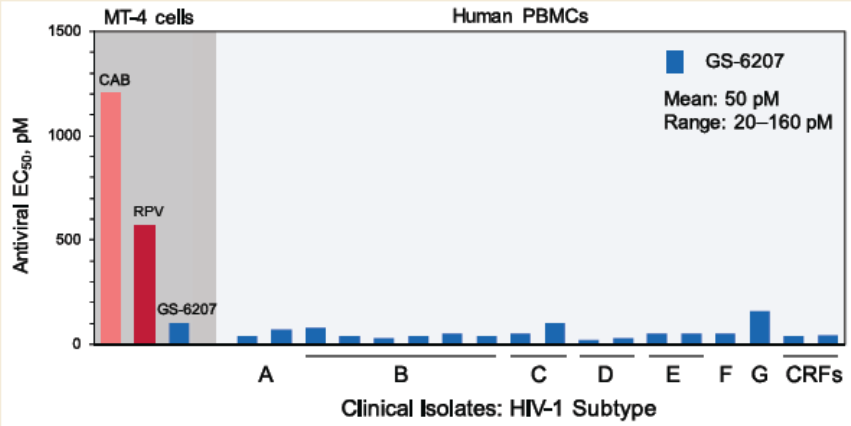
EFV, RPV = efavirenz and rilpivirine (NNRTIs, non-nucleoside reverse transcriptase inhibitors); DTG = dolutegravir (INSTI, integrase strand transfer inhibitor); ATV = atazanavir (PI, protease inhibitor); SI = CC_{50}/EC_{50} ratio

[a] EC_{50}, CC_{50} and Hill slope values (mean ± SD) obtained from at least 3 independent experiments performed in quadruplicate

[b] $EC_{95} = EC_{50} \times (95/5)^{1/\text{hillslope}}$; $paEC_{95}$ = human serum shift X EC_{95}

- GS-6207 is more potent than currently marketed ARV drugs

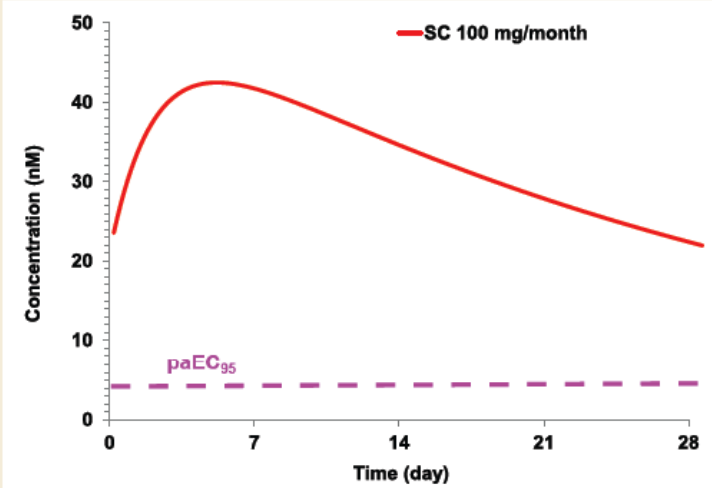
Figure 1. GS-6207 Antiviral Activity Against a Panel of HIV-1 Clinical Isolates



PBMCs, peripheral blood mononuclear cells; CAB, cabotegravir (INSTI); RPV, rilpivirine (NNRTI); CRFs, circulating recombinant forms

- GS-6207 is a potent inhibitor of all major HIV-1 subtypes

Figure 9. Simulated Steady-State Human Plasma PK Following Monthly SC Doses of Formulation A



- Predicted 100 mg monthly SC dose in human

References

1. Tse WC, et al. 2017 CROI Conference; Seattle, WA. Abstract # 38.
2. Pang KS and Rowland M, J Pharmacokinet Biopharm 1977; 5:655-680.

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Alessandra Manca

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