STRATEGIE LONG-ACTING NEL TRATTAMENTO DELL'INFEZIONE DA HIV: PRO E CONTRO

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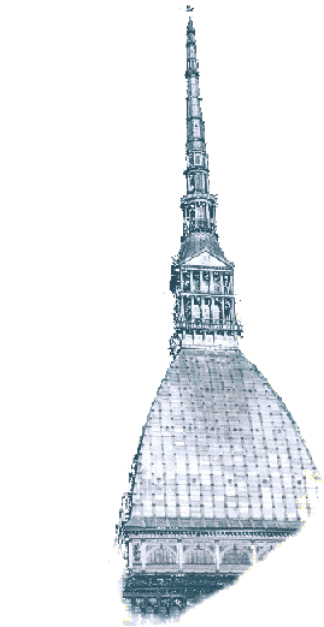

Financial Disclosures

- Abbvie
- BMS
- GS
- MSD
- Janssen
- ViiV
- Pfizer
- Novartis
- Astellas
- Basilea

- **Principles and Hypotheses supporting the development of Long-Acting Antiretrovirals (LA-ARVs)**

- **What is available in terms of pharmacological and clinical information**

- **Potential advantages/opportunities and disadvantages/risks**

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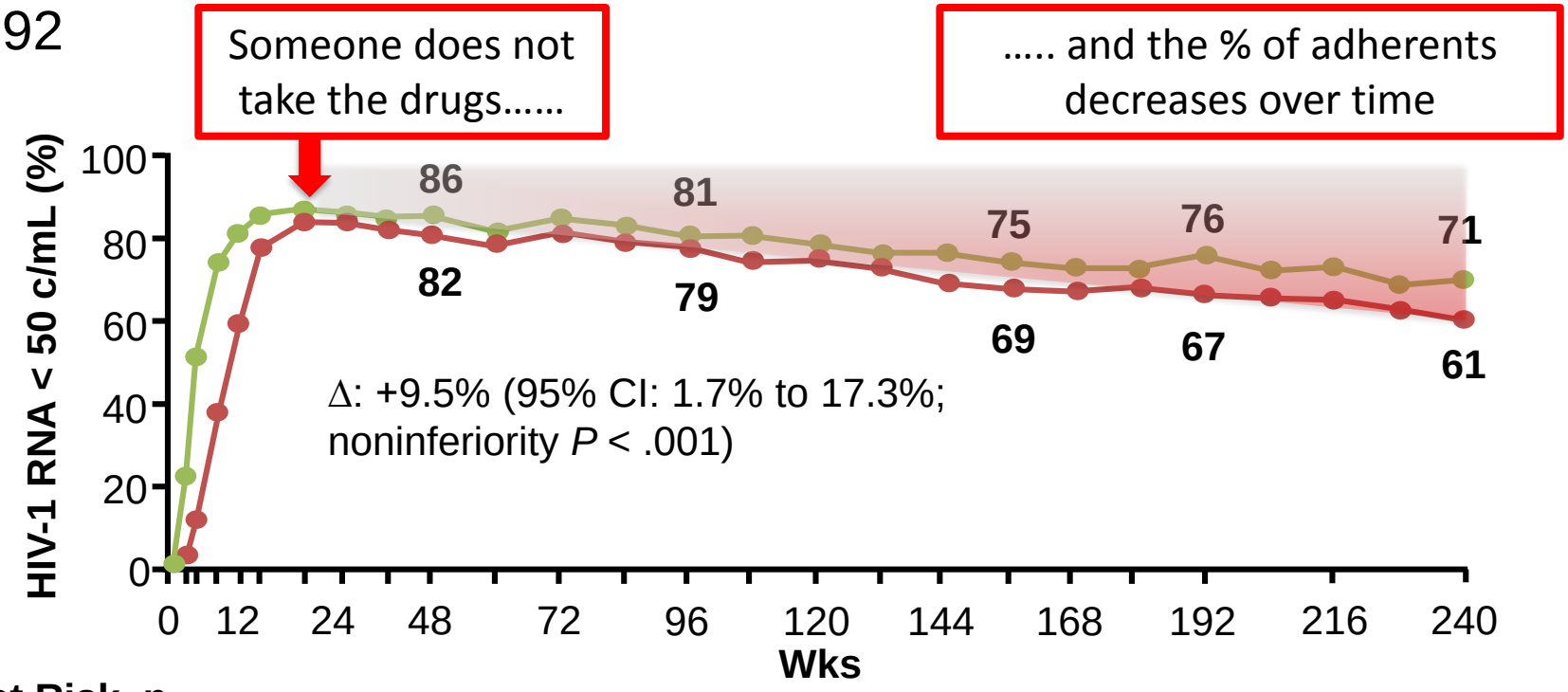
On the Therapeutic side - PROs

(imaging LA parenteral formulation of an entire regimen)

- Adherence to conventional therapy is suboptimal in a sizeable proportion of pts, even with the most tolerable and easy to take regimen (e.g. STR)
- Selective non-adherence is consistently reported in clinical trials and common practice
- Patients are aging and concurrent medications are often required
- Prior experience with PEG-IFN vs conventional IFN formulations consistently showed increased rates of therapeutic success, with higher and sustained [IFN] over time
- Community VL likely to be reduced by higher prevalence of 100% adherent patients

STARTMRK: RAL vs EFV in Treatment-Naive Patients: 5-Yr Final Report

- RAL noninferior to EFV in HIV-1 RNA < 50 c/mL at Wk 48 (primary endpoint; ITT, NC = F analysis); superior from Wk 192



Pts at Risk, n

RAL	281	276	279	280	281	281	277	280	281	281	277	279
EFV	282	282	282	281	282	282	281	281	282	282	282	279

Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;63:77-85.

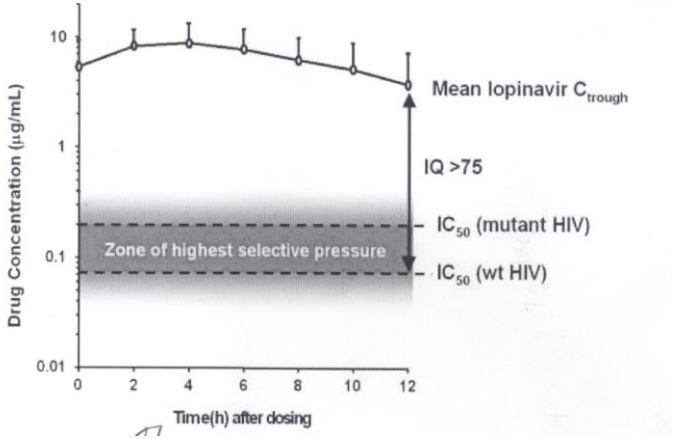
Occurrence of Selective Ritonavir Nonadherence and Dose-Staggering in Recipients of Boosted HIV-1 Protease Inhibitor Therapy

Jonathan Shuter,[1,2] Julie A. Sarlo,[1] Richard A. Rode,[3] and Barry S. Zingman[1,2,4]

[1]AIDS Center and Division of Infectious Diseases, Montefiore Medical Center, Bronx, New York, USA; [2]Albert Einstein College of Medicine, Bronx, New York, USA; [3]Abbott Laboratories, Abbott Park, Illinois, USA; [4]Einstein/Montefiore Center for AIDS Research, Bronx, New York, USA

HIV Clin Trials 2009;10(3):135–142

Results: The final study population consisted of 36 subjects. Three subjects (8.3%) were selectively nonadherent to ritonavir, 17 (47.2%) staggered any doses of ritonavir, and 3 (8.3%) staggered more than 5% of their ritonavir doses. Two of these three were also selectively nonadherent to ritonavir. There was no evident impact of these behaviors on HIV viral load (VL); all subjects who were selectively nonadherent to or frequently staggered doses of ritonavir had VL <75 copies/mL at 24 weeks. **Conclusions:** Selective ritonavir nonadherence and dose-staggering occurs in a small but significant minority of boosted PI recipients.



Darunavir without ritonavir is 37% bioavailable

Primary resistance to darunavir leads to significant in class resistance

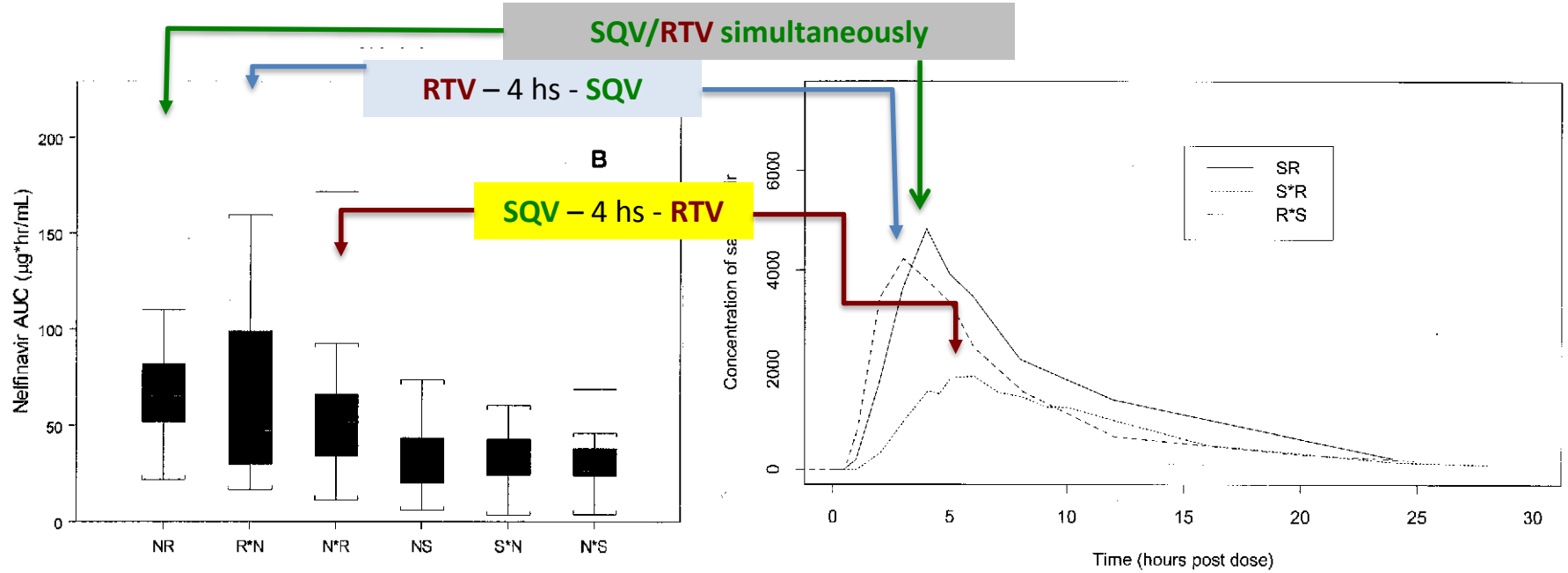
Darunavir package insert

Effect of simultaneous versus staggered dosing on pharmacokinetic interactions of protease inhibitors (Clin Pharmacol Ther 2003;73:406-16.)

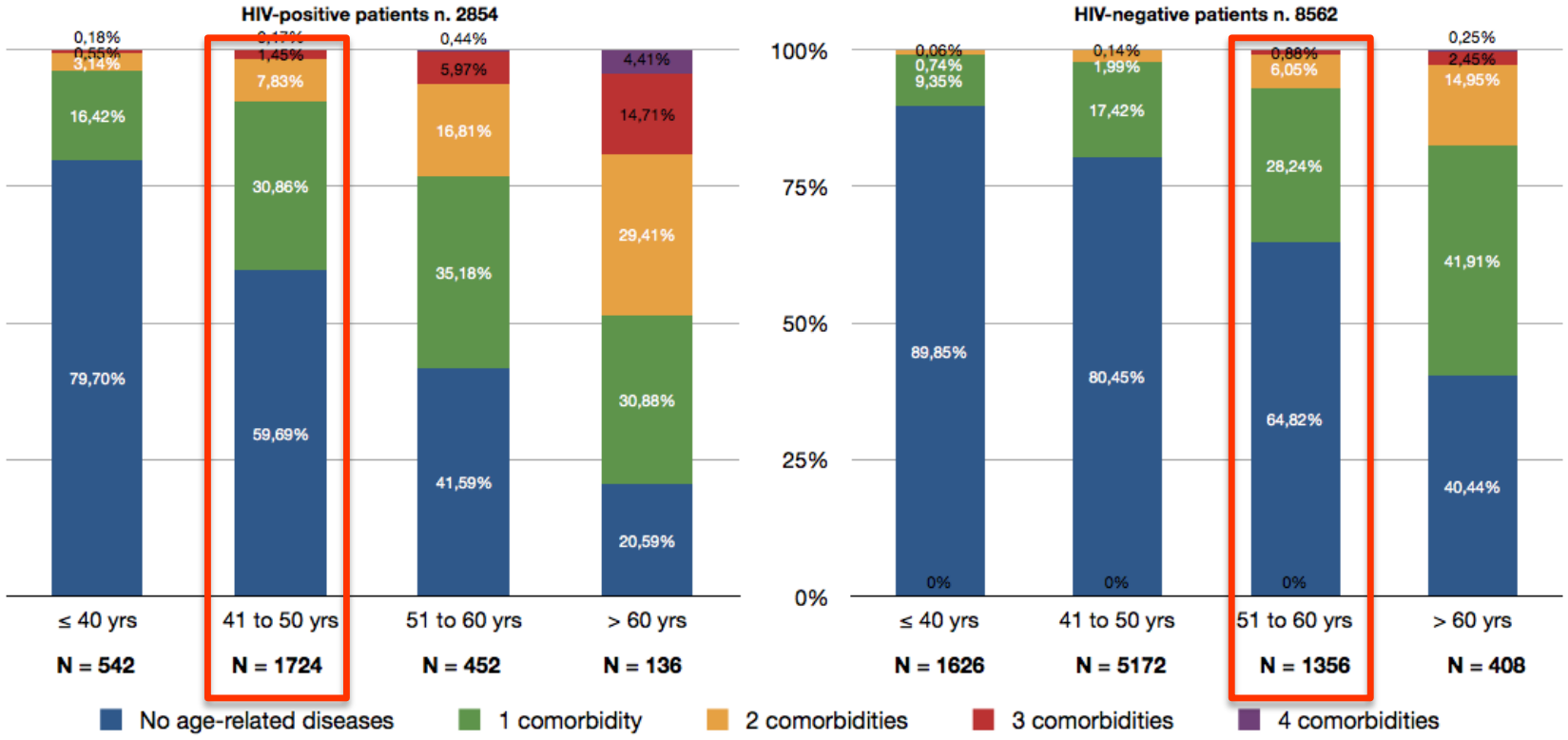
Carla B. Washington, PhD, Charles Flexner, MD, Lewis B. Sheiner, MD, Susan L. Rosenkranz, PhD, Yoninah Segal, MS, Judith A. Aberg, MD, Terrence F. Blaschke, MD, and the AIDS Clinical Trials Group Protocol 378 (ACTG 378) Study Team,
Stanford and San Francisco, Calif, Baltimore, Md, and Boston, Mass

Objective: **The aim of this study was to determine whether pharmacokinetic interactions between the protease inhibitors saquinavir soft gel, nelfinavir, and ritonavir are affected by the timing of administration.**

Study design: **We used an open-label, 6-period, incomplete Latin square crossover study in 18 human immunodeficiency virus–negative subjects. Each received single oral doses of 2 of the 3 protease inhibitors during each of 6 periods. Single doses were given either simultaneously or separated by 4 hours.**



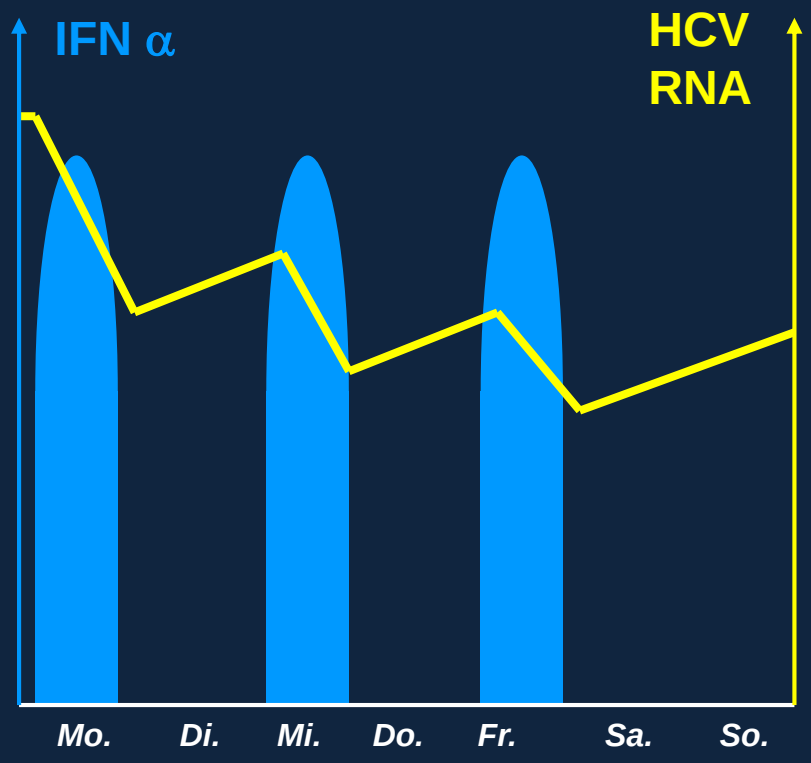
Poly-patology prevalence in cases and controls, stratified by age categories

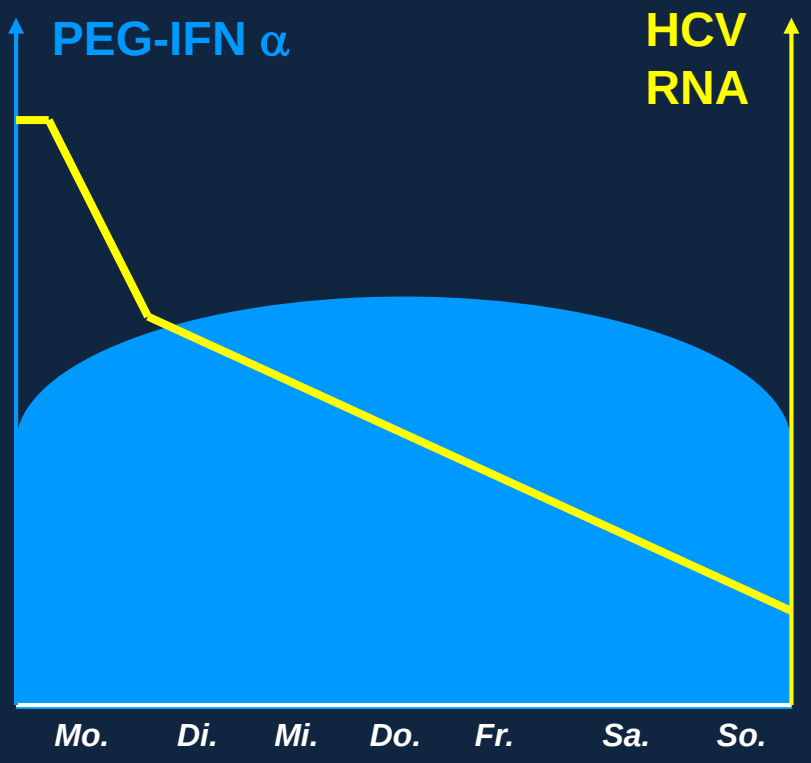


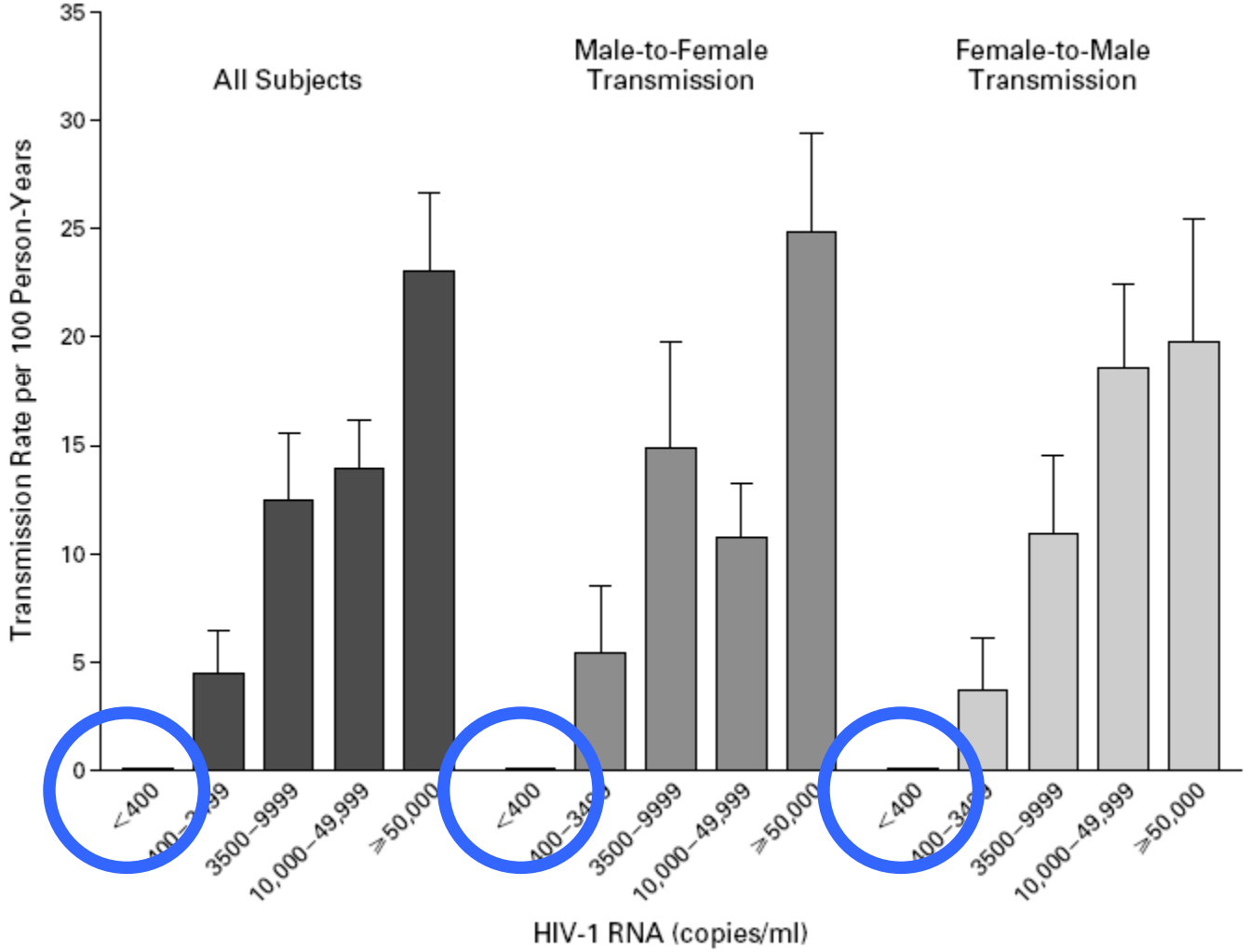
Pp	**3.9%**	**9.0%**	**20.0%**	**46.9%**	**Pp**	**0.5%**	**1.9%**	**6.6%**	**18.7%**

Guaraldi G, et al. CID 2011; 11: 1120-6

Comparison of Pharmacokinetic Profiles: PEG-IFN alfa vs. IFN alfa

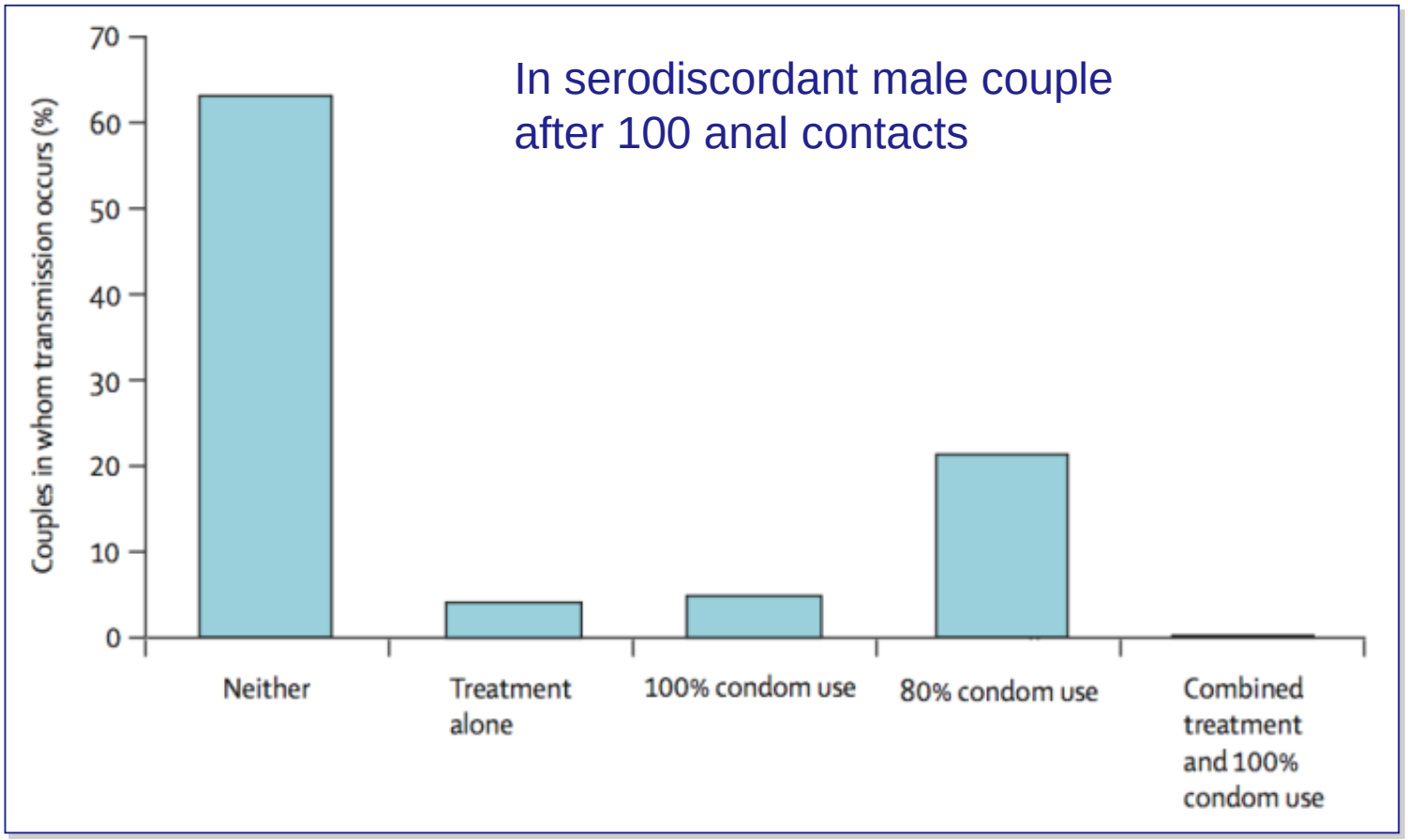





All Subjects
Male-to-Female Transmission
Female-to-Male Transmission
Transmission Rate per 100 Person-Years
35
30
25
20
15
10
5
0
<400
3500–9999
10,000–49,999
≥50,000
HIV-1 RNA (copies/ml)

Swiss statement ~~challeng~~ confirmed

(based on math. Model by Wilson et al.)



Garnett &Gazzard, The Lancet, 27.7.2008, editorialcomment

- Principles and Hypotheses supporting the development of Long-Acting Antiretrovirals (LA-ARVs)

- **What is available in terms of pharmacological and clinical information**

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SSAT040

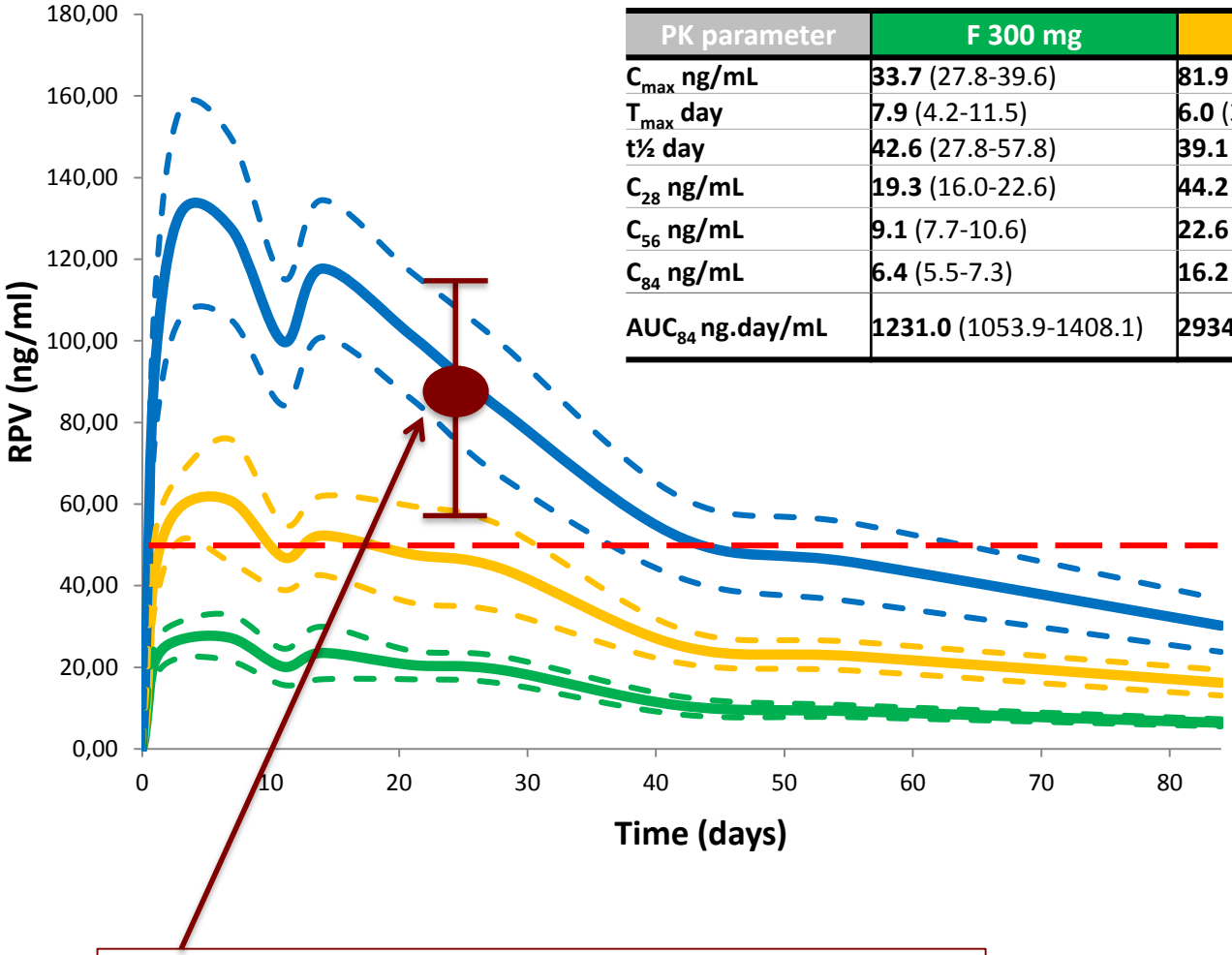
***A pharmacokinetic evaluation of the exposure and distribution of TMC278LA for use as pre-exposure prophylaxis, in plasma and genital tract / rectal compartments, following a single intramuscular dose at different doses in HIV negative healthy volunteers*. Jackson AGA, et al. In press**

- **HIV negative volunteers (60 female, 6 male)**
- **Aged 18 – 50 years**
- **Low behavioural risk for infection**
- **Female: > 50% of enrolled; self-identified African or African-Caribbean ancestry**
- **Administered 300 (n = 20), 600 (n = 20), 1200 (n = 20) mg RPV-LA (G001 formulation) intramuscularly (gluteus maximus)**
- **Sampling:**
  - **plasma *PK***
  - **cervicovaginal fluid (CVF; females) & rectal fluid (RF; males) *PK***
  - **tissue biopsies: vaginal (VT; females) & rectal (RT; males) *PK***
  - **cervicovaginal lavage (CVL; females) *PK & PD***

Day	**0**	**0 (4 h)**	**0 (8h)**	**1**	**3**	**7**	**11**	**14**	**21**	**28**	**42**	**56**	**84**
Plasma PK													
Genital/rectal fluid PK													
Tissue Biopsy (vaginal/rectal)PK													
CVL for PK and PD													

PLASMA 300, 600 & 1200 mg doses:

Dose proportionality: geometric mean (90% CI)



PK parameter	F 300 mg	F 600 mg	F 1200 mg
C_{max} ng/mL	**33.7** (27.8-39.6)	**81.9** (68.7-95.1)	**160.2** (137.5-182.9)
T_{max} day	**7.9** (4.2-11.5)	**6.0** (3.4-8.6)	**6.2** (4.3-8.1)
t½ day	**42.6** (27.8-57.8)	**39.1** (33.4-44.9)	**38.2** (29.8-46.6)
C_{28} ng/mL	**19.3** (16.0-22.6)	**44.2** (33.6-54.7)	**82.9** (66.6-99.1)
C_{56} ng/mL	**9.1** (7.7-10.6)	**22.6** (19.1-26.1)	**45.3** (35.8-54.9)
C_{84} ng/mL	**6.4** (5.5-7.3)	**16.2** (13.0-19.3)	**30.2** (23.7-36.6)
AUC_{84} ng.day/mL	**1231.0** (1053.9-1408.1)	**2934** (2568.5-3300.4)	**5981.6** (5155.9-6807.4)

TARGET?

Rilpivirine C_{trough} (ng/mL) dosed 25 mg QD at steady state in clinical studies

Jackson AGA, et al. In press

-A subject tested positive for HIV antibodies on study day 84

-HIV viral load on study day 56 = 370 copies,/mL
-HIV viral load on study day 84 = 175060 copies,/mL

-Received the lowest studied dose of 300 mg IM

-Plasma [RPV] = 24.3 ng/mL on day 28
10.5 ng/mL on day 42 (presumed exposure to HIV)
6.8 ng/mL on day 56
7.5 ng/mL on day 84

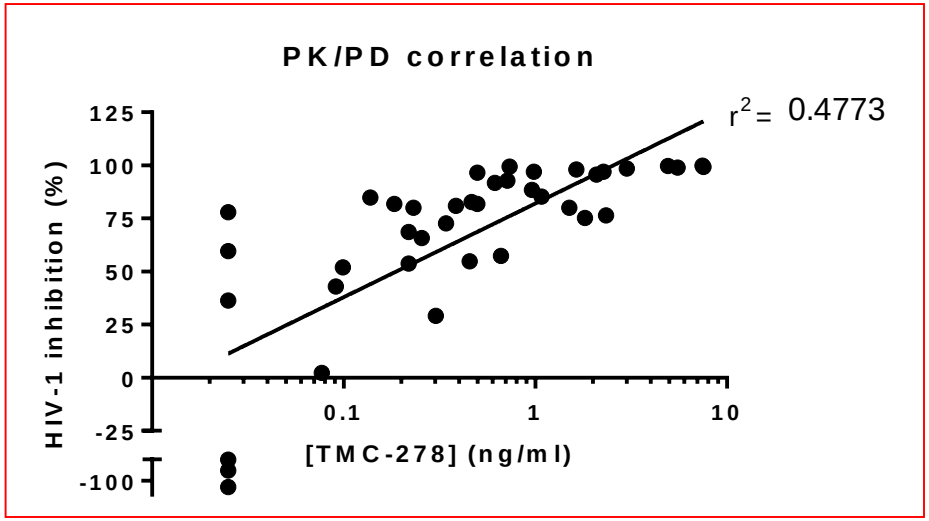
-CVF [RPV] = 32.9 ng/mL on day 28
18.3 ng/mL on day 42 (presumed exposure to HIV)
11.2 ng/mL on day 56
14.0 ng/mL on day 84

May suggest that higher exposures of RPV are needed to protect against HIV infection

Jackson AGA, et al. In press

SSAT040: PD data

- CVL samples collected by aspiration of 10 mL normal saline (after cervical lavage) at baseline, 28 and 56 days post-dose
- N = 10 on 300mg and N = 10 on 1200mg
- Antiviral activity determined against HIV-1BaL challenge of TZM-bl cells
- PK/PD correlation established using all data points from both doses

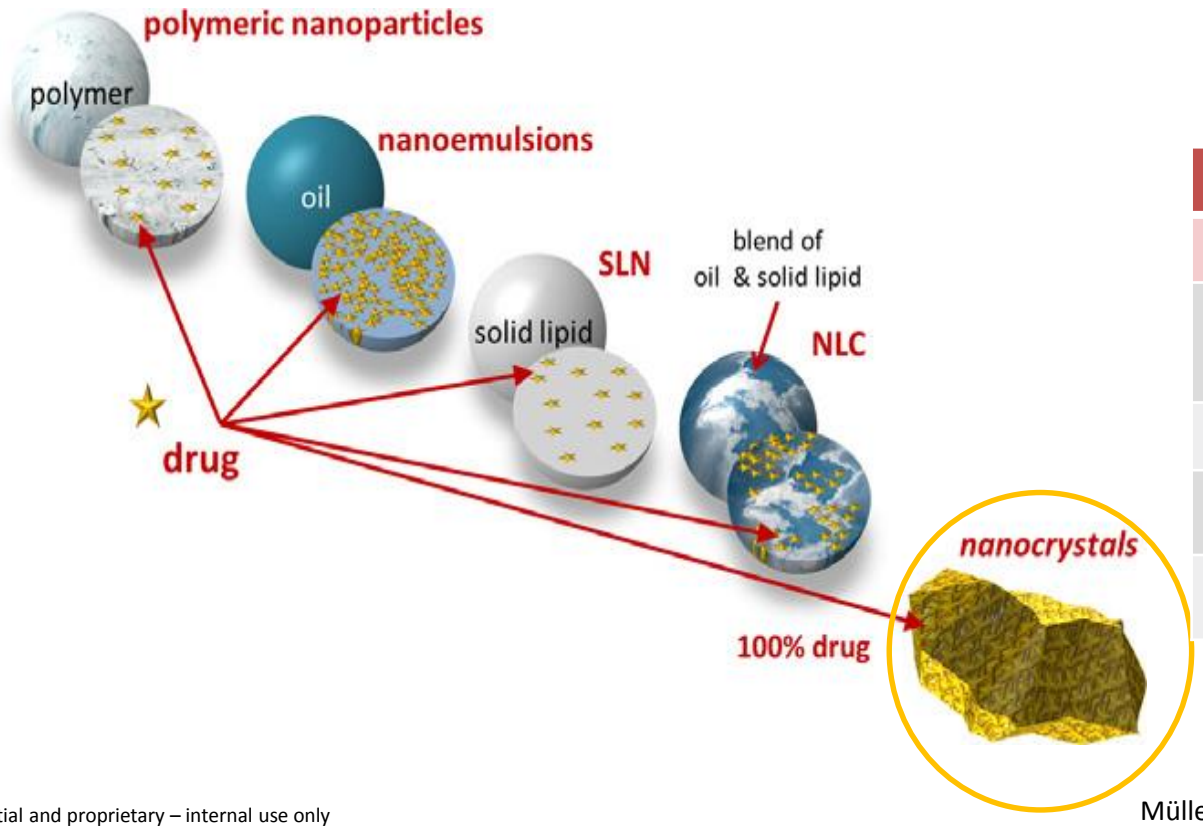


Thanks to Betsy Harold and Pedro Mesquita, Albert Einstein College of Medicine.

Jackson AGA, et al. In press

Cabotegravir nanocrystals

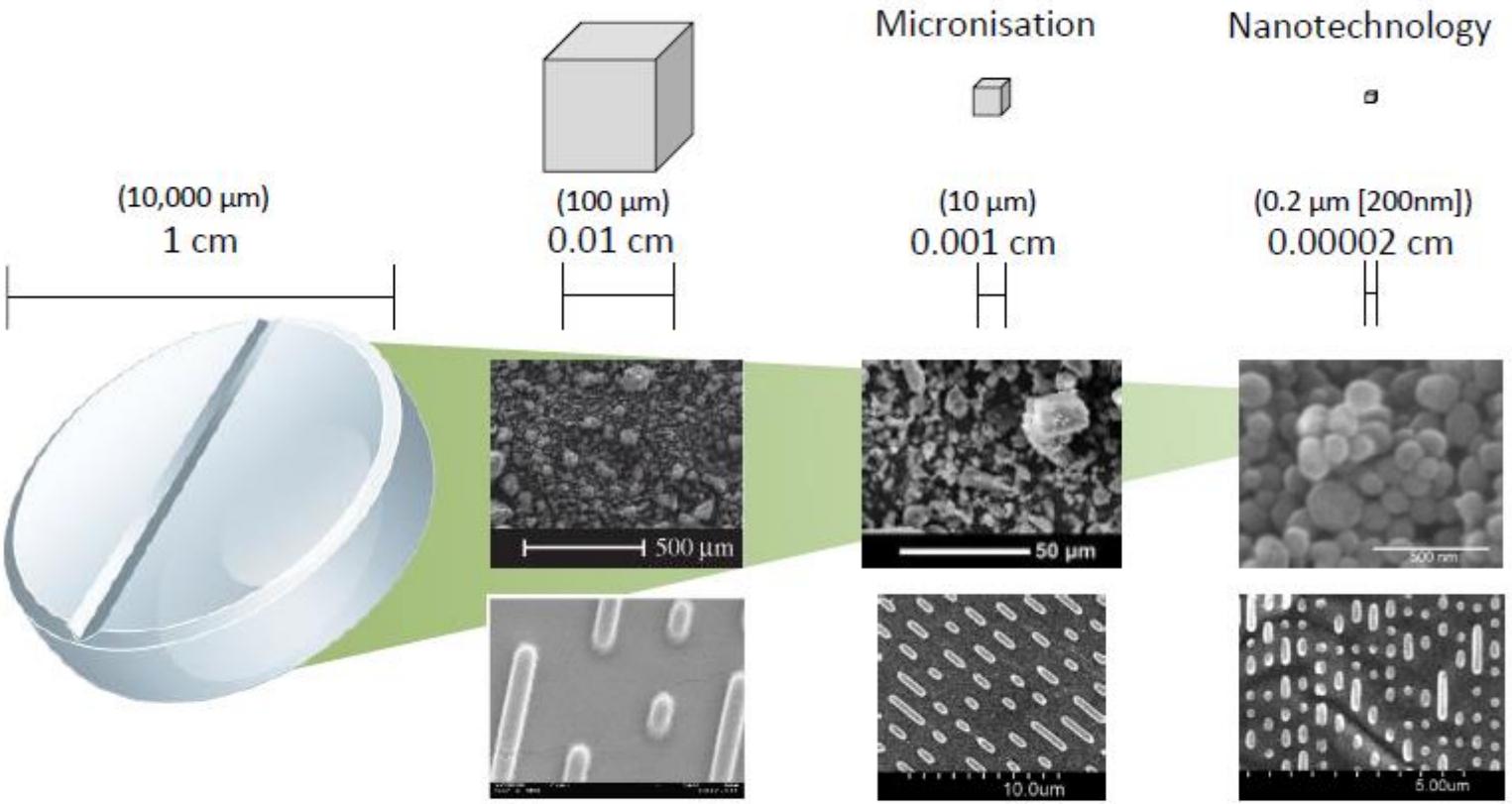
- **Drug nanocrystals are particles made from 100% drug**; typically, they are stabilized by surfactants or polymeric steric stabilizers.
- The high loading makes them very efficient in transporting drug to or **into cells**, reaching a sufficiently high therapeutic concentration for the pharmacological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

Drug formulation – size in context



Vinyl record features

1 particle
Dimensions =
100x100x100 µm

CD features

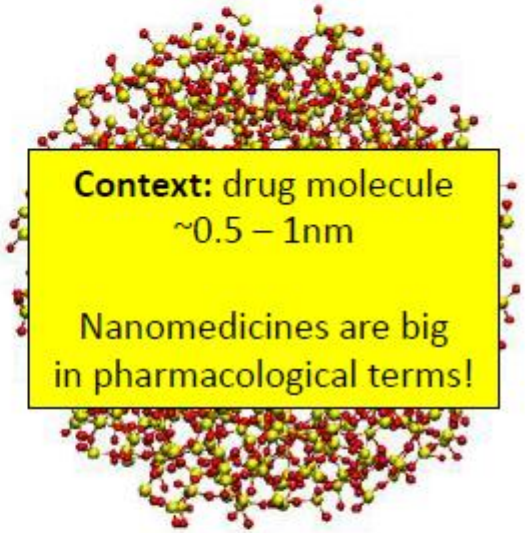
1000 particles
Dimensions =
10x10x10 µm

DVD features

125,000,000 particles
Dimensions =
0.2x0.2x0.2 µm

Nanomedicine - size in perspective

Beach ball diameter: 61 cm



Earth diameter: 12,742 km

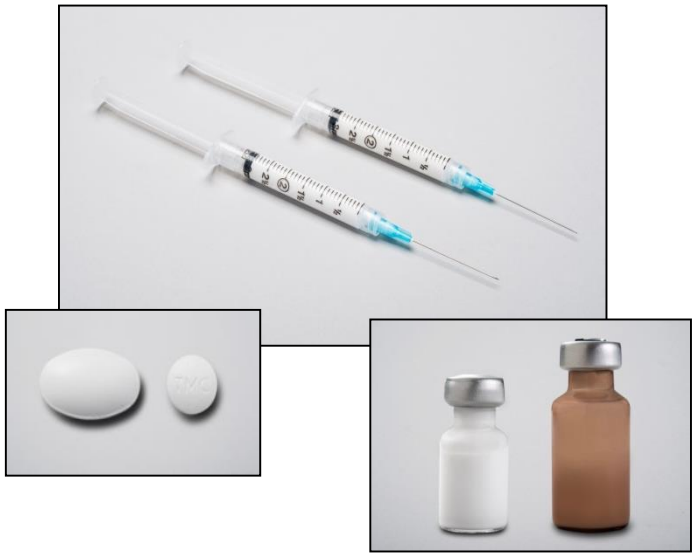
Polymeric nanoparticle: 30 nm

Approximately 20 million times smaller

Approximately 20 million times smaller

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

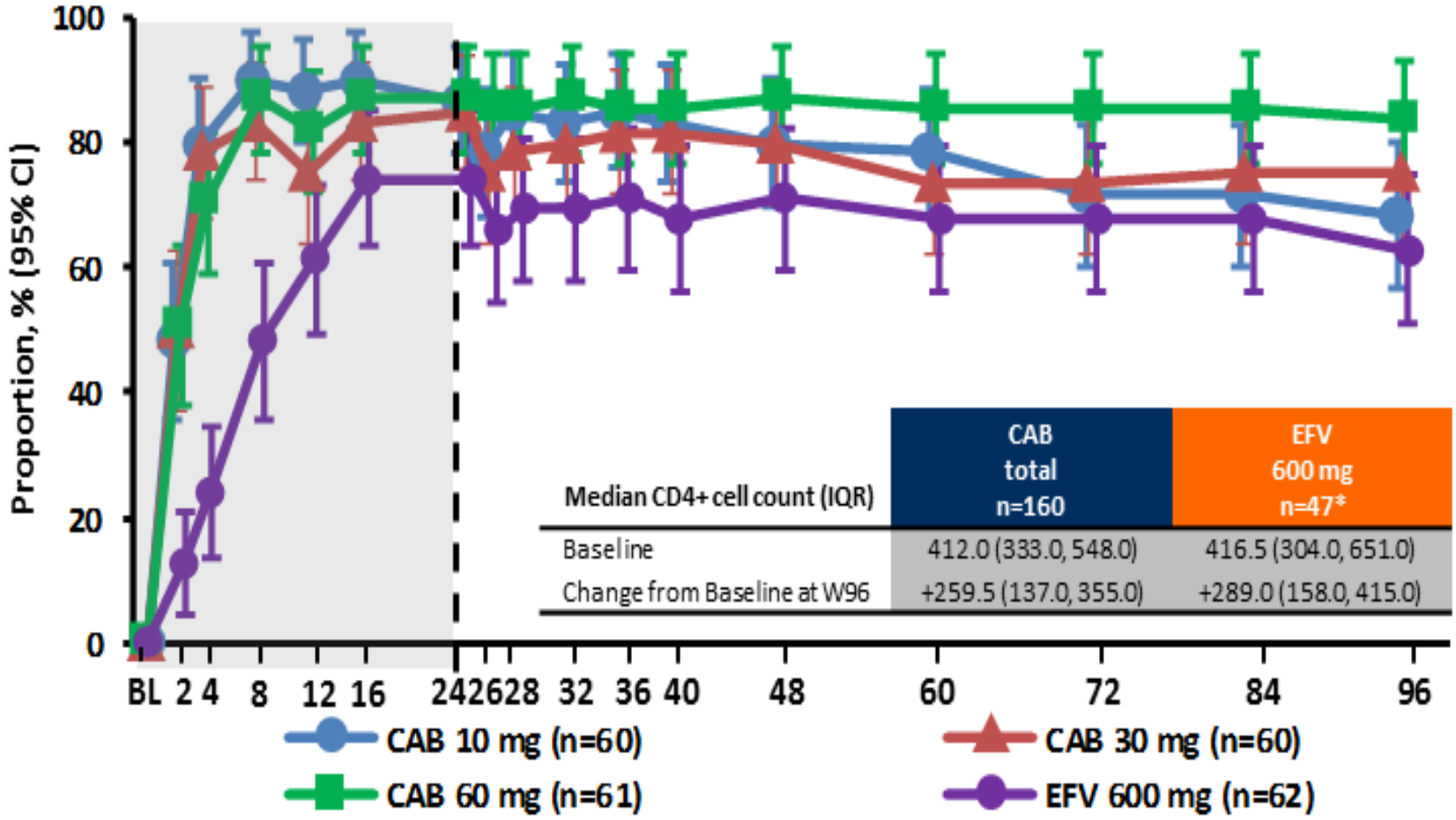


Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

Cabotegravir LA and RPV LA

Attribute	CAB LA	RPV LA
		
Drug concentration	200 mg/mL	300 mg/mL
Refrigeration/stability	No; store up to 30°C 24 months	Yes; store at 2–8°C 36 months (>8–25°C for ≤24 hours)
Protect from light	No	Yes
Dose – monthly	400 mg (2 mL)	600 mg (2 mL)
Dose – bimonthly	600 mg (3 mL)	900 mg (3 mL)
Dosage instructions/needle gauge	HCP administration Gluteal IM 23 G	HCP administration Gluteal IM 23 G
$t_{1/2}$ with single dose (range or SD)	~40 days (25–54 days)	44–61 days (±24 days)
Drug interactions	Low liability as perpetrator or victim	Low liability as perpetrator; victim of CYP3A4 induction/inhibition

LATTE Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Median CD4+ cell count (IQR)	CAB total n=160	EFV 600 mg n=47*
Baseline	412.0 (333.0, 548.0)	416.5 (304.0, 651.0)
Change from Baseline at W96	+259.5 (137.0, 355.0)	+289.0 (158.0, 415.0)

Margolis et al. CROI 2015; Seattle, WA. Poster 554LB.h

Protocol-Defined Virologic Failure (96 weeks)

	744 total n=181	EFV n=62
Subjects with PDVF during Induction	**3* (2%)**	**3 (5%)**

*1 subject per 744 dose

No NRTI, NNRTI or INI treatment-emergent mutations

	744 total n=160	EFV n=47
Subjects with PDVF during Maintenance	**2** (1%)**	**1 (2%)**
IN genotypic results at BL and time of PDVF	1	1
INI-r mutations	**1**	**0**
PR/RT genotypic results at BL and time of PDVF	2	1
NRTI-r mutations	**0**	**0**
NNRTI-r mutations	**1**	**0**

**744 10 mg – treatment emergent INI (Q148R) and NNRTI (E138Q) at W48; 744 FC = 3; RPV FC = 2

- 744 and RPV concentrations <50% of expected; extreme calorie restricted diet W40-W48

**744 30 mg – PDVF at W36; no treatment-emergent mutations

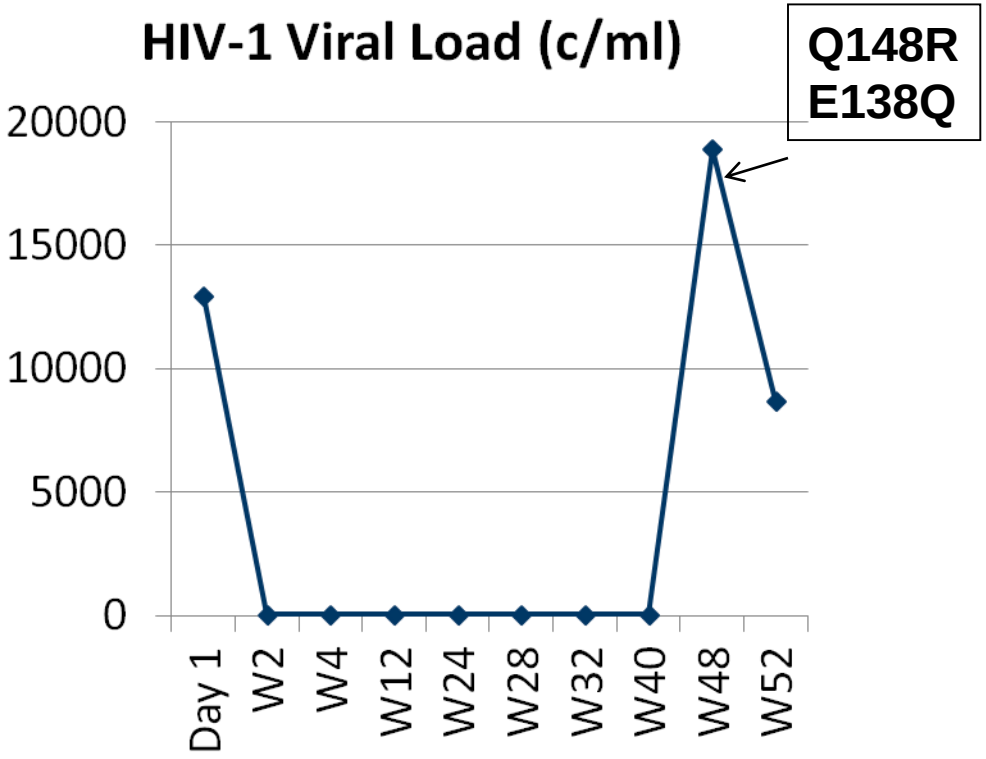
PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4
OR confirmed HIV-1 RNA ≥200 c/mL at or after Week 16 or after prior suppression to <200 c/mL

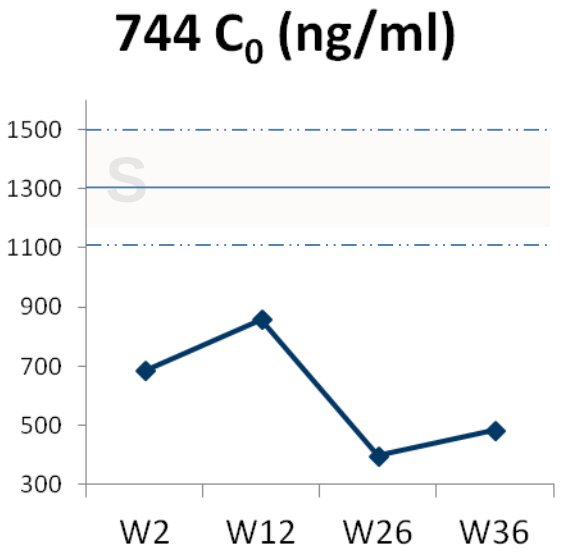
Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

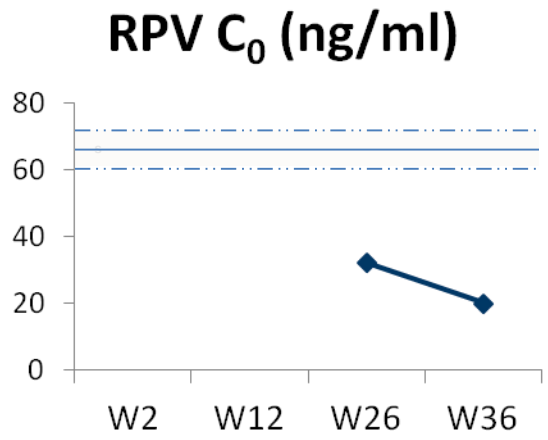
744 10 mg + RPV 25 mg

Low 744 and RPV plasma drug concentrations

Severe diet (650 kcal/day) between W40-W48



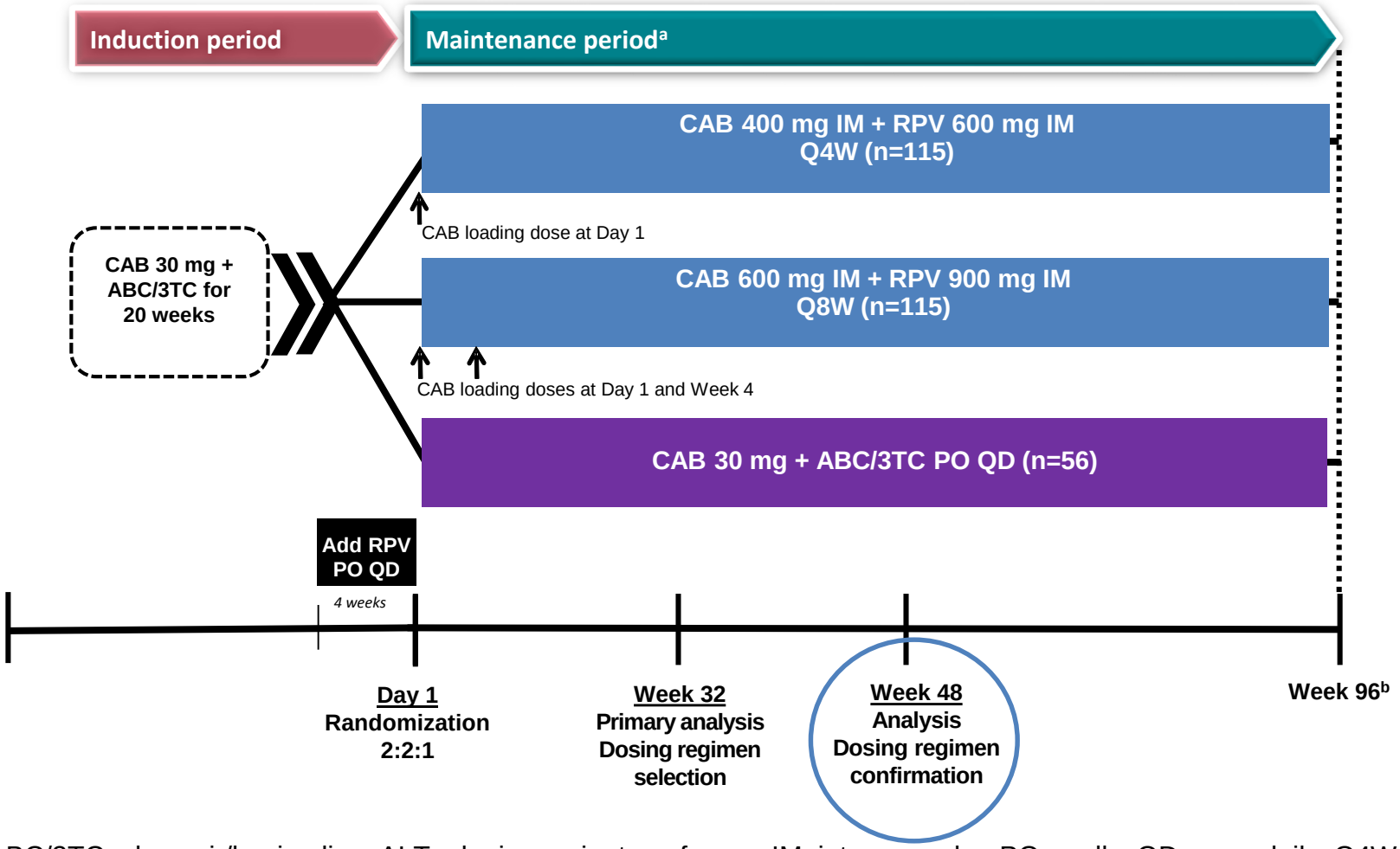




In Vitro SDM	DTG	744	RAL	EVG
Q148R (IC50 FC)	1.2	5.1	47	240

ston, MA. Abstract 91LB.

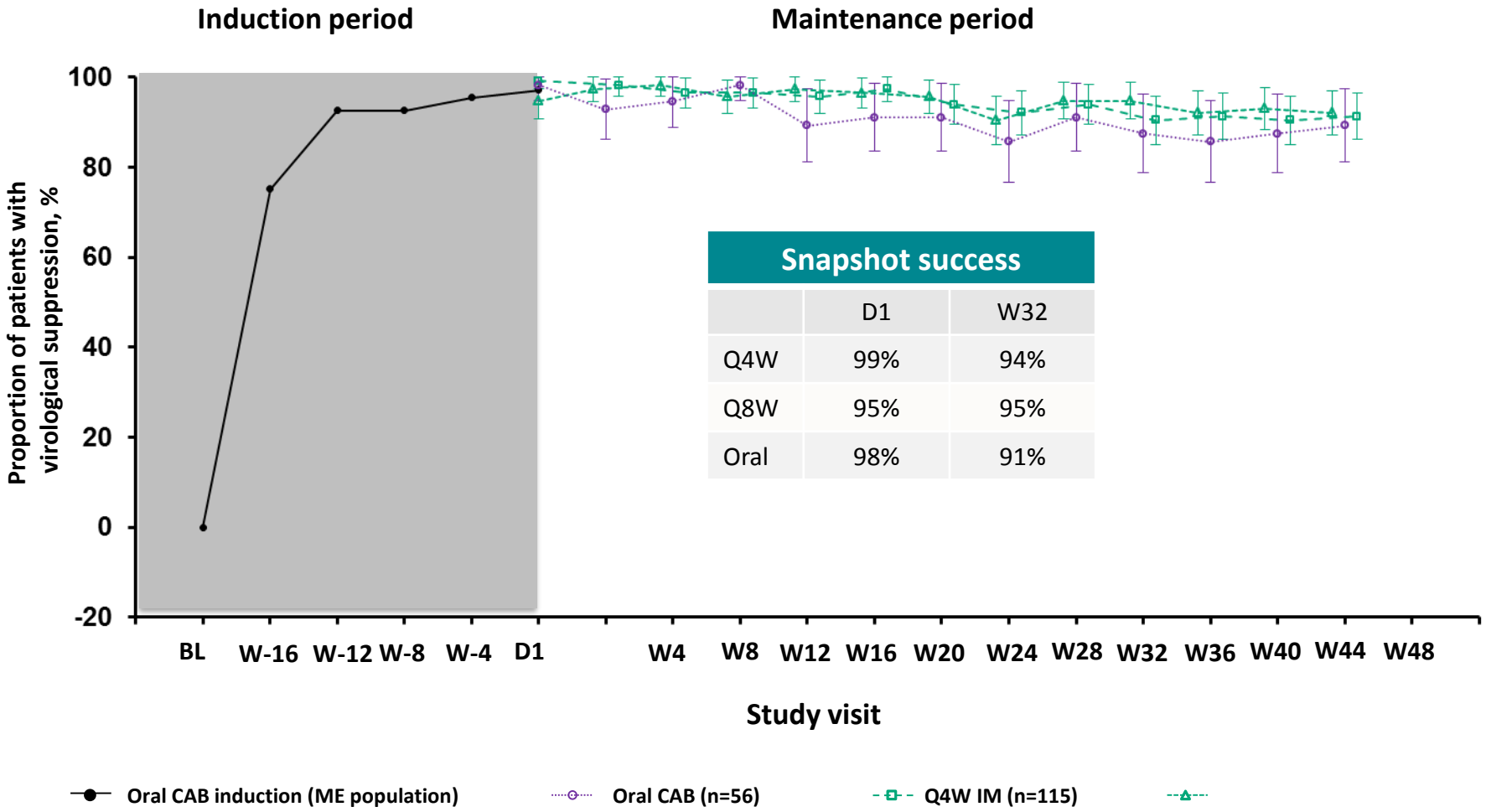
LATTE-2 Study Design



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.

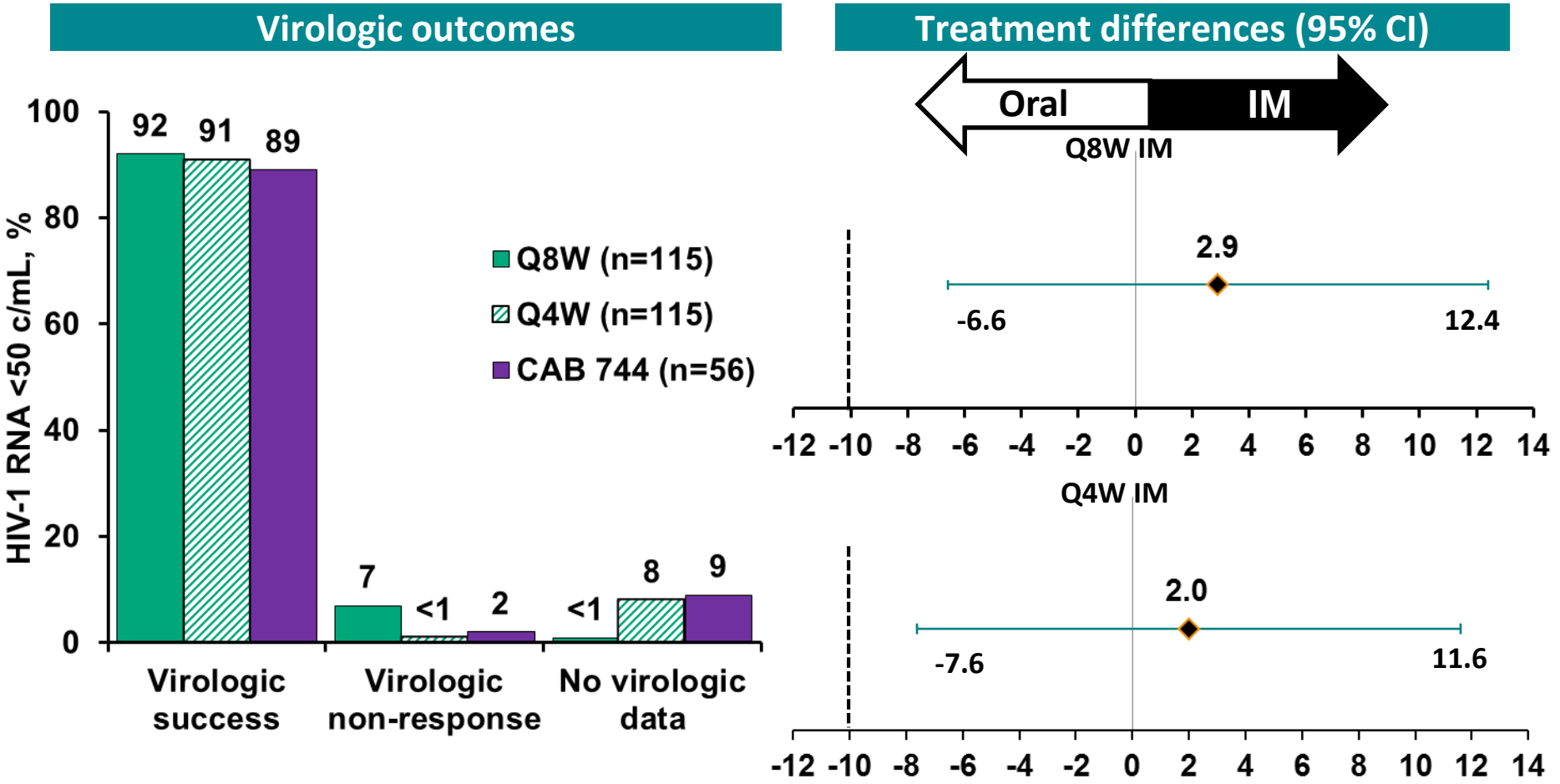
LATTE-2 Week 48 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Snapshot success		
	D1	W32
Q4W	99%	94%
Q8W	95%	95%
Oral	98%	91%

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

HIV-1 RNA <50 c/mL at Week 48
ITT-ME (Snapshot)



Both Q8W and Q4W comparable to Oral CAB at Week 48[a]

- [a]Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

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

Protocol-Defined Virologic Failure (PDVF): Genotype

Maintenance period[a]	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF	2 (1%)[b]	0	1 (2%)
INI-r mutations	1[c]	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	1[c]	0	0

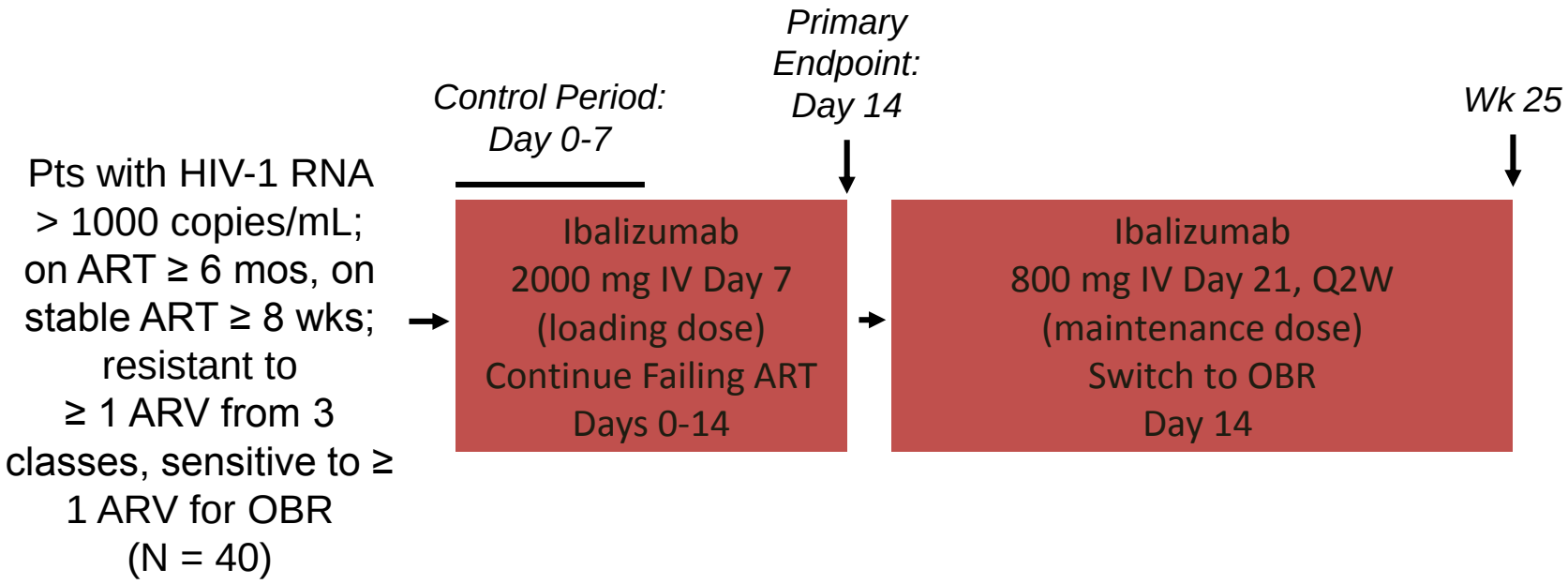
- NNRTI—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); INI—**Q148R** (FC CAB=5.1**;** Dolutegravir=1.38)[c]
- No additional PDVFs beyond W48 on any arm (all subjects through W72)[d]

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 $\log_{10}$ c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. [a]One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. [b]One PDVF at Week 4: **no detectable RPV at Week 4 and Week 8**, suggesting maladministration. [c]One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). [d]Contains data beyond W48.

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

TMB-301: Long-Acting Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14
- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance



Lewis S, et al. CROI 2017. Abstract 449LB.

Efficacy, Safety of Ibalizumab Through 24 Wks

- Primary endpoint: 83% with ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14 vs 3% at end of control period (*P* < .0001)
  - 60% with ≥ 1.0 $\log_{10}$ HIV-1 RNA decrease
  - Mean decrease by Day 14: 1.1 $\log_{10}$

Wk 24 Virologic Outcome	Ibalizumab + OBR
≥ 1.0 $\log_{10}$ HIV-1 RNA decrease, %	55
≥ 2.0 $\log_{10}$ HIV-1 RNA decrease, %	48
HIV-1 RNA < 50 copies/mL, %	43
HIV-1 RNA < 200 copies/mL, %	50
Mean HIV-1 RNA decrease from baseline, $\log_{10}$	1.6

- 9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation
- 9 other pts discontinued
  - Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal (n = 3)
  - Lost to follow-up (n = 2)
- No cases of anti-ibalizumab antibodies

Lewis S, et al. CROI 2017. Abstract 449LB.

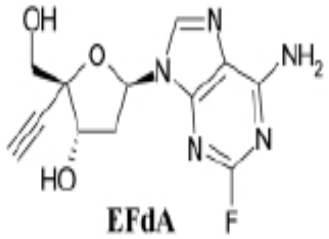
CD01 Extension: Long-term, Maintenance PRO 140 Monotherapy Following Initial ART

- PRO 140: humanized IgG4 CCR5 mAb
- Single-arm, open-label phase IIb extension study[1]
  - Maintenance PRO 140 given at 350 mg SC/wk for ≤ 3 yrs in pts stable on initial ART from CD01 study (N = 16)
- Wkly PRO 140 maintenance SC injection generally well tolerated
  - No drug-related severe AEs or d/c for AEs
  - Infrequent, mild, transient administration-site reactions in < 10% of pts
- HIV-1 RNA < 40 copies/mL maintained in majority of pts
  - > 40 wks: 13/16 pts (81.3%)
  - > 2 yrs: 10/16 pts (62.5%)
  - 1 pt d/c due to relocation; 5 pts had VF
- CD4+ cell counts stable through study
- No anti-PRO 140 antibodies detected
- Ongoing phase IIb/III studies of PRO 140 monotherapy[2] and in combination with ART[3]

1. Lalezari J, et al. CROI 2017. Abstract 437.
2. ClinicalTrials.gov. NCT02859961.
3. ClinicalTrials.gov. NCT02483078.

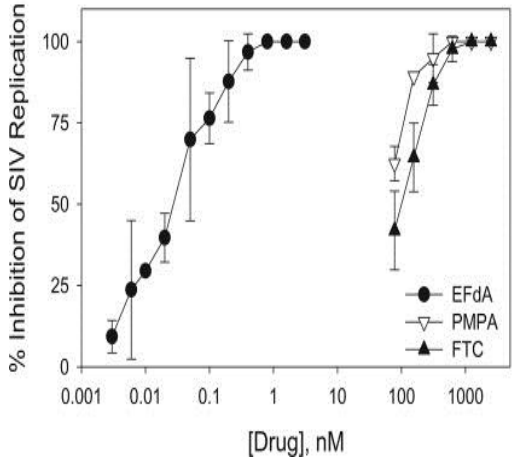
4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) MK8591

- EFdA (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Sub-nanomolar potency in vitro[1] and prolonged suppression of SIV in macaque model[2]
- Prolonged persistence of triphosphate form in PBMC and macrophage
- Potential for once weekly dosing
- Long-acting formulations under development



EFdA

A.



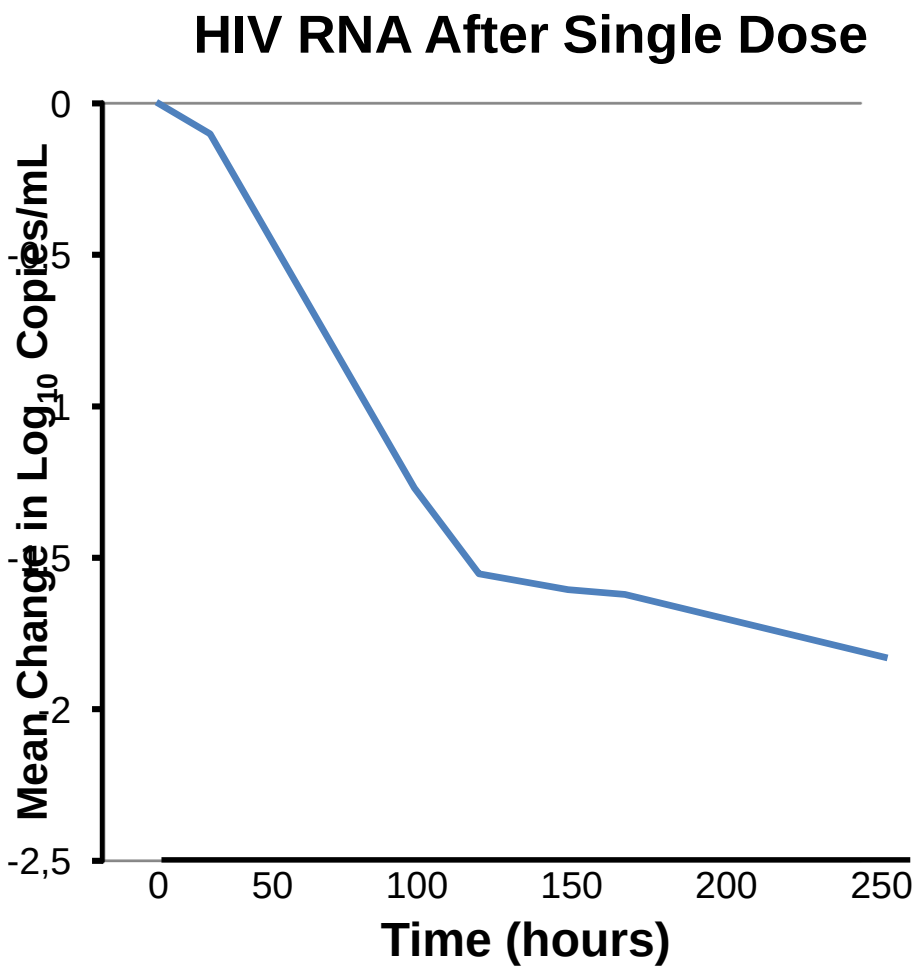
B.

	EC_{50} (nM)	EC_{95} (nM)
EFdA	0.04 +/- 0.01	0.4
PMPA	67.5 +/- 6.5	240
FTC	108.6 +/- 9.2	580

[1]Michailidis et al J Biol Chem 284: 35681-91; 2009 [2]Murphey-Corb et al AAC 56:4707-12; 2012

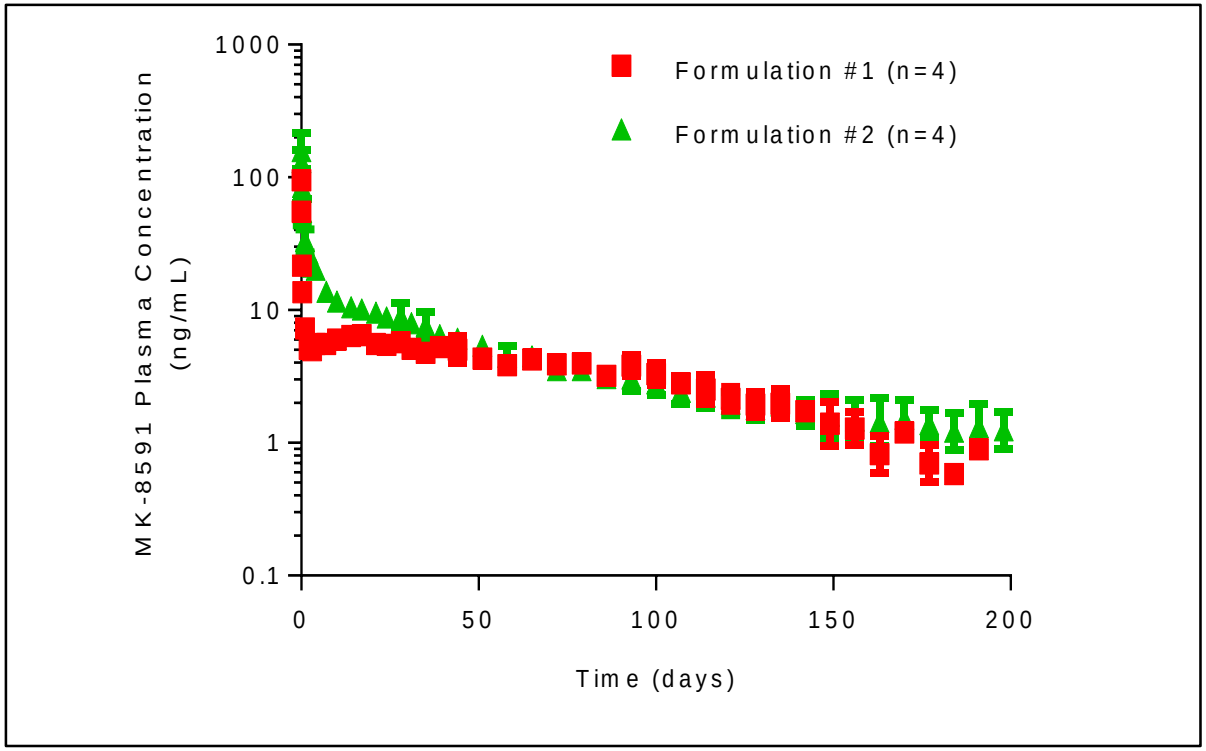
MK-8591: Reduction in HIV RNA for at Least 10 Days After Single Oral Dose

- 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



Friedman E, et al. 23rd CROI. Boston, 2016. Abstract 437LB.

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



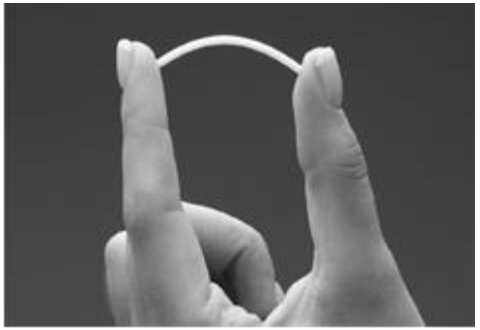
- >180-day extended release from solid state formulations after a single injection in rats.
- Data suggest the potential to provide coverage for durations up to 1 year.

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

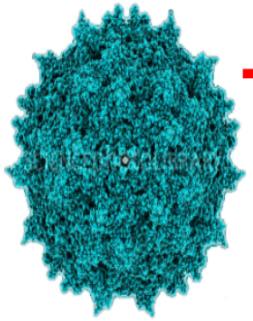
Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals

- Vectored delivery of combinations of antibody-based therapy or protein based therapy



Recombinant AAV (rAAV) features



- Transfects both dividing & non-dividing cells
- No host-genome integration & Stable Expression
- Ease to produce at high viral titer (Helper Free)
- Do not elicit significant immune response *in vivo*
- Can be used for in vivo gene deliveries

LA ARV Implants – Tenofovir Alafenamide

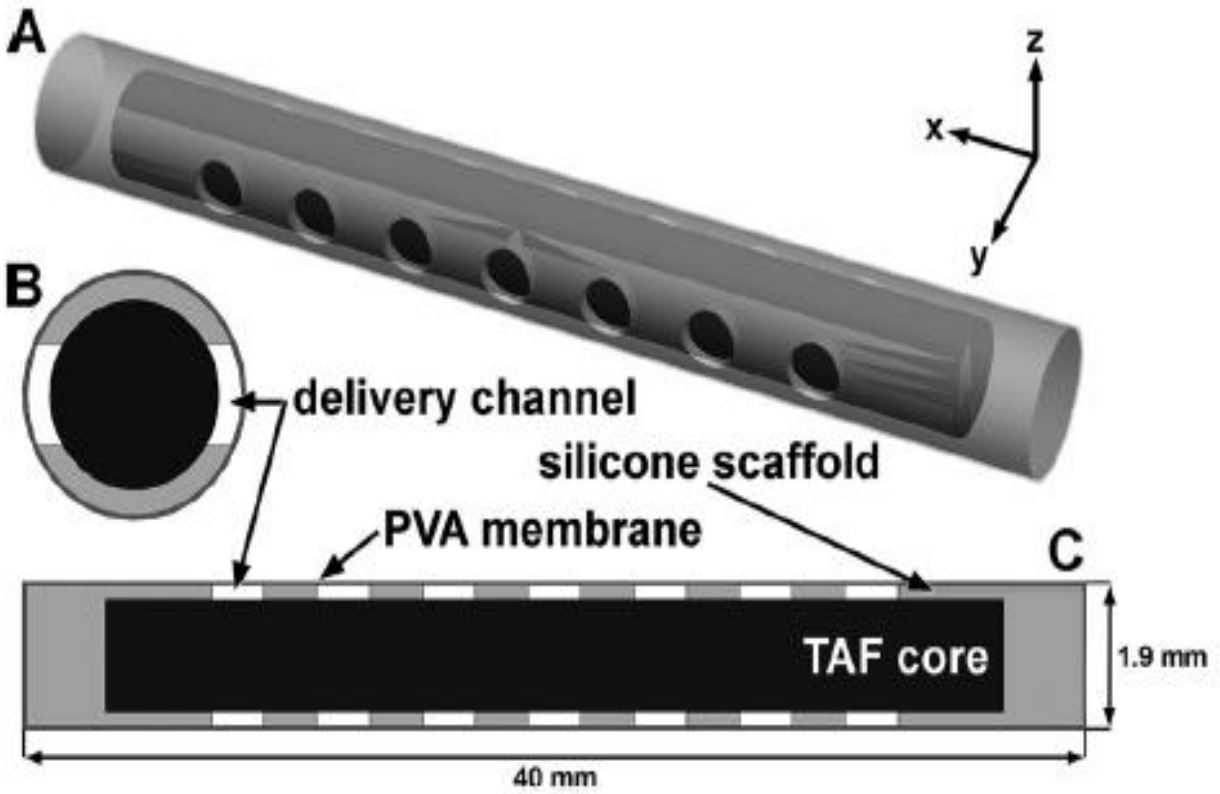


FIG 1 Three-dimensional model (A) and cross-sectional drawings (B and C) of TAF implant. The TAF core (black) inside the silicone scaffold with PVA membrane coating is shown (not to scale). Cross sections were sliced through the *y-z* (B) and *x-y* planes (C).

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

LA ARV Implants – Tenofovir Alafenamide

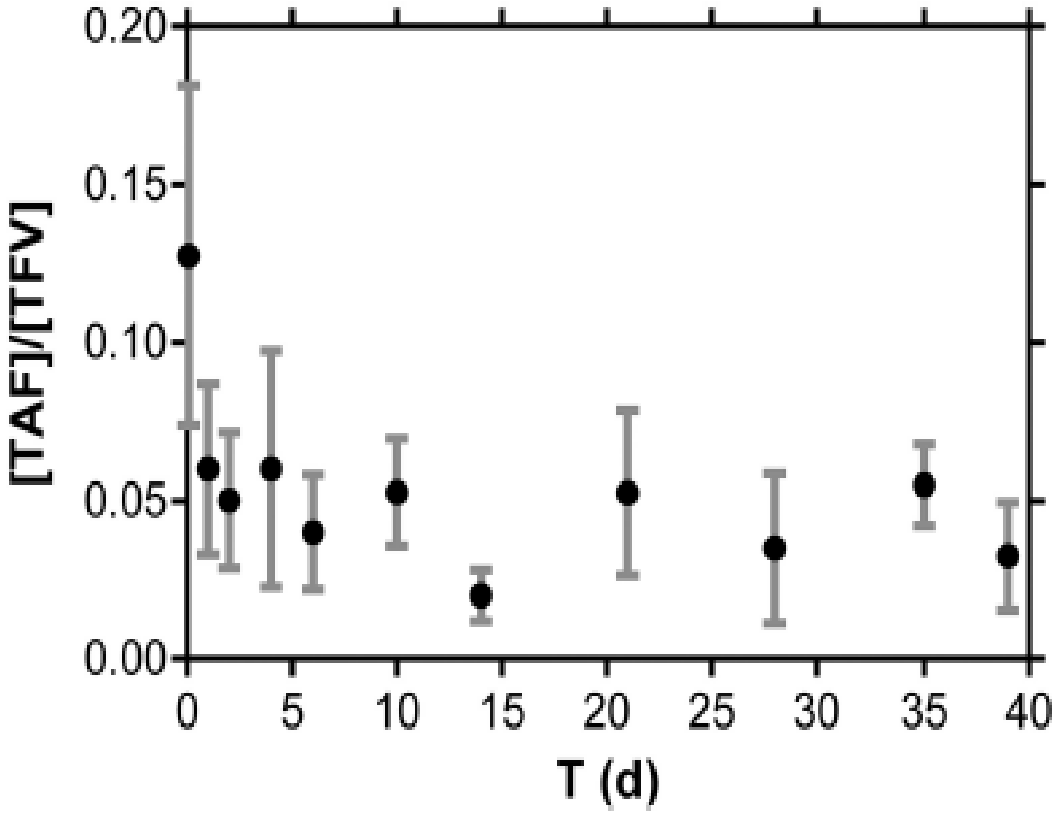


FIG 4 Molar TAF:TFV plasma concentration ratios are stable throughout the 40-day study. Each data point represents the means ± standard deviations from four beagle dogs.

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

- Principles and Hypotheses supporting the development of Long-Acting Antiretrovirals (LA-ARVs)

- What is available in terms of pharmacological and clinical information

- **Potential advantages/opportunities and disadvantages/risks**

PROs

(imaging LA parenteral formulation of an entire regimen)

- **Supervised administration might increase adherence (treatment)**
- **Parenteral administration circumvents 1st pass liver metabolism, thus possibly reducing the effect of P450 cytochrome isoenzymes, the need of boosting agents and drug-drug interactions**
- **Long-lasting delivery fits with the time-dependent PD of ARVs**
- **Long-lasting delivery might reduce peak concentrations (less AEs)**
- **Costs likely to be reduced both in terms of pharmaceutical expenditure and general management of antiretroviral therapy**
- **Proof of concept trial based on induction-maintenance strategy (LATTE) gave rise to promising results**

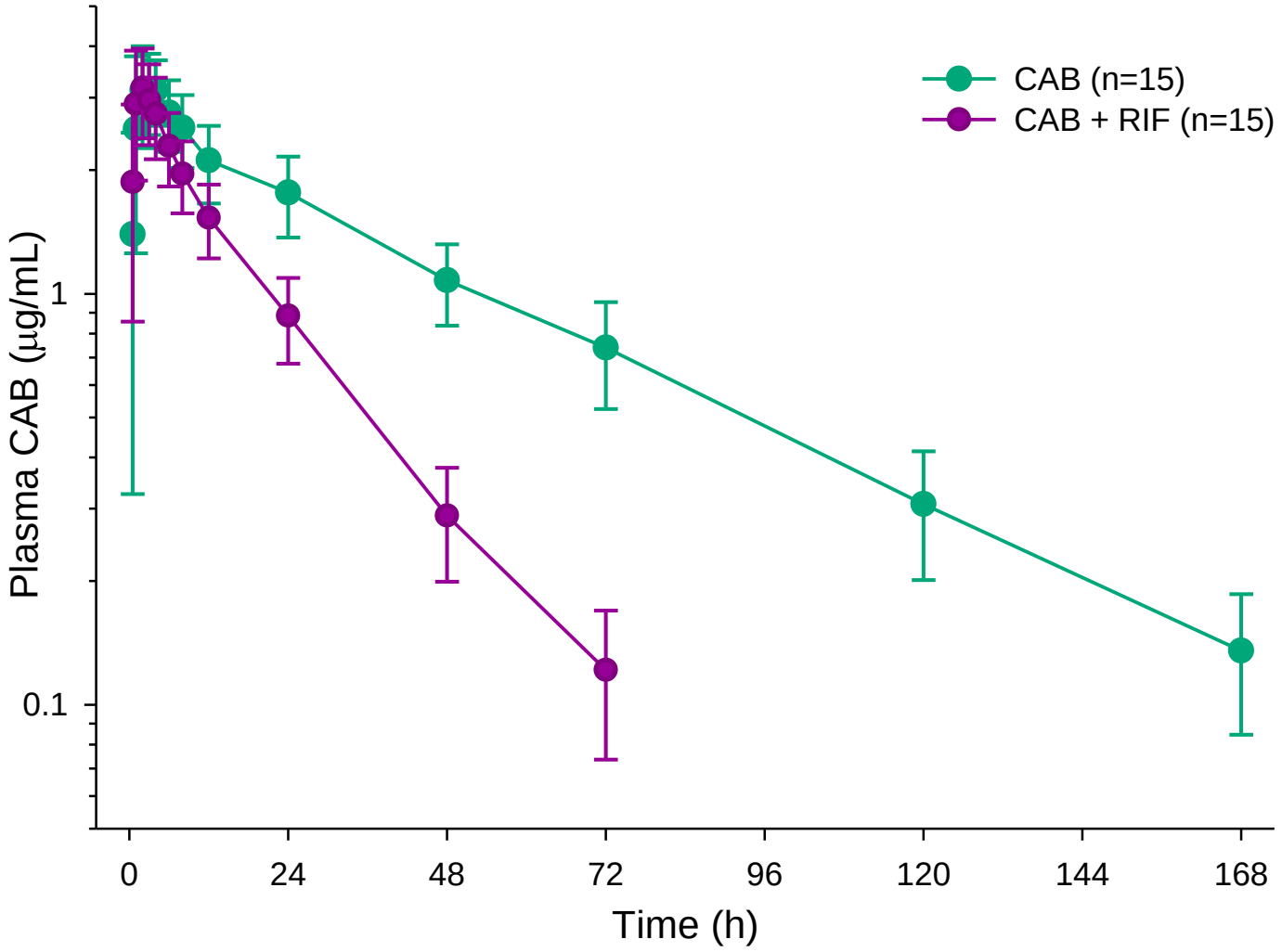
Cabotegravir DDI summary

- **Primarily metabolised via UGT1A1 with minor UGT1A9 component**
- **Favourable drug interaction profile**

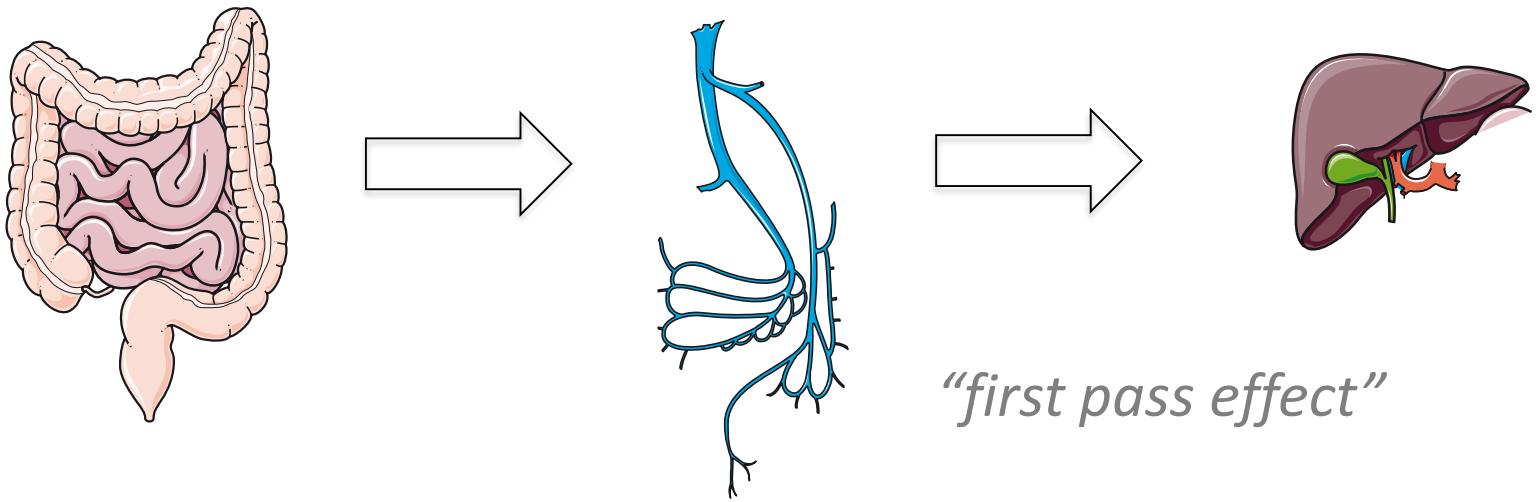
- As a victim of DDIs, no clinically significant interactions of cabotegravir with:
  - Etravirine, rilpivirine
- Administration with polyvalent cations requires separation
  - Cabotegravir should be taken 2 hours before or 4 hours after polyvalent-cation-containing products (e.g. multivitamins, antacids)

- As perpetrator of DDIs:
  - Cabotegravir causes no clinically significant effects on:
    - Midazolam (CYP3A probe)
    - Rilpivirine
    - Oral contraceptives (levonorgesterol/ethinyl oestradiol)
  - *In vitro*, no inhibitory effects on multiple CYPs or UGTs
  - Inhibitor of organic anion transporter (OAT1 and OAT3)
    - Avoid with methotrexate

Rifampin Decreases Cabotegravir Exposure



Ford et al. Clin Pharm 2016; Washington, DC. Abstract O_18.



“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

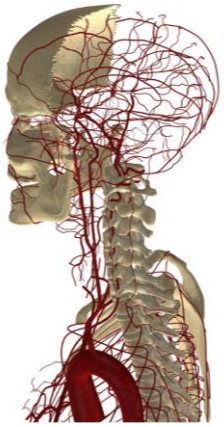
Blood flow distribution in an anatomically detailed arterial network model: criteria and algorithms

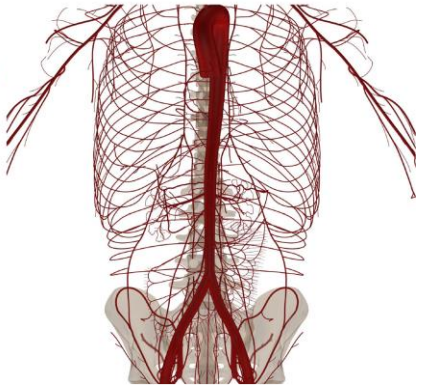
Pablo J. Blanco · Sansuke M. Watanabe · Enzo A. Dari
Marco Aurélio R. F. Passos · Raúl A. Feijóo

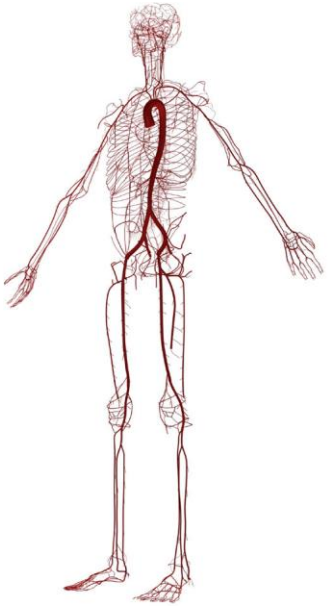
Biomech Model Mechanobiol (2014) 13:1303–1330

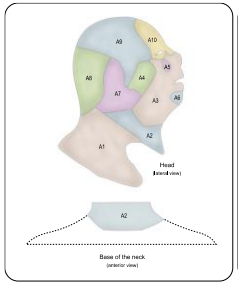
Table 5 Description of specific organs and their blood supply

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	

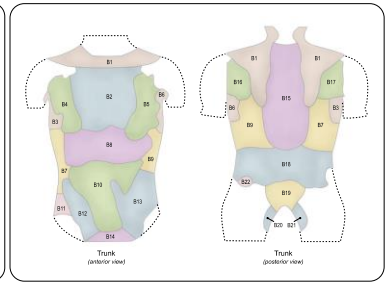




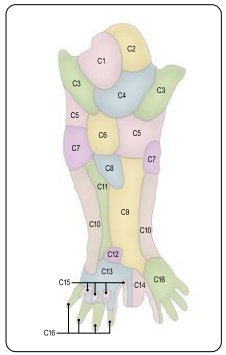




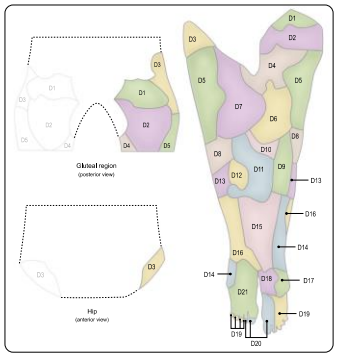
(a) Head and neck



(b) Trunk

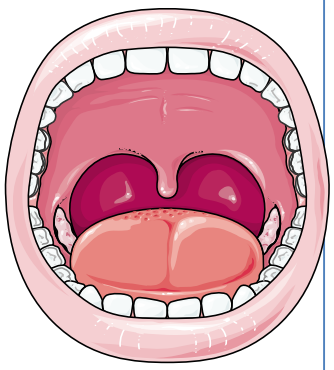


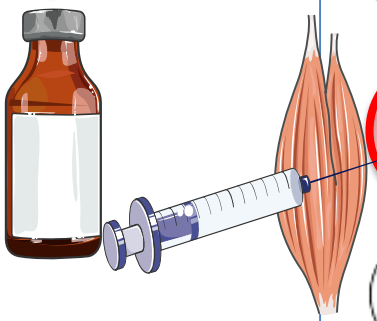
(c) Upper limb



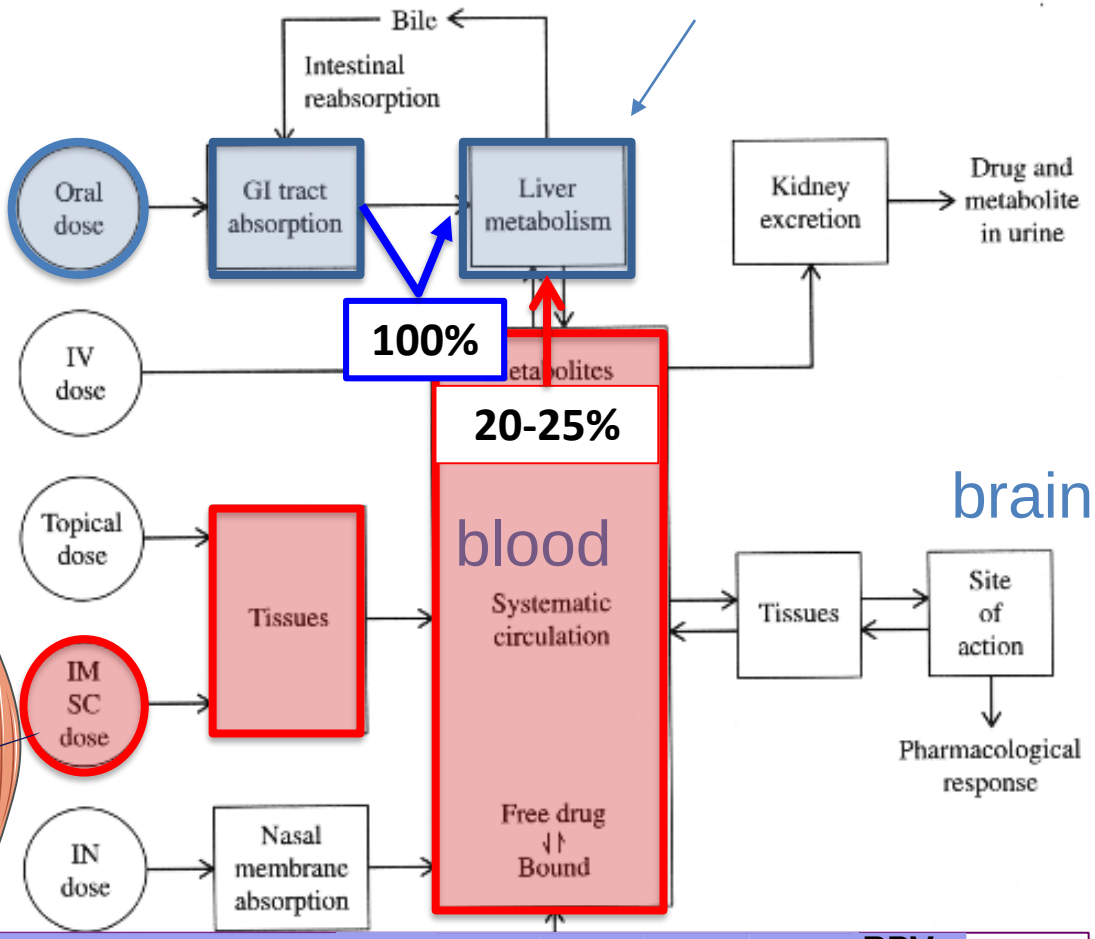
(d) Lower limb

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

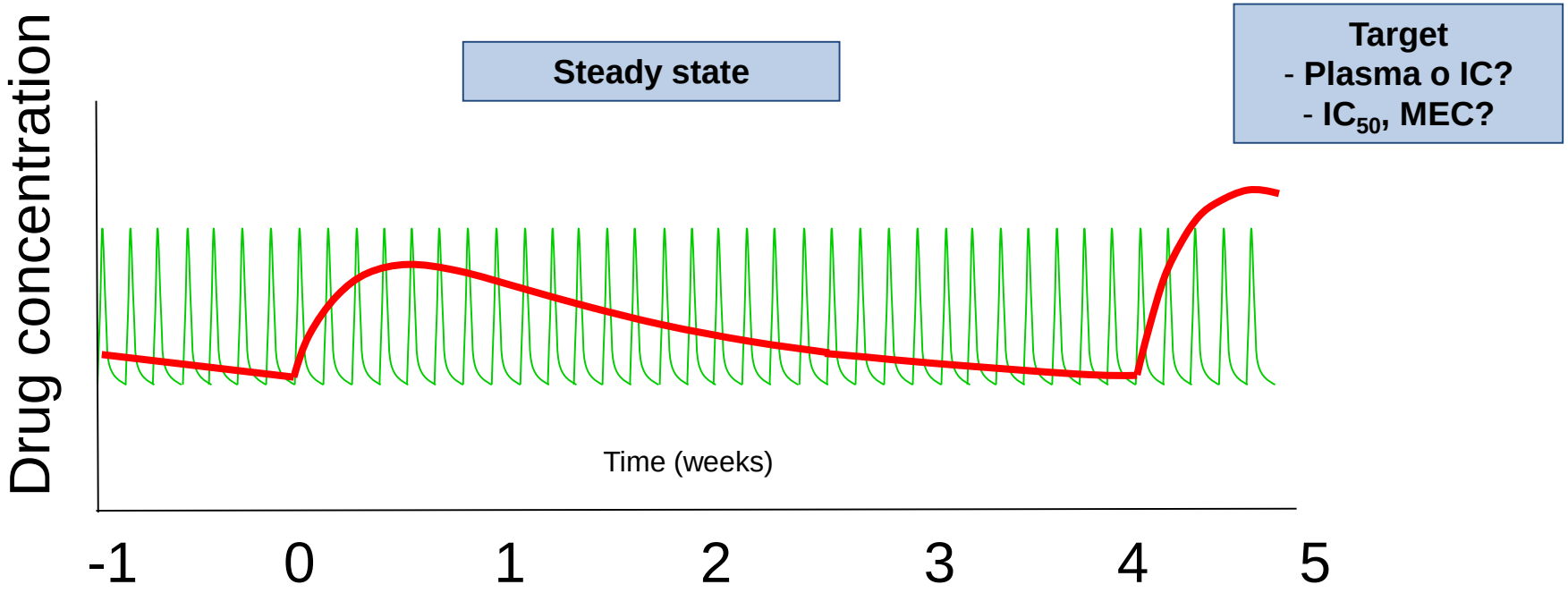


	DLV	EFV	ETV	NVP	RPV	RPV + F/TAF
Medroxyprogesterone (IM depot injection)	♦	♦	♦	♦	♦	♦
Medroxyprogesterone (oral)	■	■	■	■	♦	♦

●/○	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

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



CONs

(imaging LA parenteral formulation of an entire regimen)

- Supervised administration might decrease adherence (prevention), + fear of IM injections
- Also depending on the performance of the LA formulation, the choice of ARVs for LA-ARV might be problematic as fluctuations of drug [c] should remain into the therapeutic interval with low inter-patient variability, with some risks with several drugs
- Periodicity of drug administration should be carefully defined with a sort of “standard deviation” (e.g. + or – 7 days for the new administration as referred to the scheduled day)
- The co-formulation of LA GSK1265744 and RPV seems rather unbalanced in terms of T > MEC
- Injection site inflammation

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