Clinical pharmacology of long acting agents for HIV prevention and treatment

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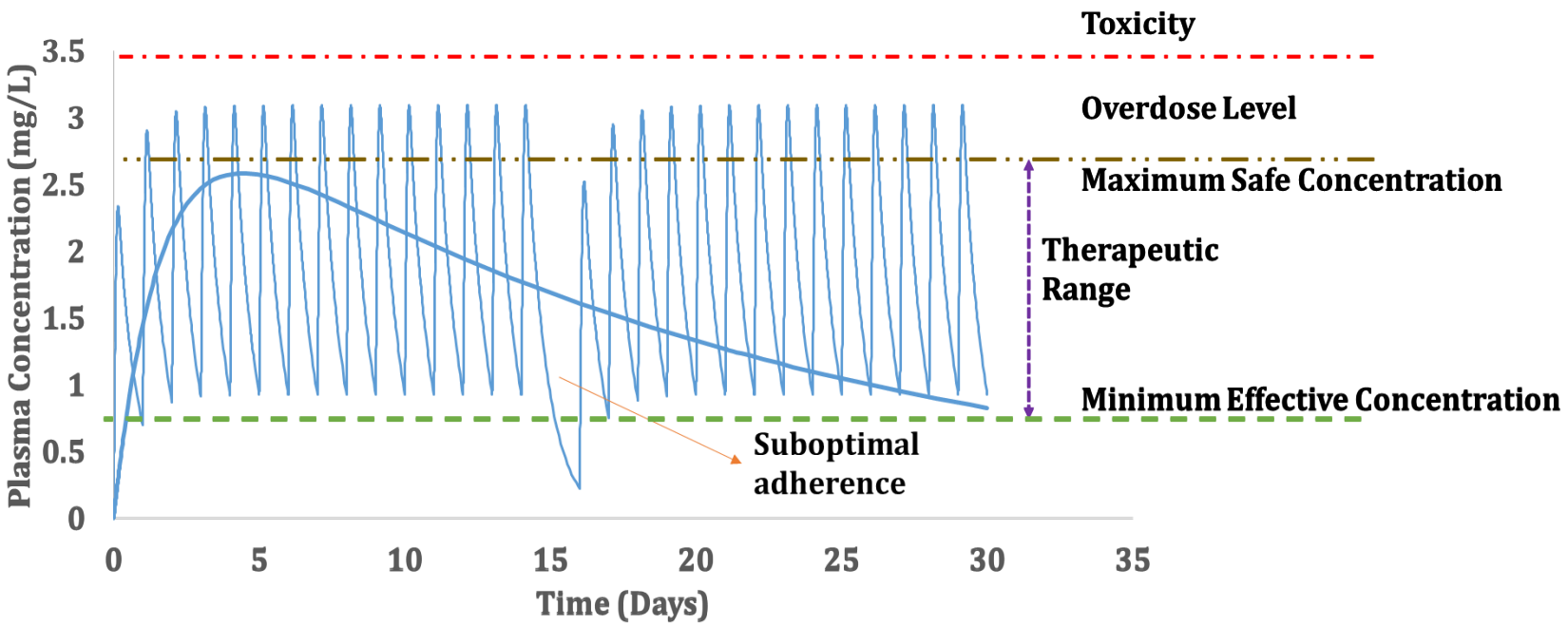
Long-acting?

- What do we mean?
- Why long-acting drugs?
- Are drug concentrations the same for everyone?
- What is the PK tail? Do we need to worry about it?
- What about drug-drug interactions (DDIs)?
- What do PLWH want?
- What about PrEP?

Definition

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

Long-acting PK

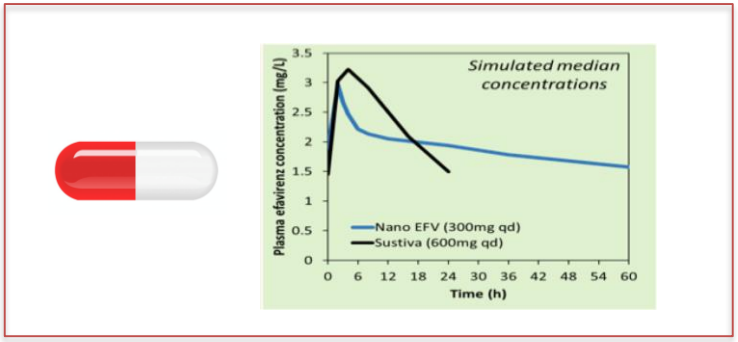


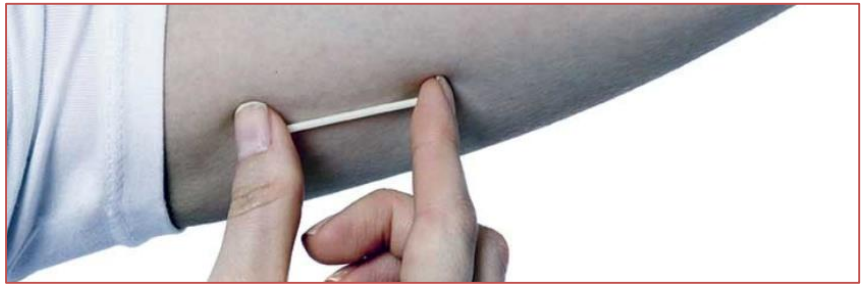
Long-acting: benefits

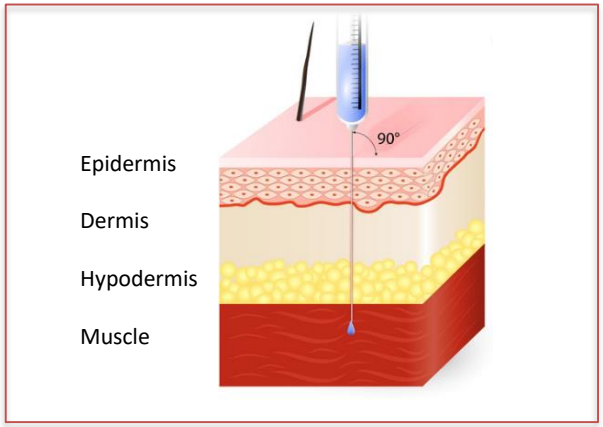
- Sustained release results in prolonged half-life
- Infrequent dosing
- Potential lower total dose
- Protection of health privacy
- Protection of poor adherence

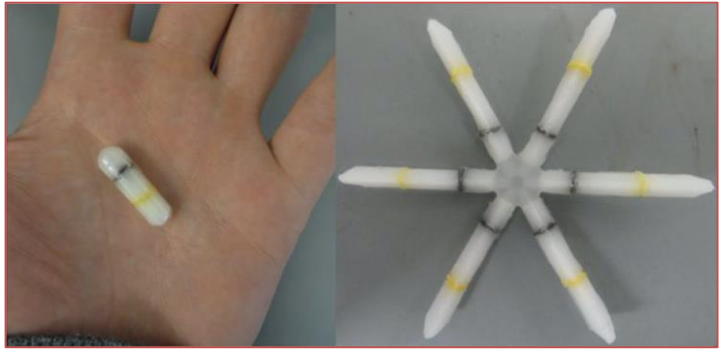
- When not administered orally, the GI barrier is bypassed

How to deliver long-acting drugs





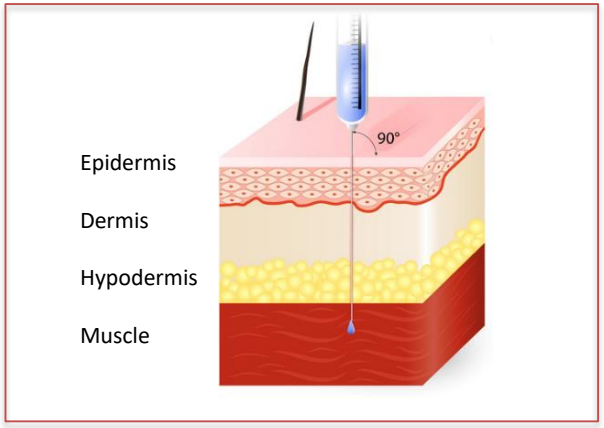




Owen et al. CROI 2017; Bellinger et al. Science Translational Medicine 2016; Benhabbour et al. Nature Communications 2019; Margolis et al. Lancet 2017

How to deliver long-acting drugs

Intramuscular injection



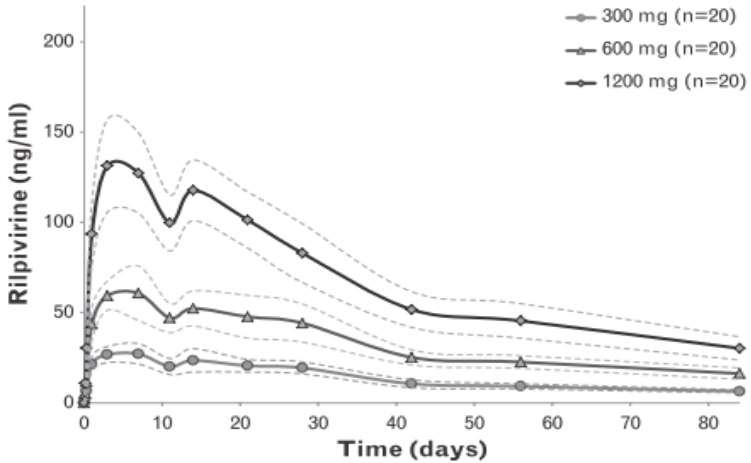
Margolis et al. Lancet 2017

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



continued to those groups who cannot, or do not, reach appropriate healthcare. Substantial challenges remain before the beginning of the end of AIDS. Treatment adherence and stigma remain major hurdles in the fight against the HIV-1 pandemic. The care cascade suggests that as few as 35% of blacks, who know their infected status, have 'undetectable' plasma viral load (<50 HIV-1 RNA copies/ml, c/ml) in the USA [2]. The annual rate of new HIV infections is still increasing in young women in sub-Saharan Africa and young black men who have sex with men (MSM) in the USA.

PHARMACOLOGY OF ORAL RILPIVIRINE

Rilpivirine (RPV) is a potent, next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI)

Janssen Research and Development, Turnhoutseweg, Beerse, Belgium

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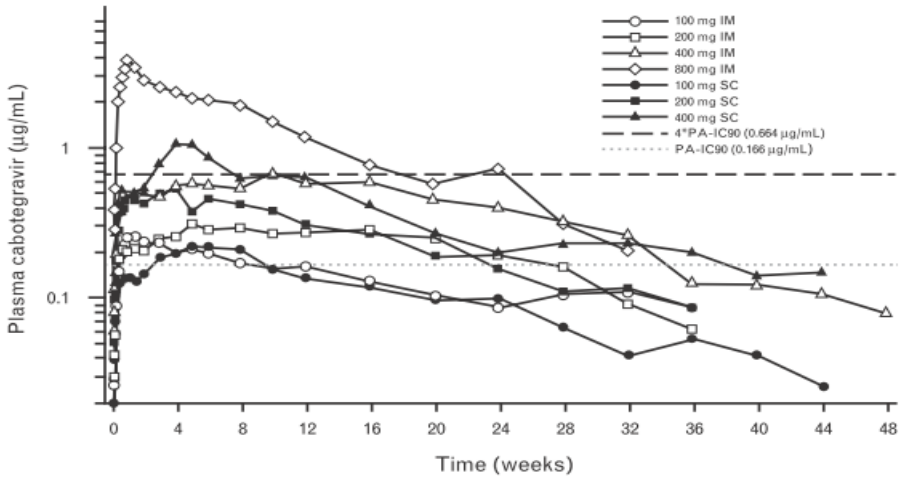
Curr Opin HIV AIDS 2015, 10:233–238

DOI:10.1097/COH.0000000000000164

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



the emergence of drug resistance, and reducing the risk of HIV transmission [2,3]. Long-acting antiretrovirals capable of achieving prolonged exposures at therapeutic concentrations may enable simplified treatment regimens that do not necessitate daily administration.

Cabotegravir (GSK1265744) is a potent integrase strand transfer inhibitor and a structural analogue of dolutegravir. Cabotegravir's unique physiochemical and pharmacokinetic properties have permitted its formulation and delivery both as an oral tablet for daily administration and as a long-acting

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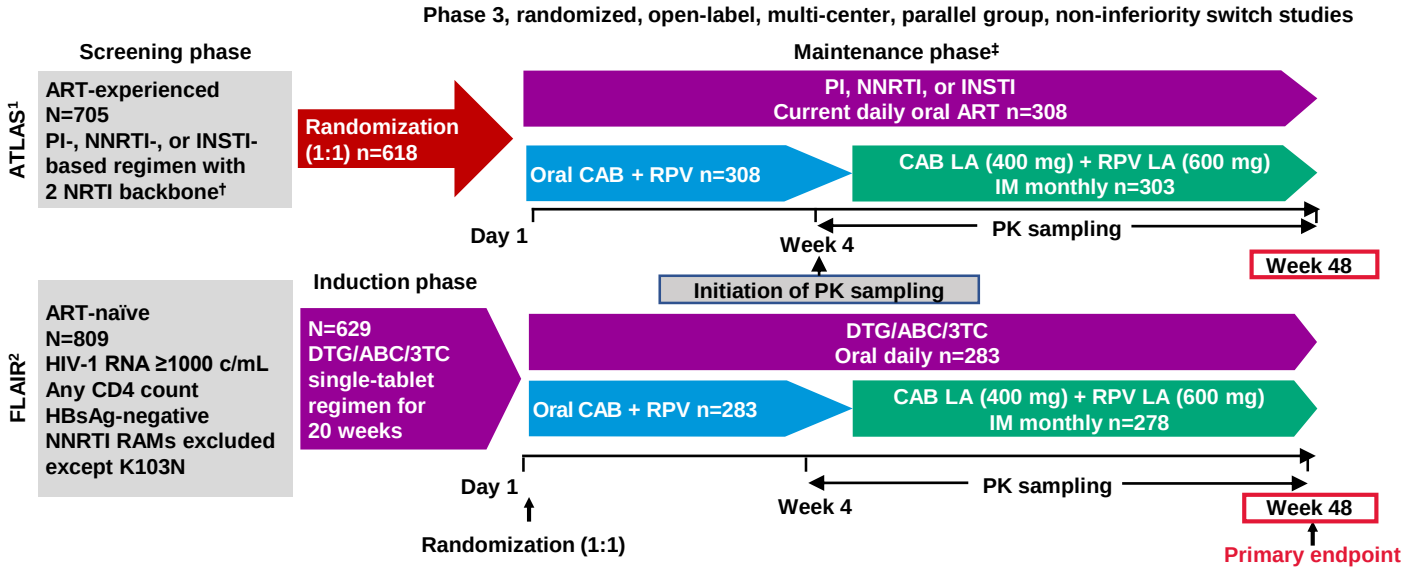
Curr Opin HIV AIDS 2015, 10:239–245

DOI:10.1097/COH.0000000000000168

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)



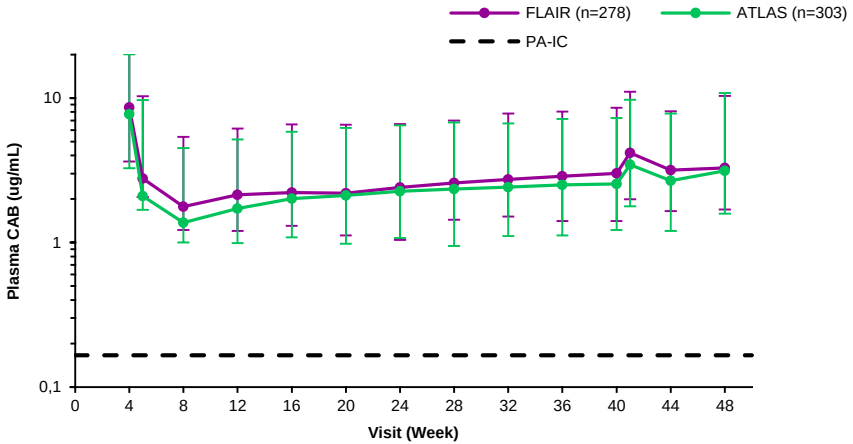
Swindells et al. CROI 2019; Orkin et al. CROI 2019

Long-acting: unanswered questions

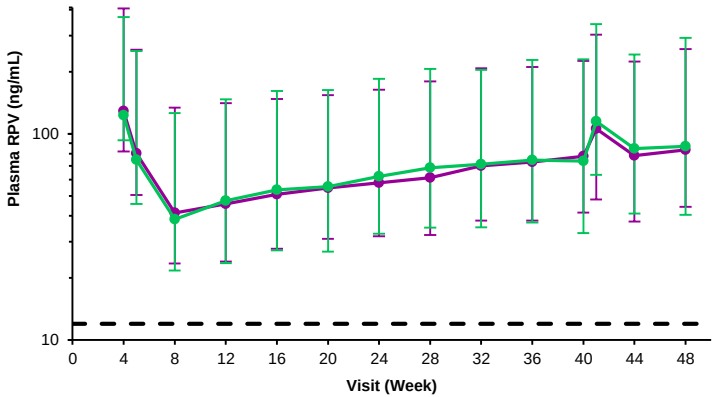
- Pregnancy
- Pediatrics
- Reduction of volume of injection
- Drug exposure – same for all?
- Drug interactions
- Long term safety
- Need for oral lead in period

LA CAB and RPV PK

Median (5th and 95th percentile) plasma CAB PK following CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks



Median (5th and 95th Percentile) plasma RPV PK following CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks



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 mL 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)§

Patel et al. IDWeek 2019

CAB PK by sex at birth and baseline BMI

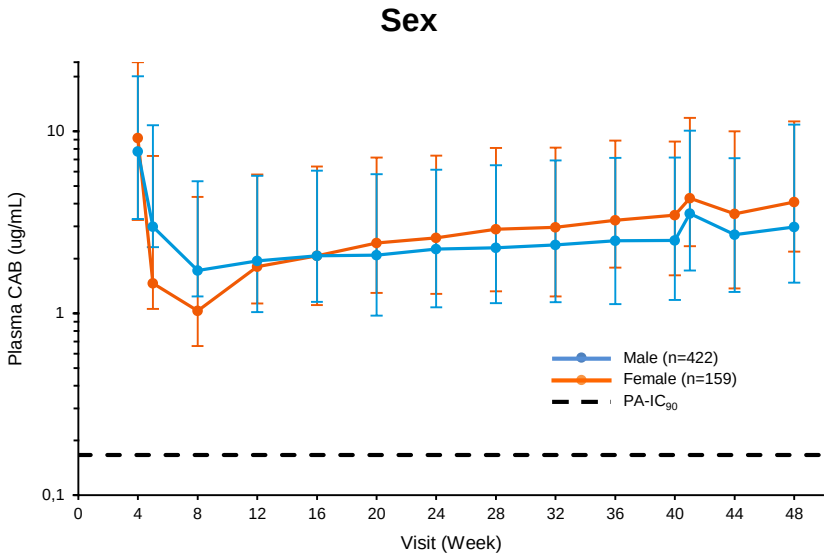
- 4 weeks following the first injection, median CAB levels were lower in females than males by 40%
- CAB troughs at Week 48 were slightly higher in females than males

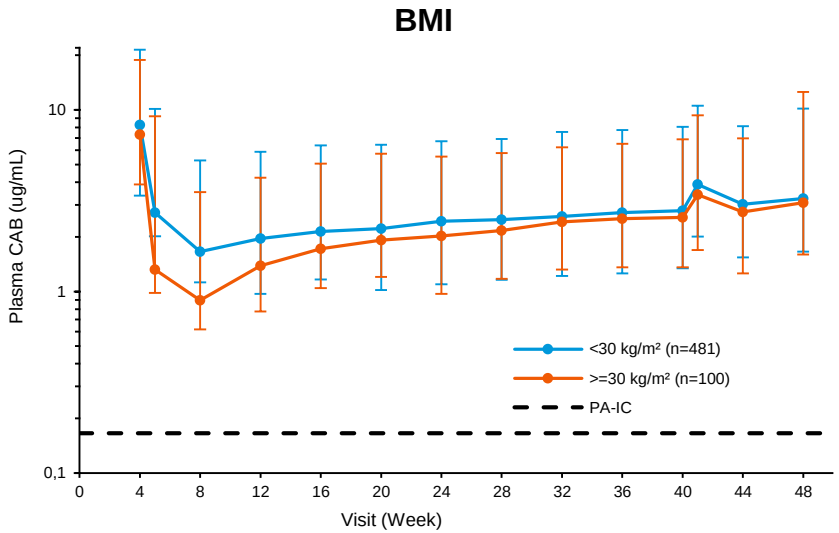
- 4 weeks following the first injection, median CAB levels were lower in individuals with body mass index (BMI) ≥30 kg/m^2 by 46% vs. those with BMI <30 kg/m^2
- CAB troughs at Week 48 were similar regardless of BMI

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

Patel et al. IDWeek 2019

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

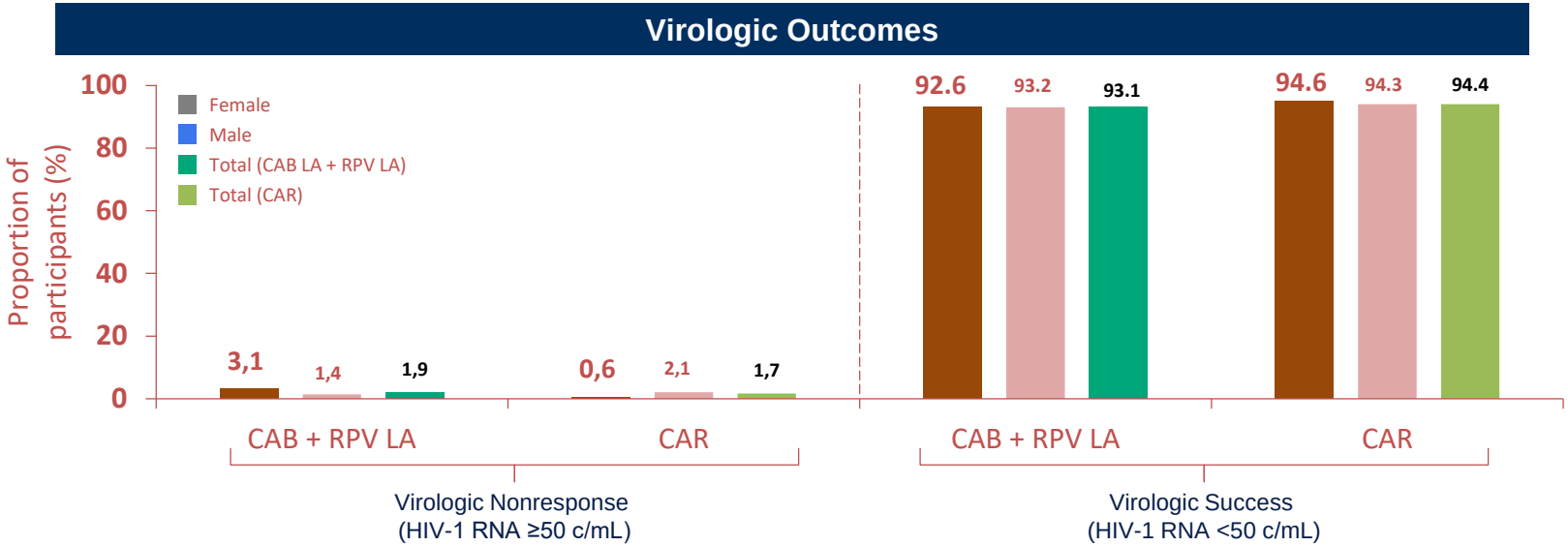




Protein-adjusted 90% inhibitory concentration (PA-IC_{90}) for CAB is 0.166 µg/mL [Margolis et al. Lancet 2017]

Patel et al. IDWeek 2019

High Rates of Virologic Success Was Observed in Both Men and Women in ATLAS and FLAIR



At Week 48, virologic non-response was infrequent, with 92.6% of women having virologic success with the LA regimen

CAB, cabotegravir; CAR, current antiretroviral; LA, long-acting; RPV, rilpivirine.

Quercia et al. EACS 2019

ATLAS and FLAIR Confirmed Virologic Failures* Were Infrequent: CAB LA + RPV LA Arm CVFs in Women at W48

Country, HIV-1 Subtype	Study	SVF Timepoint	Viral Load at SVF/CVF (c/mL)	BMI >30 kg/m²	Baseline RAMs (PBMC/HIV-1 DNA; Day 1)		SVF Timepoint RAMs (HIV-1 RNA)		Drug Sensitivity at SVF§ (Fold Change)		
					RT	INSTI‡	RT	INSTI‡			
Russia, A/A1	ATLAS	Week 8	79,166 / 25,745	No	E138E/A	None	E138A	None	**RPV (2.4)**	CAB (0.8)	DTG (0.9)
France, AG	ATLAS	Week 12	695 / 258	Yes	V108V/I E138K	None	V108I E138K	None	**RPV (3.7)**	CAB (1.2)	DTG (1.0)
Russia, A1	FLAIR	Week 20	373 / 456	Yes	None	None	E138E/A/K /T	Q148R	**RPV (7.1)**	**CAB (5.2)**	DTG (1.0)
Russia, A1	FLAIR	Week 48	488 / 440	Yes	None	None	E138K	Q148R	RPV (1.0)	**CAB (9.4)**	DTG (1.1)

- Seven (1.2%, LA; and 1.2%, CAR) confirmed virologic failures (CVFs) occurred in each arm, with 5/7† (LA) and 2/7 (CAR) arising in women
- Plasma CAB and RPV concentrations for women at the time of failure were below the population means but within the range for the large majority of individuals who maintained virologic suppression

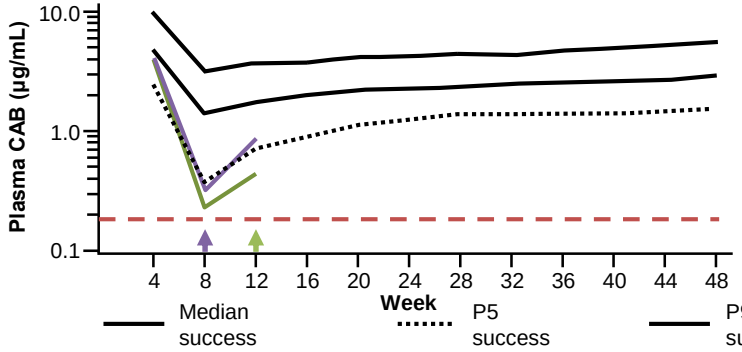
*Where CVF is defined as rebound as indicated by two consecutive plasma HIV-1-RNA levels ≥200 c/mL after prior suppression to <200 c/mL. †One participant in FLAIR had oral CAB/RPV dosing interrupted due to a false-positive pregnancy test and upon re-initiation of oral therapy, had suspected VF that was confirmed. ‡L74I is not considered an INSTI RAM by IAS-US guidelines and has no impact on CAB activity. §Monogram biological/clinical cutoffs are: RPV=2.0, CAB=2.5, and DTG=4.0.
BMI, body mass index; CAB, cabotegravir; CAR, current antiretroviral; CVF, confirmed virologic failure; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; PBMC, peripheral blood mononuclear cell; RAM, resistance-associated mutation; RPV, rilpivirine; RT, reverse transcriptase; SVF, suspected virologic failure; VF, virologic failure.

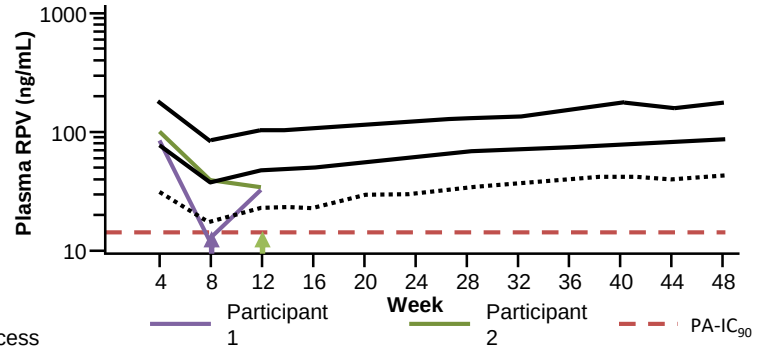
Quercia et al. EACS 2019

ATLAS and FLAIR: Individual Concentration-Time Profiles for CAB and RPV CVFs Compared with Median Profiles for Successes

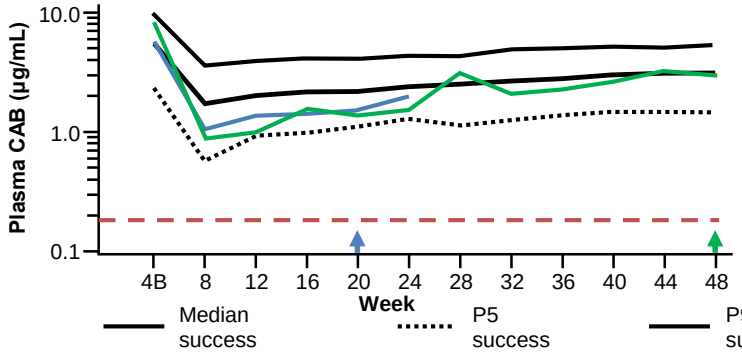
In ATLAS and FLAIR, CAB and RPV concentration-time profiles for women with CVF were within the range of exposures that show efficacy in most participants, indicating that other factors may have contributed to failure

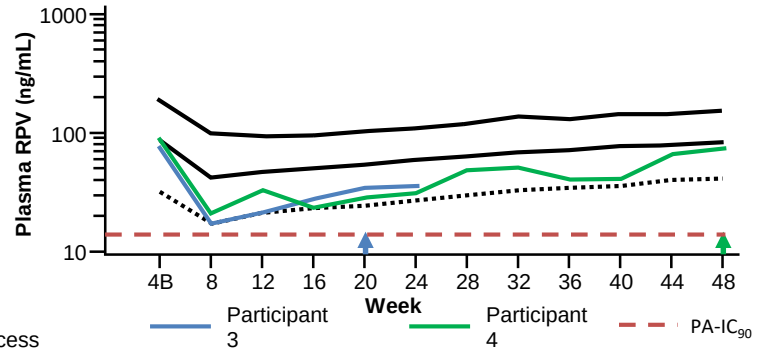
ATLAS





FLAIR



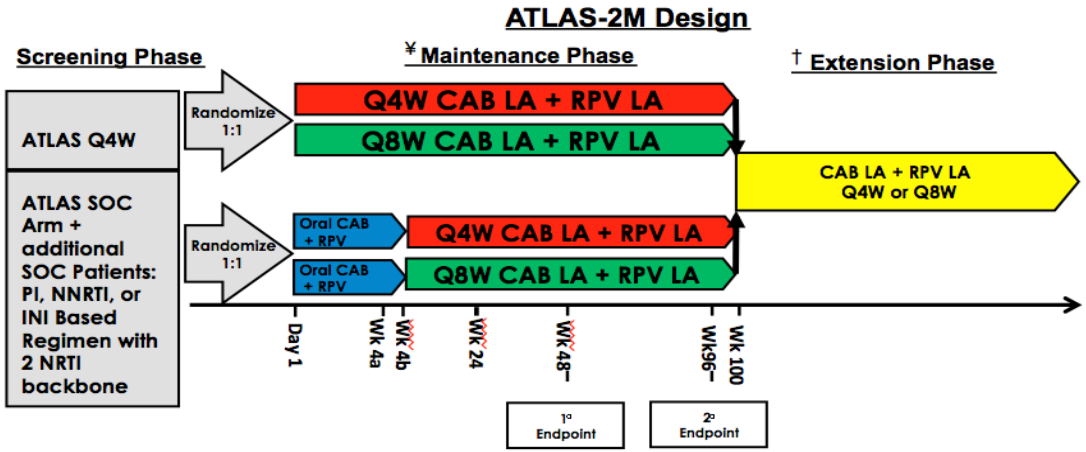


$PA\text{-}IC_{90}$ for CAB is 0.166 µg/mL. $PA\text{-}IC_{90}$ for RPV is 12 ng/mL.
CAB, cabotegravir; CVF, confirmed virologic failure; $PA\text{-}IC_{90}$, protein-adjusted 90% inhibitory concentration; RPV, rilpivirine.

Quercia et al. EACS 2019

ATLAS 2M

- Positive LATTE-2 Week 96 results enabled Q8W program
- Randomized, open-label, multicentre, non-inferiority design
- Primary goal: demonstration of non-inferiority of Q8W to Q4W dosing to extend dosing options for PLHIV
  - 4% NI Margin
  - Endpoint: proportion of participants with HIV-RNA ≥50 copies/mL at Week 48 using FDA snapshot algorithm

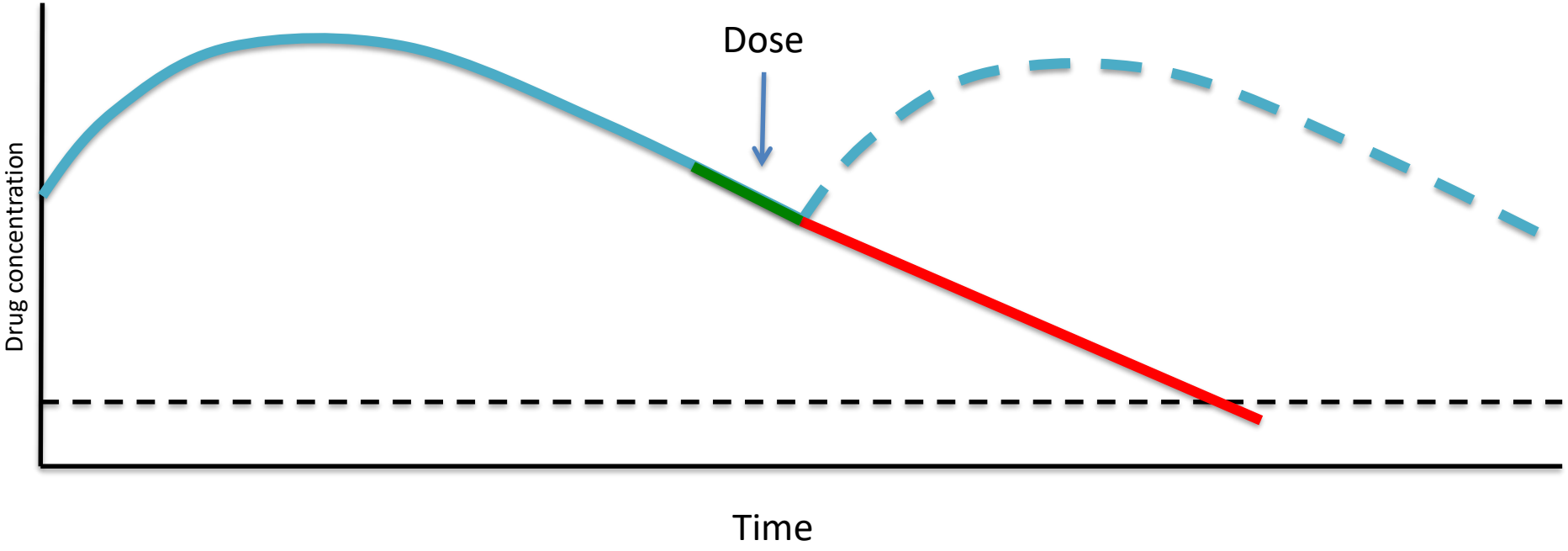


N=1049, randomized 1:1 to each arm and stratified by prior CAB + RPV exposure

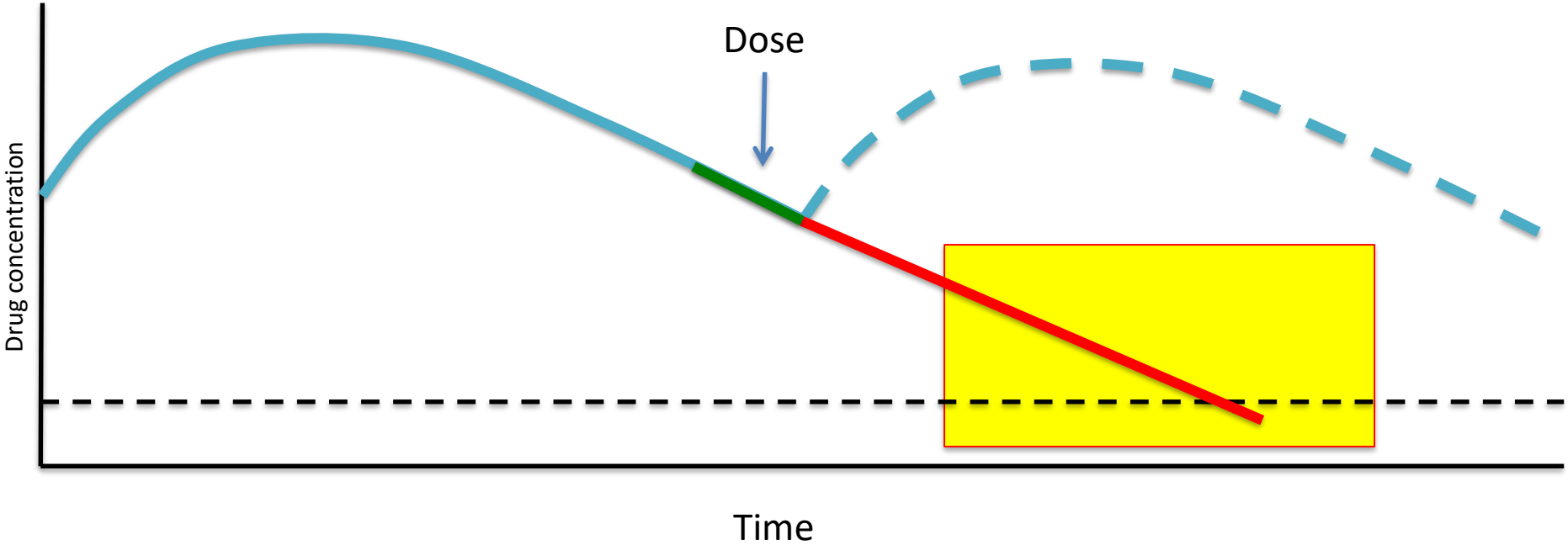
¥ ATLAS participants on Q4W arm – transition to ATLAS-2M Day 1 onwards CAB LA (400 mg) + RPV LA (600 mg) IM every 4 weeks or CAB LA (600 mg) + RPV LA (900 mg) IM every 8 weeks
New ATLAS-2M participants naïve to LA at Day 1 – all participants initiate 4-week oral lead in followed by LA injections.
Q4W arm - loading dose of CAB LA (600 mg) + RPV LA (900 mg) IM at Wk 4b, then CAB LA (400 mg) + RPV LA (600 mg) IM every 4 weeks
Q8W arm - initial dose of CAB LA (600 mg) + RPV LA (900 mg) at Wk 4b and Wk 8, then continue same IM dose every 8 weeks

† Optional Extension Phase to continue randomized CAB LA + RPV LA Q4W or Q8W at Wk 100

Missed dose PK

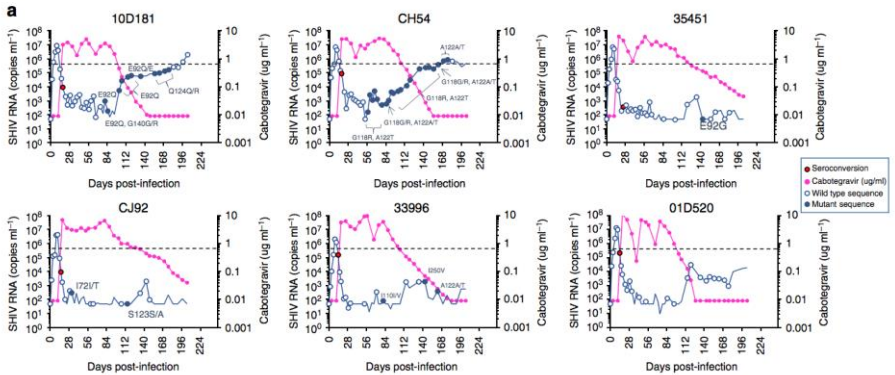


Missed dose PK



Development of resistance in presence of sub-optimal drug concentrations

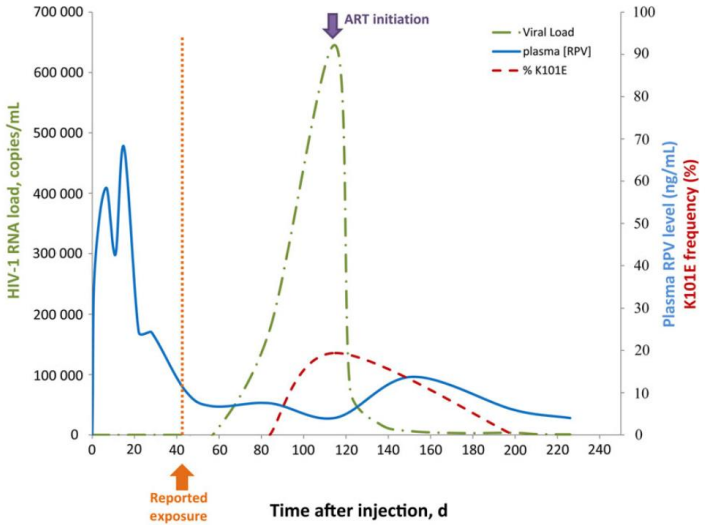
CAB



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

Development of resistance in presence of sub-optimal drug concentrations

RPV



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

Bridging strategies

Simulated concentration-versus-time profiles

a) No delay (Sim# 1)

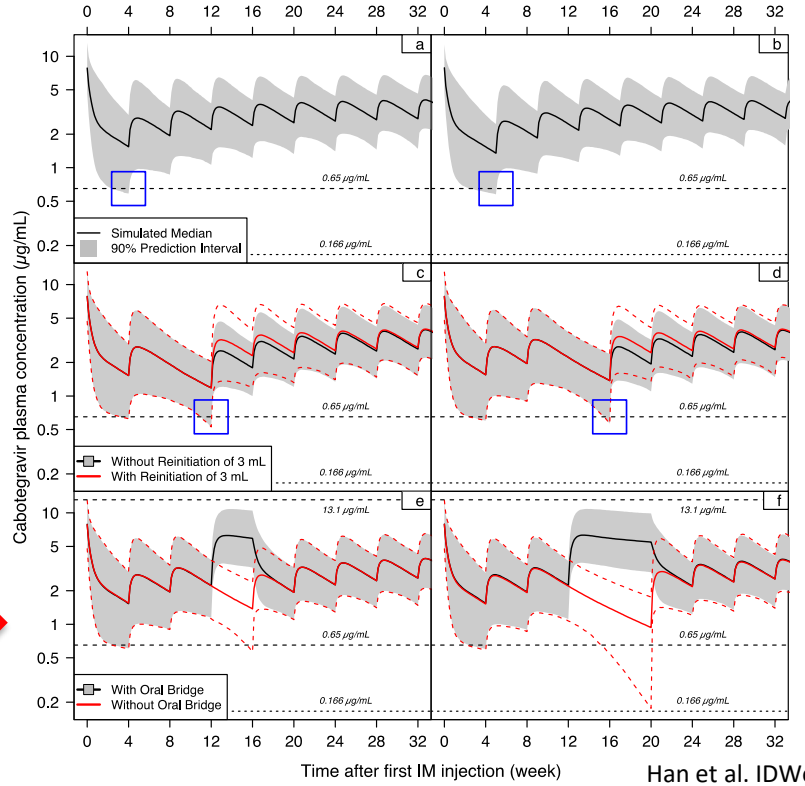
b) Injection 2 delayed by 1 week (Sim# 2)

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)

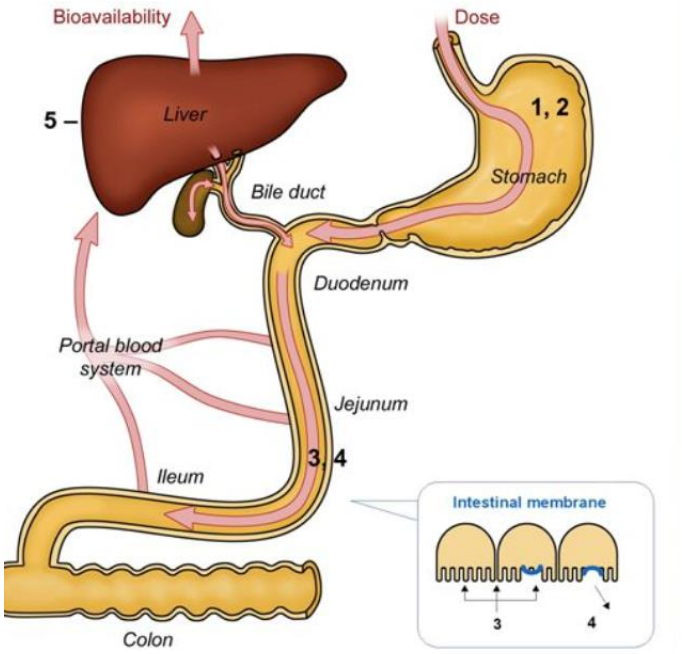
e) Injection 4 delayed by 4 weeks with/ without **oral bridge** (Sim# 25 & 32)

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



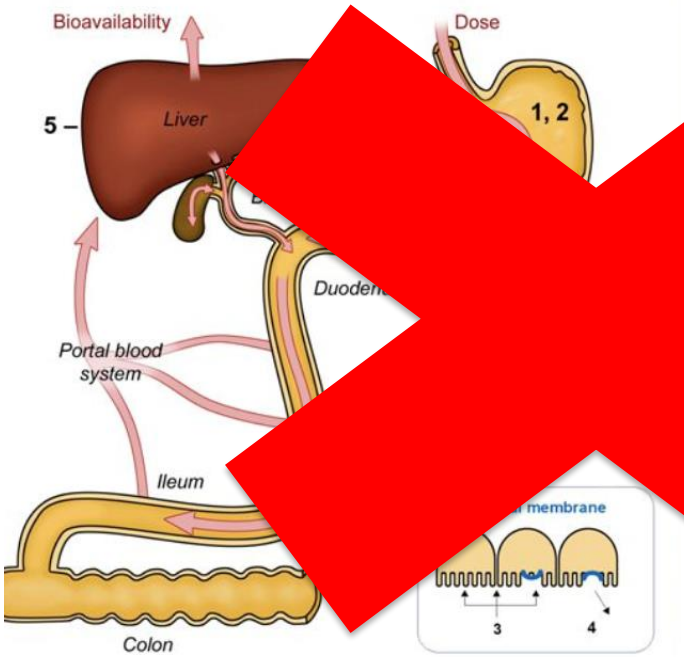
Han et al. IDWeek 2019

Drug-drug interactions



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

Drug-drug interactions



ndent absorption

chelation

st pass metabolism

t transmembrane transporters

The Journal of Infectious Diseases

MAJOR ARTICLE

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

Rajith K. R. Rajoli,[1,] **Paul Curley,[1]** **Justin Chiong,[1]** **David Back,[1]** **Charles Flexner,[2]** **Andrew Owen,[1]** **and Marco Siccardi[1]**

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

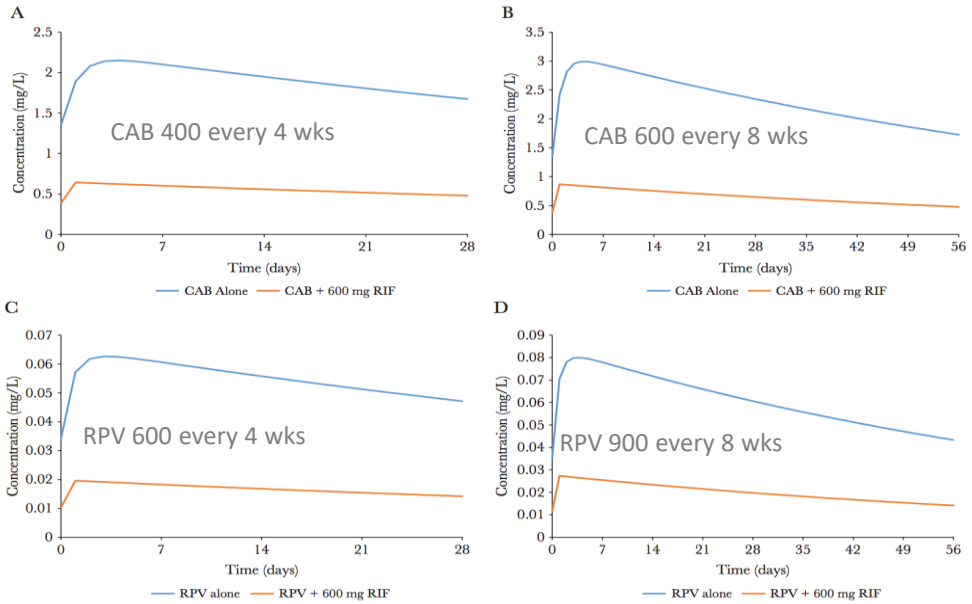
Background. Cabotegravir and rilpivirine are 2 long-acting (I interaction with rifampicin, a first-line antituberculosis agent, has predict drug–drug interactions (DDIs) between these LA antiretr cokinetic (PBPK) modeling.

Methods. The designed PBPK models were qualified (accord data for oral formulations of cabotegravir, rilpivirine, and rifampi paring the DDI between oral cabotegravir and oral rilpivirine with kinetic prediction of DDIs.

Results. PBPK models predicted a reduction in both area und of LA cabotegravir of 41%–46% for the first maintenance dose co concentrations were predicted to decrease by 82% for both AUC_0 coadministered with rifampicin.

Conclusions. The developed PBPK models predicted the thec tramuscular formulations. According to these simulations, it is like will result in subtherapeutic concentrations of both drugs.

Keywords. PBPK modeling; cabotegravir; rifampicin; long-ac



CAB PrEP

THE LANCET
HIV

Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial

Martin Markowitz, Ian Frank, Robert M Grant, Kenneth H Mayer, Richard Elion, Deborah Goldstein, Chester Fisher, Magdalena E Sobieszczyk, Joel E Gallant, Hong Van Tieu, Winkler Weinberg, David A Margolis, Krischan J Hudson, Britt S Stancil, Susan L Ford, Parul Patel, Elizabeth Gould, Alex R Rinehart, Kimberly Y Smith, William R Spreen

Summary

Background Cabotegravir (GSK1265744) is an HIV-1 integrase strand transfer inhibitor with potent antiviral activity and a long half-life when administered by injection that prevented simian-HIV infection upon repeat intrarectal challenge in male macaques. We aimed to assess the safety, tolerability, and pharmacokinetics of long-acting cabotegravir injections in healthy men not at high risk of HIV-1 infection.

Methods We did this multicentre, double-blind, randomised, placebo-controlled, phase 2a trial at ten sites in the USA. Healthy men (aged 18–65 years) deemed not at high risk of acquiring HIV-1 at screening were randomly assigned (5:1), via computer-generated central randomisation schedules, to receive cabotegravir or placebo. Participants received oral cabotegravir 30 mg tablets or matching placebo once daily during a 4 week oral lead-in phase, followed by a 1 week washout period and, after safety assessment, three intramuscular injections of long-acting cabotegravir 800 mg or saline placebo at 12 week intervals. Study site staff and participants were masked to treatment assignment from enrolment through week 41 (time of the last injection). The primary endpoint was safety and tolerability from the first injection (week 5) to 12 weeks after the last injection. We did analysis in the safety population, defined as all individuals enrolled in the study who received at least one dose of the study drug. This study is registered with ClinicalTrials.gov identifier, NCT02076178.

Findings Between March 27, 2014, and Feb 23, 2016, we randomly assigned 127 participants to receive cabotegravir (n=106) or placebo (n=21); 126 (99%) participants comprised the safety population. Most participants were men who have sex with men (MSM; n=106 [83%]) and white (n=71 [56%]). 87 (82%) participants in the cabotegravir group and 20 (95%) participants in the placebo group completed the injection phase. Adverse events (n=7 [7%]) and injection intolerability (n=4 [4%]) were the main reasons for withdrawal in the cabotegravir group. The frequency of grade 2 or higher adverse events was higher in participants in the long-acting cabotegravir group (n=75 [80%]) than in those in the placebo group (n=10 [48%]; p=0·0049), mostly due to injection-site pain (n=55 [59%]). No significant differences were noted in concomitant medications, laboratory abnormalities, electrocardiogram, and vital sign assessments. Geometric mean trough plasma concentrations were 0·302 μg/mL (95% CI 0·237–0·385), 0·331 μg/mL (0·253–0·435), and 0·387 μg/mL (0·296–0·505) for injections one, two, and three, respectively, indicating lower than predicted exposure. The geometric mean apparent terminal phase half-life estimated after the third injection was 40 days. Two (2%) MSM acquired HIV-1 infection, one in the placebo group during the injection phase and one in the cabotegravir group 24 weeks after the final injection when cabotegravir exposure was well below the protein-binding-adjusted 90% inhibitory concentration.

Interpretation Despite high incidence of transient, mild-to-moderate injection-site reactions, long-acting cabotegravir was well tolerated with an acceptable safety profile. Pharmacokinetic data suggest that 800 mg administered every 12 weeks is a suboptimal regimen; alternative dosing strategies are being investigated. Our findings support further investigation of long-acting injectable cabotegravir as an alternative to orally administered pre-exposure prophylaxis regimens.

PLOS | MEDICINE

RESEARCH ARTICLE

Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

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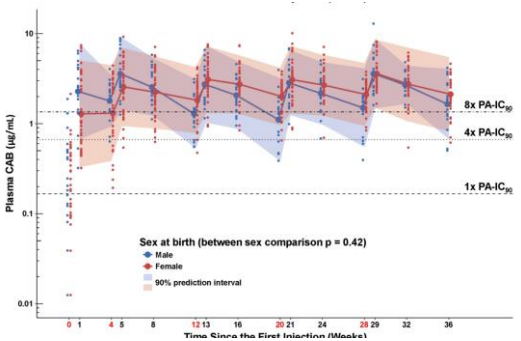
CAB LA 600 mg every 8 weeks met PK targets for both male and female study participants



HPTN 083
an HIV prevention clinical trial

HPTN 084
Long-acting Injectable For the Epidemic

aidsinfo.nih.gov/drugs/513/cabotegravir

What do patients want?

AIDS and Behavior
https://doi.org/10.1007/s10461-019-02703-5

ORIGINAL PAPER

Transgender Women's Concerns and Preferences on Potential Future Long-Acting Biomedical HIV Prevention Strategies: The Case of Injections and Implanted Medication De

Christine Tagliaferri Rael[1] · Michelle Martinez[2,4] · Rebecca Gig
Will Mellman[2] · Pablo Valente[2,4] · George J. Greene[5] · Susan G. S
Richard T. D'Aquila[7] · Alex Carballo-Diéguez[1] · Thomas J. Hope[8]

PLOS ONE

Experiences with long acting injectable ART: A qualitative study among PLHIV participating in a Phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain

sios[1], Miguel Gorgolas[2], Maria-Luisa Montes[3],
[5], Jerome deVente[6], Gary J. Richmond[7], Sarah
, David Margolis[8], Miranda Murray[9]

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are, Raleigh-Durham, North Carolina, United States of America,
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ATLAS PRO Conclusions

- High levels of overall acceptability indicate that LA treatment meets participants' expectations and supports the therapeutic potential of monthly CAB + RPV LA
- Most participants considered LA injections and ISRs to be "totally" or "very acceptable" and had low rates of discontinuation
- Of the participants who switched to the LA arm, 97% of CAB + RPV LA study participants preferred monthly IM administration over previous oral therapy and expressed high levels of treatment satisfaction

PRO analyses from the FLAIR study of LA therapy are presented in ***Poster MOPEB258***[1]*; Week 48 ATLAS and FLAIR combined results are presented in* ***Poster MOPEB257***[2]

CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; LA, long-acting; PRO, patient-reported outcome; RPV, rilpivirine.
1. Chounta V, et al. IAS 2019; Mexico City, Mexico. Poster MOPEB258.
2. Overton ET, et al. IAS 2019; Mexico City, Mexico. Poster MOPEB257.

Murray M, et al. IAS 2019; Mexico City, Mexico. Oral MOAB0103.

Taylor & Francis

HIV Clinical Trials

ISSN: 1528-4336 (Print) 1945-5771 (Online) Journal homepage: https://www.tandfonline.com/loi/yhct20

Satisfaction and acceptability of cabotegravir long-acting injectable suspension for prevention of HIV: Patient perspectives from the ECLAIR trial

Miranda I. Murray, Martin Markowitz, Ian Frank, Robert M. Grant, Kenneth H. Mayer, Krischan J. Hudson, Britt S. Stancil, Susan L. Ford, Parul Patel, Alex R. Rinehart, William R. Spreen & David A. Margolis

Qualitative Thematic Analysis of Soc Media Data to Assess Perceptions of of Administration for Antiretroviral Treatment Among People Living Witl

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Vasiliki Chounta,[4] Kristen A. Deger[1]

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IDWeek 2019™; October 2-6, 2019; Washington, DC

Perceptions of and Preferences for Oral or Long-Acting Injectable Antiretroviral Treatment Regimens in the United States and Canada

CP. Garris,[1] S. Heidenreich,[2] E. Arthurs,[3] K. Cutts,[4] FA. Spinelli,[1] H. Collacott,[2] E. Lowman,[5] H. Rice,[6] B. Lebouché,[7] GN. Chua,[2] H. Gelhorn[4]

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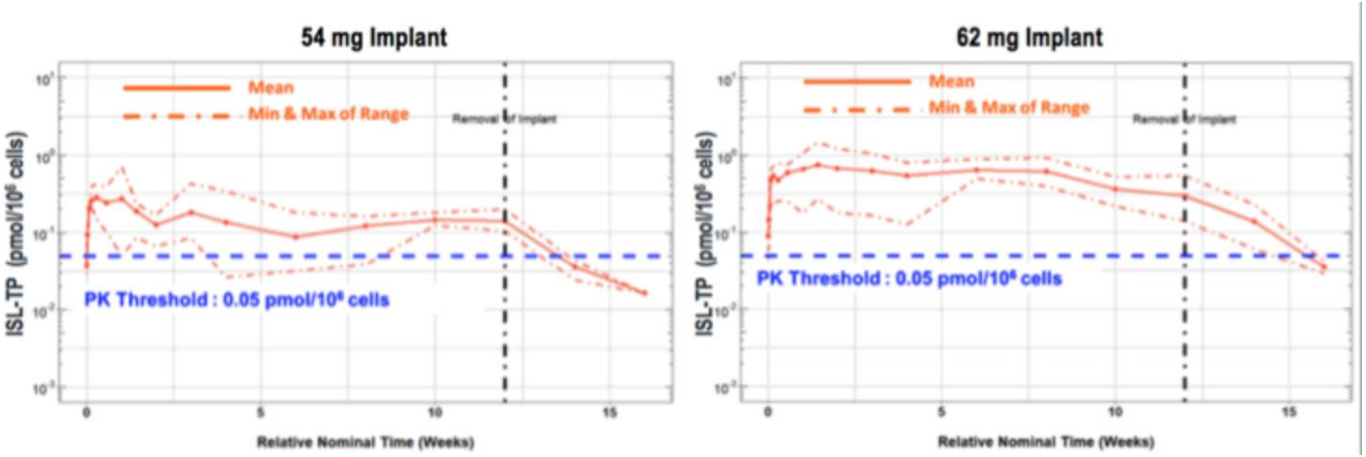
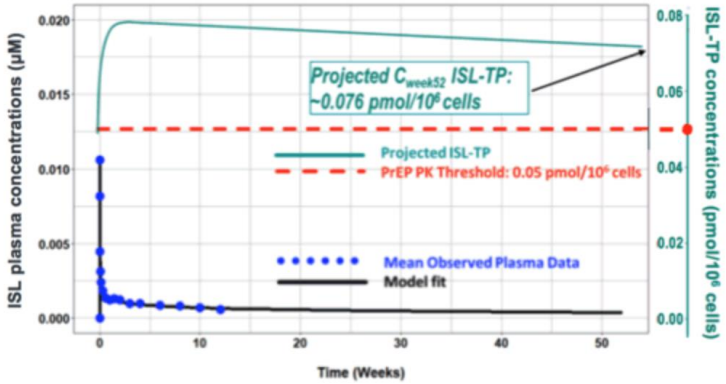
IDWeek 2019™; October 2-6, 2019; Washington, DC

ISLATRAVIR (ISL)

First-in-human trial of MK-8591-eluting implants demonstrates concentrations suitable for HIV PrEP for at least one year



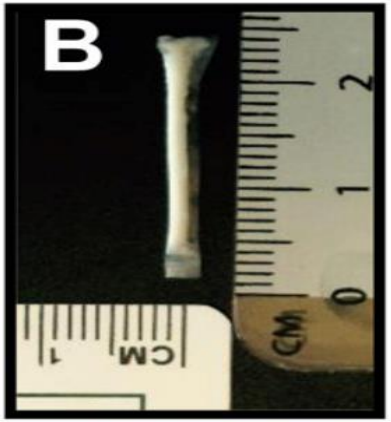


Matthews et al. IAS 2019

Pharm Res. 2016 July ; 33(7): 1649–1656. doi:10.1007/s11095-016-1904-6.

A Tunable, Biodegradable, Thin-Film Polymer Device as a Long-Acting Implant Delivering Tenofovir Alafenamide Fumarate for HIV Pre-exposure Prophylaxis

Erica Schlesinger[1], **Daniel Johengen**[2], **Ellen Luecke**[5], **Ginger Rothrock**[3], **Ian McGowan**[4], **Ariane van der Straten**[5,6], and **Tejal Desai**[2,§]



TAF Thin Film Polycaprolactone Device Prototypes:

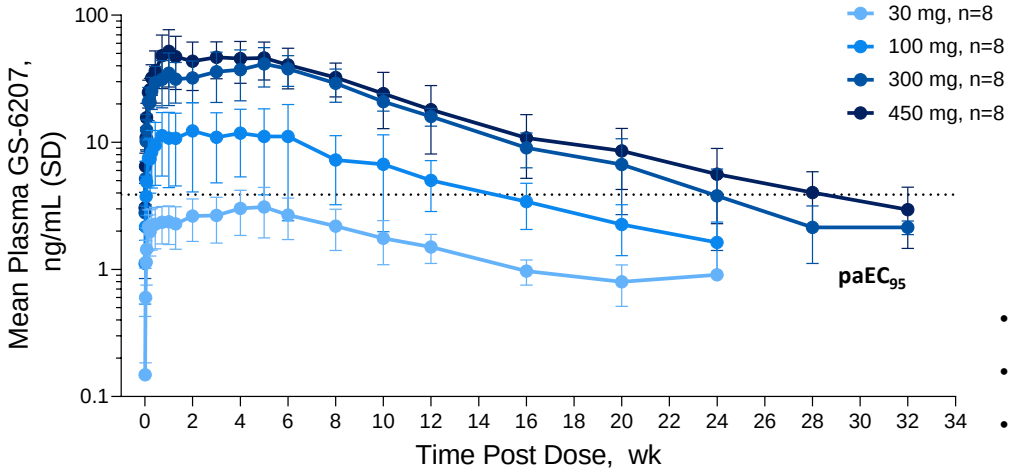
(A) 2.5mm diameter, 40mm long prototypes loaded with 230mg 1:1 TAF:PEG300 (w/w)

(B) 0.6mm diameter, 20mm long prototype loaded

GS-6207 Capsid Inhibitor: Phase 1 First in Human Safety and PK of Subcutaneous Single Dose

Phase 1, randomized, blinded, placebo-controlled, single dose, dose-ranging study in healthy volunteers[1]

GS-6207 Exposure Following SC Injection



SC Dose	IQ_{w12}*
450 mg	4.7
300 mg	4.1
100 mg	1.3
30 mg	0.4

- Rapid rise in concentrations with systemic exposure maintained for ≥ 24 wks
- Doses ≥ 100 mg exceeded paEC95 for ≥ 12 wks
- Apparent terminal $t_{1/2}$ 32-45 days, consistent across doses

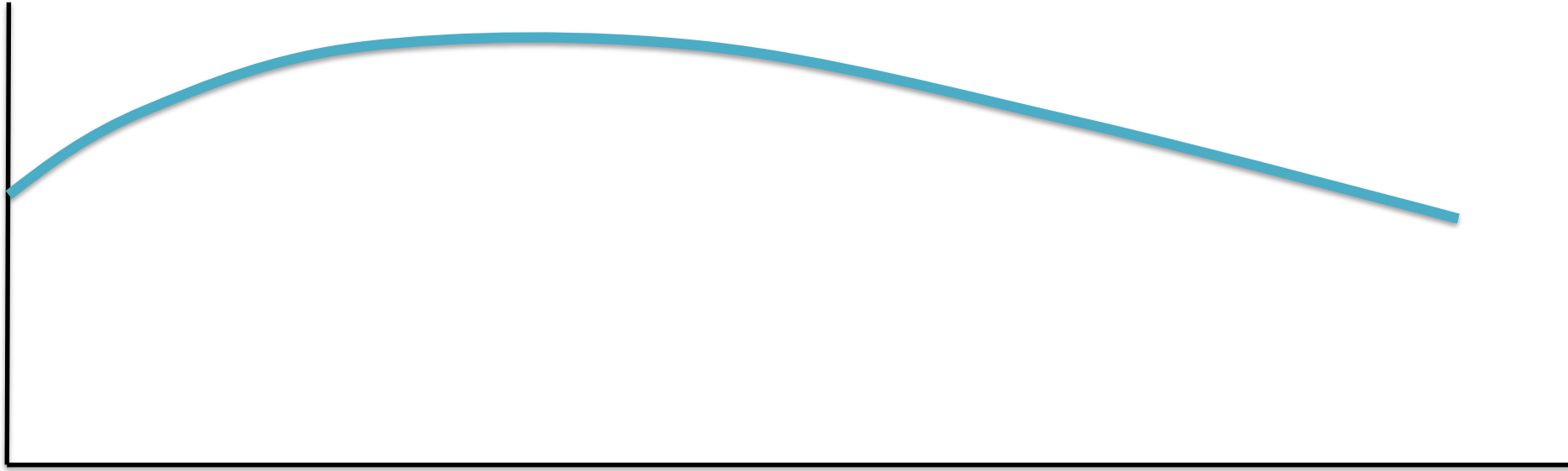
First-in-human data support continued clinical development of GS-6207 as a long-acting ARV for HIV treatment or prevention

– * IQ = C_{w12}/$paEC_{95}$; $paEC_{95}$ = 3.87 ng/mL
– † Pooled assessment of blinded safety data
– *paEC95, protein adjusted 95% effective concentration; Cw12, GS-6207 plasma concentration on Day 84; IQ, inhibitory quotient.

Begley R, et al. EACS 2019. Basel, Switzerland. Oral PS13/1

Conclusions

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



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