Clinical pharmacology of less drug regimens

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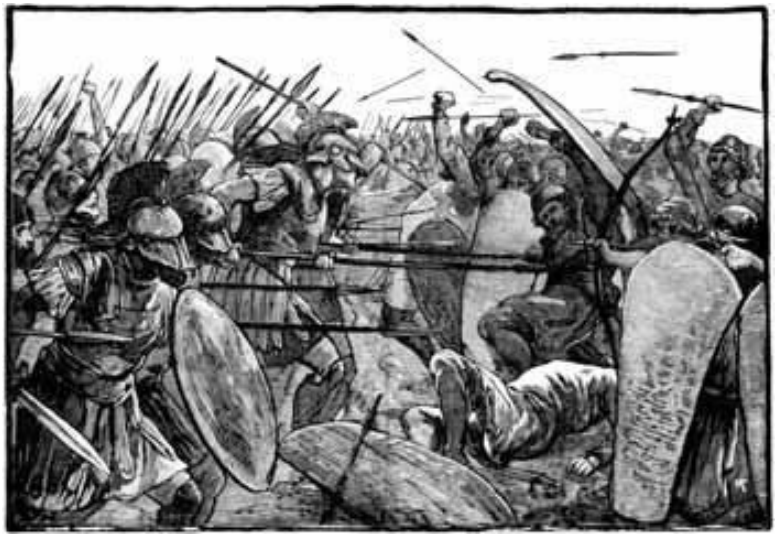
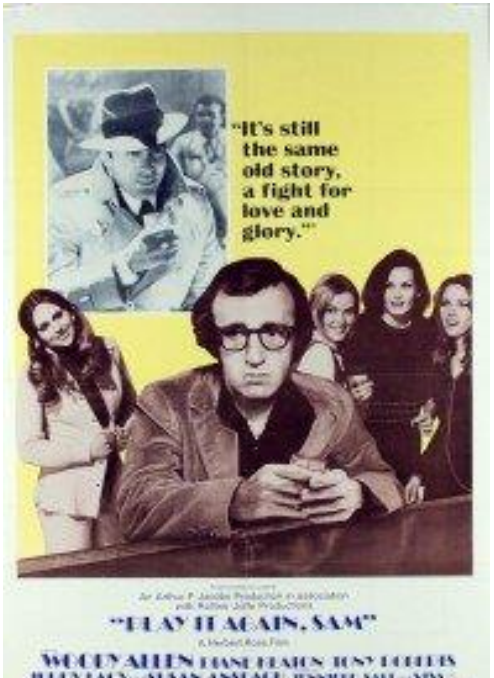
Outline

- ✓ **Forgiveness of PI/r in dual regimen (or the battle of Thermopilae)**

- ✓ **Maraviroc dosing with PI/r (or “Play it again, Sam”)**





PI/r-based dual regimen in naive patients

(as compared to triple regimens)

Study	Regimen	Efficacy	Resistance	Lipids	Renal	Bone
ACTG 5142	LPV/r + EFV					
Progress	LPV/r + RAL					
SPARTAN	ATV + RAL				?	?
NEAT 001	DRV + RAL					
1078	ATV + MVC 150 qd					?
VEMAN	LPV + MVC 150 qd					?
MODERN	DRV/r + MVC 150 QD			?	?	?
GARDEL	LPV/r + 3TC				?	?

equal
better
worse
slightly worse

Facts

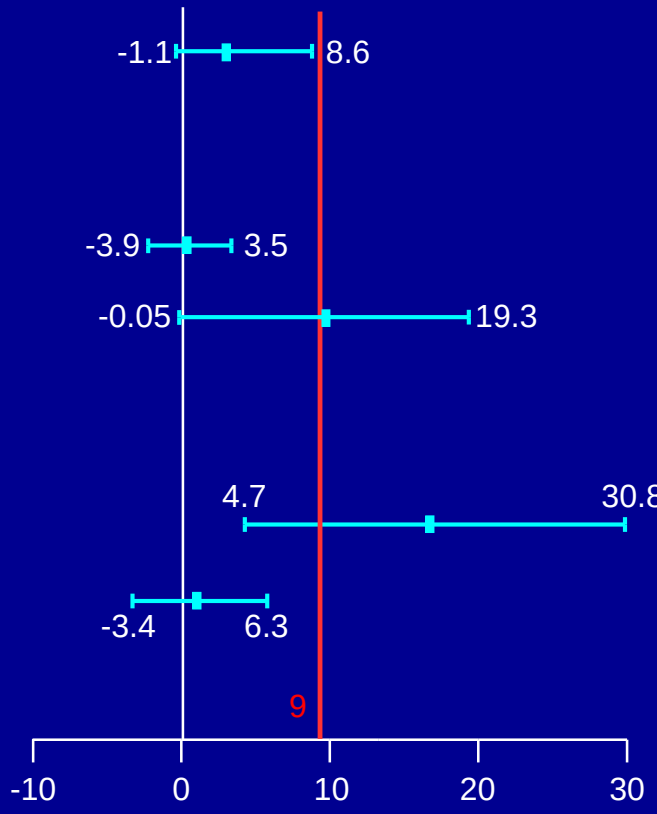
- In naives, dual regimen based on DRV/r **QD** or ATV/r showed lower efficacy as compared to **BID** LPV/r-based regimens, especially, but not only, in pts with HIV-RNA > 100k.

- In stable patients (switch), limited data are available, but no differences have been reported as compared to triple therapy (ATV/r + 3TC, DRV/r + MVC, LPV/r + 3TC).

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*

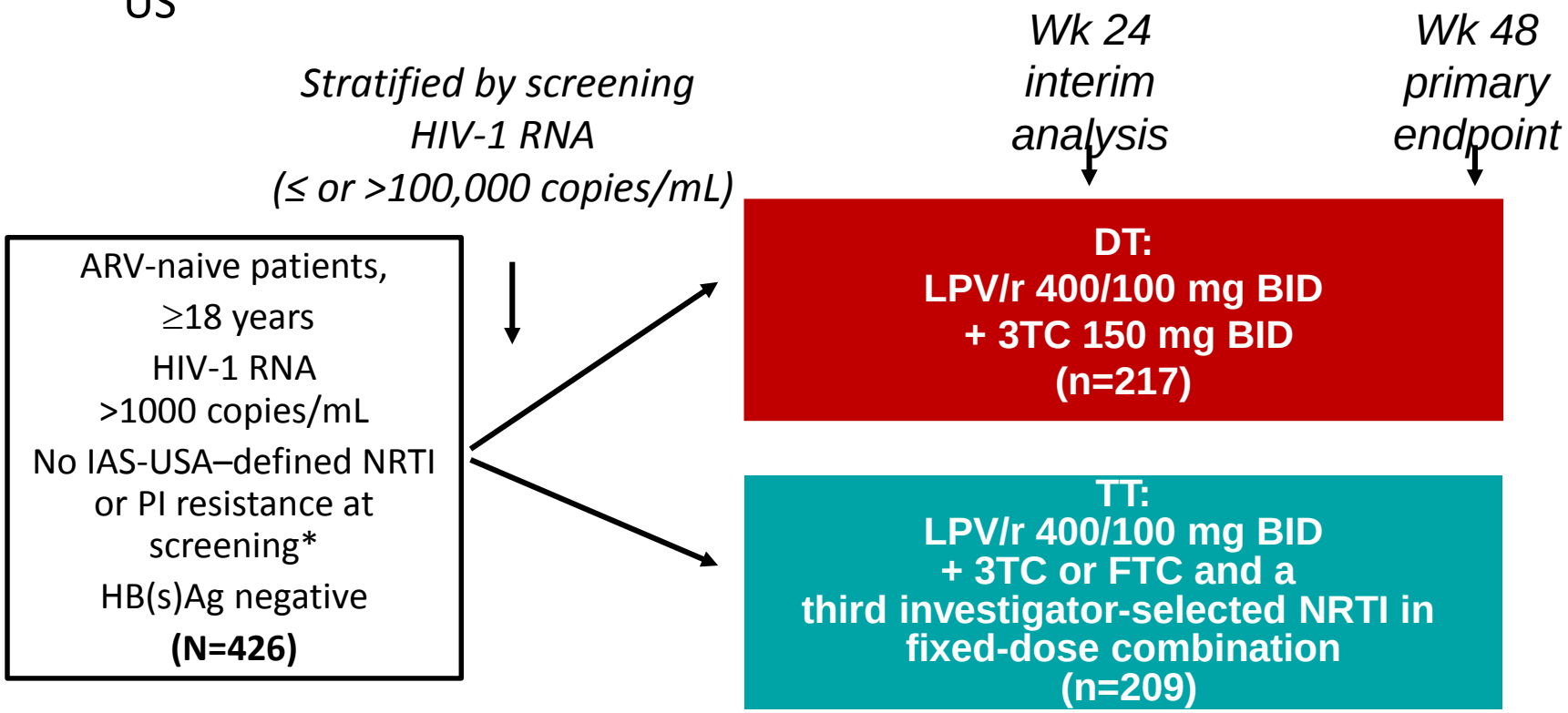


Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity

Study Design

- Phase III, randomized, international, controlled, open-label study
- Study included adult patients from Argentina, Chile, Mexico, Peru, Spain, US

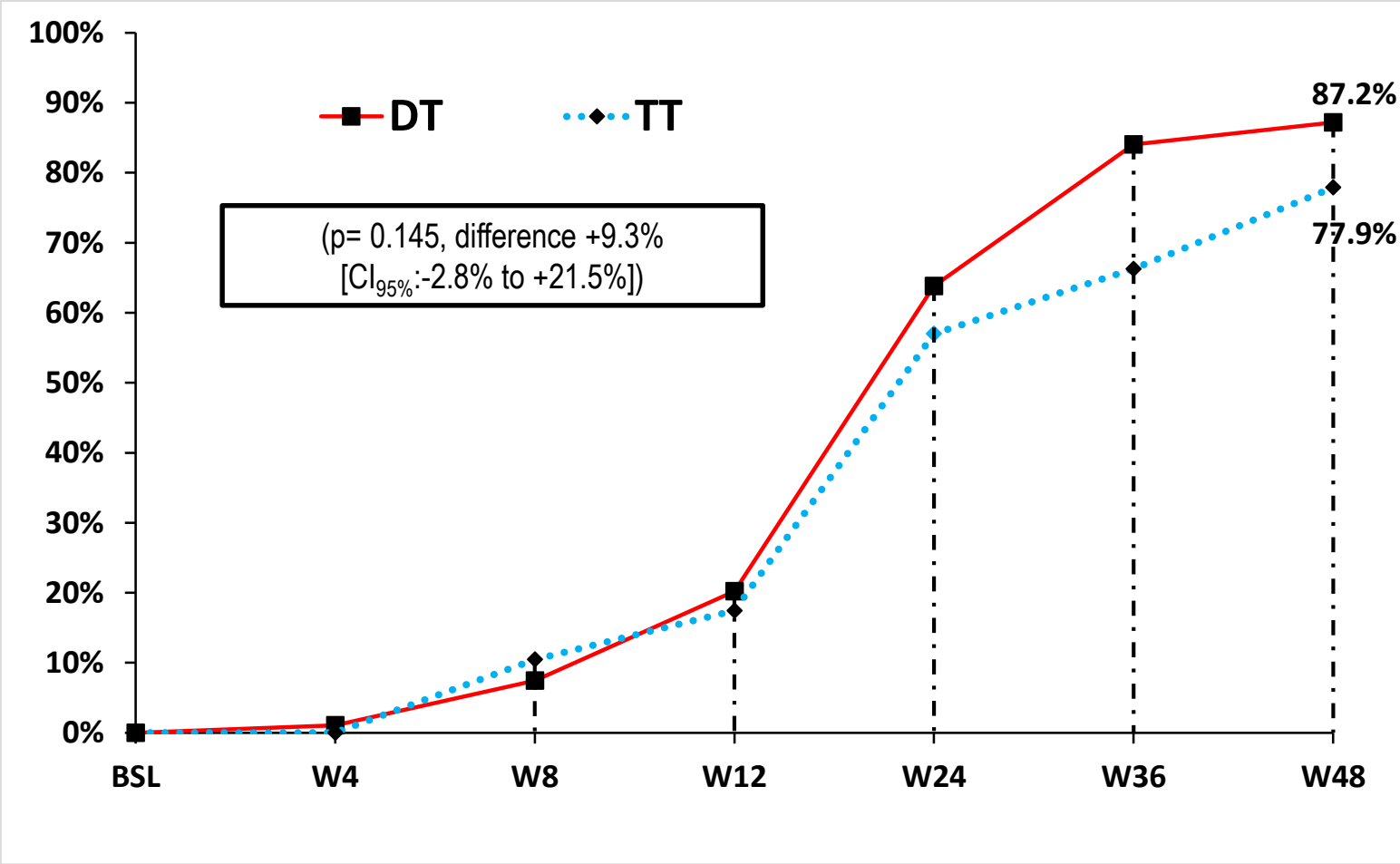


*Defined as ≥1 major or ≥2 minor LPV/r mutations

LPV major mutations include the following mutations: V32I; I47V/A; L76V; V82A/F/T/S

Cahn et al. Lancet Infect Dis 2014

Viral load <50 copies/mL at week 48 (ITTe),
baseline VL > 100.000 copies/mL

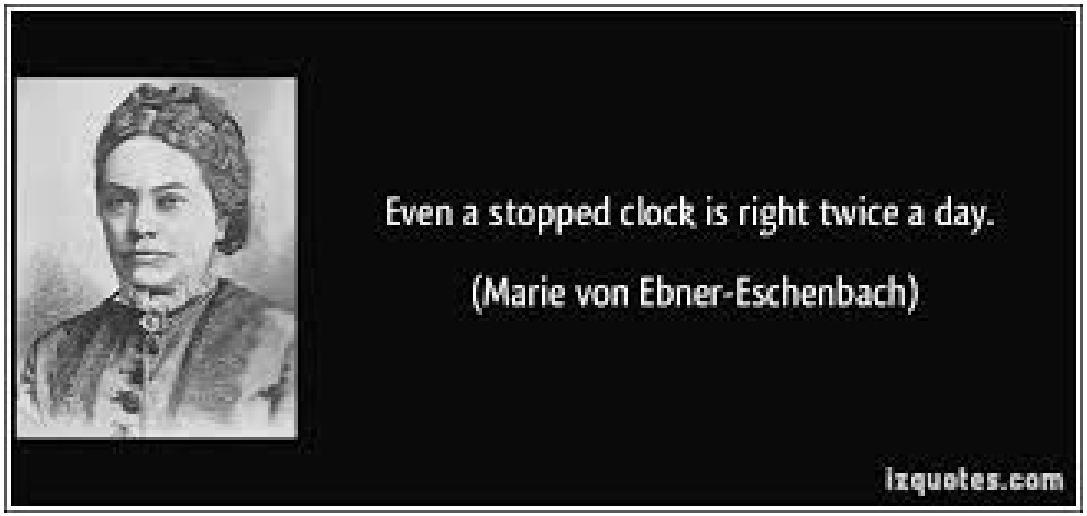


- Cahn et al. Lancet Infect Dis 2014

Pharmacological issues of dual regimens - 1

Why **bid** PI/r (LPV/R) **better** than **qd** PI/ (ATV/r and DRV/r)?

- Sample sizes, study designs
- Patient populations
- Potency of 2nd drug (RAL, MVC, 3TC)
- ***PK?***



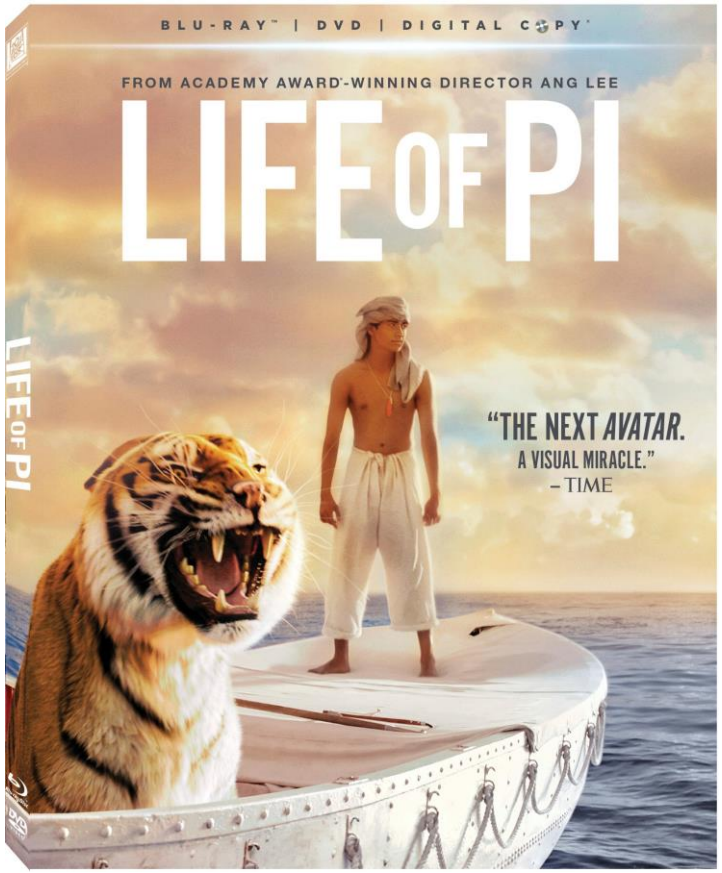
Limited “forgiveness” of boosted PI

- Regularly interspersed missed dose may pose a problem for PI/r **(short half-life)** and not for NNRTIs (long half-life)
- Average adherence to PI/r best predictor of virological efficacy

(Parienti, CID 2010)

Selective nonadherence to RTV more frequent than supposed

(Shuter HIV Clin Trials 2009, Calcagno IWCPA 2010)



The “tail” studies

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2011, p. 4218–4223 Vol. 55, No. 9
0066-4804/11/$12.00 doi:10.1128/AAC.01747-10

Pharmacokinetics of Once-Daily Darunavir-Ritonavir and Atazanavir-Ritonavir over 72 Hours following Drug Cessation[▽]

Marta Boffito,[1]* Akil Jackson,[1] Alieu Amara,[2] David Back,[2] Saye Khoo,[2] Chris Higgs,[1] Natalia Seymour,[1] Brian Gazzard,[1] and Graeme Moyle[1]

St. Stephen's Centre, Chelsea and Westminster Hospital, London, United Kingdom,[1] and Department of Pharmacology, University of Liverpool, Liverpool, United Kingdom[2]

Antiviral Therapy 13:901–907

Original article

Pharmacokinetics of atazanavir/ritonavir once daily and lopinavir/ritonavir twice and once daily over 72 h following drug cessation

Marta Boffito[1], Laura Else[2], David Back[2], Jessica Taylor[1], Saye Khoo[2], Marta Sousa[1], Anton Pozniak[1], Brian Gazzard[1] and Graeme Moyle[1]*

[1]St Stephen's Centre, Chelsea and Westminster Hospital, London, UK
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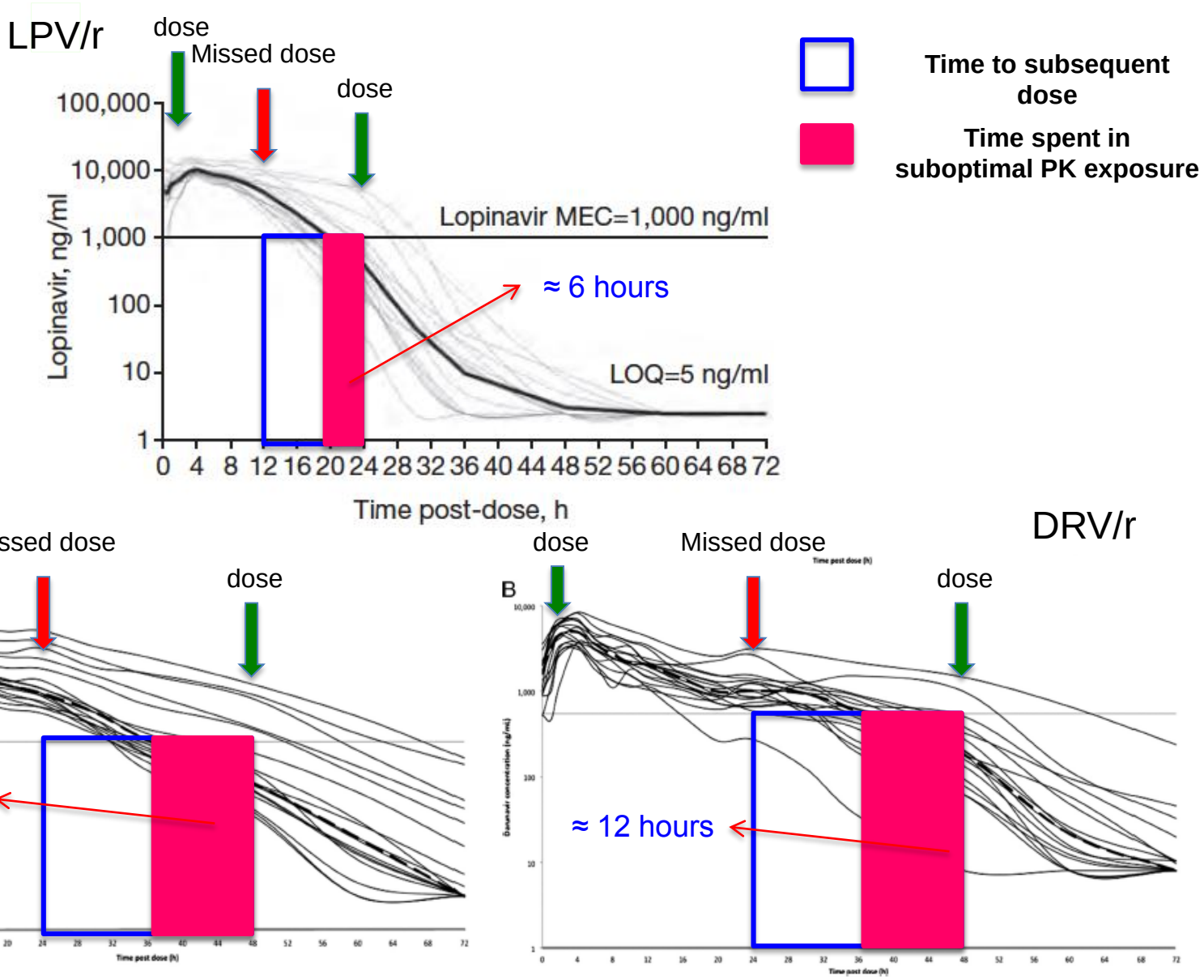
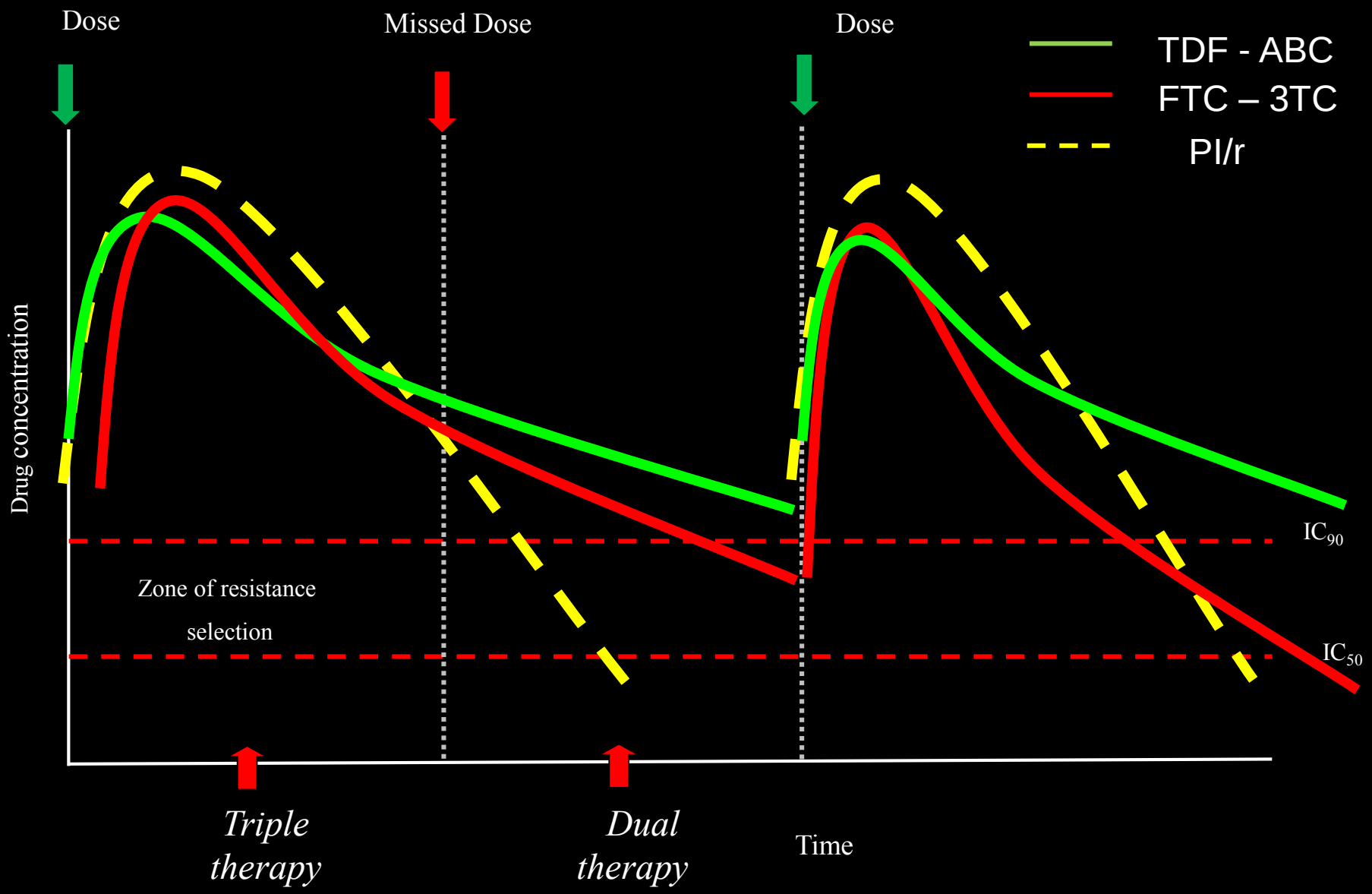
Which forgiveness in case of single dose missed? A comparison based on “tail”studies

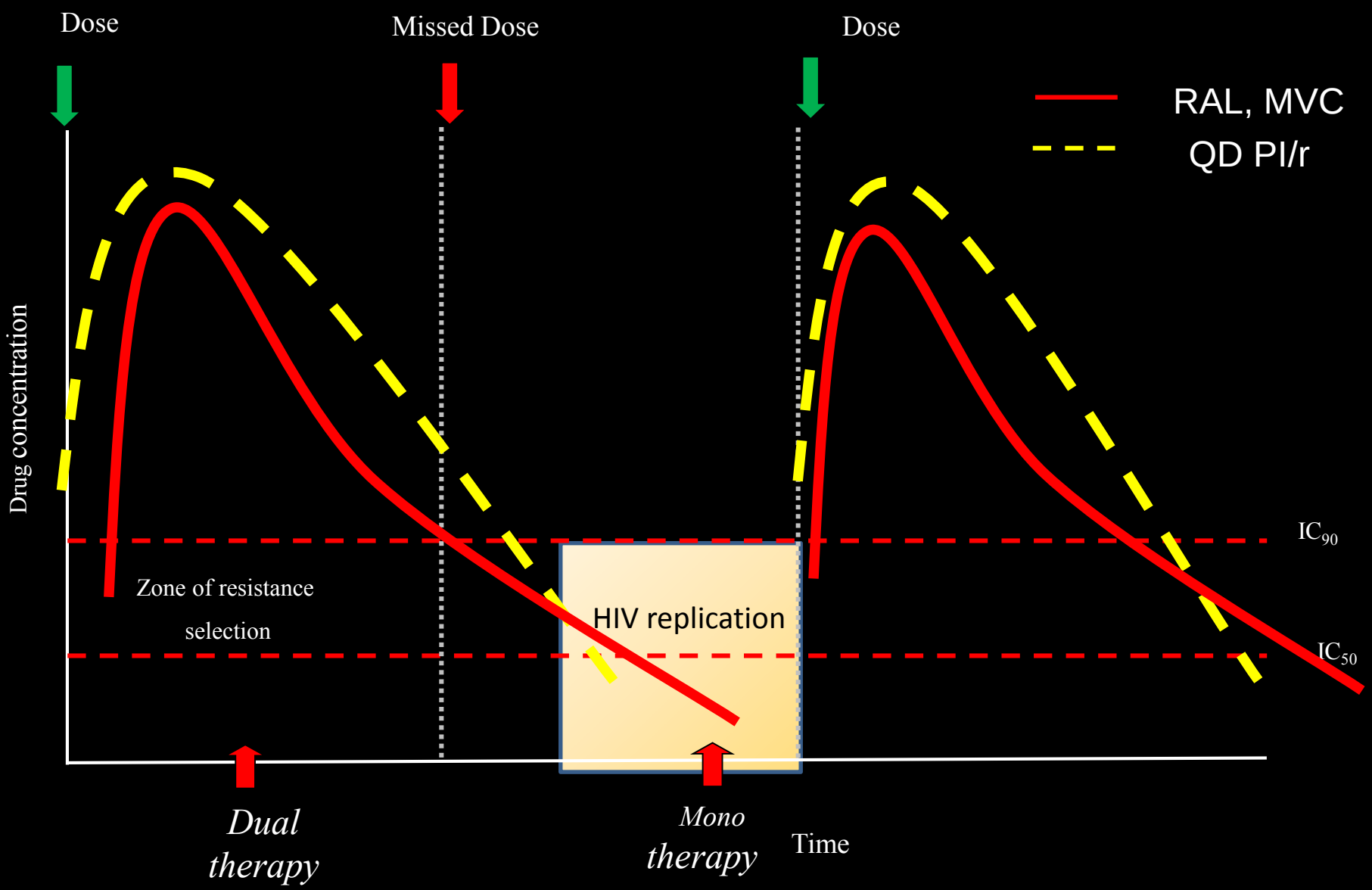


Boffito et al. AAC 2011 Sep;55(9):4218–23. 2.Boffito M, et al. AT 2008

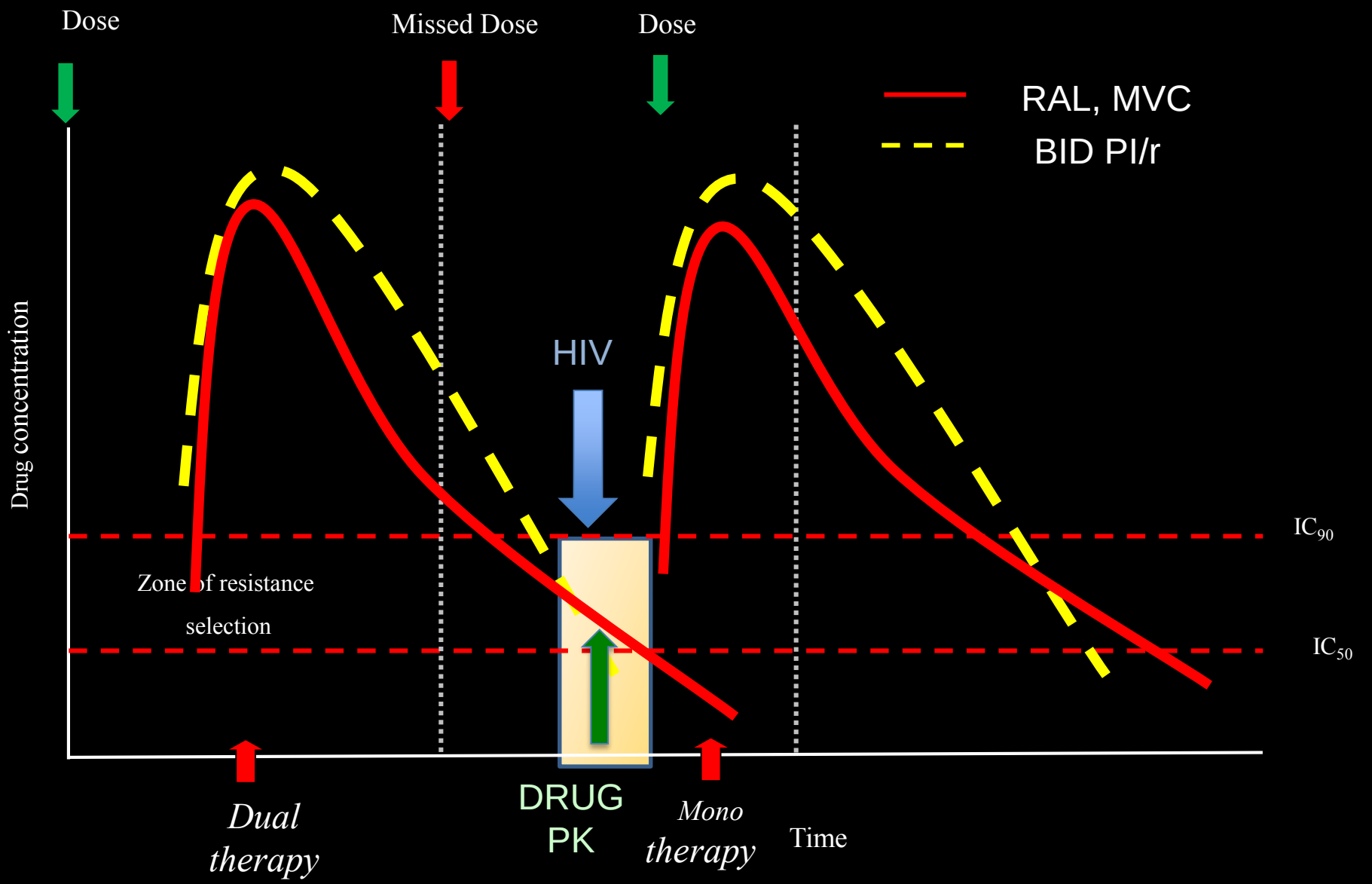
Forgiveness of NUCs-based regimens



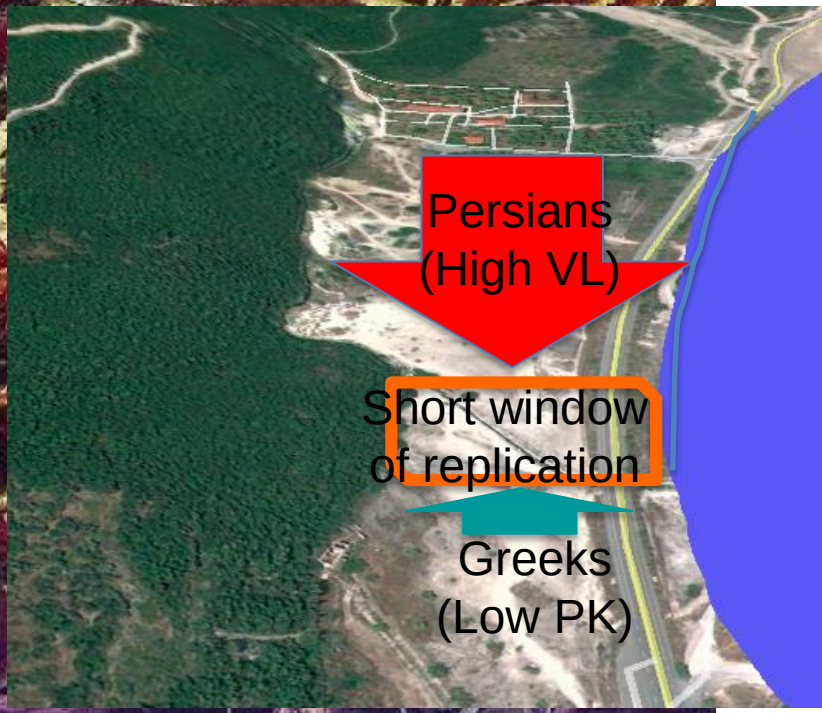
Limited forgiveness without NUCs?



Limited forgiveness without NUCs?



Battle of Thermopylae, 480 BC



Pharmacological issues of dual regimens - 1

In viremic patients who miss or delay a single drugs dose, QD PI/r-based regimens offer more prolonged opportunities of viral replication as compared to BID PI/r regimen.

In the clinical setting:

-to take into account in **viremic (and/or not fully adherent)** patients who need for clinical reasons a NUC-sparing regimen

-probably lower impact **in stable patients** (switch)

A future for dual regimens?

- ❑ STRs are for many but not for everyone (resistance, toxicity, cost)

- ❑ Dolutegravir as a new”backbone” for dual regimens, due to (boosted PI-like) high genetic barrier?

- ✓ DTG + RPV as a switch (DORISS, ViiV study)
- ✓ DTG + 3TC in naive (PADDLE)
- ✓ …..

Pharmacological issues of dual regimens - 2

Which maraviroc dosing when administered with PI/r?

Why 150 mg qd dosing has been selected for dual regimens?

1. In post-hoc re-analysis of MOTIVATE trial no concentration-efficacy relationship was found between QD and BID arms[1] :

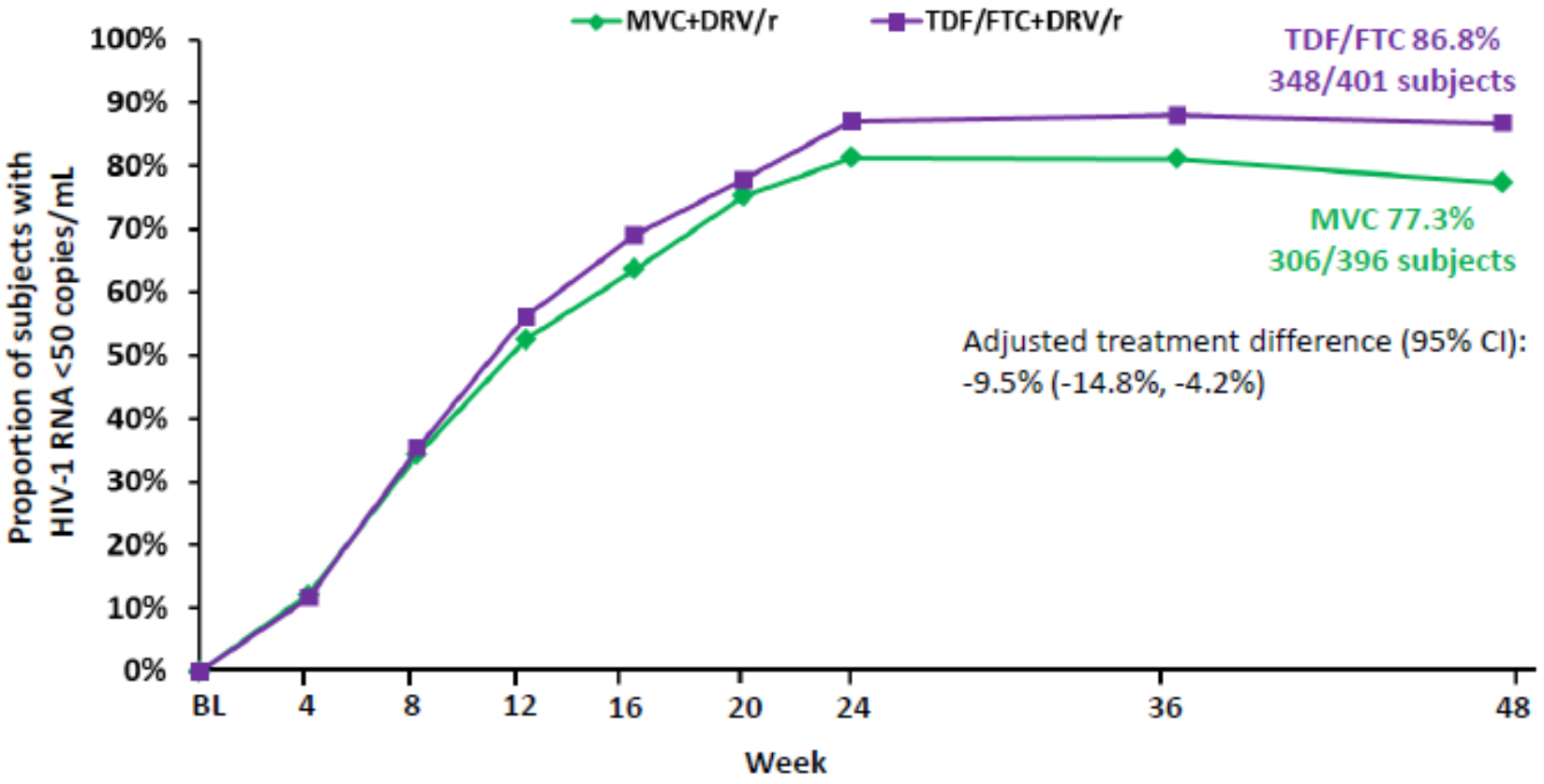
- "***both 150 QD and 150 BID dosing with boosted PI deliver concentration near the top of concentration-response curve"****

2. Initial encouraging results with small randomized studies (ATV/r and LPV/r) in naive patients.

Keep in mind: DRV use was not allowed in MOTIVATE…

[1]Jacqmin P, CPT Pharmacometrics Syst Pharmacol. 2013

HIV-1 RNA <50 copies/mL Over Time

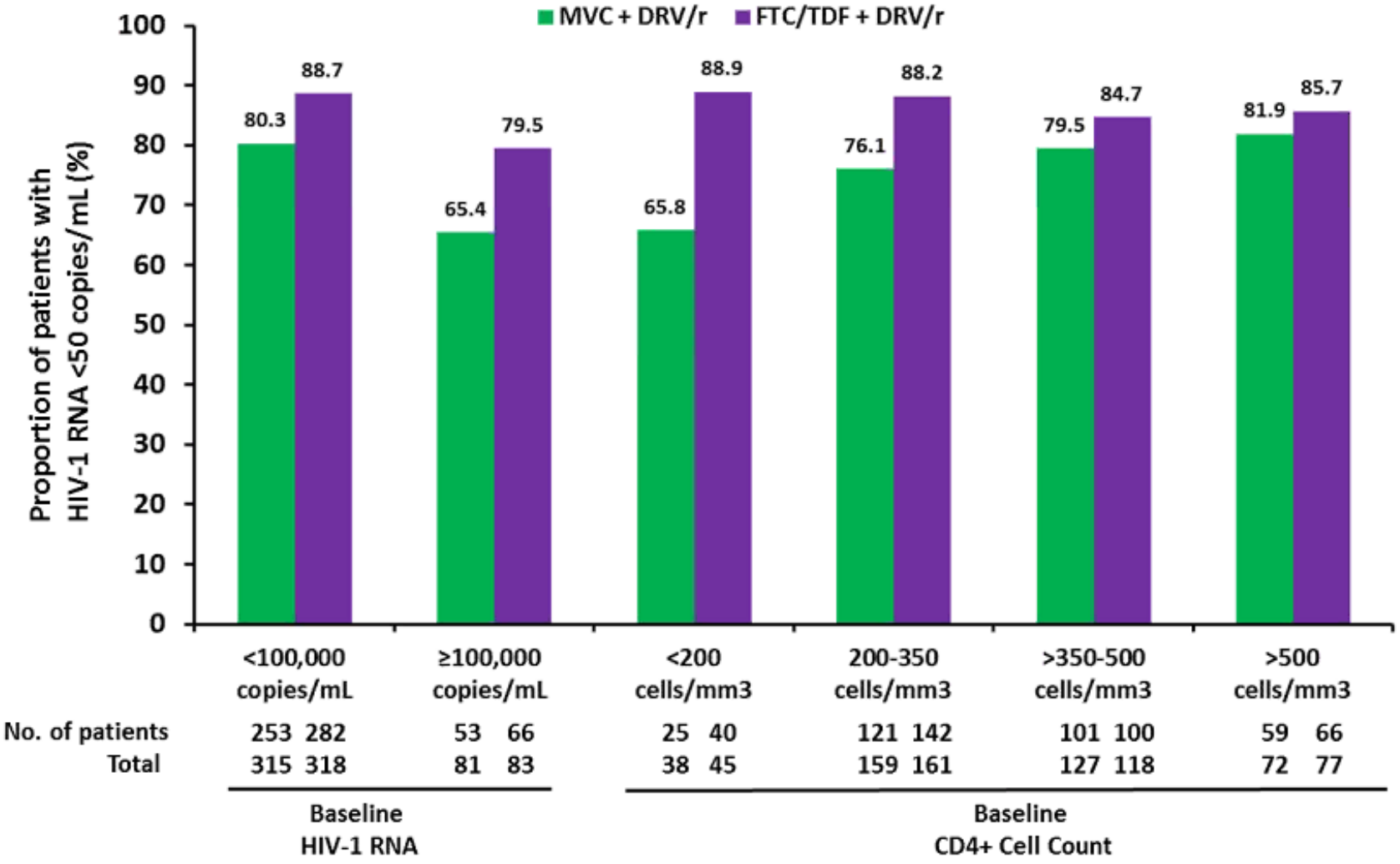


Mean CD4+ cell count changes at Week 48 (mean ± SD, cells/mm³)	
MVC + DRV/r	195.3 ± 175.7
TDF/FTC + DRV/r	193.9 ± 175.7

Stellbrink et al. IAC 2014; Melbourne, Australia. Abstract TUAB0101.

20th International AIDS Conference; July 20-25, 2014; Melbourne, Australia

Treatment Response at Week 48 by Key Subgroups



Stellbrink et al. IAC 2014; Melbourne, Australia. Abstract TUAB0101.

20th International AIDS Conference; July 20-25, 2014; Melbourne, Australia

"Although this investigational two-drug regimen was inferior to the three-drug regimen in this study, maraviroc remains a valuable antiretroviral therapy when used in combination with other antiretrovirals ***and dosed twice daily in adults*** with confirmed CCR5-tropic HIV."

Dr. John Pottage, Chief Scientific and Medical Officer, ViiV Healthcare.

PK of MVC 150 mg with PIs
(median values from different trials)

	DRV /r QD[1]	ATV/r[3]	LPV/r[2]
Ctrough ng/ml	39	37	59
Caverage ng/ml	128	180	179
Cmax ng/ml	415	650	601
Half-life hrs	10.3	-	9.8
AUC ng.h/ml	3073	4330	4694
Clearance l/h	48	-	32

MVC exposure higher with ATV/r and LPV/r than with DRV/r QD

[1]MIDAS study, Taiwo et al , JAIDS 2013; [2]VEMAN study, Calcagno et al, JAC 2013; 078 study, Mills et al; JAIDS 2013

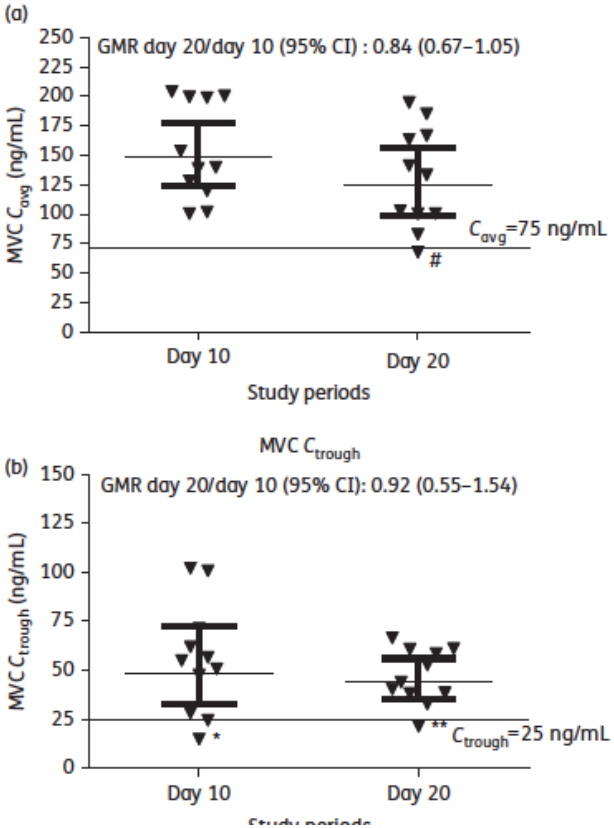
J Antimicrob Chemother
doi:10.1093/jac/dkt006

Journal of Antimicrobial Chemotherapy

Pharmacokinetic profile and safety of 150 mg of maraviroc dosed with 800/100 mg of darunavir/ritonavir all once daily, with and without nucleoside analogues, in HIV-infected subjects

Borja Mora-Peris[1]*, Adam Croucher[2], Laura J. Else[3], Jaime H. Vera[1,2], Saye Khoo[3], George Scullard[2], David Back[3] and Alan Winston[1,2]

[1]Department of Medicine, Faculty of Medicine, Imperial College London, St Mary's Hospital Campus, Norfolk Place, London W2 1PG, UK; [2]Department of HIV and Genitourinary Medicine, Imperial College Healthcare NHS Trust, St Mary's Hospital, Praed Street, London W2 1NY, UK; [3]Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

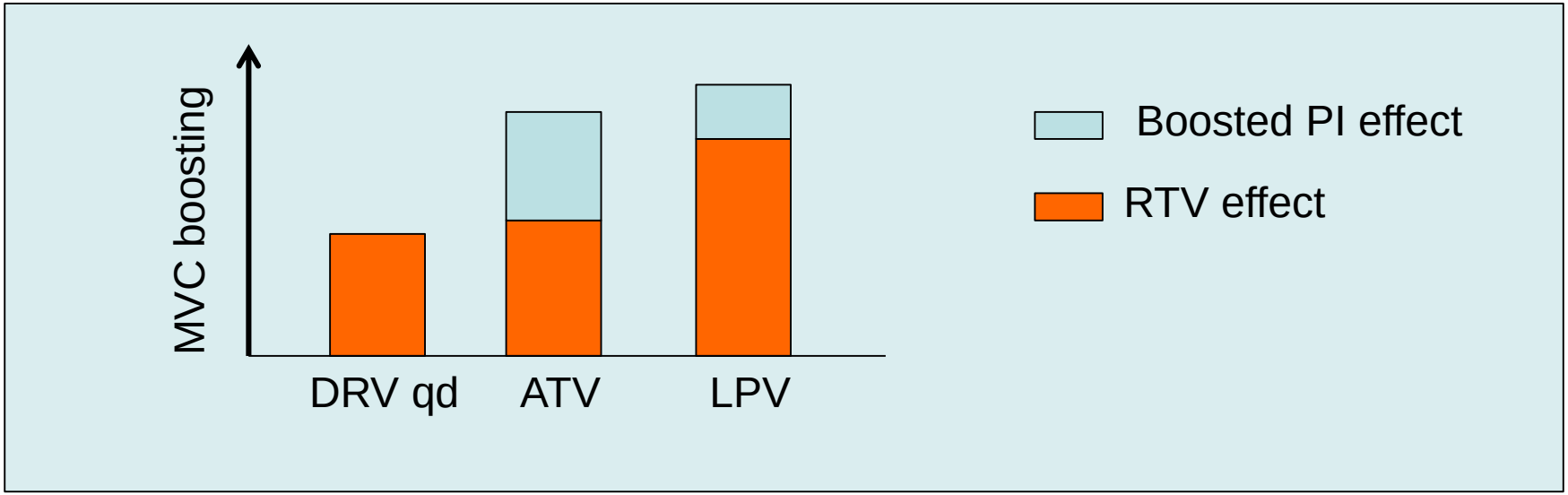


In 3 out of 11 subjects**, maraviroc Ctrough and Cavg were below 25 and 75 ng/mL,** respectively

Within this novel nucleoside-sparing regimen, maraviroc exposure is **dependent on ritonavir exposure,** which was slightly reduced in the absence of tenofovir/emtricitabine.

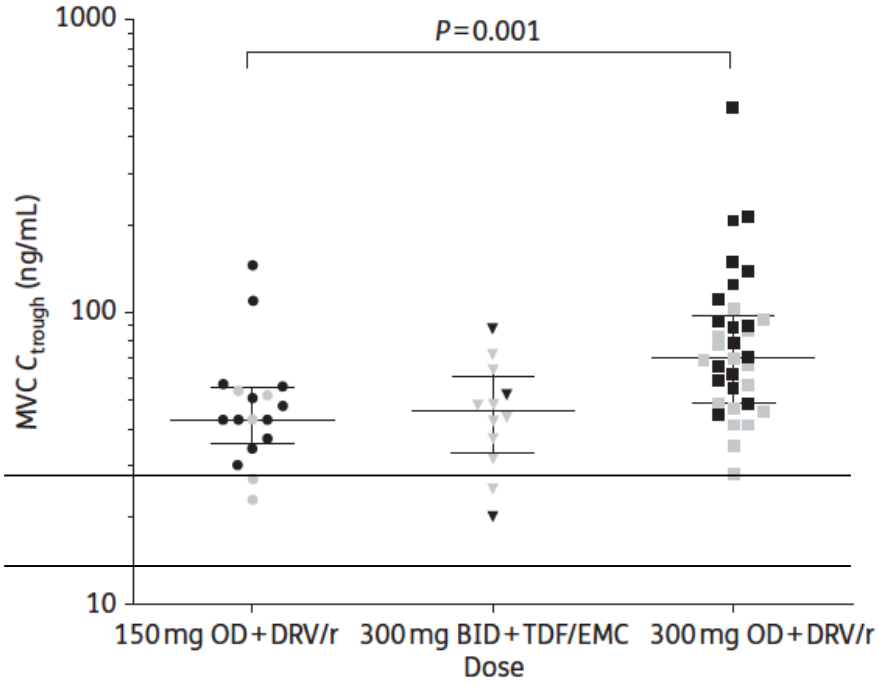
MVC 150 Qd – Facts & thoughts

trial	Study drugs	Virological Efficacy	Immunological efficacy
MODERN	**DRV/R + MVC 150 QD**	Inferior (stopped)	?
A4401078	**ATV/R + MVC 150 QD**	Inferior (slightly)	equal
VEMAN	**LPV/rR+ MVC 150 QD**	equal	superior



Why not MVC 300 QD + DRV/r?

1



Okoli, JAC 2012

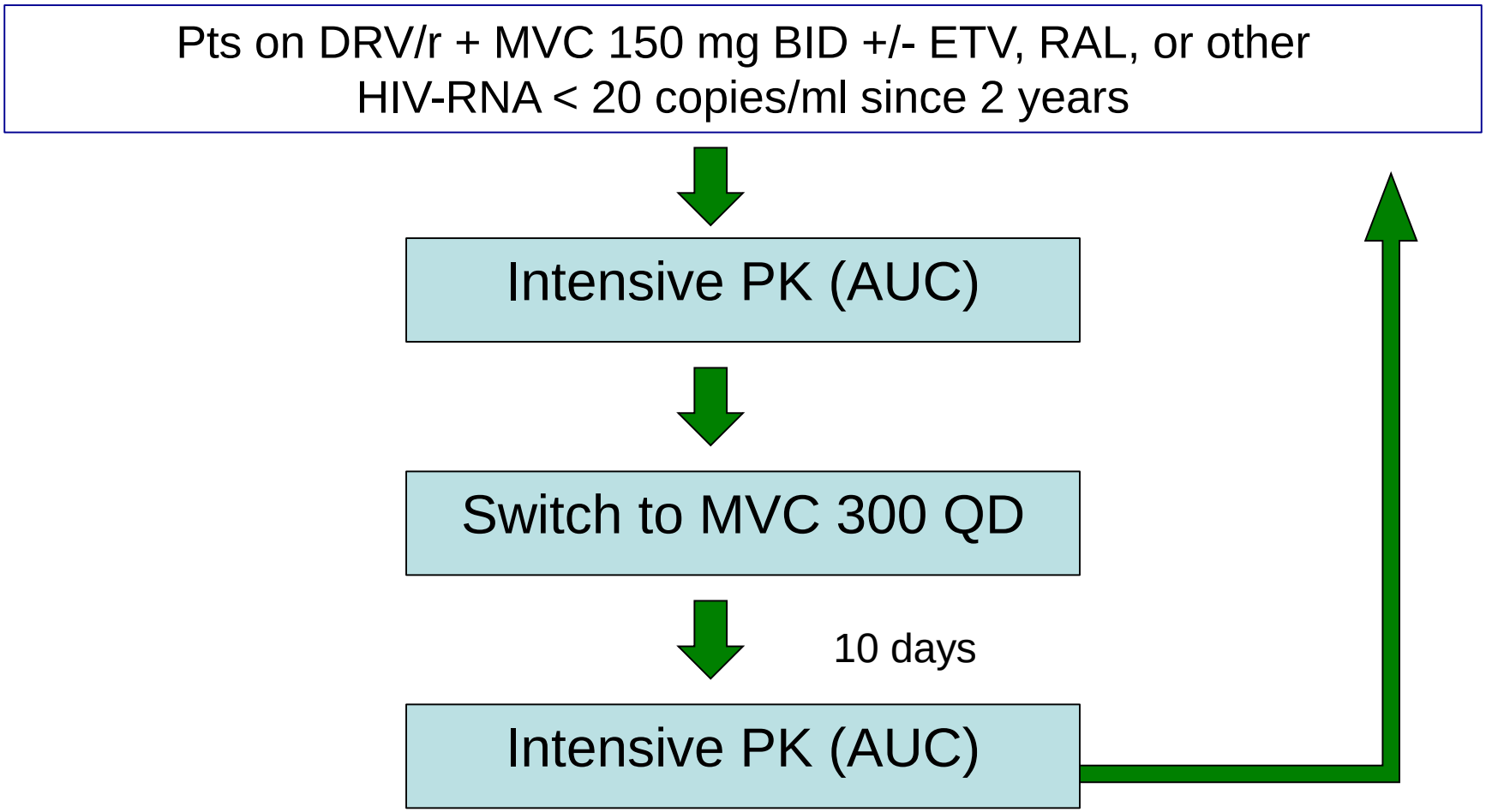
excess of MVC dose reduction can abrogate the advantage of boosting effect of PI!

2

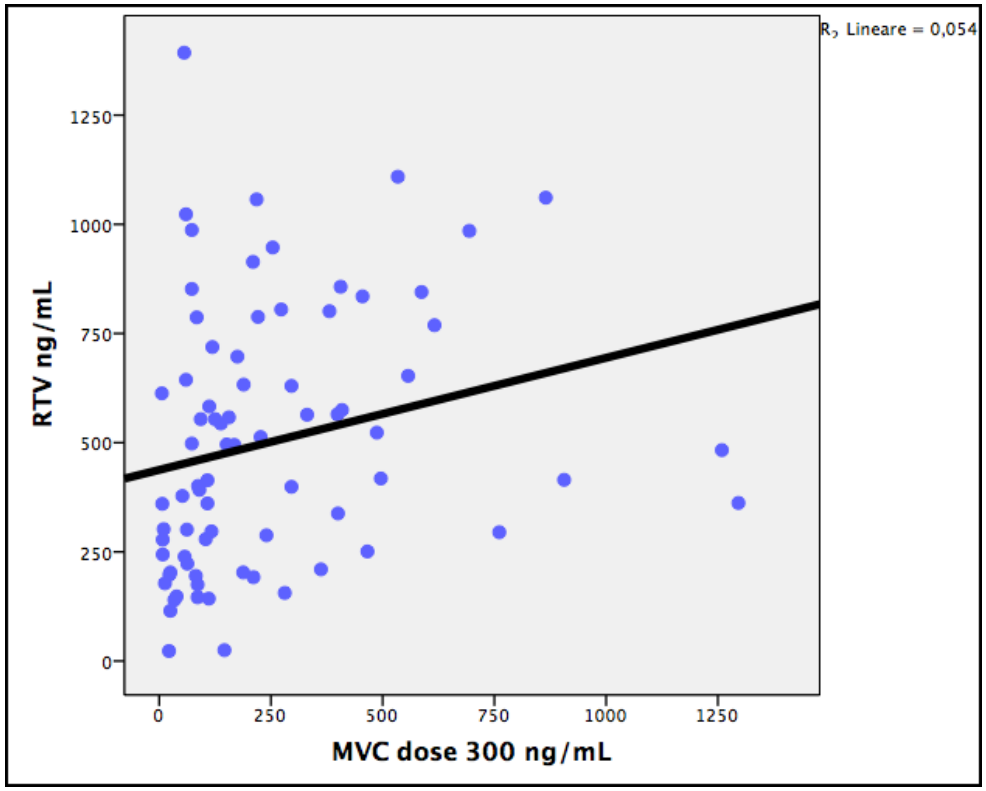
GUSTA study, switch to DRV/R + MVC 300 QD in stable patient (ONGOING)
median MVC Ctrough 58 ng/ml
(Gagliardini et al ICAR 2014)

Which data we need on MVC 300 QD (+ PI/r)?

Which data we need on MVC 300 QD (+ PI/r)?

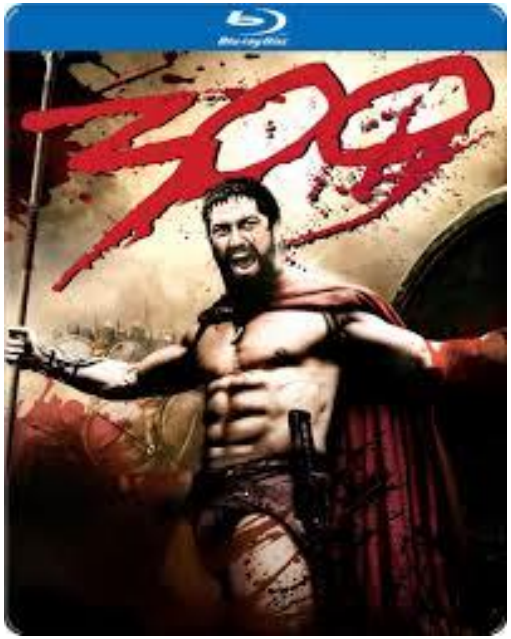


(Collaborative Torino-Milano study)



P=0.001

At 300 mg dosing, MVC exposure correlates with RTV exposure



PK of **MVC 300 QD** seems to be substantially **equivalent to standard 150 mg BID** when associated with DRV/r, potentially leading to more convenience and lower cost.

This dosage could be considered:

- ✓ for dual regimens in naive/stable patient
- ✓ as a switch in most stable patients on salvage regimens (MOTIVATE-like pts)

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ID Unit

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