15th Residential Course on Clinical Pharmacology of Antiretrovirals

January 15-17, 2020

Clinical Pharmacology of Two-drug Regimens

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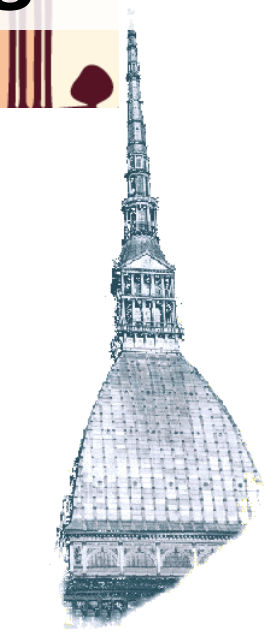
Università degli Studi di Torino
Ospedale Amedeo di Savoia



Financial Disclosures

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

Most anti-infective therapies consist of a single drug.

In many cases, however, more than a drug is necessary, for different reasons

Viruses

- HIV
- HBV
- HCV
- CMV

Mycobacteria

- *M.tuberculosis*
- *M.leprae*
- MAC & other atypical

Parasites

- *P.falciparum*
- *P.vivax*
- *P.ovale*
- *E.histolytica*
- *W.bancrofti*

Conventional bacteria

- *P.aeruginosa*
- ESβL producers (e.g. KPC)
- Endocarditis
- Polymicrobial infections
- Empiric/Rational Therapy
- *H.pylori*

Fungi

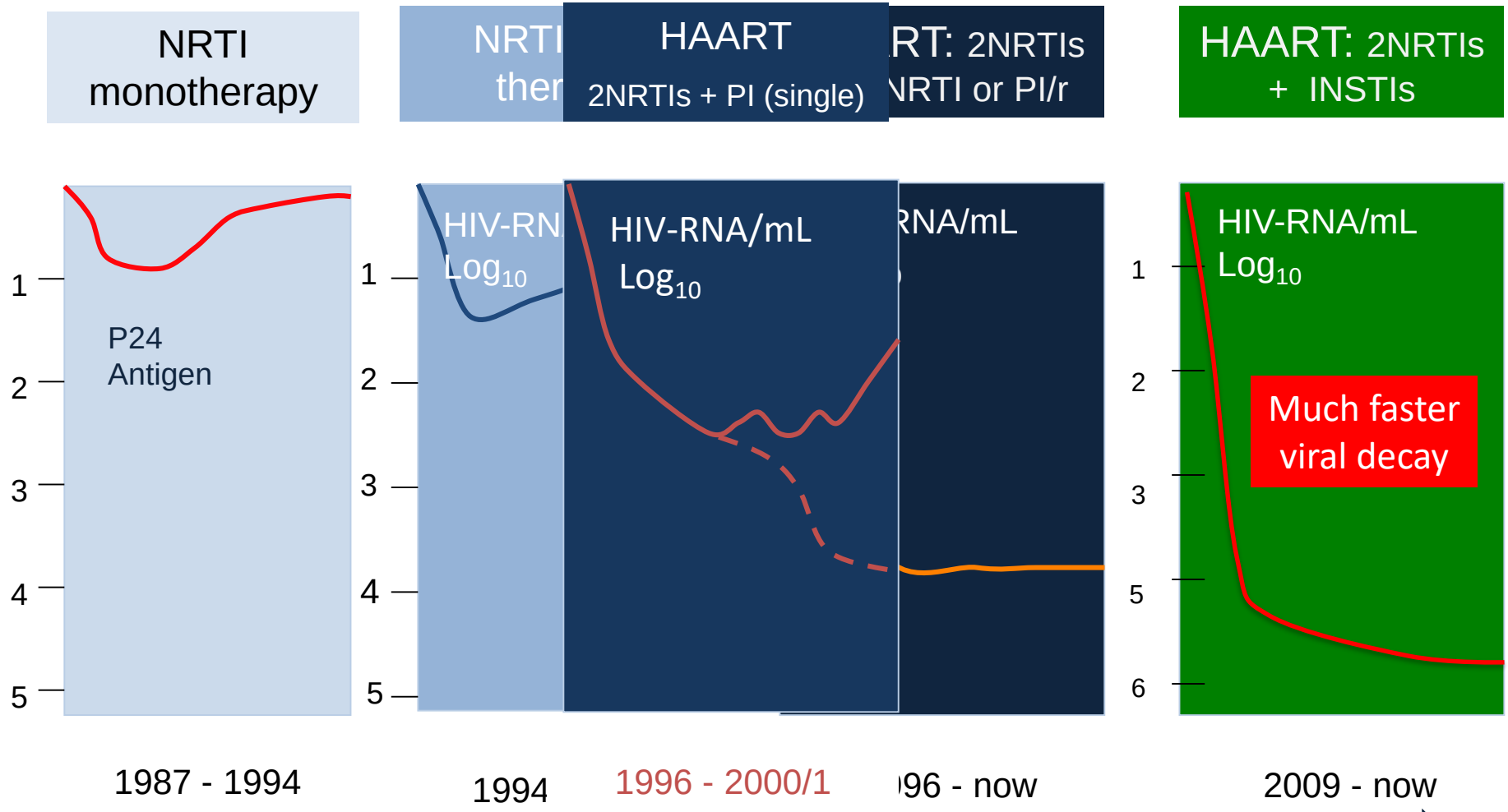
- *Cryptococcus sp.*
- *Aspergillus spp.*
- *Candida sp.*

The reasons why we use more than a drug in the treatment of some infectious diseases…

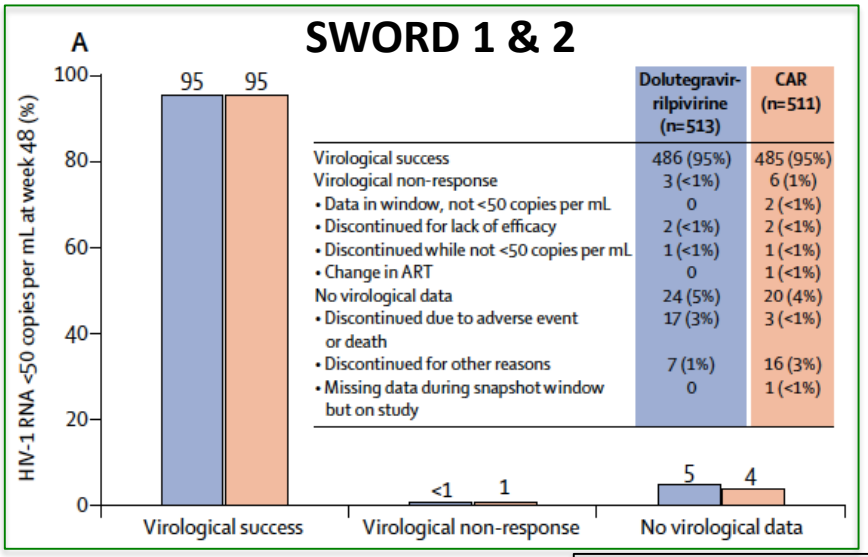
- **To increase 1 or more efficacy parameters**
  - Synergy
  - Additive effect
- **To increase the Genetic barrier**
- **To provide a wider Spectrum Coverage**
- **To provide a wider Compartment Coverage**
- **To interfere with more biosynthetic steps in the microbe life cycle**

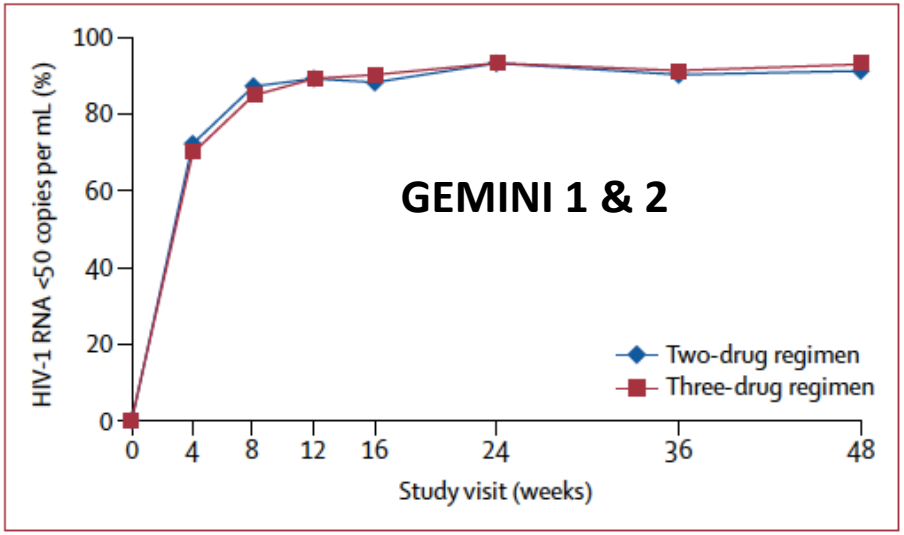
In HIV infection, until 2019 the recognized successful paradigm has been the use of 3 drugs, although the introduction of more potent drugs has improved the Pk/PD performance of antiretroviral therapy

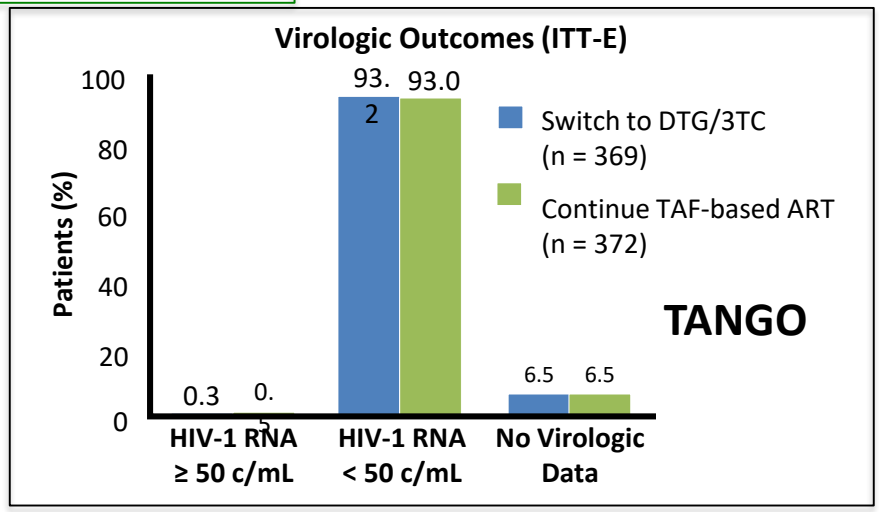
ANTIRETROVIRAL REGIMENS and their Antiviral Performance in the HIV Treatment History



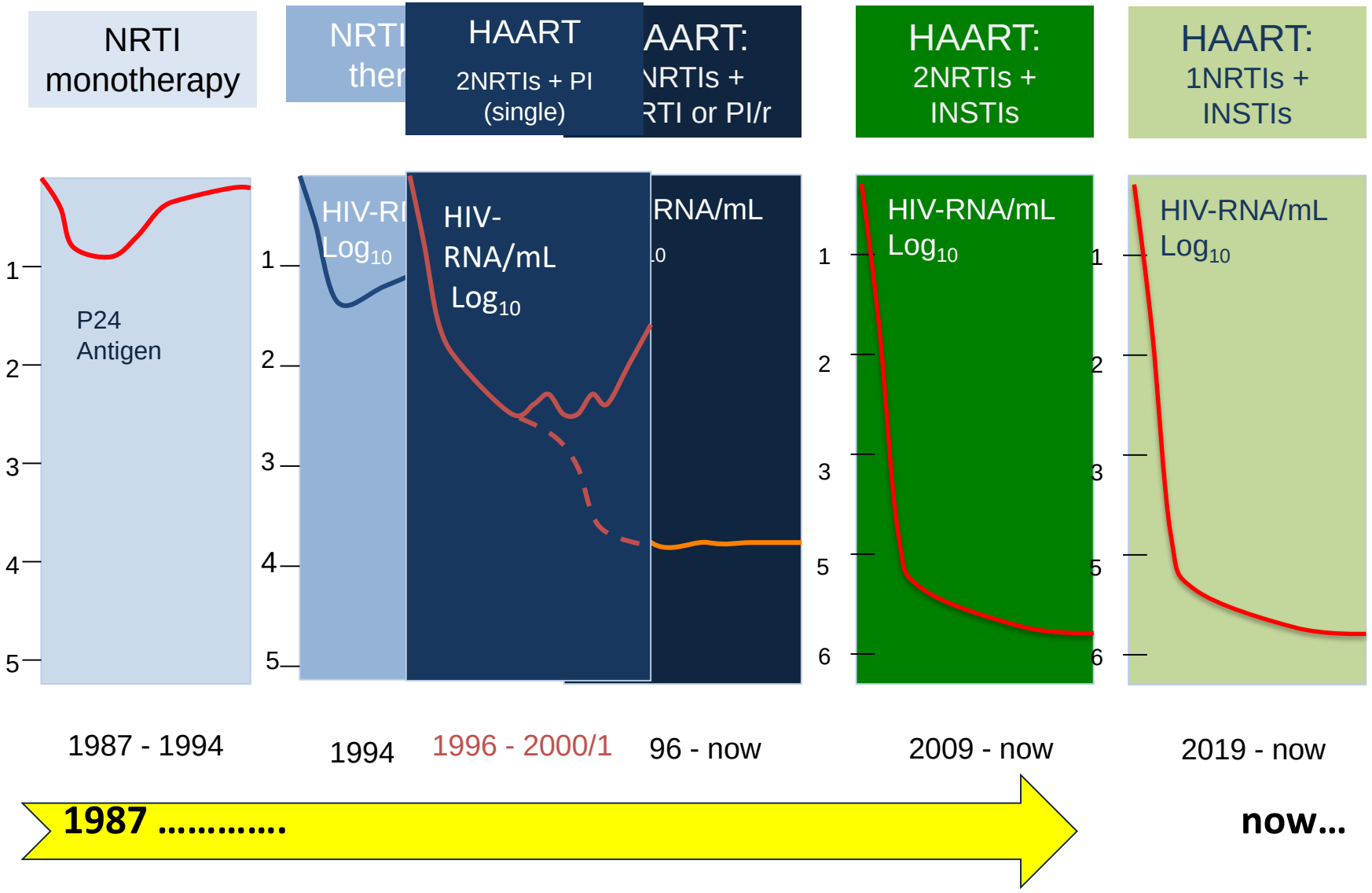
In 2019, following the release of data on comparative, controlled, registration-sized clinical trials, regimens consisting of 2 drugs rather than 3 have been approved for clinical use, both in naïve and experienced patients with HIV infection







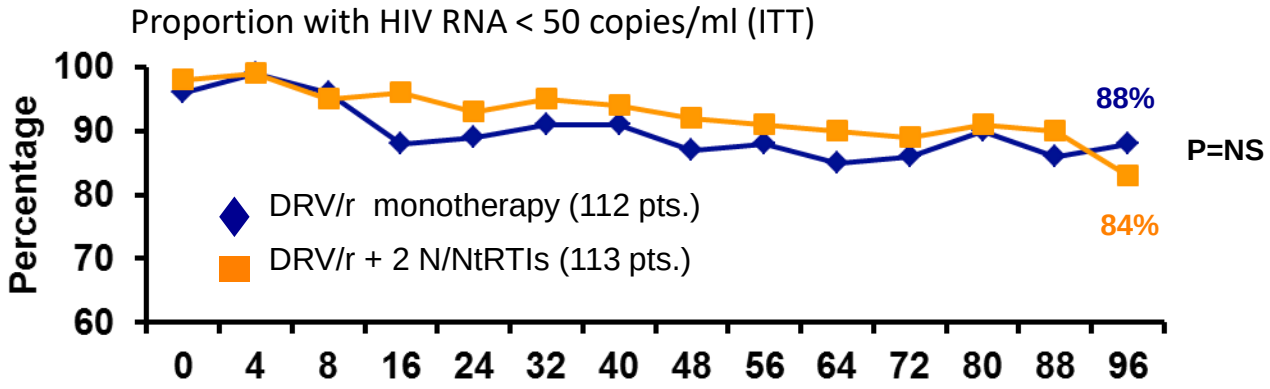
ANTIRETROVIRAL REGIMENS and their Antiviral Performance in the HIV Treatment History



Well before DTG/RPV (maintenance) and DTG/3TC (naïve and maintenance) were formally approved, numerous small-medium sized attempts have been performed to prove that 2-drug regimens or even monotherapy were successful in selected circumstances

MONOI: Switch to DRV/r ± NRTIs

Randomized study of DRV/r or DRV/r + NRTIs in Patients with HIV RNA <50 c/mL on ART and No Prior PI Failure and Naïve to DRV

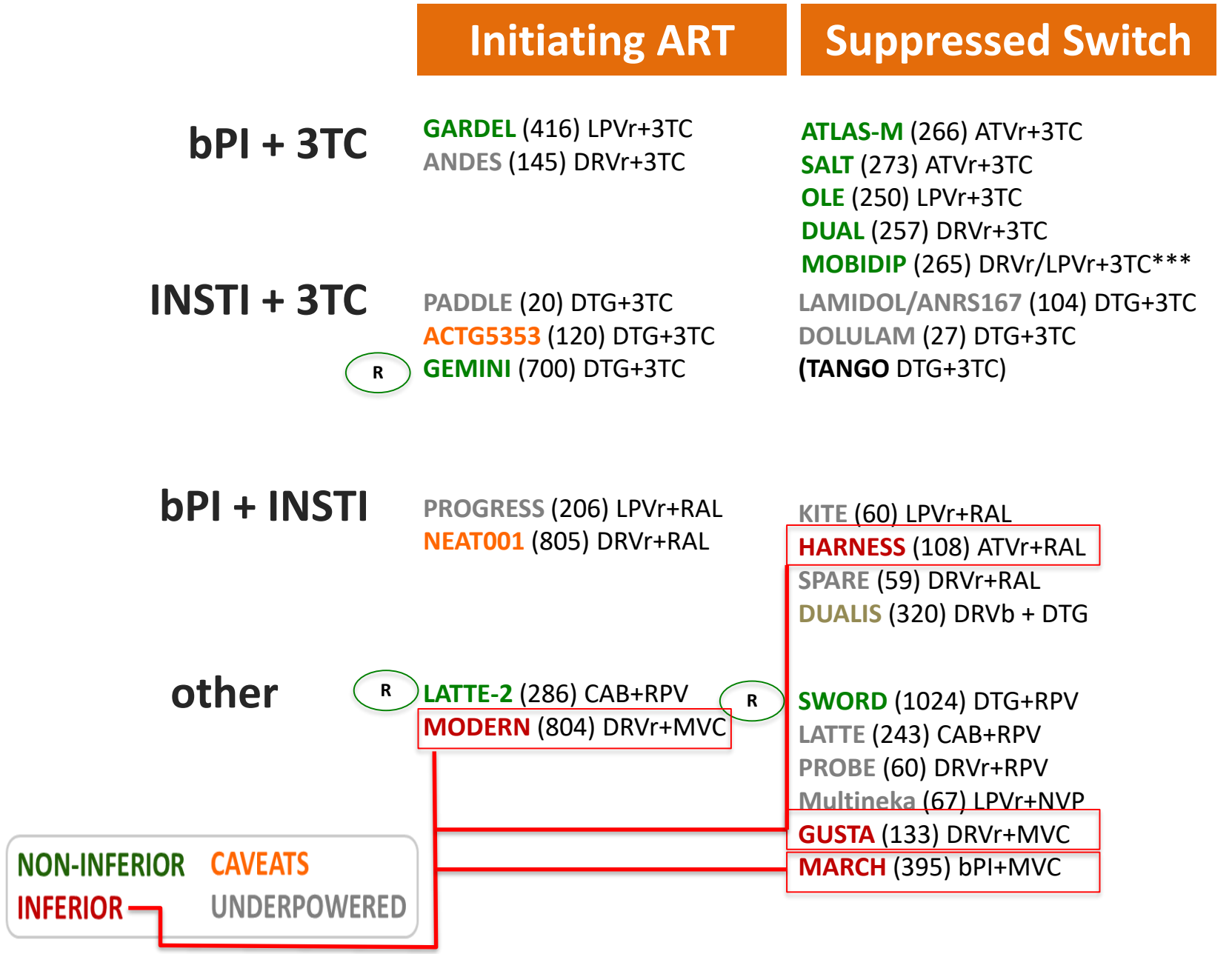


Response Predictors:

	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

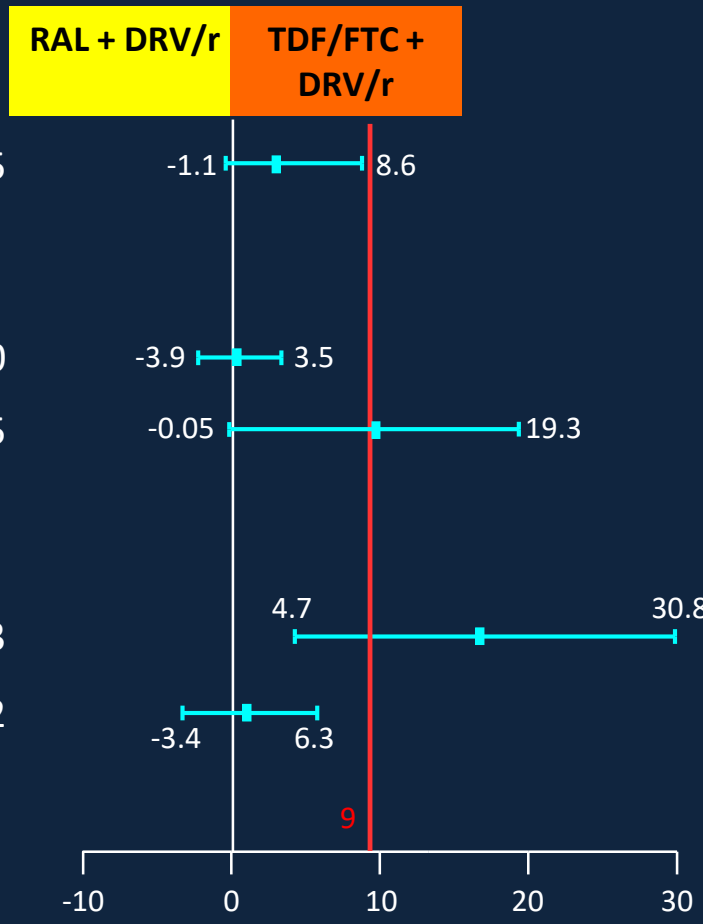
Valantin M-A, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 534.

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

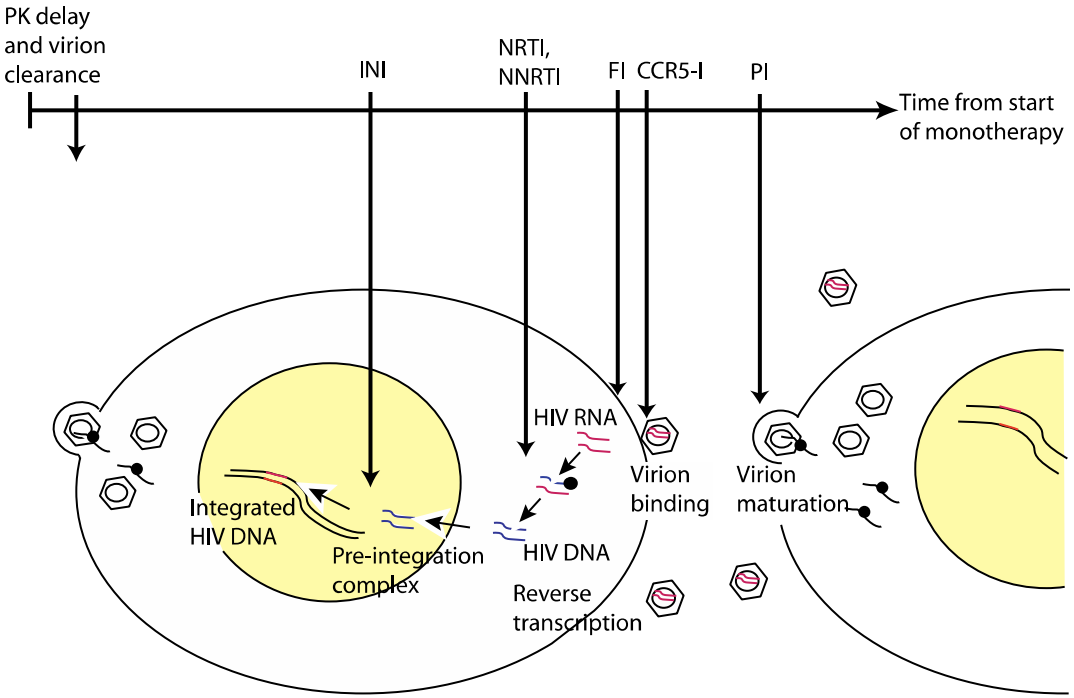


FIG. 1. The positions in the HIV life cycle affected by each drug class and their relative timing in terms of when they impact HIV RNA levels in blood.

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

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

Which are the properties of 2nd generation INSTIs that made it possible to generate the new 2-drug paradigm?

- **Intrinsic potency**

  also testified by FAST ANTIVIRAL EFFECT

- **High IQ**

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- **Genetic barrier**

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- **Clinical tolerability and safety**

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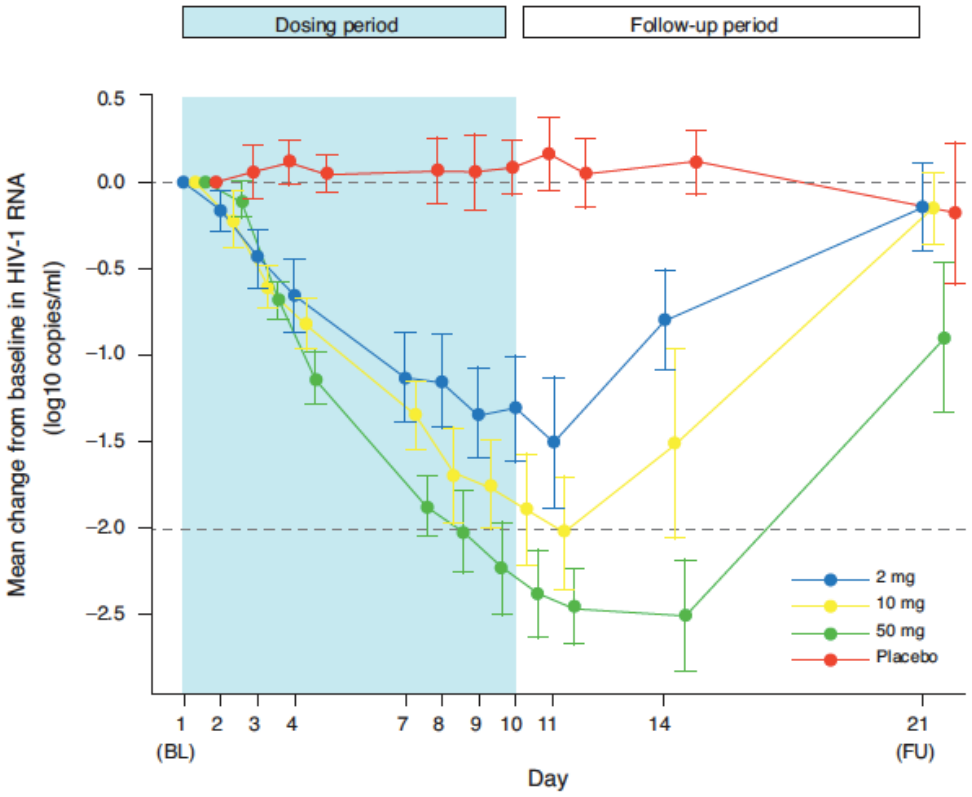
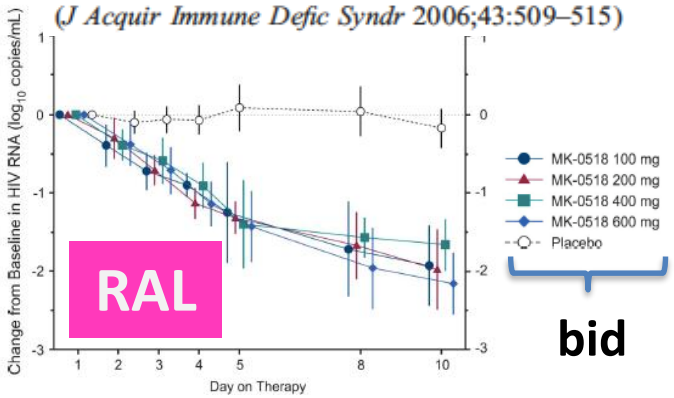
Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults

Min S, et al.

AIDS 2011, 25:1737–1745

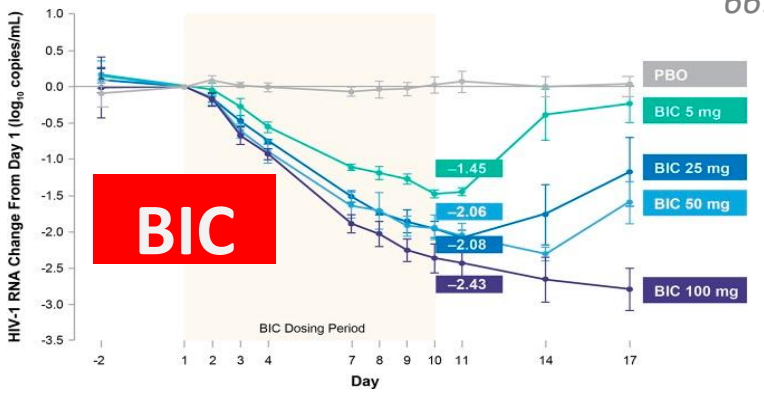


Markowitz M, et al.



Gallant JE, et al.

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



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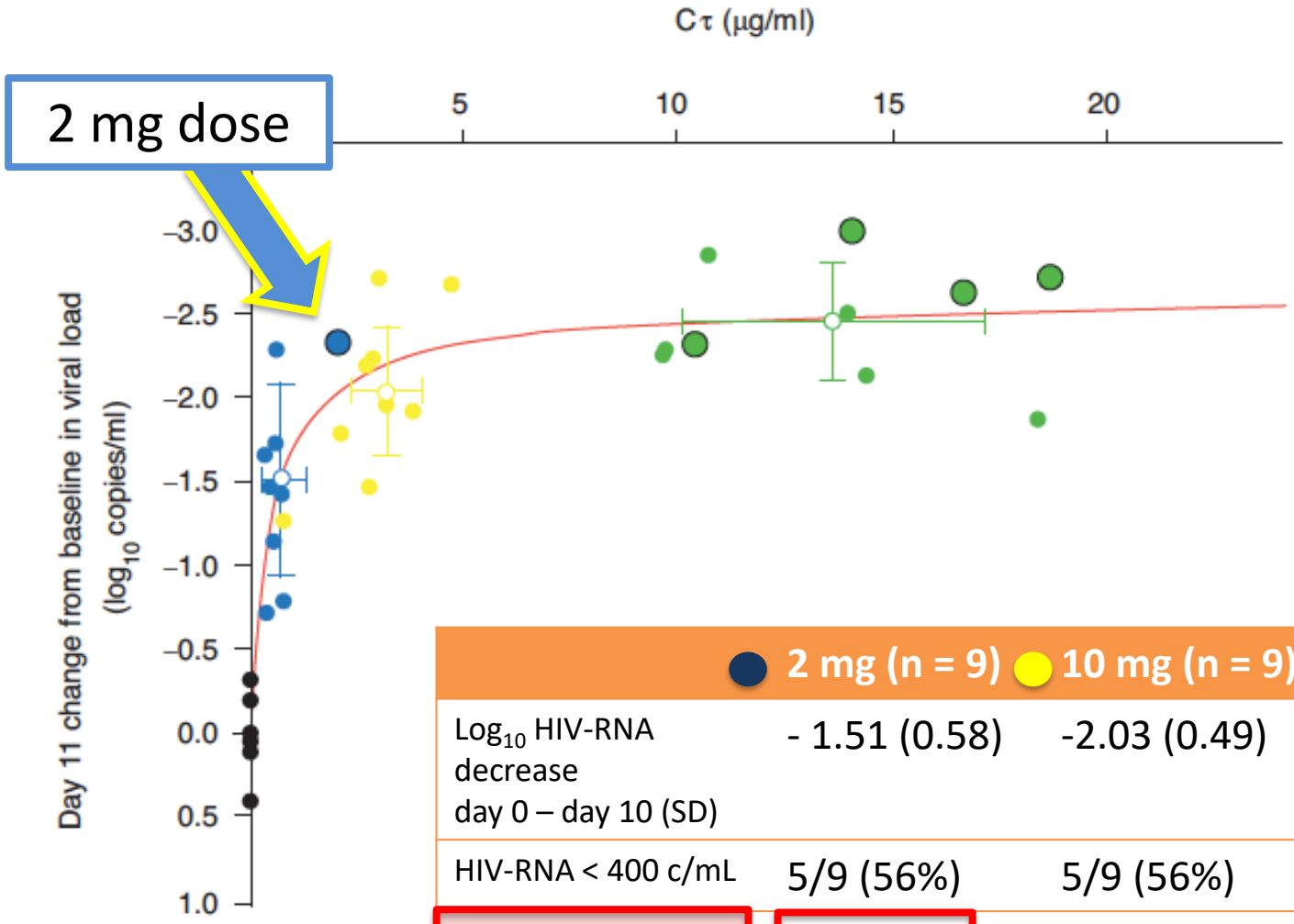
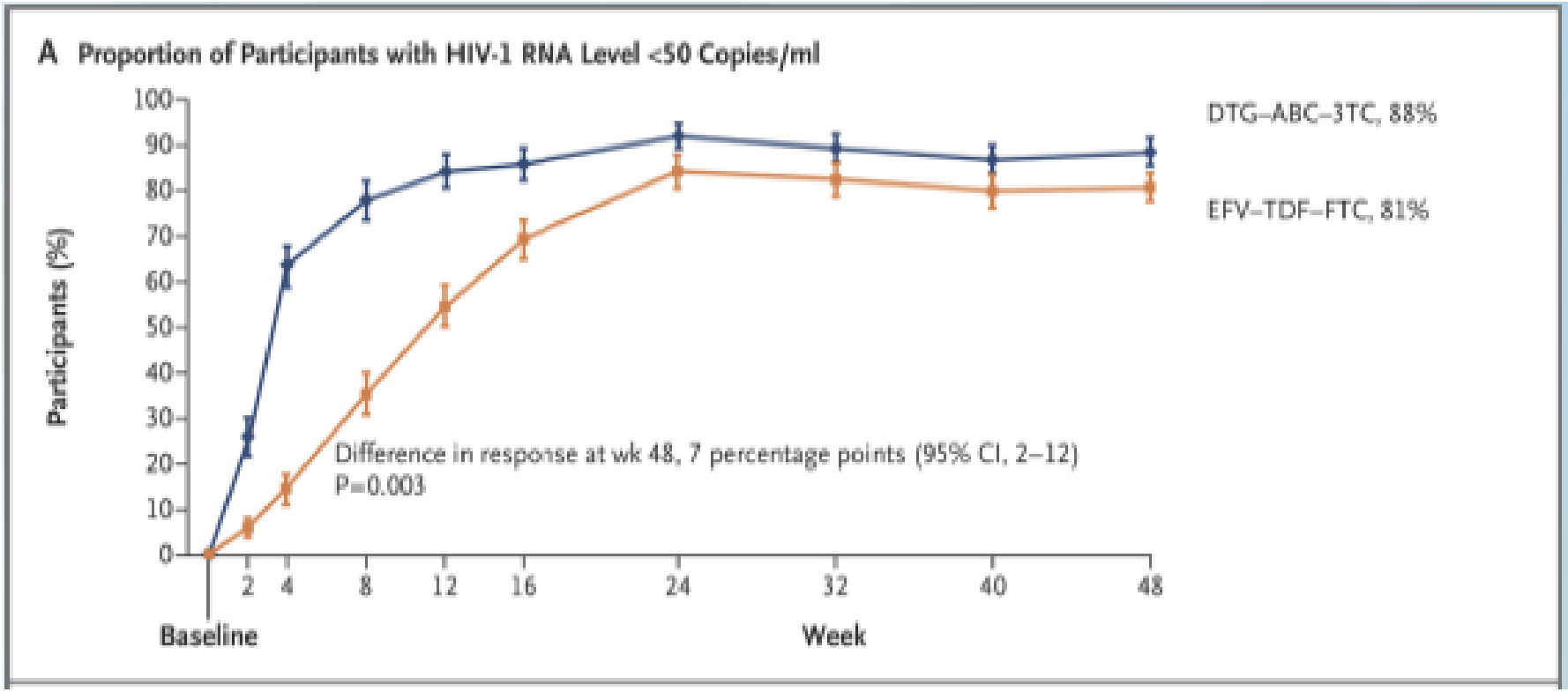


	2 mg (n = 9)	10 mg (n = 9)	50 mg (n = 10)
Log_{10} HIV-RNA decrease day 0 – day 10 (SD)	- 1.51 (0.58)	-2.03 (0.49)	-2.46 (0.35)
HIV-RNA < 400 c/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
HIV-RNA < 50 c/mL	1/9 (11%)	0	7/10 (70%)

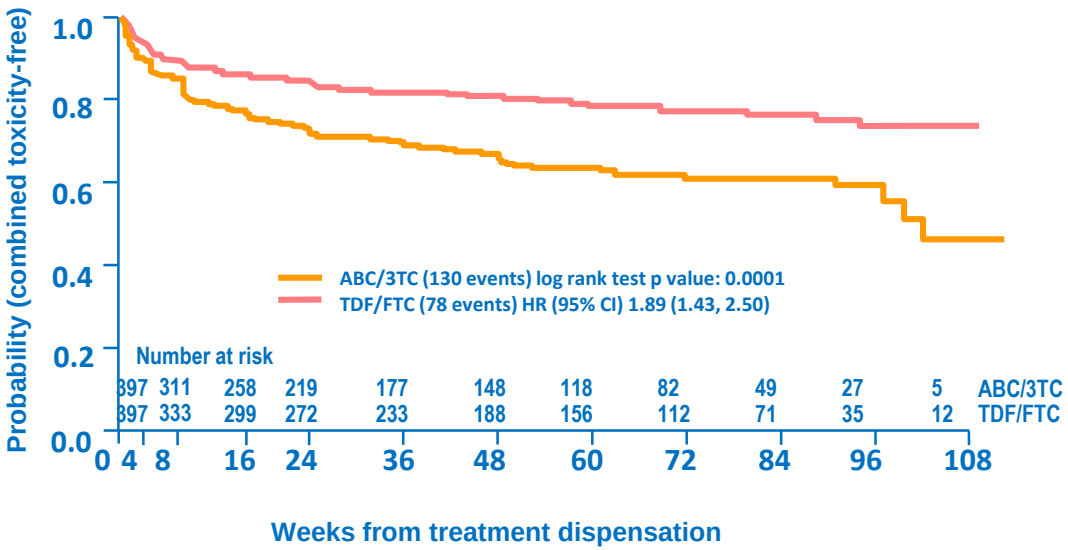


Median time to suppression:

- DTG arm: 28 d
- EFV arm: 84 d

Gandhi M, Gandhi RT. N Engl J Med 2014;371:248-259.

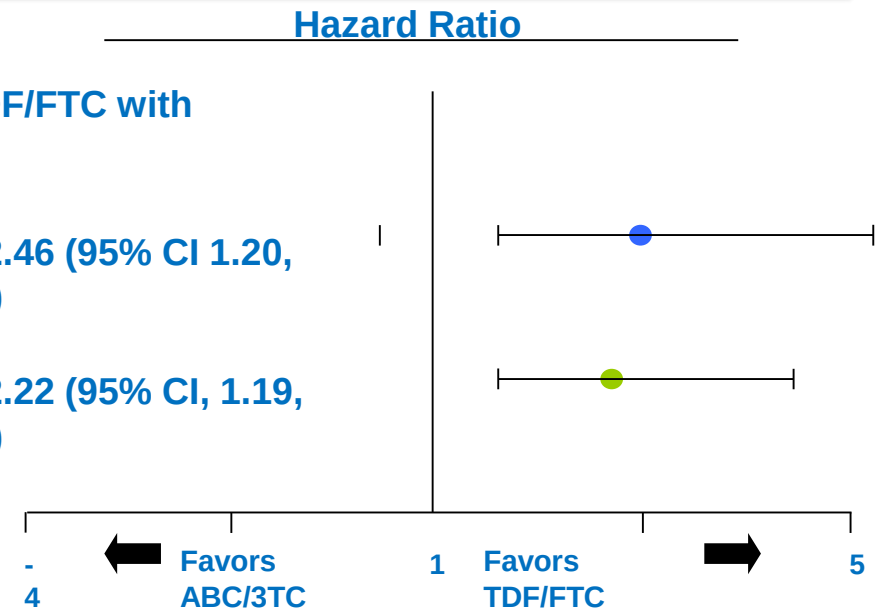
As-treated analysis of patients receiving first NRTI backbone



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

Sax et al. NEJM 2009;361:2230

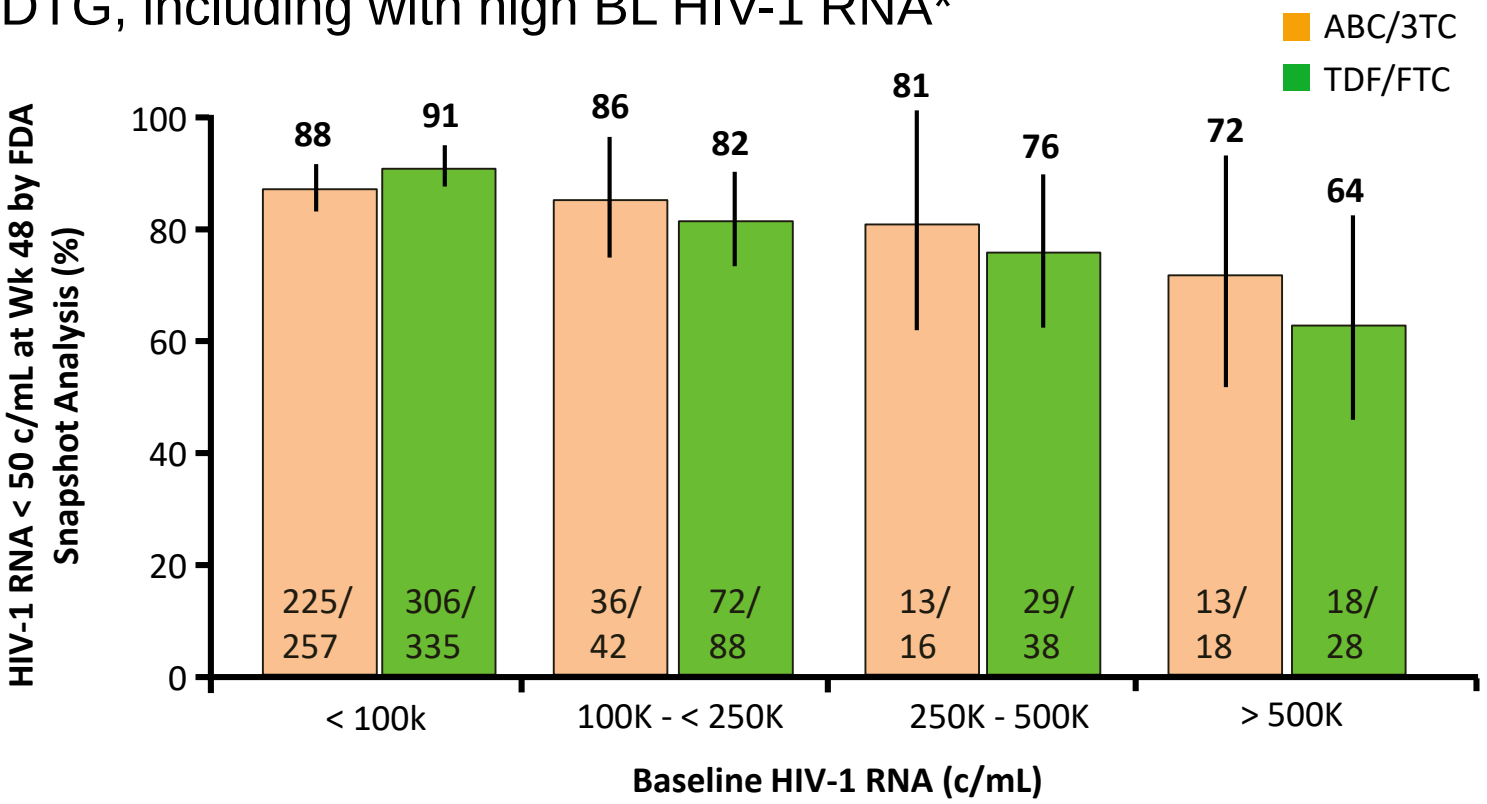
ABC/3TC vs. TDF/FTC: primary virologic endpoint (High viral load stratum at DSMB action)



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.

NMA study

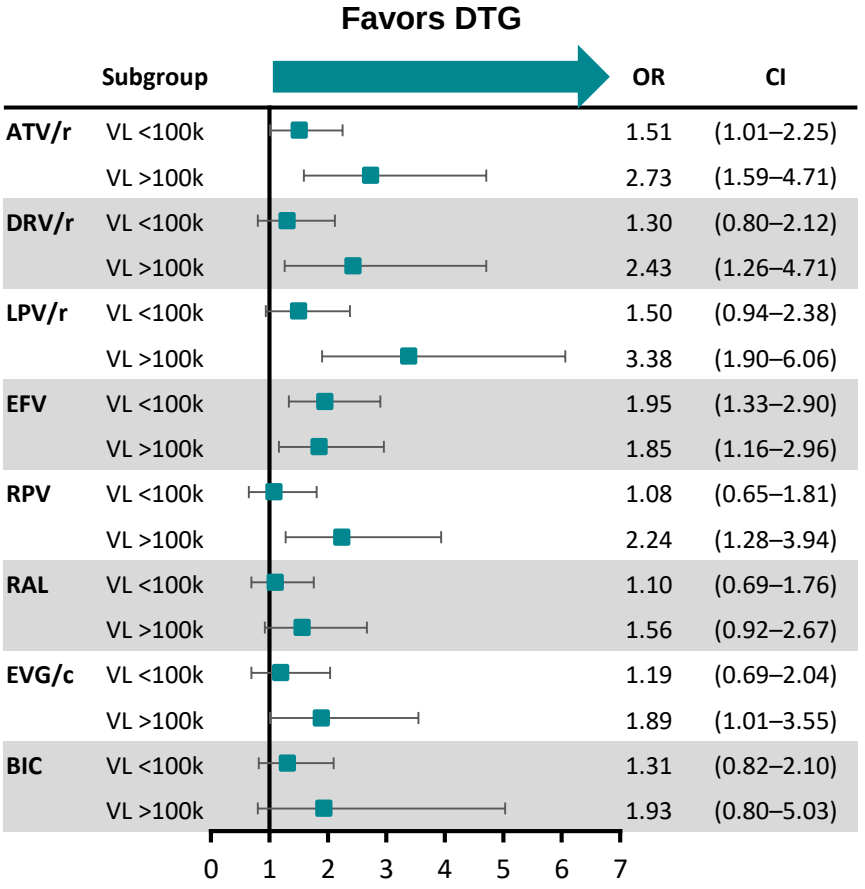
Network…… Meta…….. Analysis

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.

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JAMA®
The Journal of the American Medical Association

The inhibitory quotient. A method for interpreting minimum inhibitory concentration data. P. D. Ellner and H. C. Neu

1981; 246: 1575-78

THE INHIBITORY QUOTIENT*

HAROLD C. NEU, M.D.
Chief, Division of Infectious Diseases

PAUL D. ELLNER, Ph.D.
Director, Clinical Microbiology Services

Columbia University College of Physicians and Surgeons
New York, New York

THE past few years have seen many improvements in methods to determine the susceptibility of microorganisms to different antibacterial agents. Although most physicians continue to speak of bacteria as susceptible or resistant to an antibiotic, the use of minimal inhibitory concentrations (MICs) has become increasingly common when dealing with nosocomial pathogens which often resist older penicillins and cephalosporins. This paper will evaluate the meaning of inhibitory concentrations and peak serum concentrations as they relate to the use of antimicrobial agents in outpatient settings.[1]

THE INHIBITORY CONCENTRATION

What is an inhibitory concentration? The minimum inhibitory concentration (MIC) of an antibiotic is that amount of antimicrobial agent which will inhibit the visible growth of a microorganism, as measured by the eyes or by a machine using light scattering. The MIC is determined with generally agreed-upon numbers of bacteria, 10^4 or 10^5 colony-forming units (CFU), using a standard broth or agar medium which contains antibiotic in twofold differing concentrations. The minimal bactericidal concentration (MBC) is the lowest concentration of drug that kills 99.9% of the organisms. This is determined by removing clear fluid from tubes or wells in a plate and placing the fluid onto agar plates. Bacteria which were inhibited but not killed will grow. Although many factors, such as size of inoculum, type of medium, cation content, osmolality, and aerobic

*Presented as part of a *Symposium on Recent Developments in Oral Antibiotic Therapy: Bacampicillin Update* held by the Section on Pediatrics and the Section on Medicine of the New York Academy of Medicine December 19, 1982. This symposium was supported by a grant from Roerig, division of Pfizer Pharmaceuticals.

Address for reprint requests: Harold C. Neu, M.D., Department of Medicine, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, N.Y. 10032

$$\text{Inhibitory quotient (IQ)} = \frac{\text{Average peak level achievable in target tissue or fluid*}}{\text{Minimum inhibitory concentration (MIC) of pathogen}}$$

Fig. 1. Calculating the inhibitory quotient.

concentration data that we called the inhibitory quotient (IQ).[3] Calculated as shown in Figure 1, the IQ is a number that indicates the multiple of the MIC expected with the lowest dosage of an antimicrobial agent. Examples of typical MIC data are shown in Table I and typical blood levels in Table II.

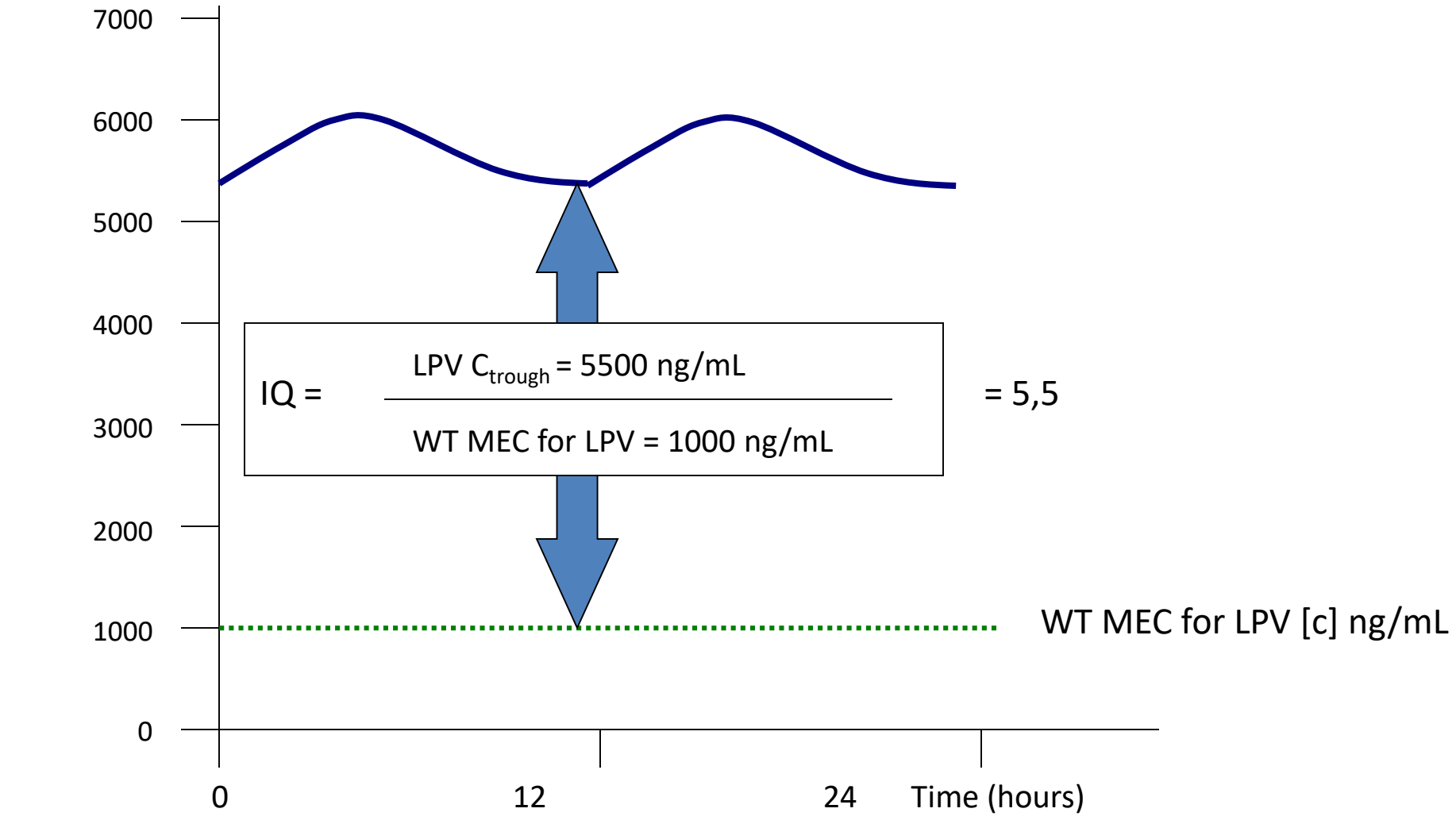
We initially applied the IQ system to parenteral therapy, but it also lends itself to use with oral agents. This method permits determination of MICs of bacterial isolates using either commercially frozen microdilution plates or such optical devices as the Autobac®. Antimicrobial agents selected for testing are those which would be used against the organisms. Concentrations used in testing are based upon those necessary to separate isolates which would be inhibited or killed from those which would survive.

In our institution, values for average peak serum levels of antibiotics are stored in a computer. Antibiotic blood levels chosen for intravenous use are those that would reflect the level achieved at the end of 20 to 30 minute infusions, while oral levels are based on the peaks known from studies in normal individuals, and may reflect a level at one hour or two hours, depending upon absorption kinetics of the particular antibiotic. Urine concentrations chosen are those found in the urine during the first several hours after administration of the drug. Certainly urine concentrations of some agents may be markedly depressed if the individual has impaired renal function with a glomerular filtration rate below 30 ml/mm and the agent in question is cleared primarily by glomerular filtration. Levels in cerebrospinal fluid, which of course apply only to parenteral therapy, are based on the much higher doses used to treat meningitis and on the presence of meningeal inflammation.

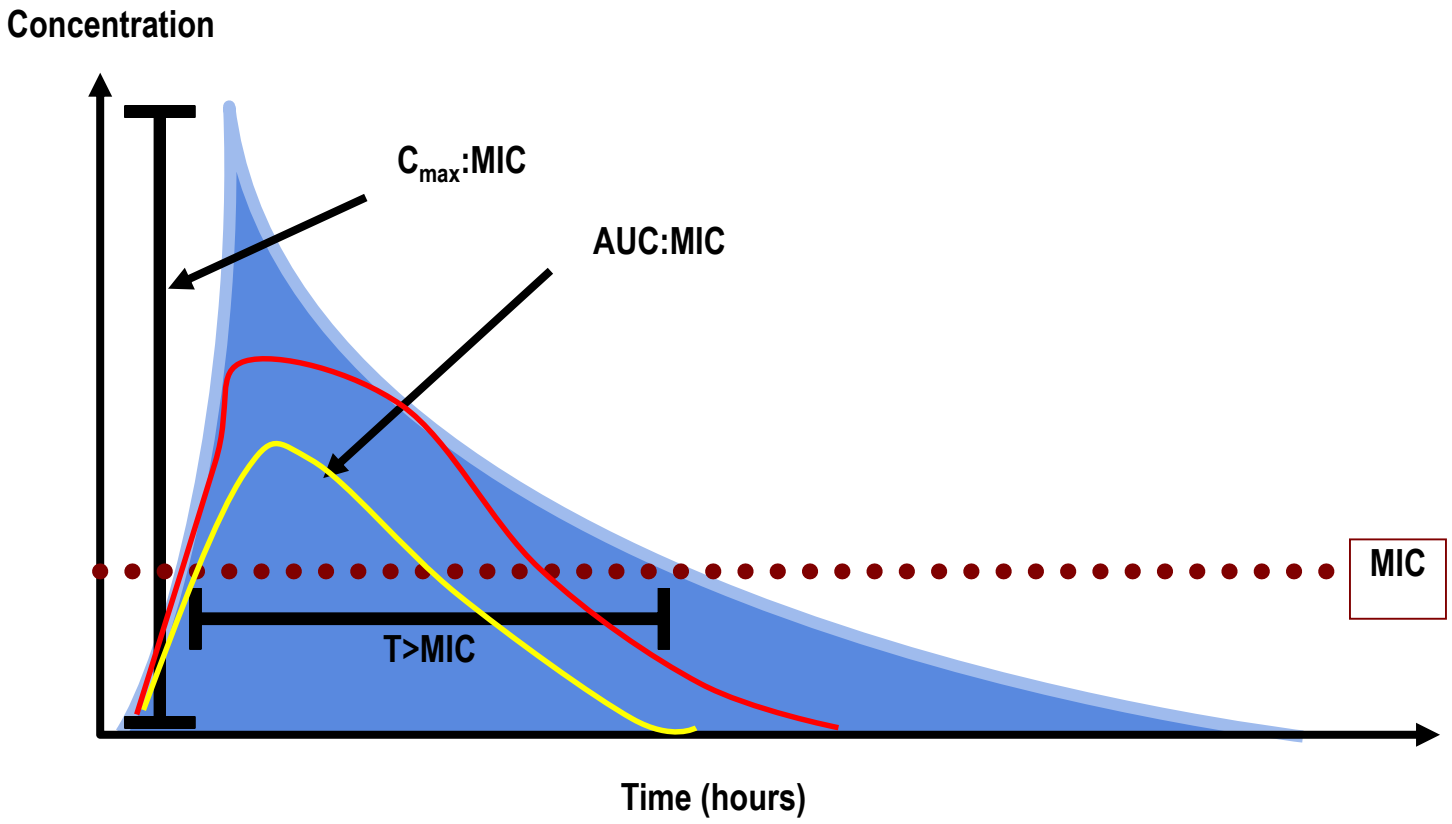
In each instance, inhibitory quotients reported to a physician are those appropriate to the body site of the specimen, such as serum, urine, bile, or

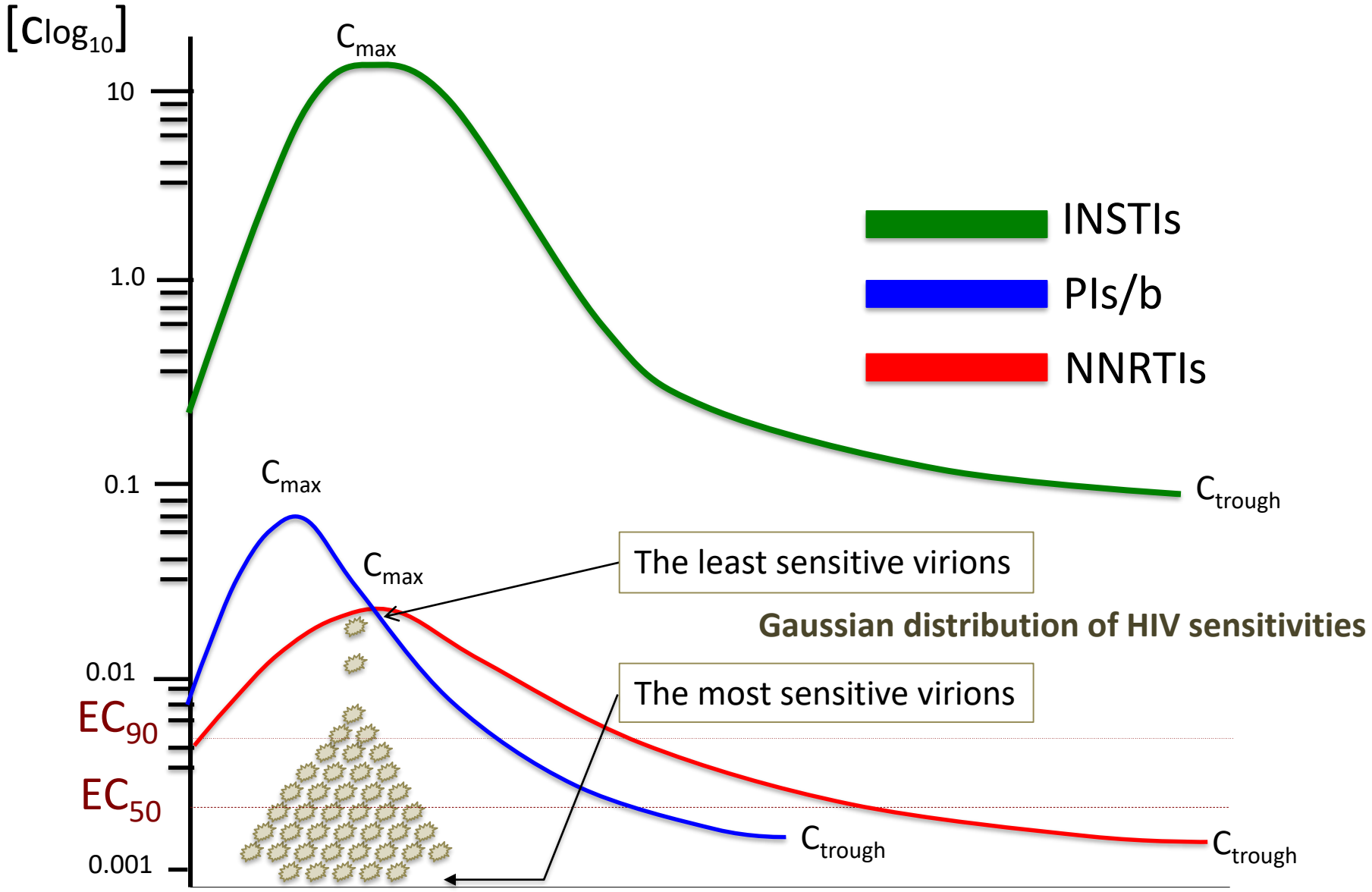
*Lung is considered part of the central body compartment due to its high blood flow and hence the serum level is used.

…the only IQ we can reliably measure as a true concentration ratio is that for the WT virus…..



Although antiretrovirals are thought to act in a **time-dependant 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**....

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10
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Cmax
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Ctrough
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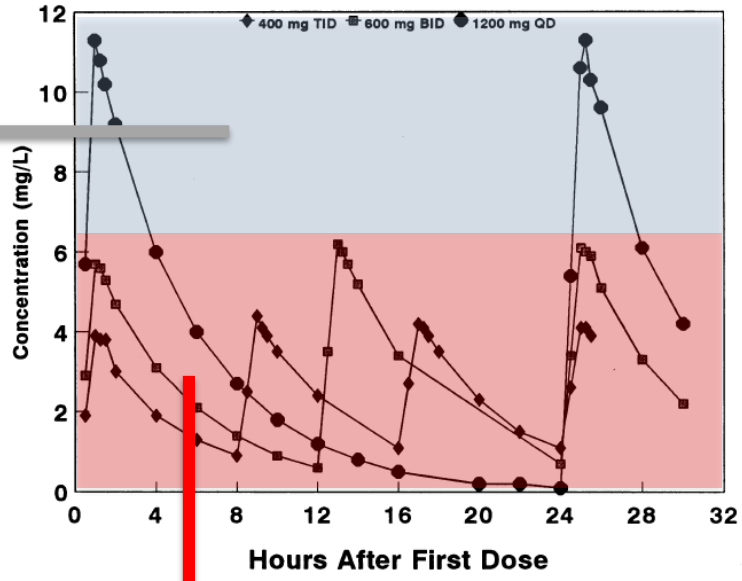
Ctrough
INSTIs
PIs/b
NNRTIs
The least sensitive virions
Gaussian distribution of HIV sensitivities
The most sensitive virions

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



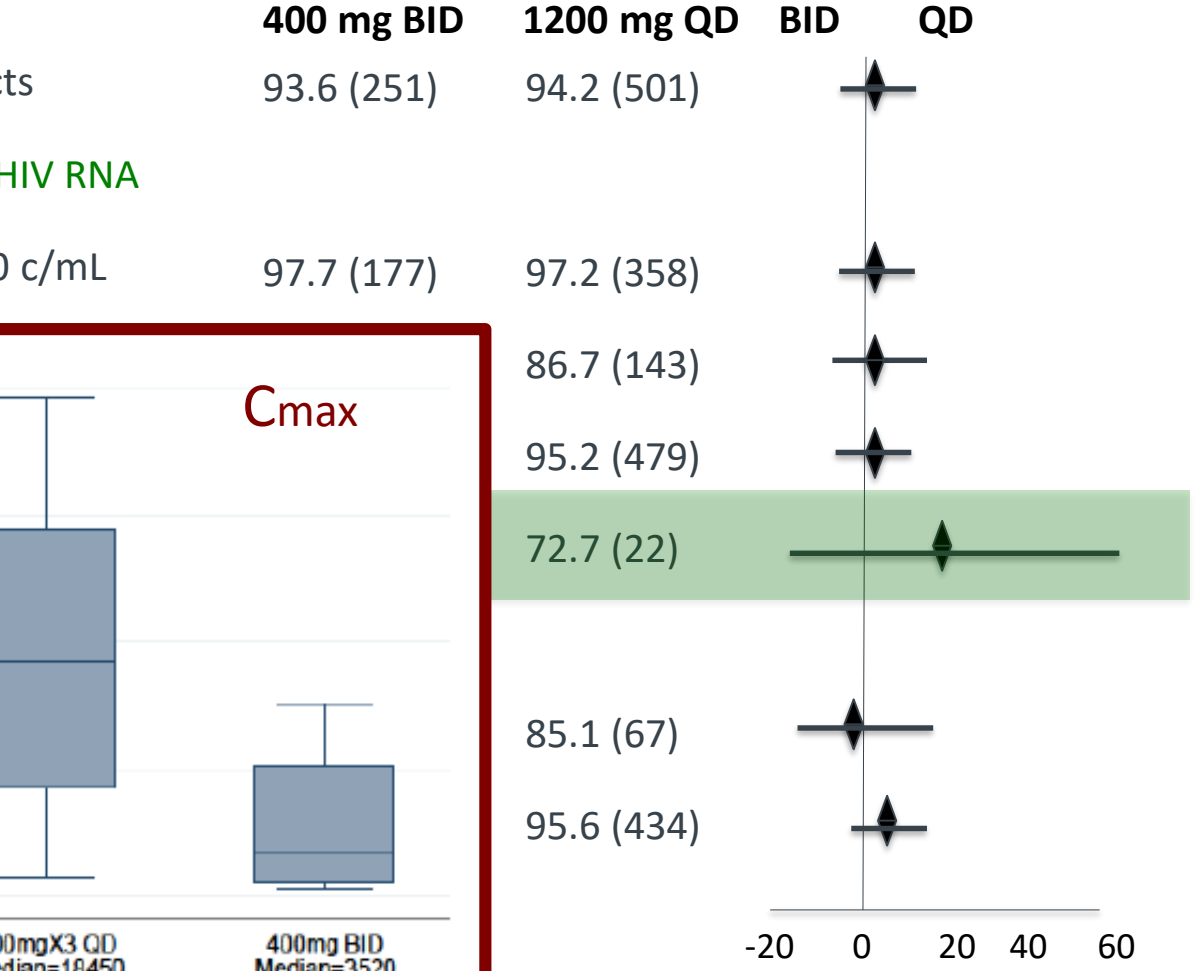
Regrowth without Resistance

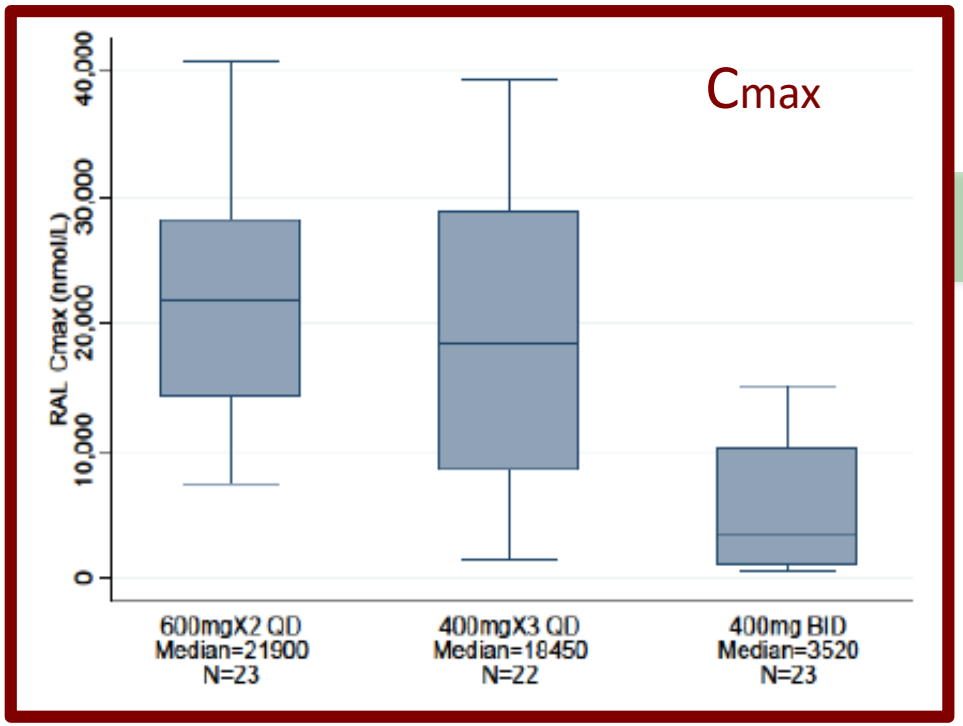
Regrowth with Resistance

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)
	86.7 (143)	
	95.2 (479)	
	72.7 (22)	
	85.1 (67)	
	95.6 (434)	





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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

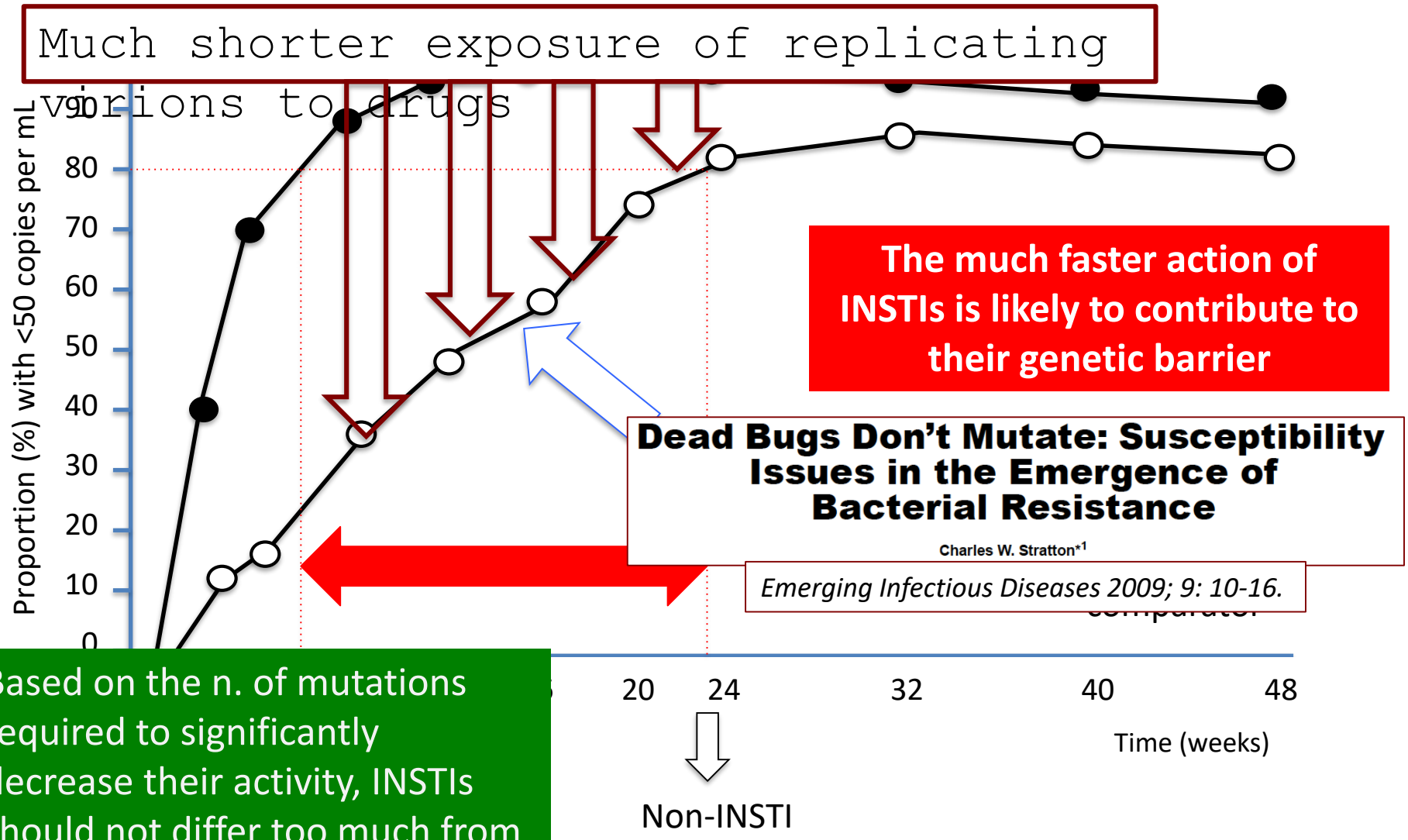
- Low rates of virologic withdrawals were observed at Week 48

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.



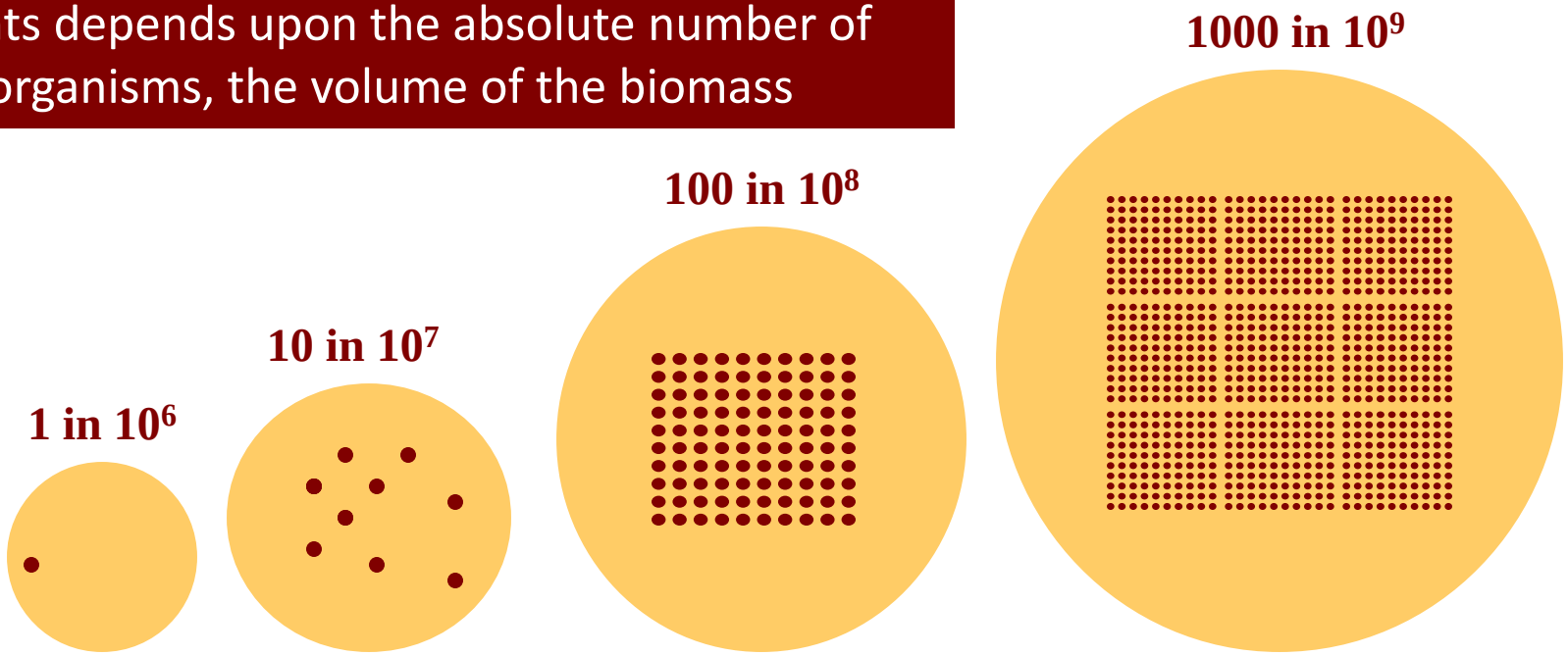
e comparison between the viral decay associated to INSTIs and the one seen with a non-INSTI 3rd drug.. The double arrow identifies the different time required to achieve 80% of viral suppression; a much shorter exposure of the viral biomass to treatment drugs is seen with INSTIs (6 weeks) as compared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

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

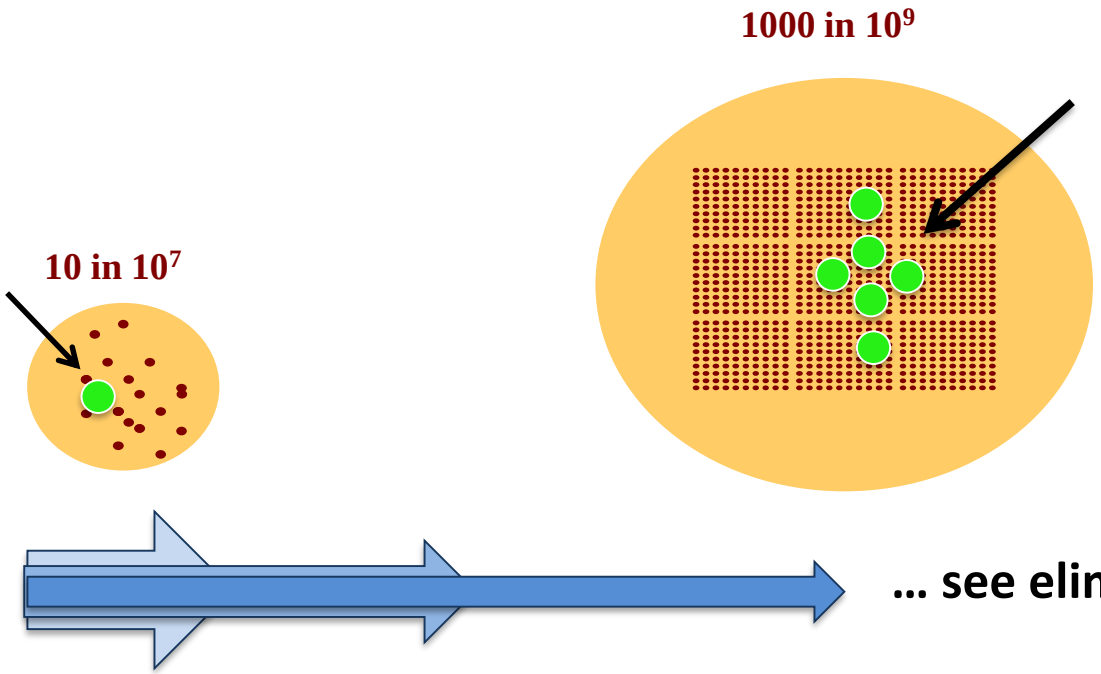


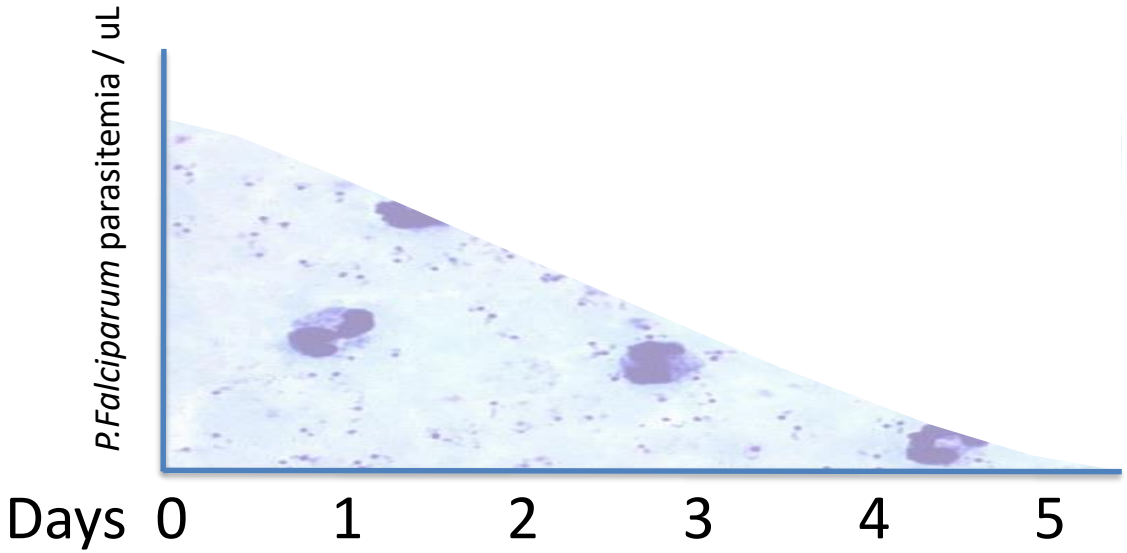
The main factors that determine the chance of genetic selection under the action of a specific "darwinian selector":

1. The spontaneous frequency of the "quasispecies" that would take a growth advantage as a result of the selector action

2. The duration of exposure to the specific selector (e.g. the drug)

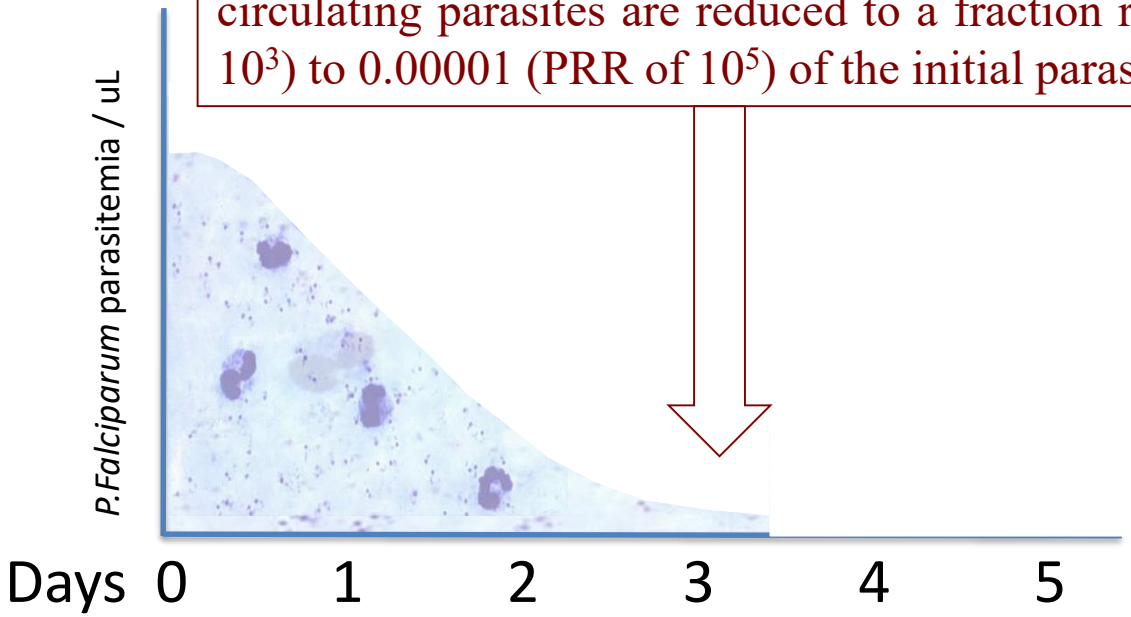
3. The absolute magnitude of the population containing that drug-R quasispecies





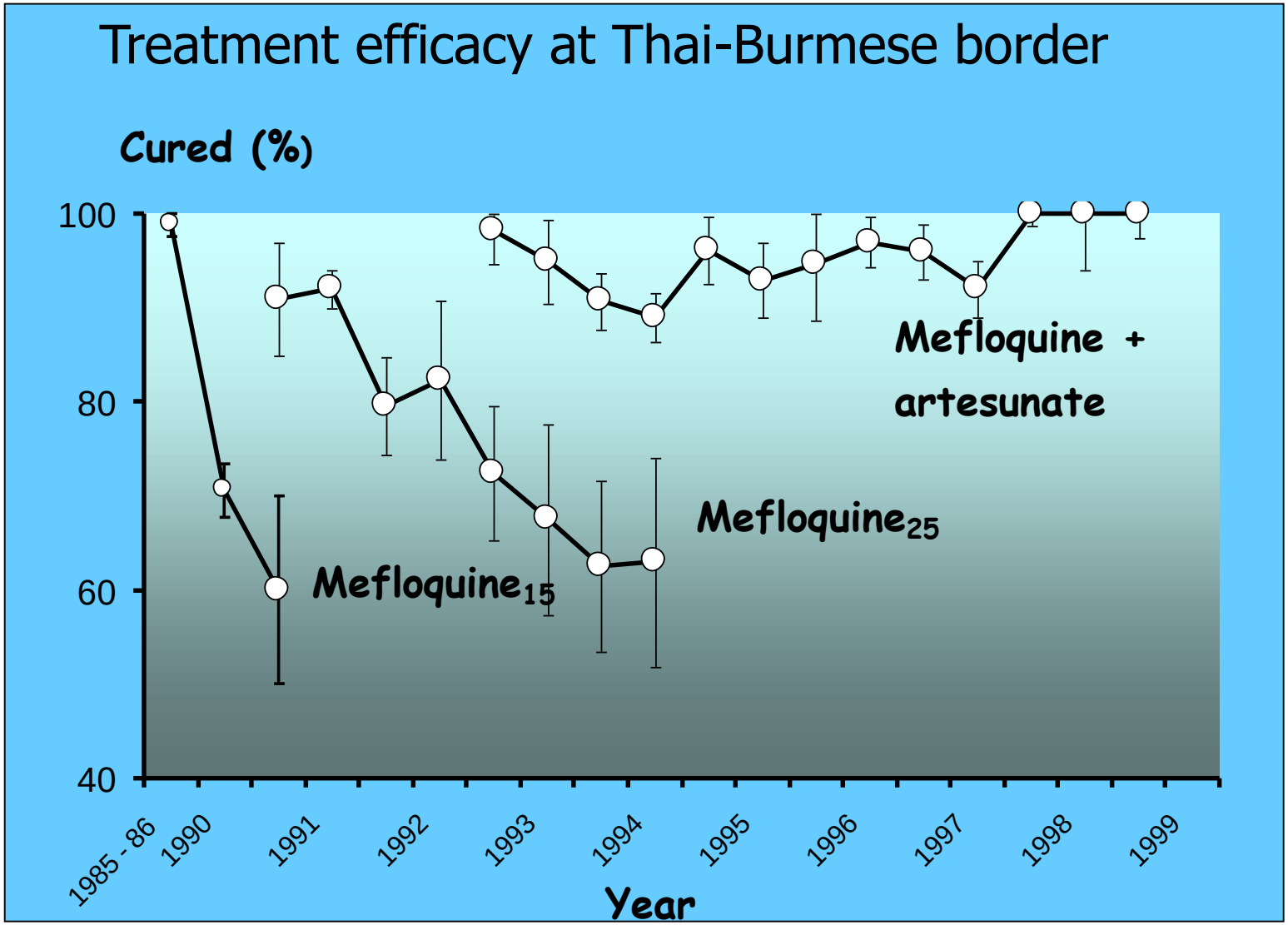
Mefloquine

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.*

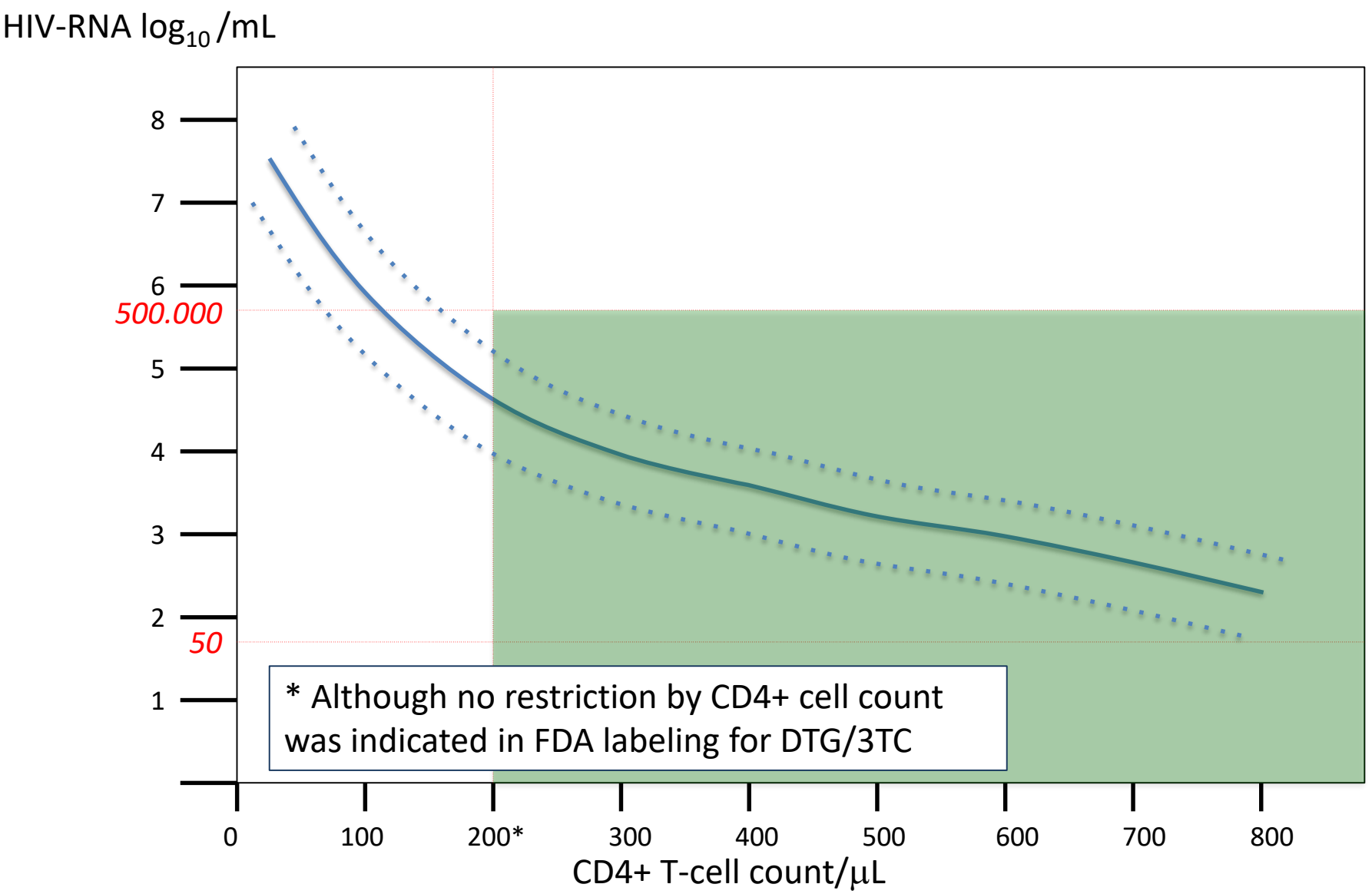


Artesunate +
Mefloquine

First demonstration project in Thailand

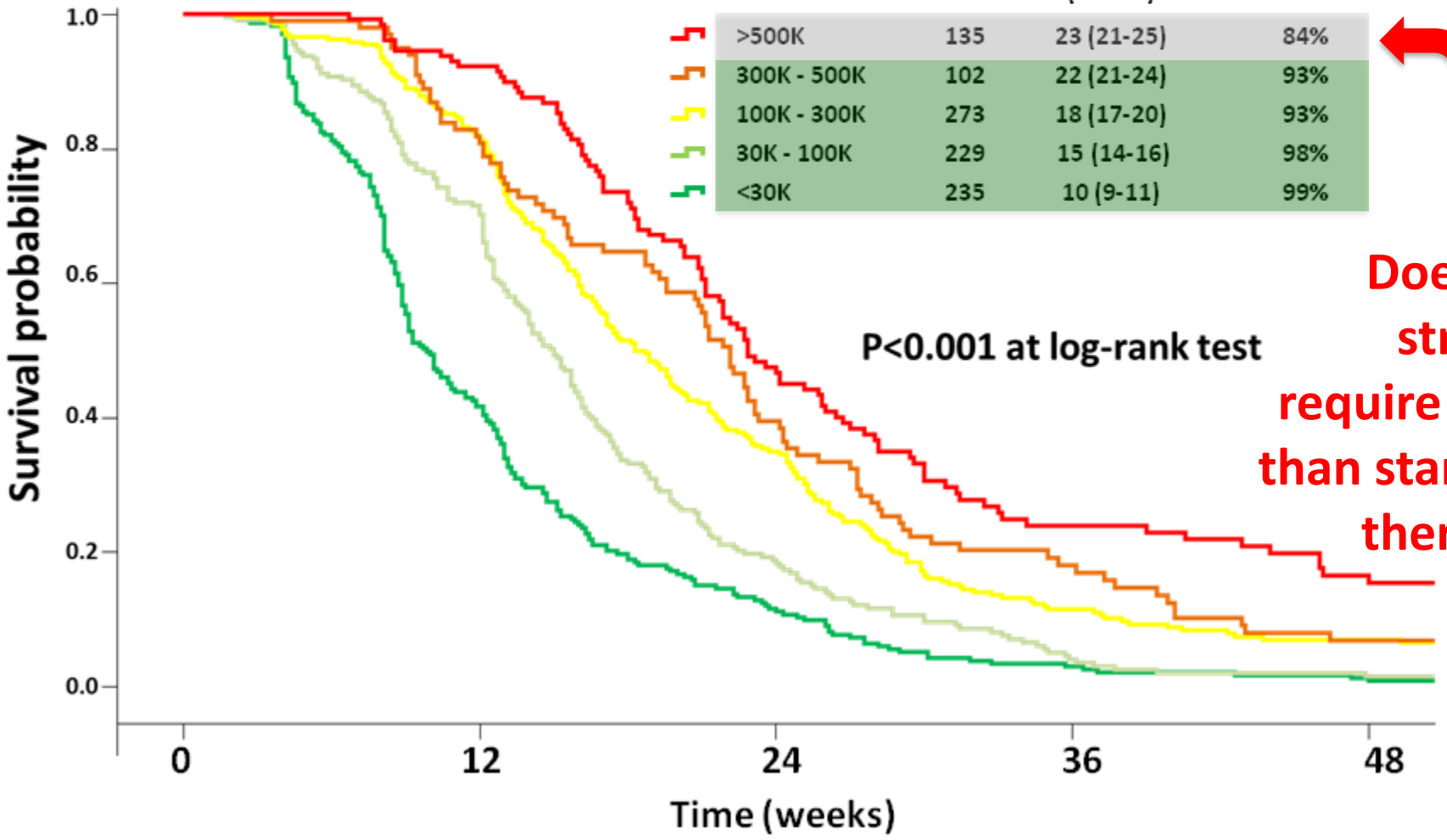


GEMINI 1&2 – derived baseline immunovirologial cut-off defining the suitable treatment-naïve patients with chronic HIV infection who are candidate for successful DTG/3TC dual therapy



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%



Does this stratum require more than standard therapy ?

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

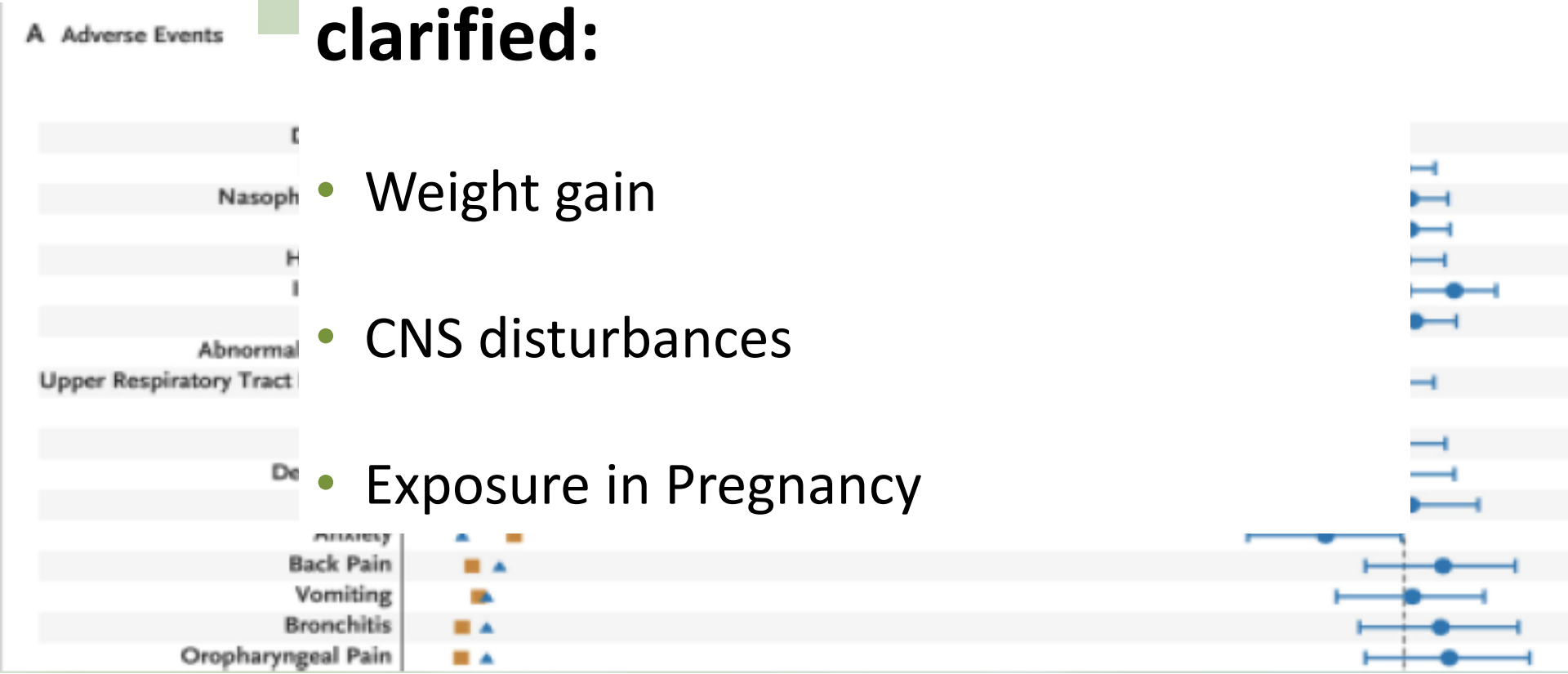
Which are the properties of 2nd generation INSTIs that made it possible to generate the new 2-drug paradigm?

- **Intrinsic potency**
  also testified by FAST ANTIVIRAL EFFECT
- **High IQ**
  also responsible for FAST ANTIVIRAL EFFECT
- **Genetic barrier**
  also due to FAST ANTIVIRAL EFFECT
- **Clinical tolerability and safety**

- Better tolerability
- Drug discontinuation due to side effects in SINGLE:

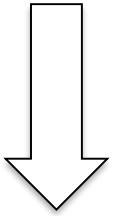
Pending issues to be further clarified:

- Weight gain
- CNS disturbances
- Exposure in Pregnancy



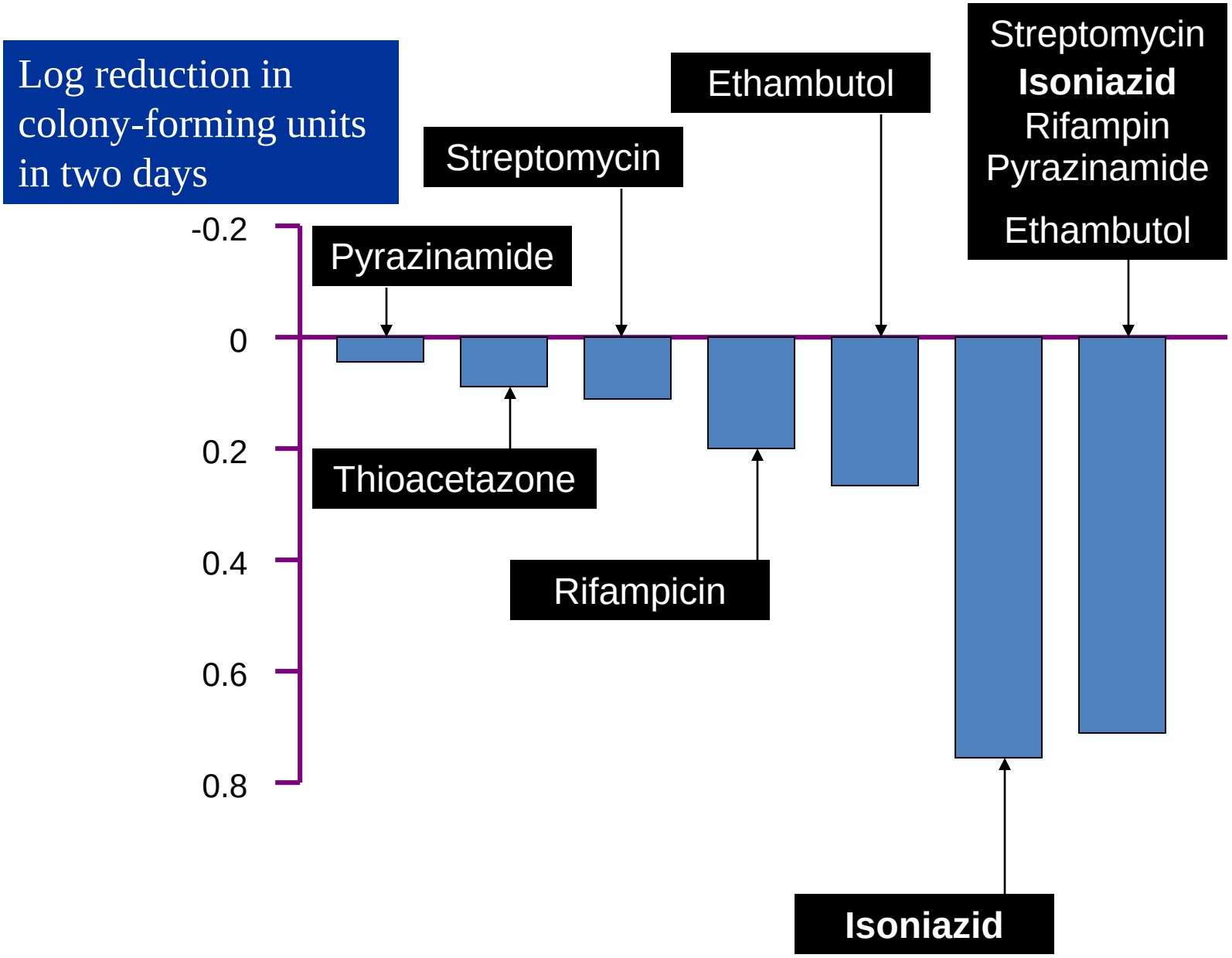
Walmsley SL et al. N Engl J Med 2013;369:1807-1818.

The reasons accounting for the few 2DR failures in clinical trials



The risk of INSTI monotherapy

- **Insufficient Pk exposure of 2nd drug**
- **Inactive 2nd drug**


Log reduction in colony-forming units in two days
Streptomycin
Ethambutol
Streptomycin
Isoniazid
Rifampin
Pyrazinamide
Ethambutol
-0.2
Pyrazinamide
0
0.2
Thioacetazone
0.4
Rifampicin
0.6
0.8
Isoniazid

MRC, 1970

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

MonoDTG

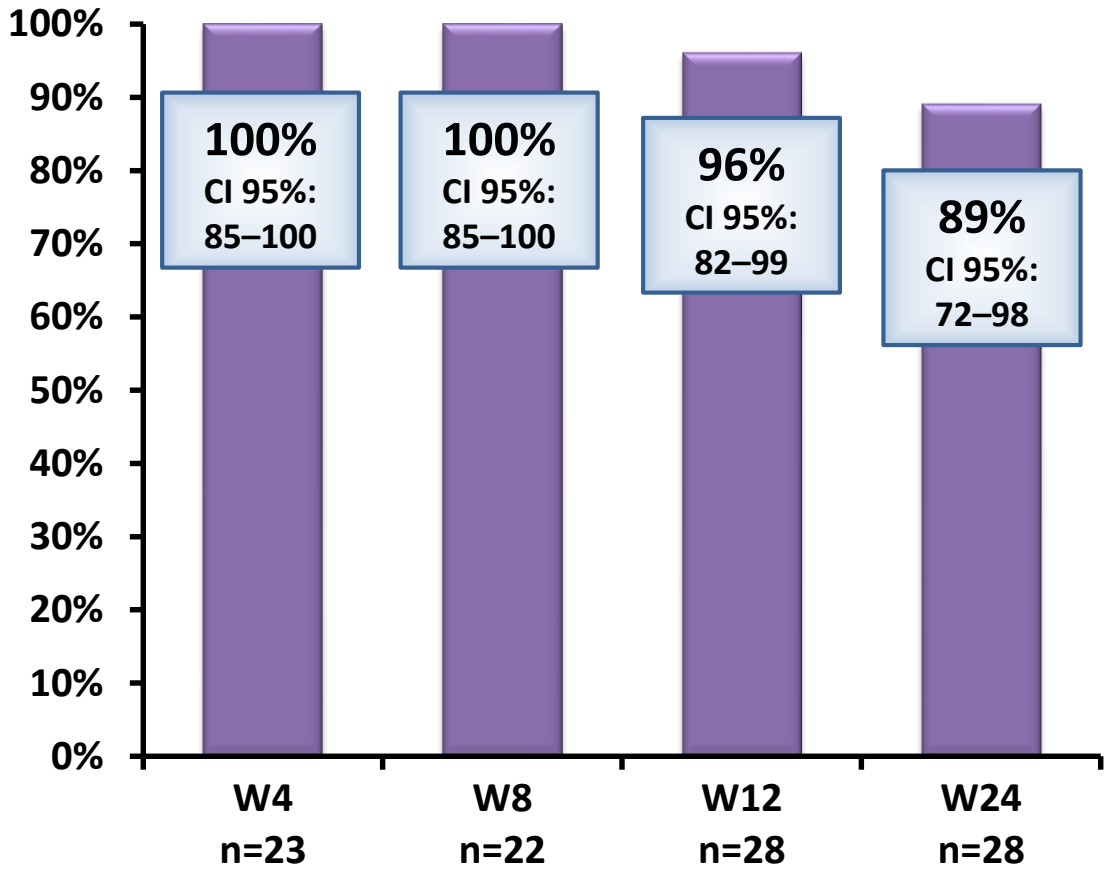
28 pts

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



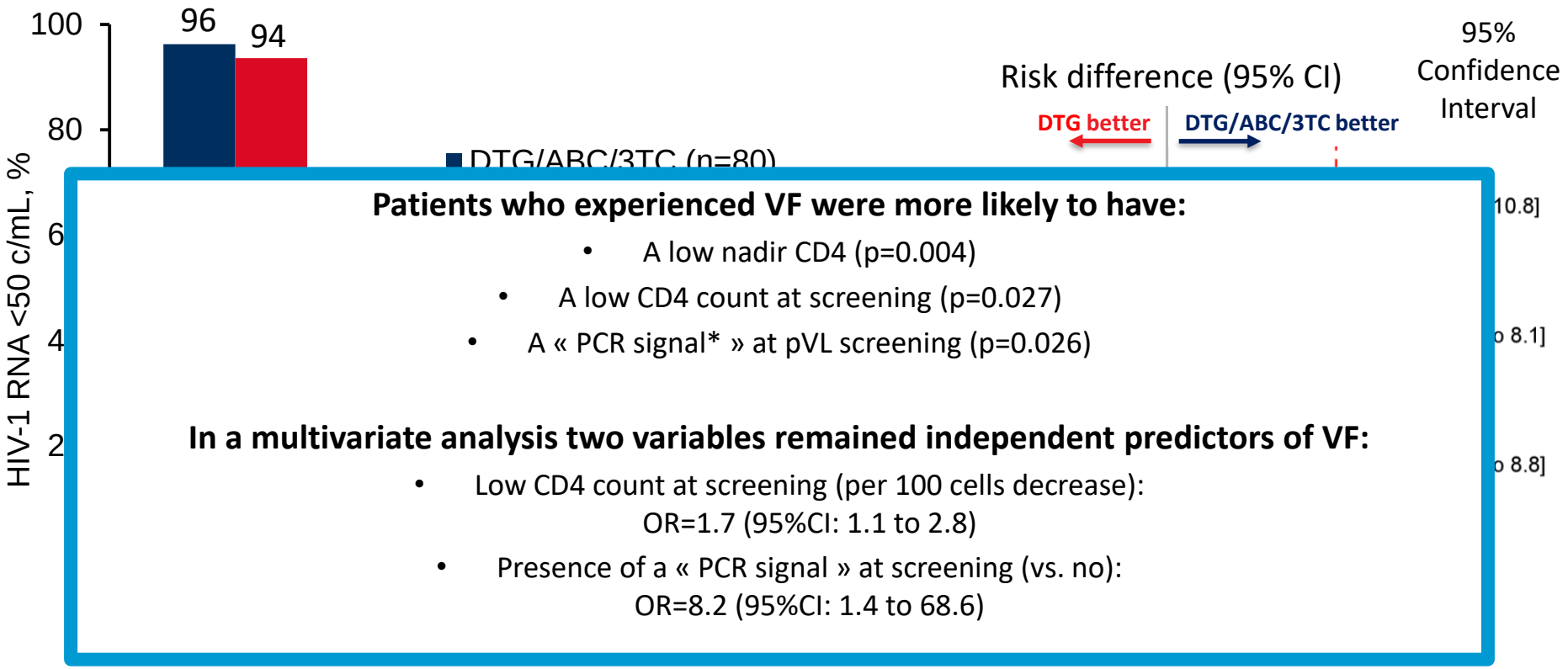
MONCAY trial

Stable, efficient and well-tolerated DTG/ABC/3TC regimen*

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

Virologic outcomes (ITT)

W24 treatment difference



Patients who experienced VF 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)

In a multivariate analysis two variables remained independent predictors of VF:

- Low CD4 count at screening (per 100 cells decrease):
  OR=1.7 (95%CI: 1.1 to 2.8)
- Presence of a « PCR signal » at screening (vs. no):
  OR=8.2 (95%CI: 1.4 to 68.6)

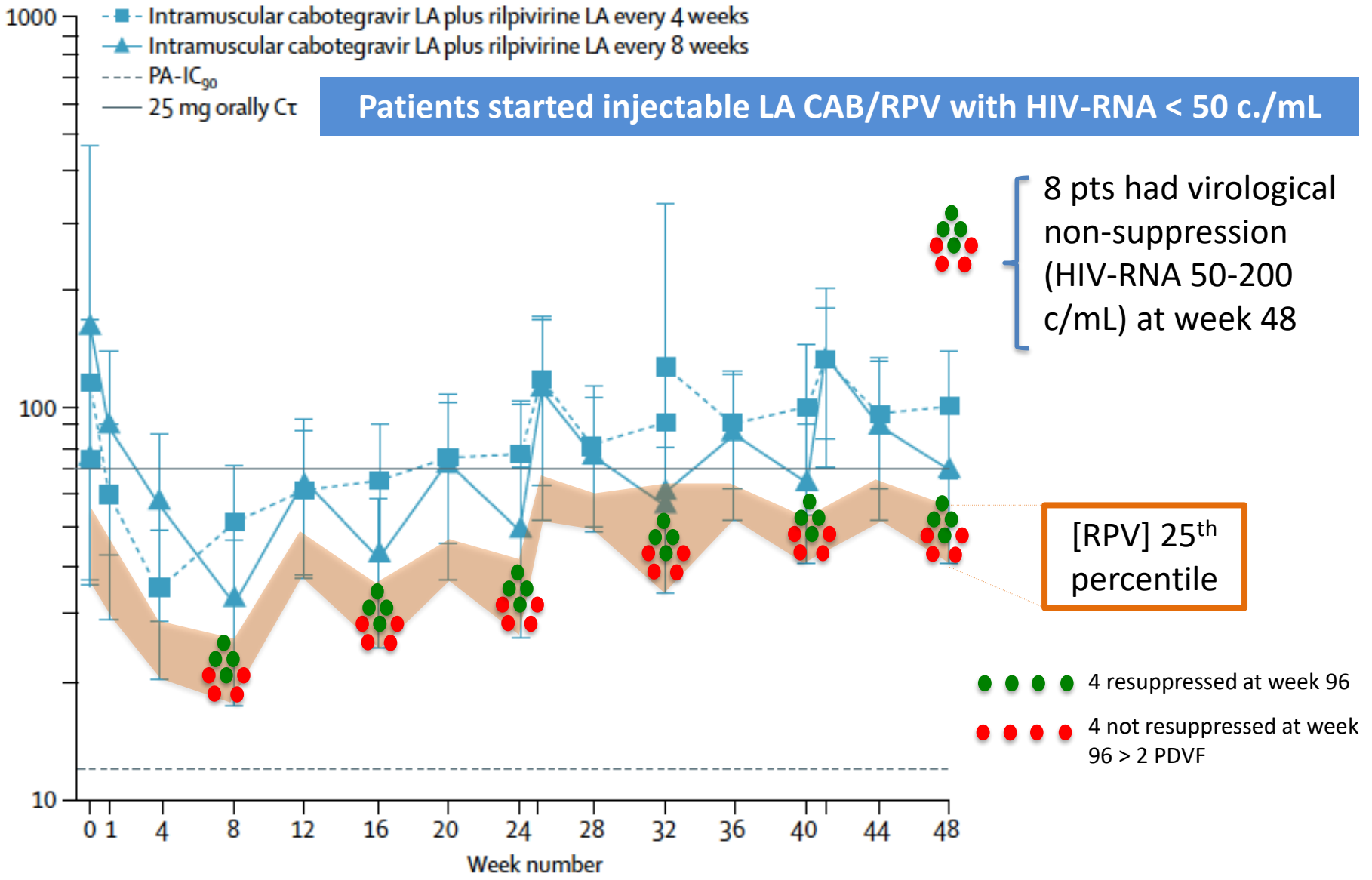
DTG was **non-inferior** to DTG/ABC/3TC **at Week 24**

with respect to snapshot in the ITT, mITT and PP population

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

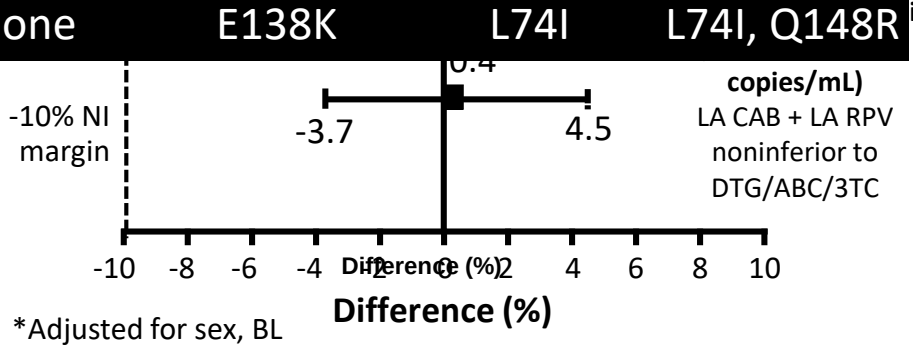
Lancet 2017; 390: 1499–510



FLAIR: Efficacy at Wk 48 in ITT-E Population

Study	Sex	Country	HIV-1 Subtype	Wk of Failure	NNRTI RAMs		INSTI RAMs	
					Baseline	Failure	Baseline	Failure
ATLAS	F	Russia	A/A1	8	E138E/A	E138A	L74I	L74I
	F	France	AG	12	V108V/I, E138K	V108I, E138K	None	None
	M	Russia	A/A1	20	None	E138E/K	L74I	L74I, N155H
FLAIR	F	Russia	A1	20	None	E138E/A/K/T	L74I	L74I, Q148R
	M	Russia	A1	28	None	K101E	L74I	L74I, G140R
	F	Russia	A1	48	None	E138K	L74I	L74I, Q148R

Nonresponse (≥ 50 c/mL) **Success (< 50 c/mL)** **Virologic Data**



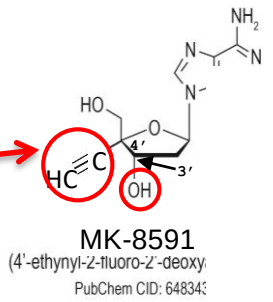
*Adjusted for sex, BL HIV-1 RNA (< vs ≥ 100,000 c/mL).

Orkin. CROI 2019. Abstr 140LB.

A new 2-DR solution not based on INSTIs

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

Translocation is inhibited by the strong interactions of the hydrophobic **4´-ethynyl group** with the hydrophobic pocket of the RT active site.

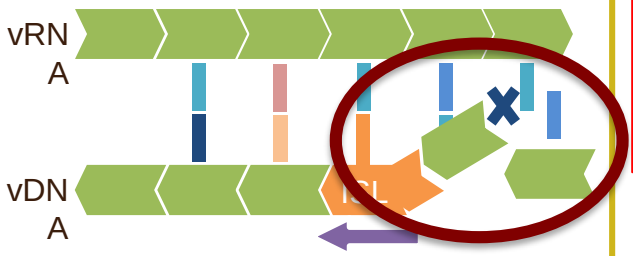


Unlike anti-HIV NRTIs but like Entecavir and Sofosbuvir, Islatravir (MK-8591) has a **3'-OH**

The **2-fluoro group** alters the electronic distribution in the adenine ring, which results in **resistance to degradation by adenosine deaminase** and in a **longer intracellular T/2**

- 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

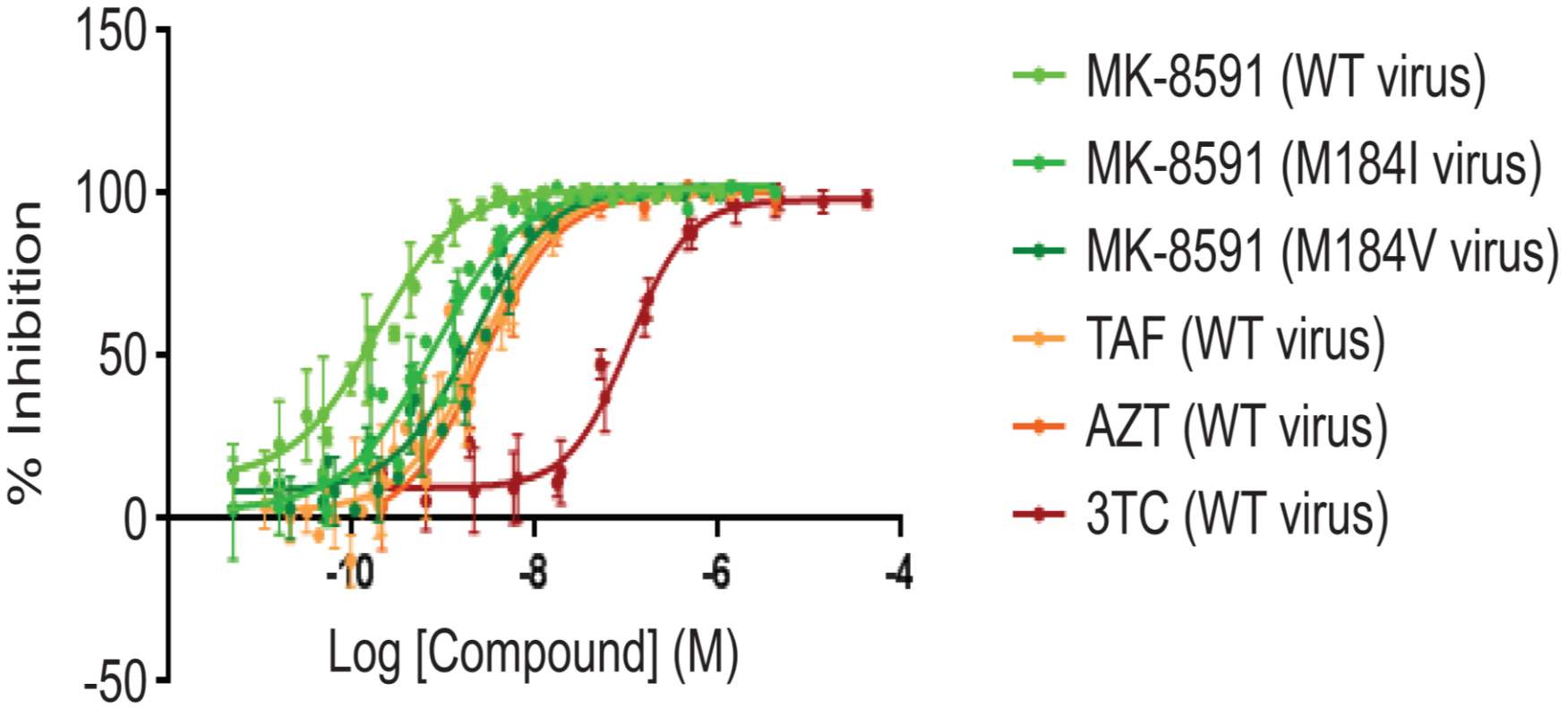
Delayed Chain Termination
due to the 4'-ethynyl and 3'-hydroxyl groups

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

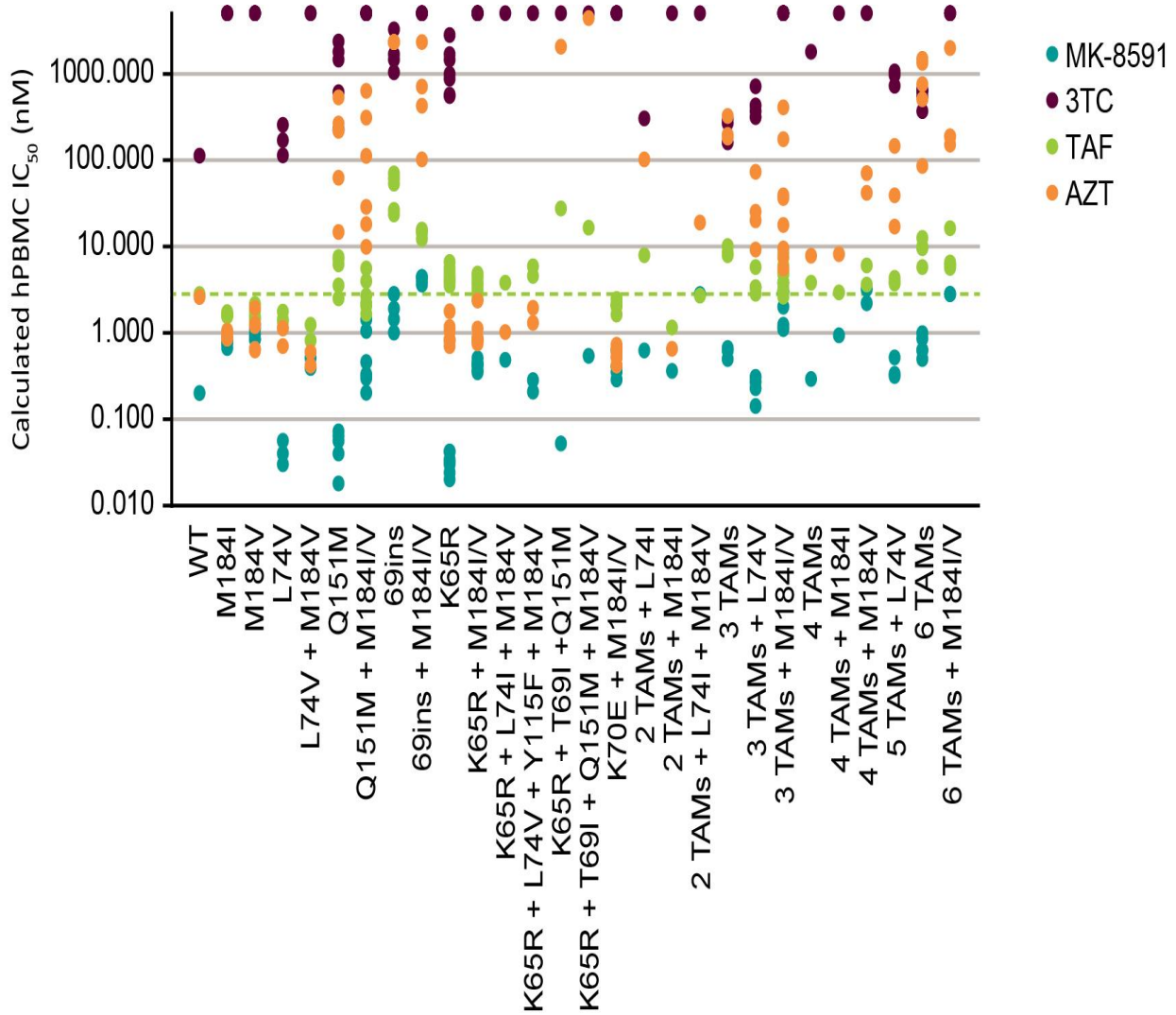
Adapted from Molina J-M, et al. Presented at IAS 2019; Oral Presentation #WEAB0402LB and Poster #LBPED46.

GROBLER, MK-8591 PK STUDY, CROI 2019

MK-8591 Exhibits Potent Antiviral Activity Against Wild-Type and NRTI-Resistant HIV-1 [1/2]



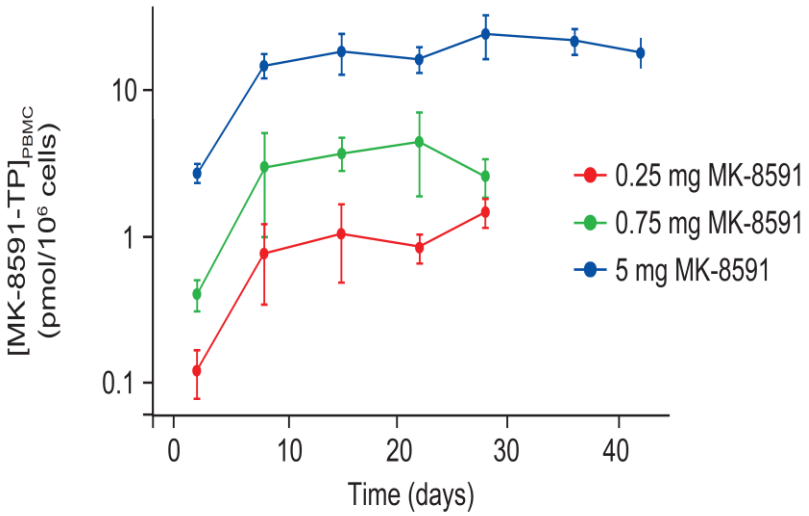
MK-8591 is More Potent Against Most Resistant Mutants Than Approved NRTIs



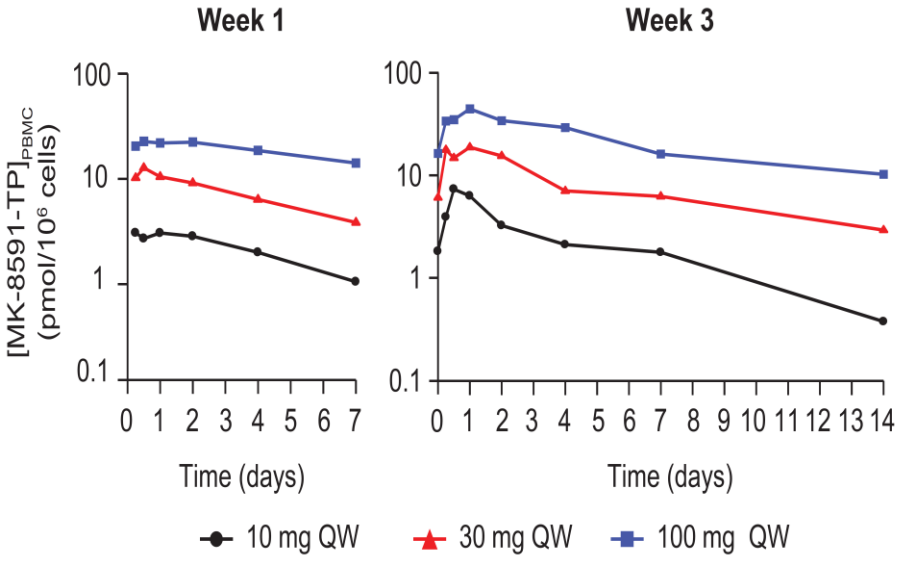
GROBLER, MK-8591 PK STUDY, CROI 2019

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

MK-8591-TP Concentration-Time Profile with QD Dosing



MK-8591-TP Concentration-Time Profile with QW Dosing



Matthews, CROI 2018
Grobler et al, CROI 2016

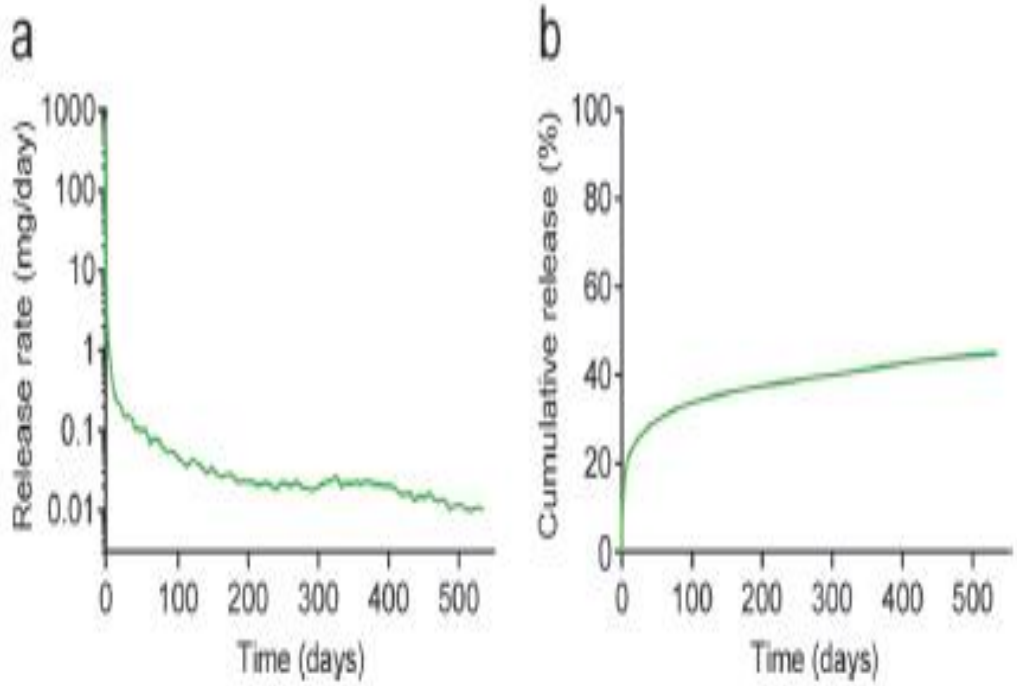
Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention

ANTIVIRAL AGENTS

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Stephanie E. Barrett,[a] Ryan S. Teller,[a] Seth P. Forster,[a] Li Li,[a] Megan A. Mackey,[a] Daniel Skomski,[a] Zhen Yang,[a] Kerry L. Fillgrove,[b] Gregory J. Doto,[c] Sandra L. Wood,[c] Jose Lebron,[c] Jay A. Grobler,[d] Rosa I. Sanchez,[b] Zhen Liu,[a] Bing Lu,[b] Tao Niu,[b] Li Sun,[b] Marian E. Gindy[a]

MK-8591 implants achieved clinically relevant drug exposures and sustained drug release, with plasma levels maintained for **greater than 6 months** that correspond to efficacious MK-8591-TP levels, resulting in a 1.6-log reduction in viral load.



In vivo MK-8591 release rate (a) and cumulative release (b) from a 60 wt% MK-8591 in PCL formulation in rat.

Barrett et al AAC October 2018 Volume 62 Issue 10 e01058-18

DORAVIRINE: the properties making it different from other NNRTIs:

- Shorter elimination half-life
- Greater potency vs RPV (no BL HIV-RNA restrictions)
- Excellent lipid profile
- No signature toxicity (e.g. no skin rash)
- Simpler metabolism (no inducer/inhibitor activities on CYP enzymes or Transporters)
- Unique resistance profile among NNRTIs

As opposite to 1st gen. NNRTIs (EFV, NVP, ETV)

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Sabrina Audagnotto

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Marino Bonasso

Ilaria De Benedetto

Stefano Biffi

Paolo Tiralongo

Micol Ferrara

Alice Trentalange

Lucio Boglione

Pino Cariti

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Ambra Barco

Tommaso Lupia

Simone Mornese Pinna

Enrica Borgogno

Silvia Scabini

Giancarlo Orofino

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