Clinical pharmacology of long-acting agents for HIV prevention and treatment

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Disclosures

Travel grants

Speaker

Advisor

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Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, and Teva.

Long-acting?

- What do we mean?
- Why LA drugs?
- Are drug concentrations the same for everyone?
- What is the PK tail & do we need to worry about it?
- What about DDIs?

Is “everyone” being studied?

LA = long-acting; PK = pharmacokinetics; DDIs = drug-drug interactions; PLWH people living with HIV

Definition

- A drug which:
  - Is slowly absorbed and slowly excreted
  - Persists in the circulation/tissues
  - Is effective over a long period of time

Objective

Prerequisite: Less frequent dosing than once daily

	Oral	Parenteral (im; sc)	Implant/device
Dosing frequency	≥ 1 week	≥ 1-2/6 months	≥ 6 months

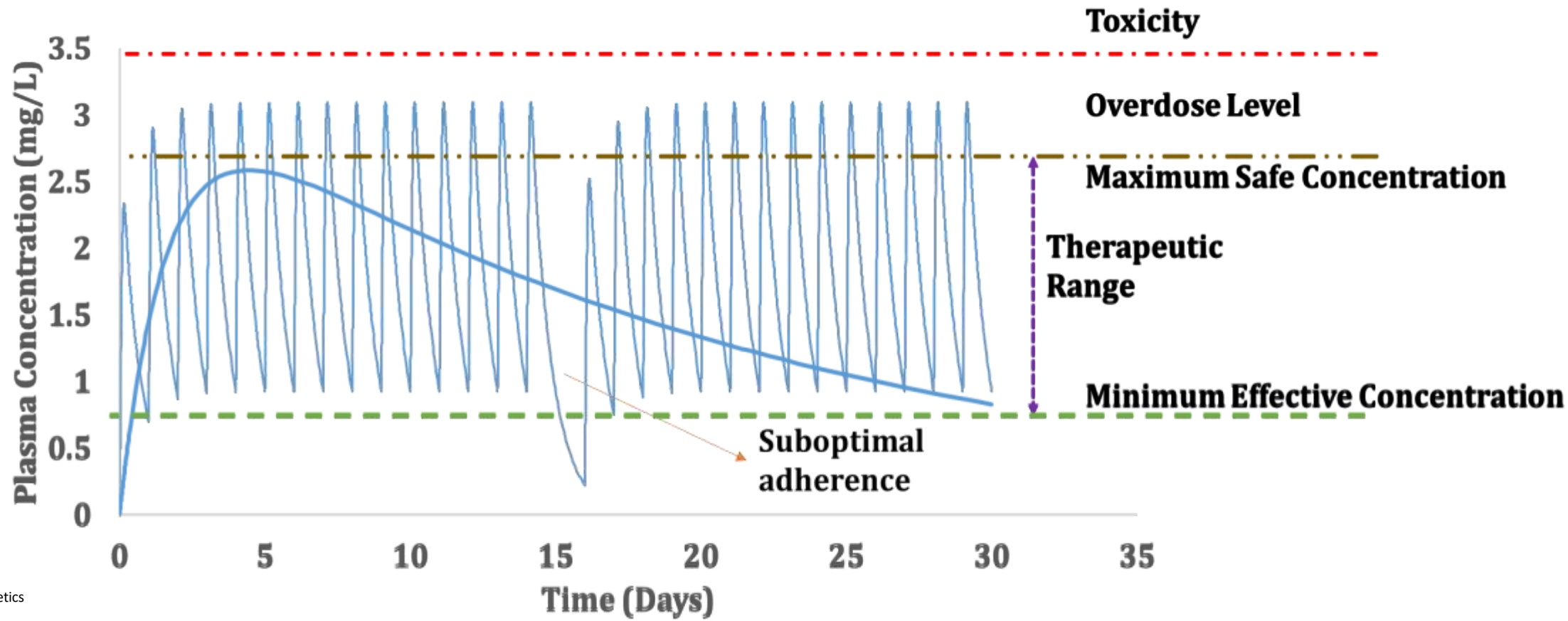
Benefits

- ❑ Increased choice
- ❑ Increased convenience/health privacy
- ❑ Simplify adherence
- ❑ Reduce API* administered

*API = Active Pharmaceutical Ingredient

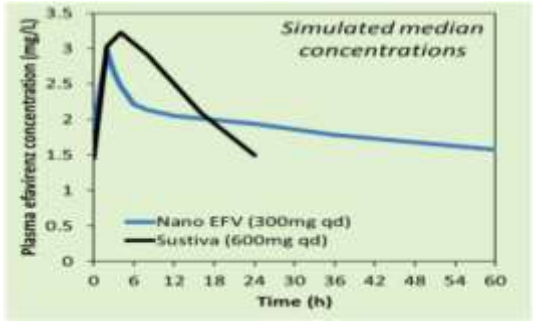
Owen et al. Adv Drug Deliv Rev 2016

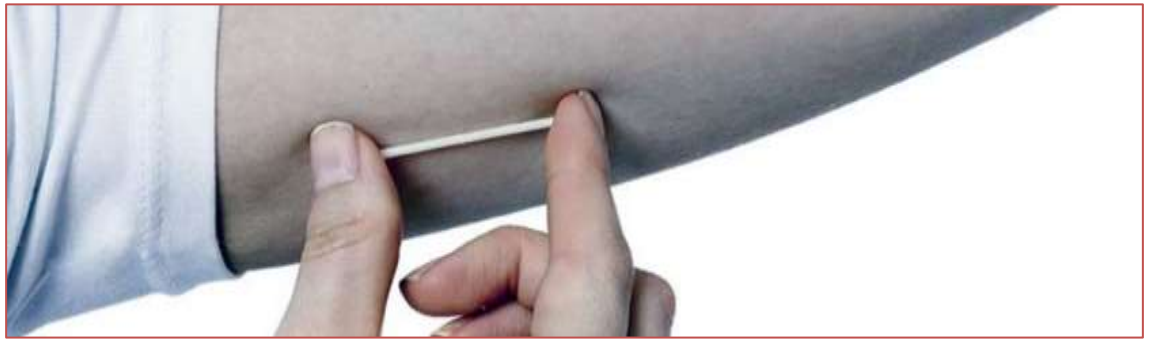
Long-acting PK



PK = pharmacokinetics

How to deliver long-acting drugs



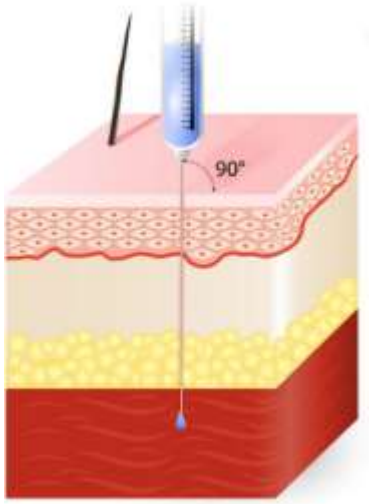


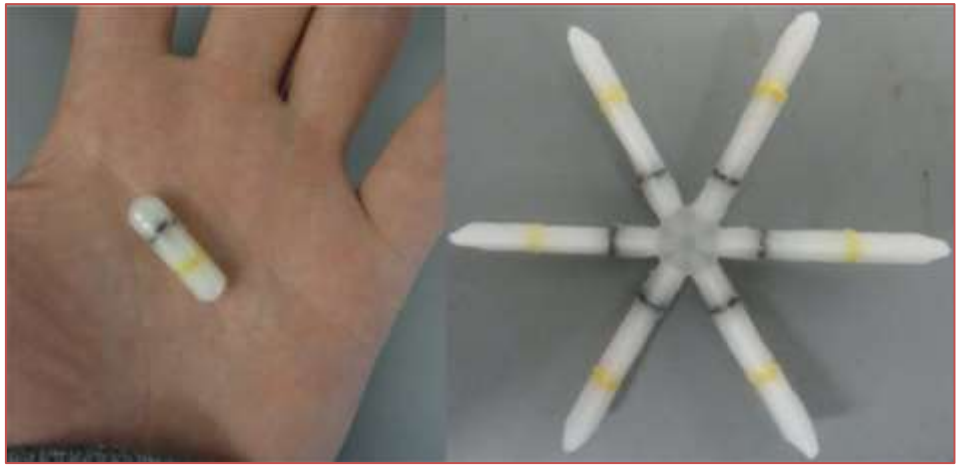
Epidermis

Dermis

Hypodermis

Muscle

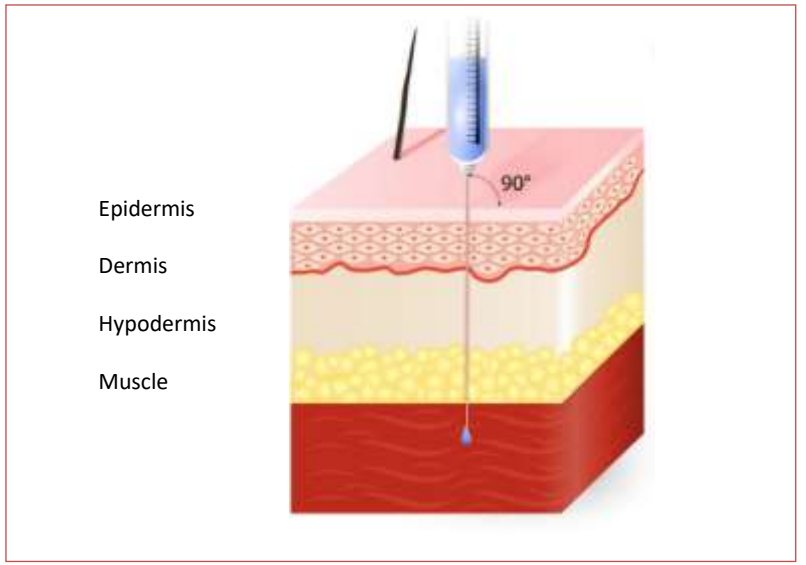




Owen et al. CROI 2017; Bellinger et al. Science Translational Medicine 2016; Benhabbour et al. Nature Communications 2019; Margolis et al. Lancet 2017

How to deliver long-acting drugs

Intramuscular injection



Margolis et al. Lancet 2017

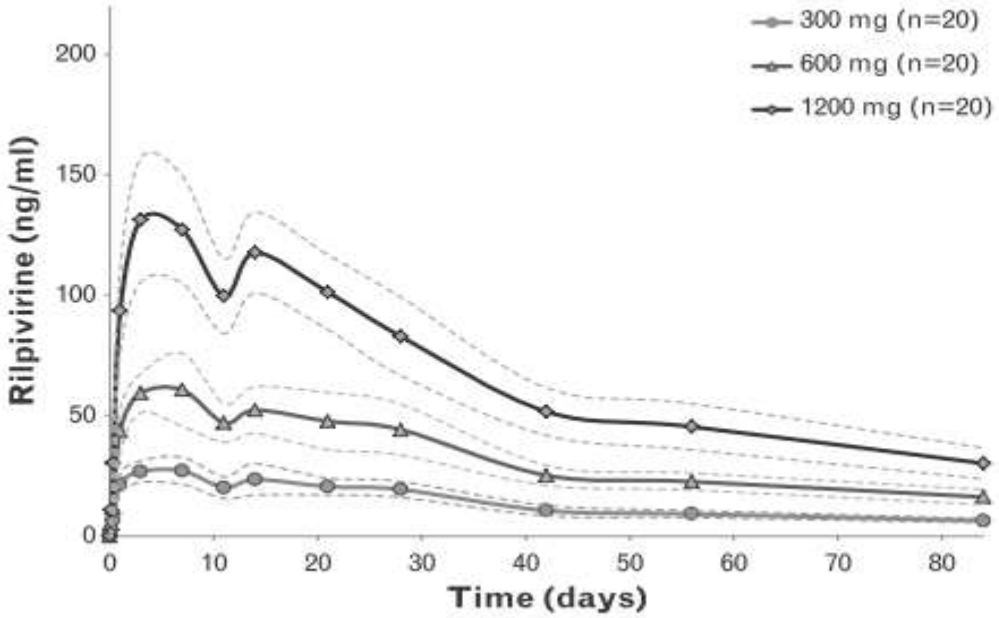
REVIEW

Formulation and pharmacology of long-acting rilpivirine

Peter E. Williams, Herta M. Crauwels, and Esther D. Basstanie

Purpose of review
Rilpivirine (RPV), a nonnucleoside reverse transcriptase inhibitor, is a potent antiretroviral (ARV) effective for HIV treatment at 25 mg daily oral dose. Its physio-chemical and pharmacological properties enable formulation of RPV as a long-acting injectable nanosuspension. This review summarizes these properties supporting the potential of intermittent parenteral administration of rilpivirine long acting (RPV LA) in both treatment and prevention of HIV-1 infection.

Recent findings
RPV is unusual among ARVs in that its stability and solubility enable aqueous suspensions with high drug loading, so that injection volumes can be minimized. Such innovative nanosuspensions are well tolerated in animals and humans after intramuscular injection and provide sustained drug concentrations in systemic circulation. The pharmacological findings support further investigations of RPV LA injections every 4 or 8 weeks, both as a single agent for potential preexposure prophylaxis and as two-drug all-injectable maintenance therapy with cabotegravir long acting.



REVIEW

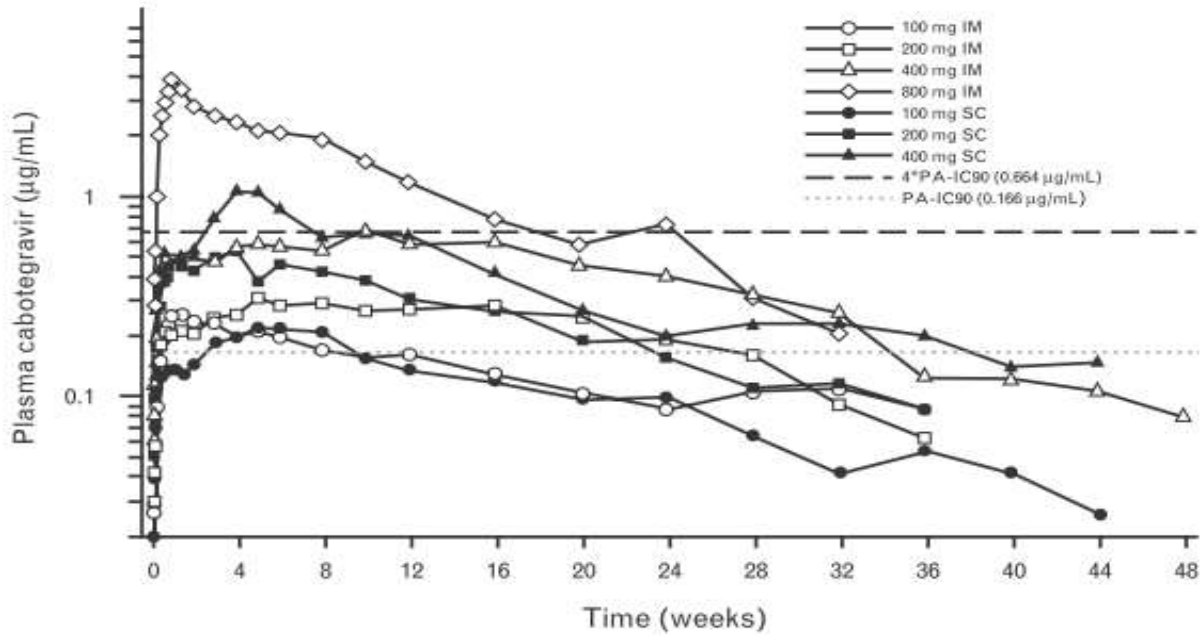
OPEN

Formulation and pharmacology of long-acting cabotegravir

Christine Trezza[a], Susan L. Ford[a], William Spreen[a], Rennan Pan[b], and Stephen Piscitelli[a]

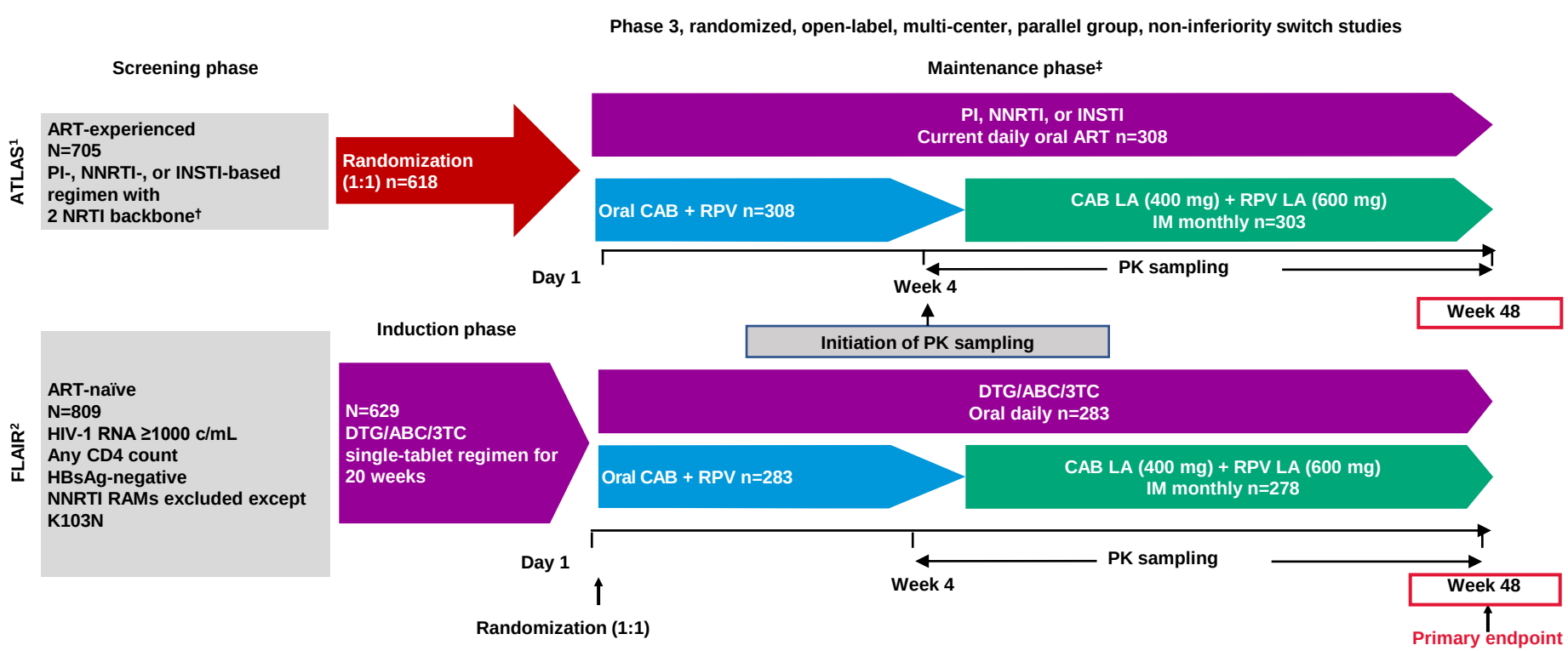
Purpose of review
Long-acting cabotegravir may provide a novel therapeutic option for both the treatment and prevention of HIV-1 infection that does not necessitate adherence to a daily regimen. The present review will highlight the unique formulation properties and pharmacologic attributes of long-acting cabotegravir nanosuspension.

Recent findings
Cabotegravir is a potent integrase strand transfer inhibitor that has been formulated as an oral tablet for daily administration and as a long-acting injectable nanosuspension. Long-acting cabotegravir is readily absorbed following intramuscular and subcutaneous administration and has an elimination half-life of approximately 40 days, allowing for administration on a monthly or less frequent schedule. Repeat-dose pharmacokinetic studies and population pharmacokinetic modeling indicate monthly and bi-monthly dosing achieves clinically relevant plasma concentrations considered effective for HIV maintenance therapy and that quarterly injections are appropriate for investigation as preexposure prophylaxis. Cabotegravir is primarily metabolized by uridine diphosphate glucuronosyltransferase 1A1 and is unlikely to be impacted



ATLAS and FLAIR

ATLAS (NCT02951052) and FLAIR (NCT02938520) are two randomized, open-label, international Phase 3 studies that demonstrated non-inferiority of switching to monthly intramuscular (IM) injections of CAB + RPV LA vs. current antiretroviral regimen (CAR)



Women enrolment target

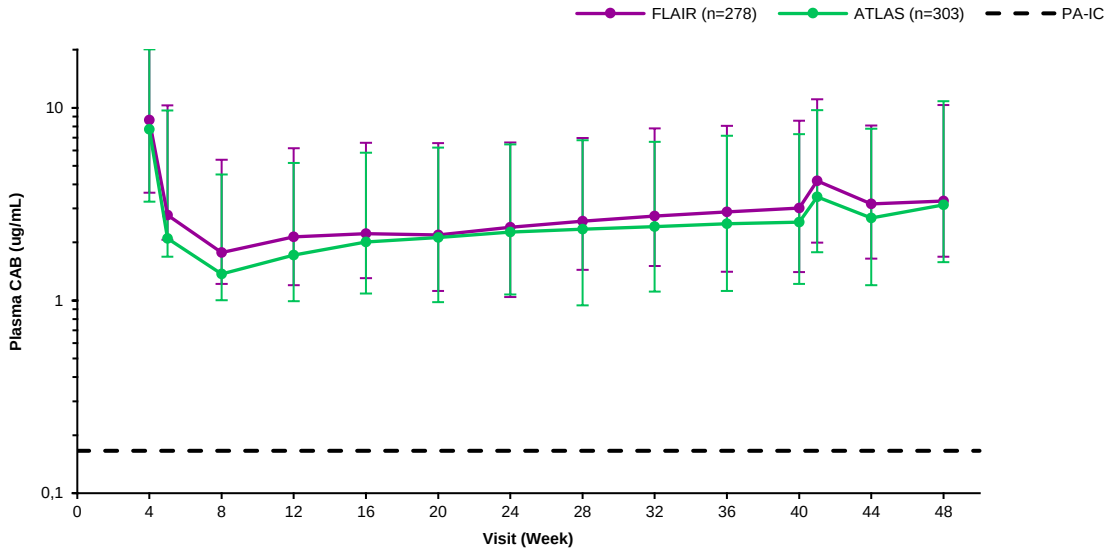
1 in 4

1 in 5

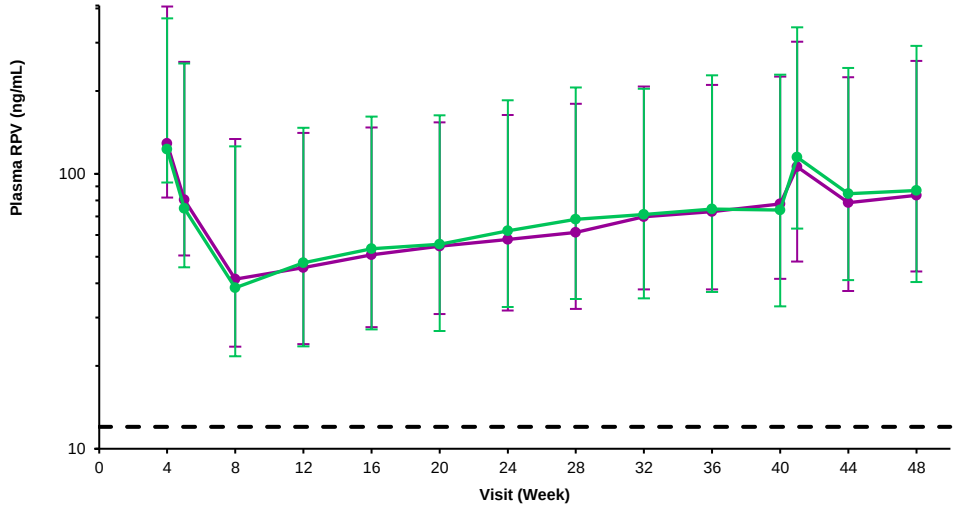
Swindells et al. NEJM 2020; Orkin et al. NEJM 2020

LA CAB and RPV PK Q4W

Median (5th and 95th centile) plasma CAB



Median (5th and 95th centile) plasma RPV PK



Oral lead-in period	Initiation dose (Week 4b)	Continuation dose Week 8 and every 4 weeks thereafter
CAB 30 mg once daily	CAB LA 600 mg IM (3 mL x 1)	CAB LA 400 mg IM (2 m L x 1)§
RPV 25 mg once daily	RPV LA 900 mg IM (3 mL x 1)	RPV LA 600 mg IM (2 mL x 1)§

LA = long-acting; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

Patel et al. IDWeek 2019

CAB PK by sex at birth and baseline BMI

- 4 weeks following the first injection, median CAB levels were lower in females than males by 40%
- CAB troughs at Week 48 were slightly higher in females than males

- 4 weeks following the first injection, median CAB levels were lower in individuals with body mass index (BMI) ≥30 kg/m^2 by 46% vs. those with BMI <30 kg/m^2
- CAB troughs at Week 48 were similar regardless of BMI

There were no differences in RPV concentrations by sex or BMI over the 48-week study period

BMI = body mass index; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

Patel et al. IDWeek 2019

CAB PK by sex at birth and baseline BMI

ALTLAS and FLAIR Baseline characteristics

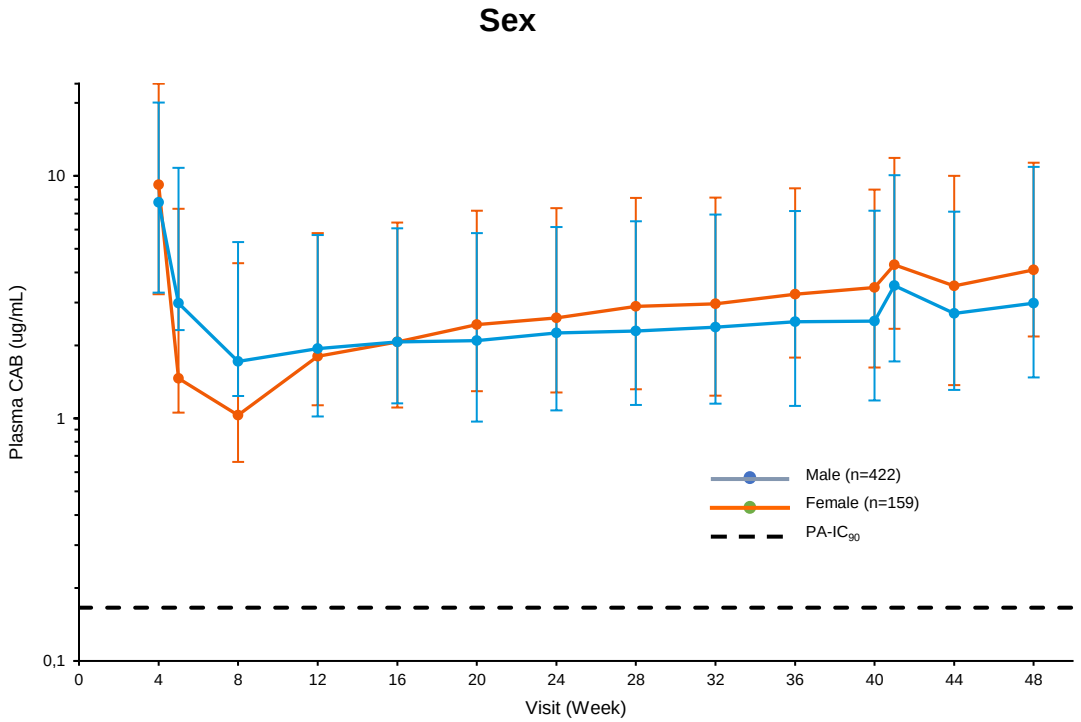
	CAB LA + RPV LA N (%)		CAR N (%)	
	Women	Men	Women	Men
Sex at birth	162 (27)	429 (73)	168 (28)	423 (72)
Age (mean in years)	41	38	43	38
BMI ≥30 (kg/m^2)	44 (27)	56 (13)	48 (29)	55 (13)
Race:				
Black or African American	59 (36)	50 (12)	69 (41)	64 (15)
White	92 (57)	338 (79)	93 (55)	315 (74)
Asian	8 (5)	26 (6)	3 (2)	25 (6)
Other	3 (2)	15 (3)	3 (2)	17 (4)
Region†:				
Europe and North America	75 (46)	316 (74)	83 (49)	322 (76)
Russian Federation	44 (27)	57 (13)	45 (27)	53 (13)
South Africa	34 (21)	15 (4)	36 (21)	18 (4)

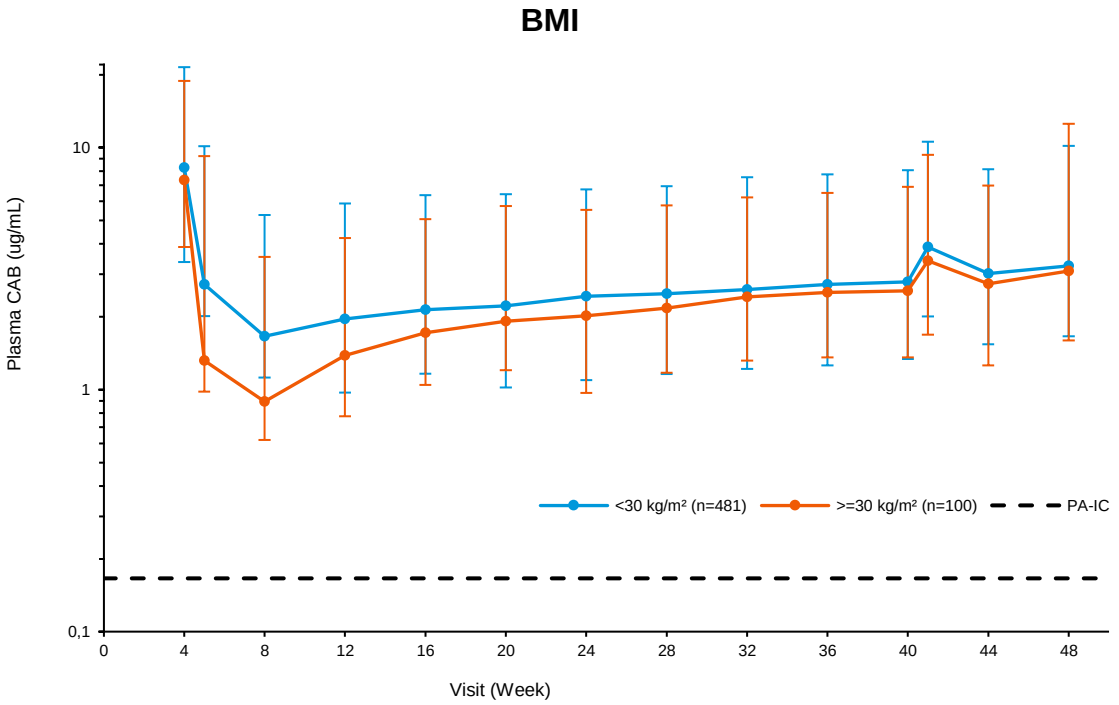
There were no differences in RPV concentrations by sex or BMI over the 48-week study period

BMI = body mass index; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

Patel et al. IDWeek 2019; Quercia et al EACS 2019

Median (5th and 95th centile) pooled CAB PK in ATLAS and FLAIR Week 4–48 by sex at birth and BMI



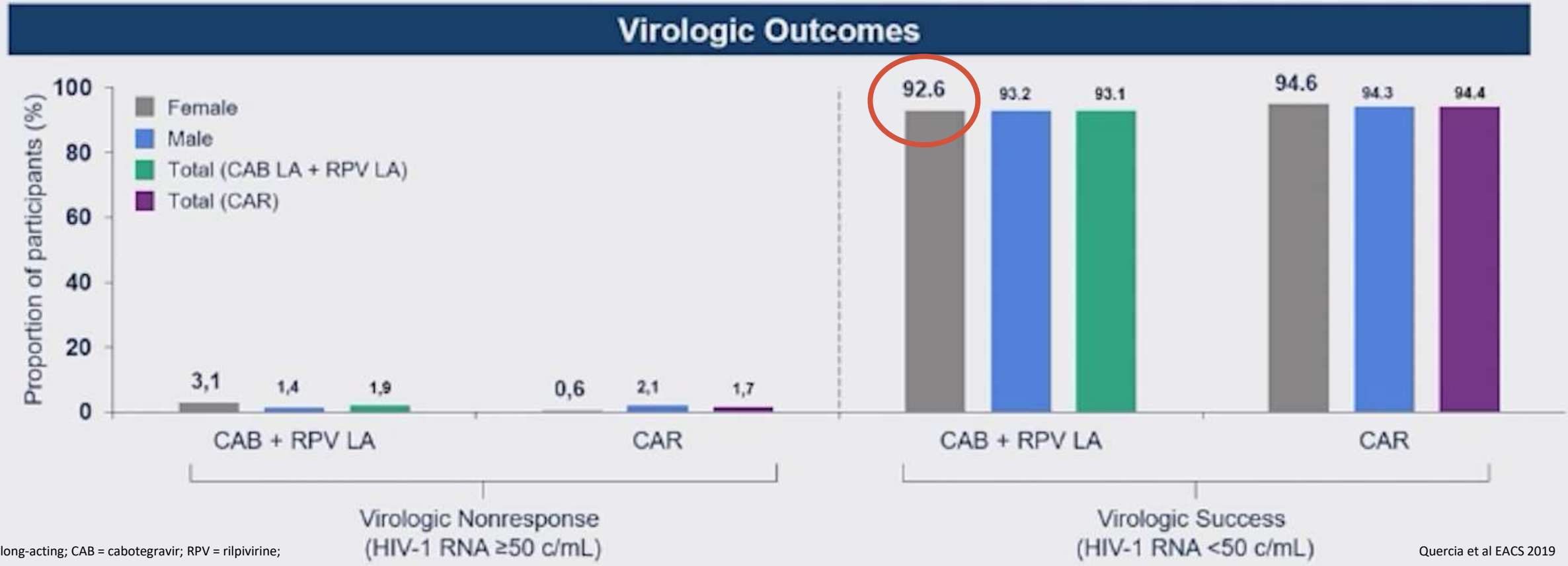


Protein-adjusted 90% inhibitory concentration ($PA\text{-}IC_{90}$) for CAB is 0.166 µg/mL [Margolis et al. Lancet 2017]

BMI = body mass index; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

Patel et al. IDWeek 2019

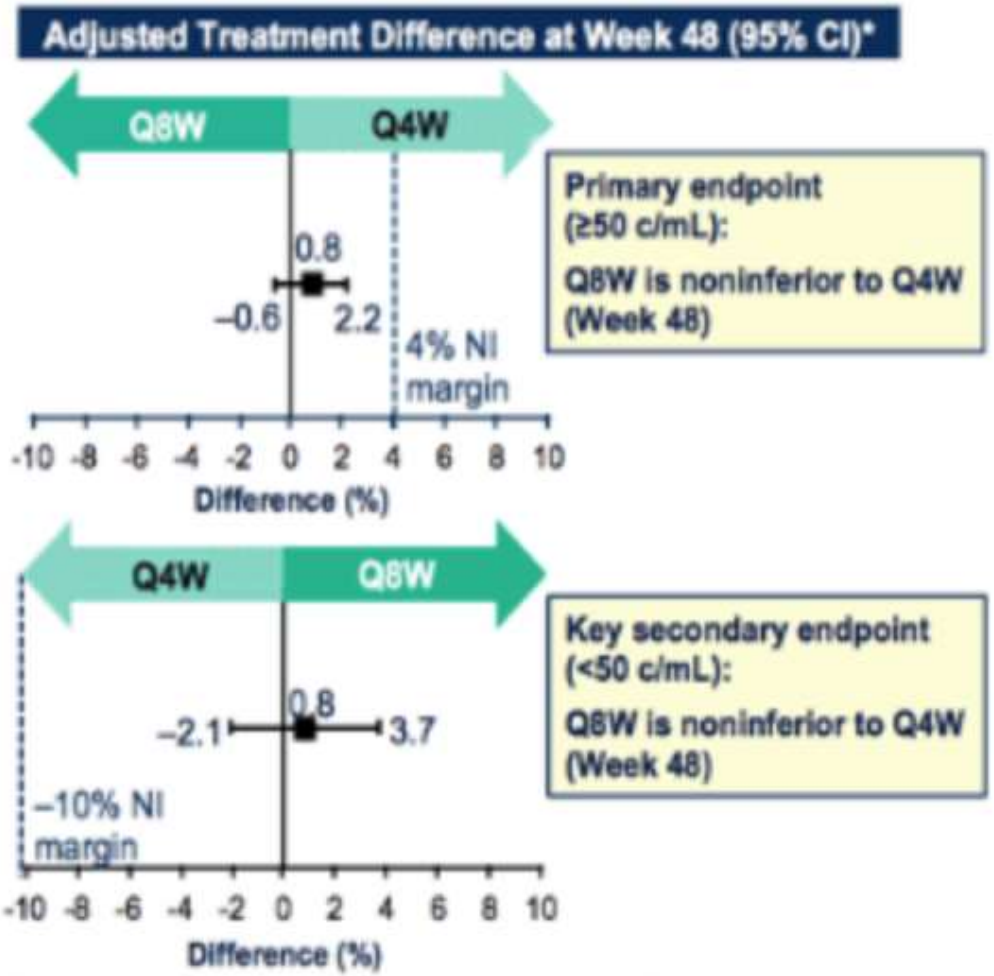
High rates of virological response in ATLAS and FLAIR in both men and women (48wk)



LA = long-acting; CAB = cabotegravir; RPV = rilpivirine;

Quercia et al EACS 2019

ATLAS 2M: results



Summary of confirmed virologic failures

	n	CVFs n (%)	CVFs with RPV RAMs*	RPV RAMs Observed at Failure	CVFs with IN RAMs*	IN RAMs Observed at Failure
Q8W	522	8 (1.5)	6/8	K101E, E138E/K, E138A, Y188L	5/8	Q148R,† N155H†
Q4W	523	2 (0.4)	1/2	K101E, M230L	2/2	E138E/K, Q148R, N155N/H

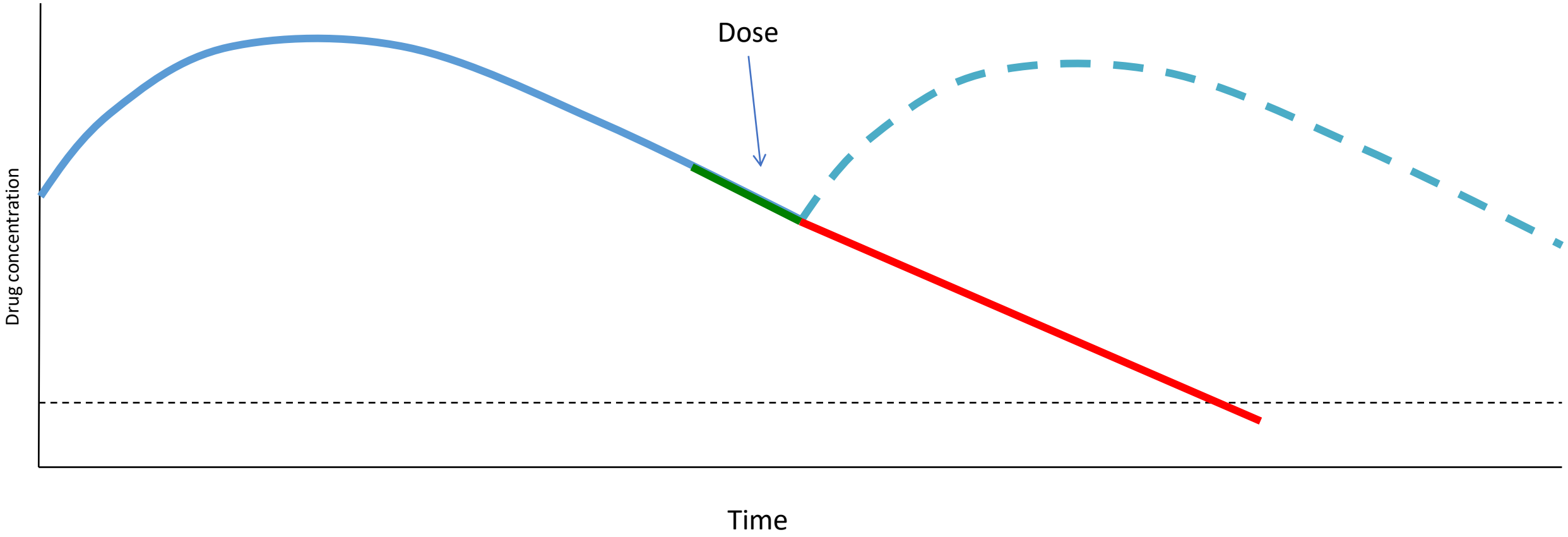
Q8W of CAB + RPV LA was:

-non-inferior to Q4W
-well tolerated (98% ISR grade1-2)
-preferred by study participants

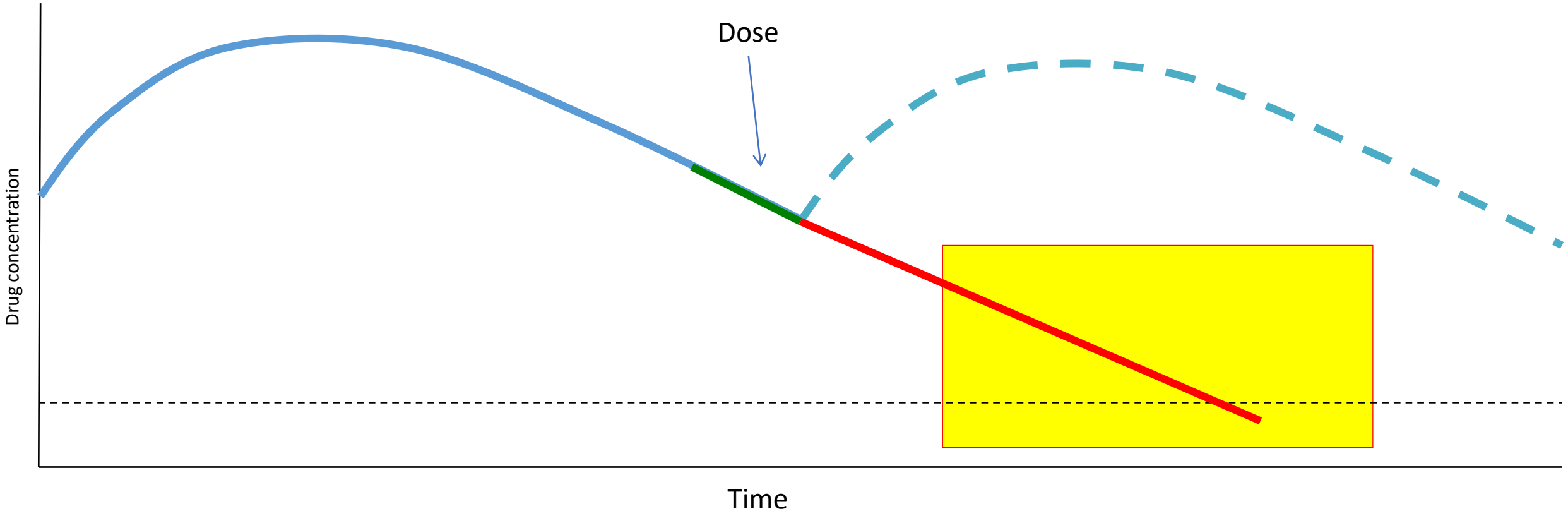
Overton et al. CROI 2020

LA = long-acting; CAB = cabotegravir; RPV = rilpivirine

Missed dose PK

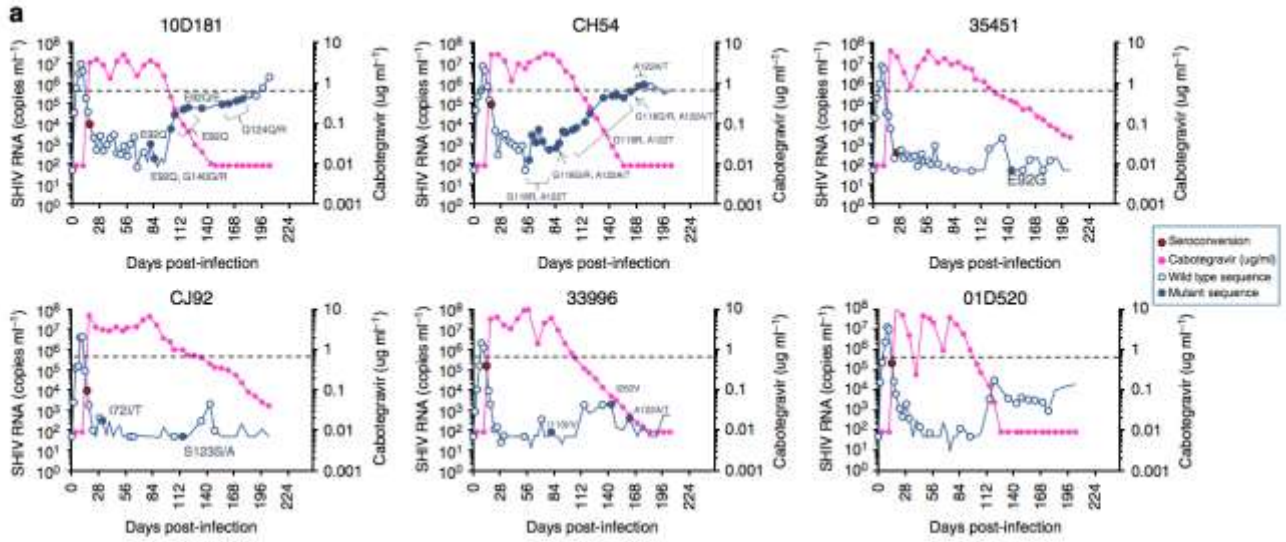


Missed dose PK

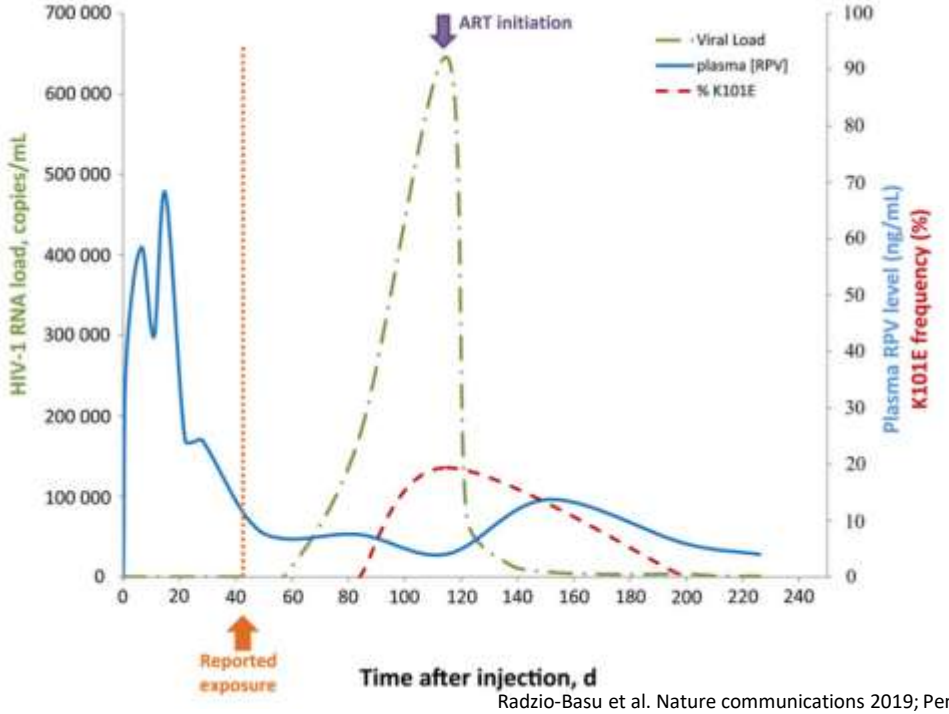


Development of resistance in presence of sub-optimal drug concentrations

CAB



RPV



LA = long-acting; CAB = cabotegravir; RPV = rilpivirine; PK = pharmacokinetics

Radzio-Basu et al. Nature communications 2019; Penrose et al. JID 2016

LA CAB: Bridging strategies

Simulated concentration-versus-time profiles

a) No delay (Sim# 1)

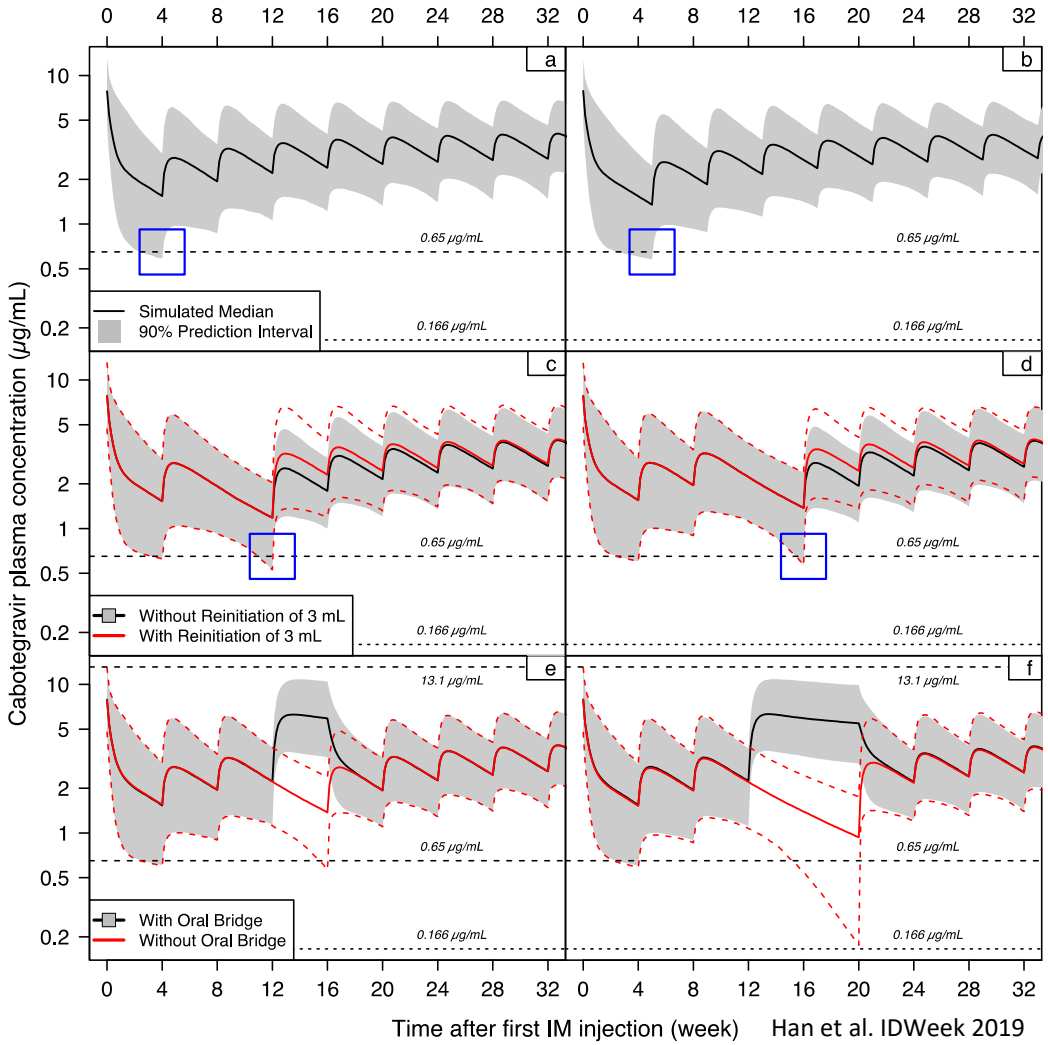
b) Injection 2 delayed by 1 week (Sim# 2)

c) Injection 3 delayed by 4 weeks with 2 mL or 3 mL reinitiation (Sim# 15 & 16)

d) Injection 4 delayed by 4 weeks with 2 mL or 3 mL reinitiation (Sim# 25 & 26)

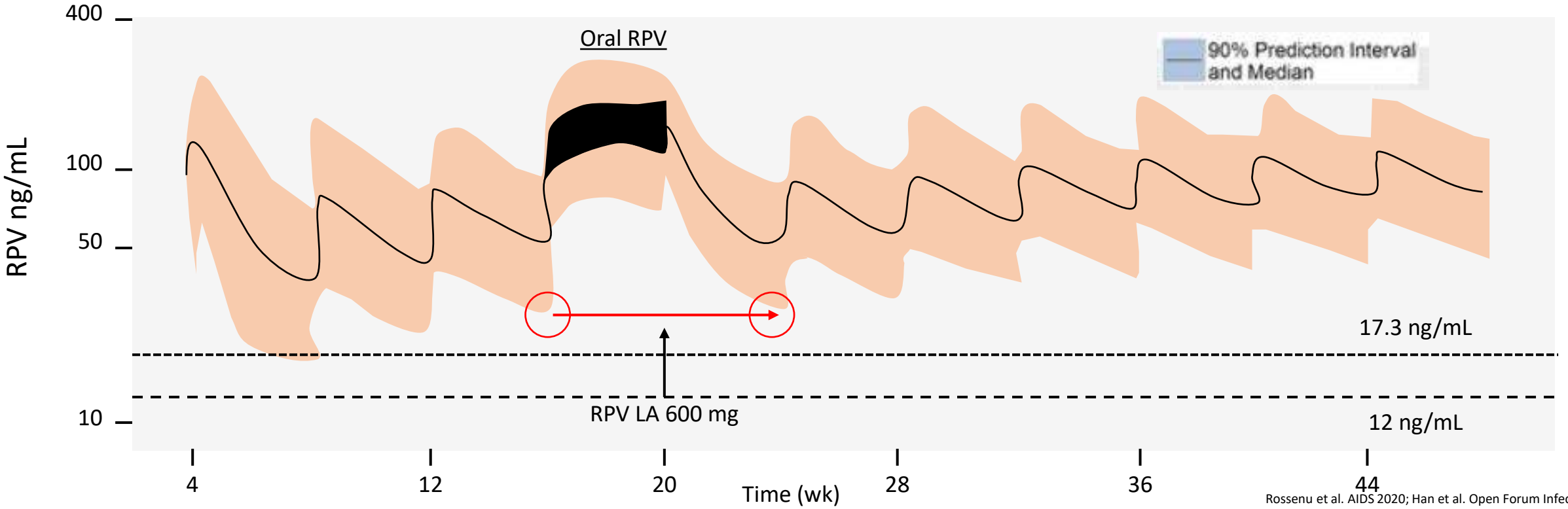
e) Injection 4 delayed by 4 weeks with/ without **oral bridge** (Sim# 25 & 32)

f) Injection 4 delayed by 8 weeks with/ without **oral bridge** (Sim# 29 & 35)



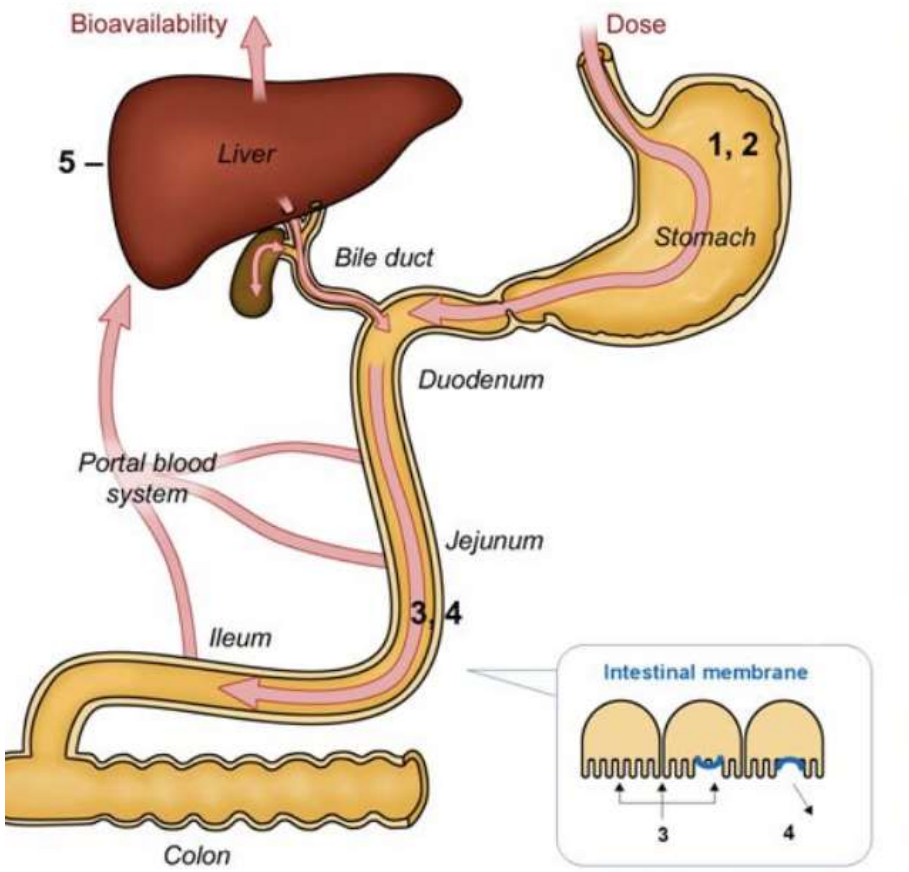
LA RPV: Bridging strategies

- **<u>Oral bridge with 25 mg RPV OD</u>**
  followed by 600 mg of RPV-LA if time between injections ≤ 2 months or 900 mg if > 2 months
- Similar to CAB LA



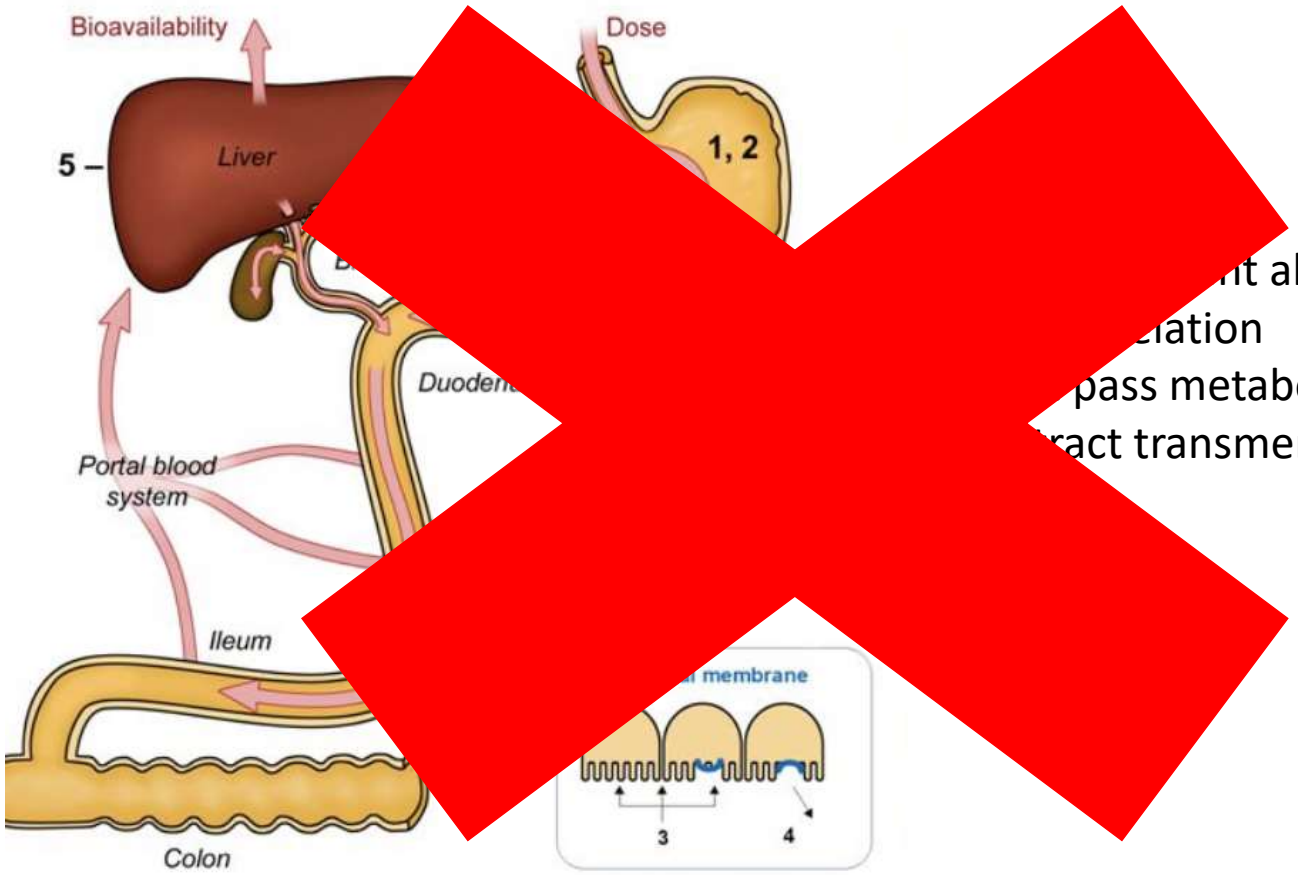
Rossenu et al. AIDS 2020; Han et al. Open Forum Infect Dis. 2019

Drug-drug interactions



pH dependent absorption
Drug chelation
First pass metabolism
GI tract transmembrane transporters

Drug-drug interactions



- nt absorption
- iation
- pass metabolism
- ract transmembrane transporters

The Journal of Infectious Diseases

MAJOR ARTICLE

Predicting Drug–Drug Interactions Between Rifampicin and Long-Acting Cabotegravir and Rilpivirine Using Physiologically Based Pharmacokin

Rajith K. R. Rajoli,[1] Paul Curley,[1] Justin Chiong,[1] David Back,[1] Charles Flexner,[2] Andrew Ow

[1] Department of Molecular and Clinical Pharmacology, University of Liverpool, United Kingdom; and [2] Johns Hopkins U Baltimore, Maryland

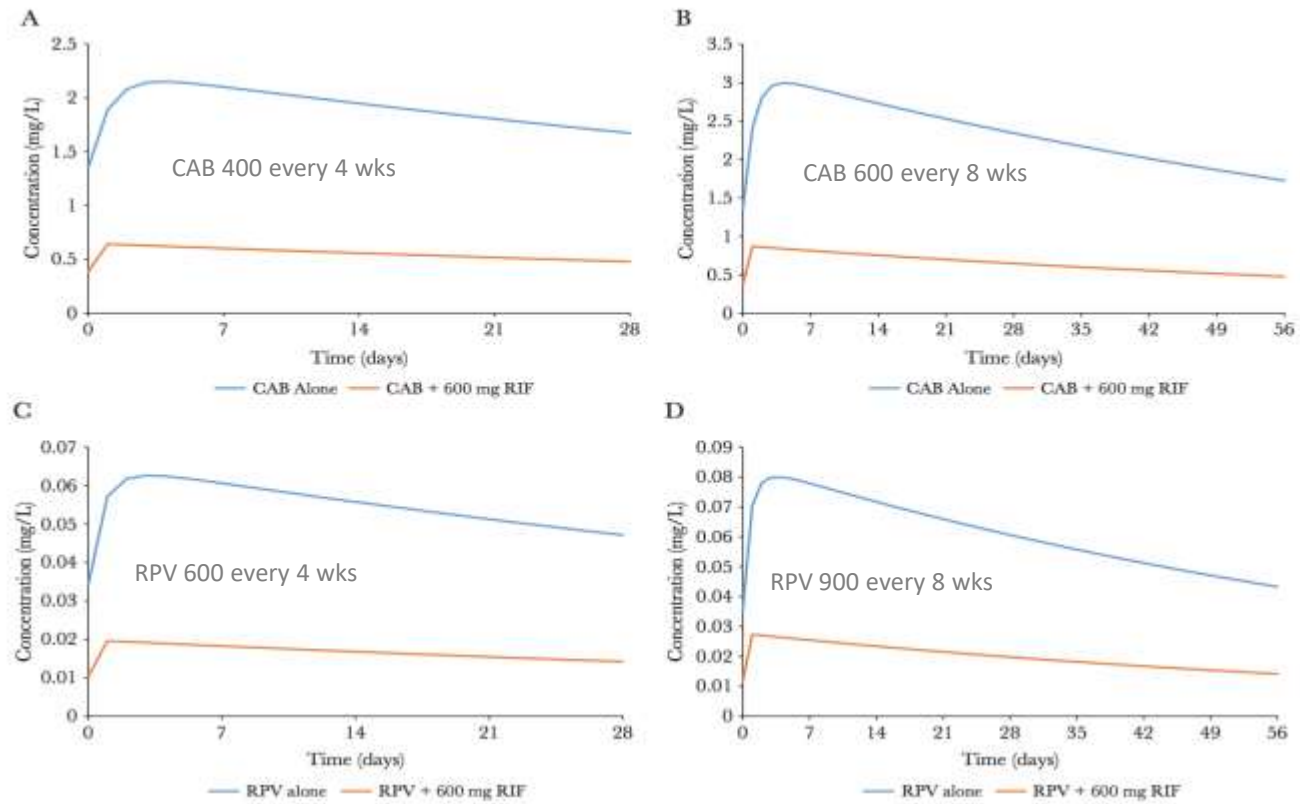
Background. Cabotegravir and rilpivirine are 2 long-acting (LA) antiretrov interaction with rifampicin, a first-line antituberculosis agent, has not been inv predict drug–drug interactions (DDIs) between these LA antiretroviral agents cokinetic (PBPK) modeling.

Methods. The designed PBPK models were qualified (according to Europ data for oral formulations of cabotegravir, rilpivirine, and rifampicin. Inductic paring the DDI between oral cabotegravir and oral rilpivirine with rifampicin. kinetic prediction of DDIs.

Results. PBPK models predicted a reduction in both area under the curve of LA cabotegravir of 41%–46% for the first maintenance dose coadministered concentrations were predicted to decrease by 82% for both $AUC_{0\text{-}28\ days}$ and C_{tr} coadministered with rifampicin.

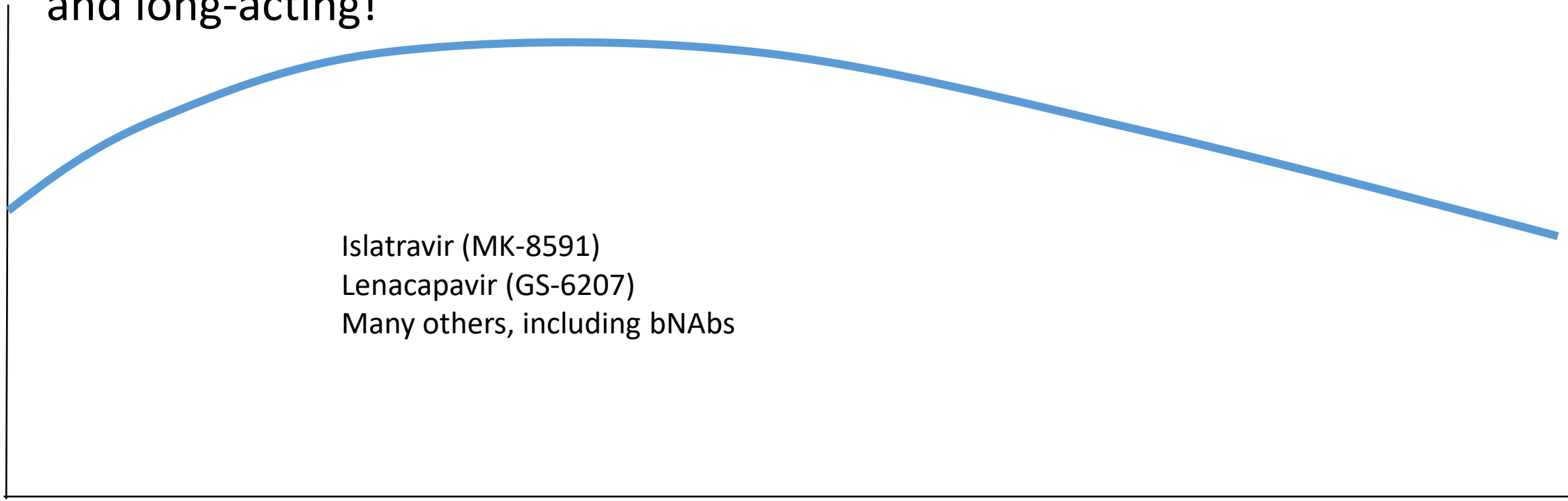
Conclusions. The developed PBPK models predicted the theoretical effect tramuscular formulations. According to these simulations, it is likely that coadn will result in subtherapeutic concentrations of both drugs.

Keywords. PBPK modeling; cabotegravir; rifampicin; long-acting; drug–d



Long acting ARV in development

- Discovering units are focused on less drugs, new mechanisms of action and long-acting!

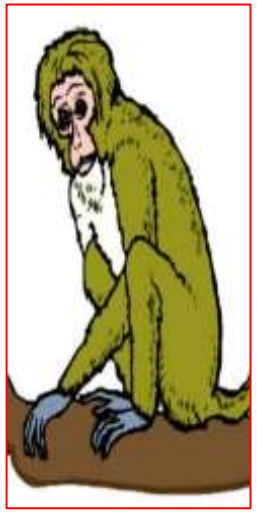


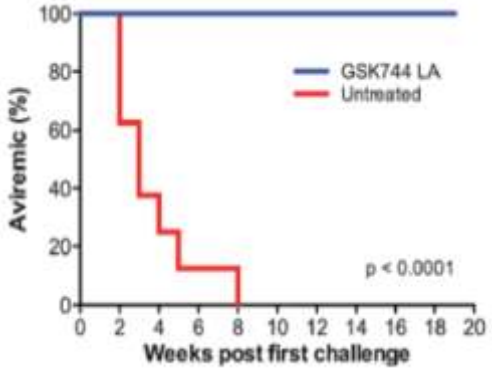
Islatravir (MK-8591)
Lenacapavir (GS-6207)
Many others, including bNAbs

Broadly Neutralizing Antibodies = bNAbs

PrEP: Cabotegravir LA

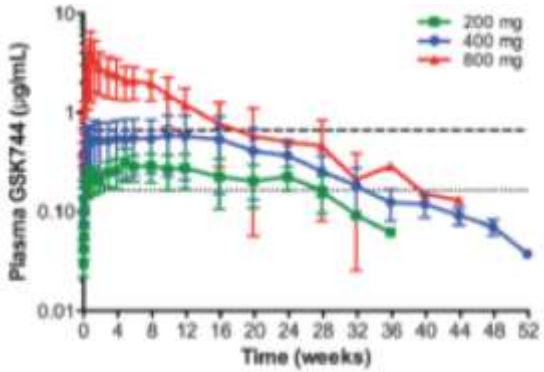
✓ ✗/✓ ✓ ✓✓





Long-acting integrase inhibitor protects macaques from intrarectal SHIV. Andrews et al. 2014

Phase I



Concentrations in:

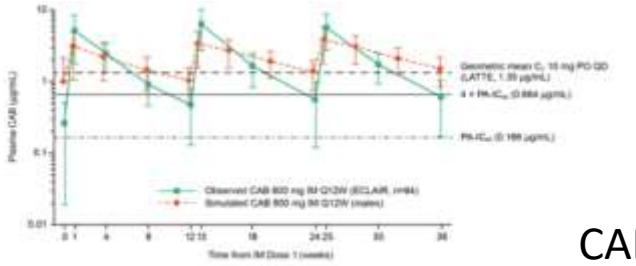
- *Female genital tract = 16%–28% of plasma*
- *Rectal tissue < 8% of plasma*

Relevance?

GSK1265744 PK in plasma and tissue after single-dose LA injectable administration in healthy subjects. J Acquir Immune Defic Syndr. Spreen et al. 2014

Phase II

ECLAIR



Markowitz et al. 2017

HPTN 077
Men and women

Phase III

CAB LA vs TDF/FTC IN MSM/TGW (>4000) 083 and women (>3000) 084 CAB LA superior to oral PrEP

Global phase III study HPTN 083 and 084

Outstanding questions

- Implementation of injection Q8w
- Adolescents? (data > 18) – sub-study analysis ongoing
- Use during pregnancy and breastfeeding
- PK tail

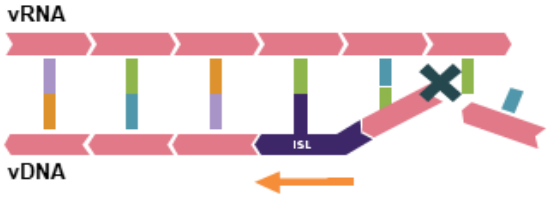
NRTTI: Islatravir (Formerly MK 8591)

- First in class nucleoside transcription translocation inhibitor (NRTTI)
- Multiple mechanisms of action contribute to high potency and high barrier to resistance including drug resistant viruses

Translocation Inhibition

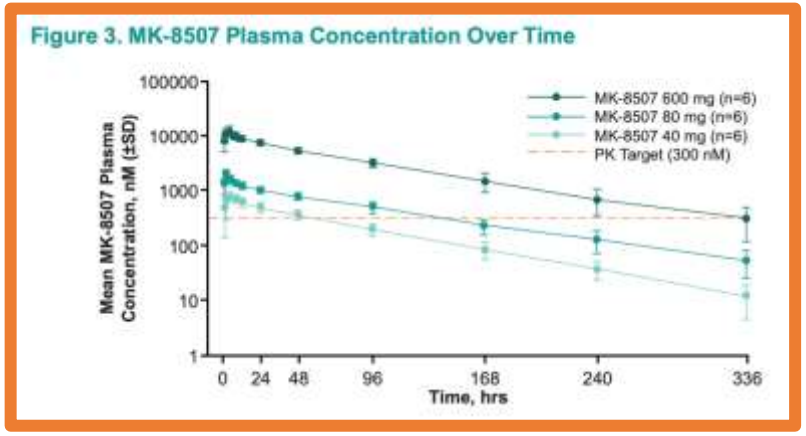
- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to RT-associated resistance-conferring mutations
- **Viral replication is inhibited**

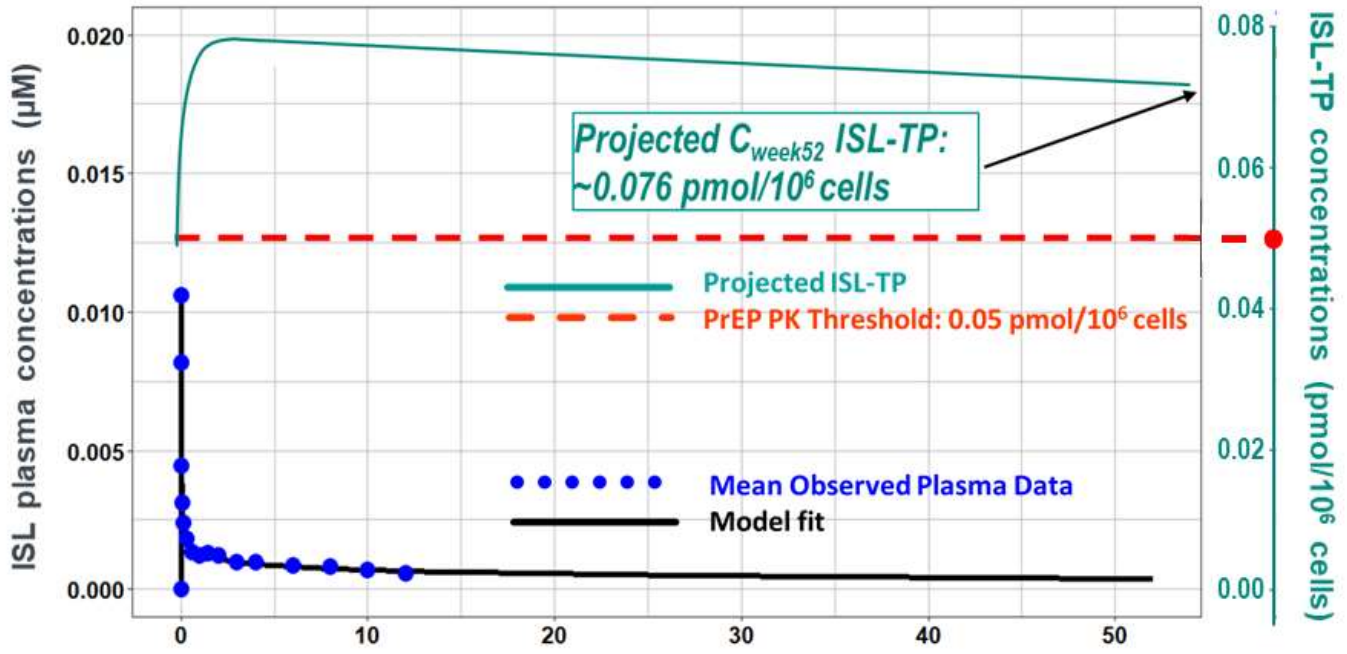
- In development as:
  - Daily oral 2DR regimen together with doravirine
  - Once weekly tablet in combination with MK8507
  - Monthly oral for PrEP
  - Implant (PrEP)



Ankrom et al. Glasgow 2020

Islatravir implant maintains concentration threshold for one year

62 mg Implant Projected to Lead to Concentrations Above Threshold for at Least 12 Months

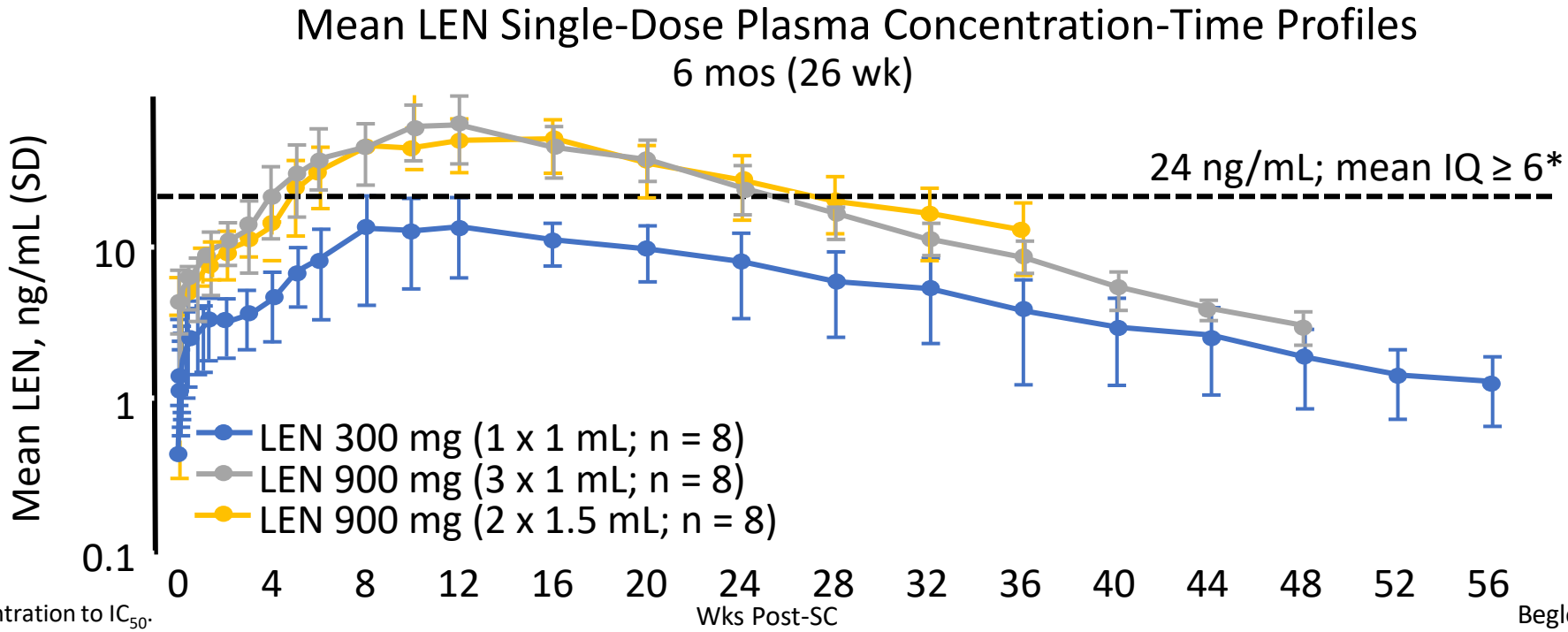


Matthews et al. IAS 2019

Lenacapavir (GS-6207) PK Profile

- Lenacapavir (GS-6207): first-in-class selective HIV-1 capsid protein inhibitor / oral and SC long-acting formulations
- Randomized, double-blind, placebo controlled, single-ascending SC dose phase I study in HIV-negative participants
- Supports 6 monthly dosing , maintained target concentrations for 26 weeks

N= 30



*IQ: ratio of LEN plasma concentration to IC_{50}.

Begley. AIDS 2020. Abstr PEB0265.

Key points

- Exciting developments with injectable/implants and other LA formulations
- Need to learn about tail, different population exposures, bridging strategies, etc
- By skipping the GI/hepatic first pass, DDIs likely be fewer but still presen /modelling important to predict DDIs in virtual patients
- Implementation challenges

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