15th Residential Course on Clinical Pharmacology of Antiretrovirals

January 15-17, 2020

New INSTIs

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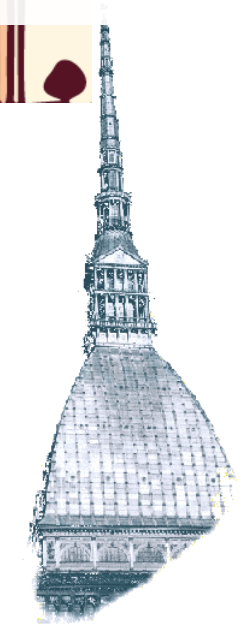

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- Abbvie
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- ViiV
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- Basilea
- Zambon
- Correvio
- Angelini

EACS European AIDS Clinical Society

Recommendations for Initiation of ART in PLWH with Chronic Infection without prior ART Exposure

Version 10.0
November 2019

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + DTG		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) III Weight increase
TAF/FTC/BIC		
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
DTG + 3TC	HBsAg negative HIV-VL < 500,000 copies/mL CD4 count > 200 cells/µL	
2 NRTIs + NNRTI		
TAF/FTC or TDF/FTC or TDF/3TC + DOR TDF/3TC/DOR		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (DOR: HIV-2)
TAF/FTC or TDF/FTC or TDF/3TC + RPV TAF/FTC/RPV TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r TAF/FTC/DRV/c	With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (DRV/r: cardiovascular risk)

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC[a] **(AI)—if HLA-B*5701 negative**
- DTG plus tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC)
- RAL[c] plus tenofovir[b]/FTC[a] (**BI** for TDF/FTC, **BII** for TAF/FTC)

Recommended Initial Regimens for Most People with HIV Just updated

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

INSTIs – based Regimens

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2018 Recommendations of the International Antiviral Society-USA Panel

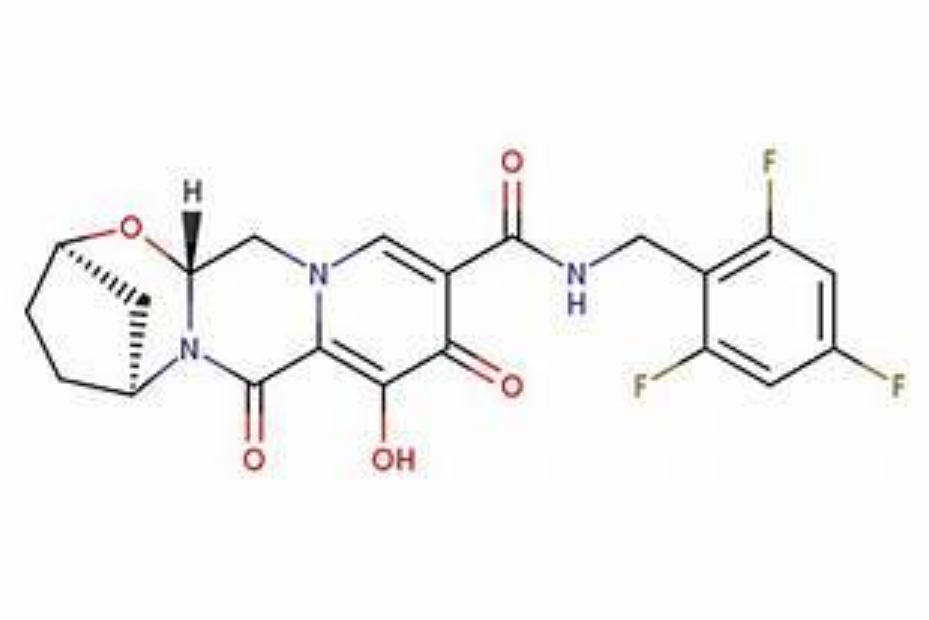
JAMA. 2018;320(4):379-396.

Generally Recommended Initial Regimens (Listed in Alphabetic Order by InSTI Component)

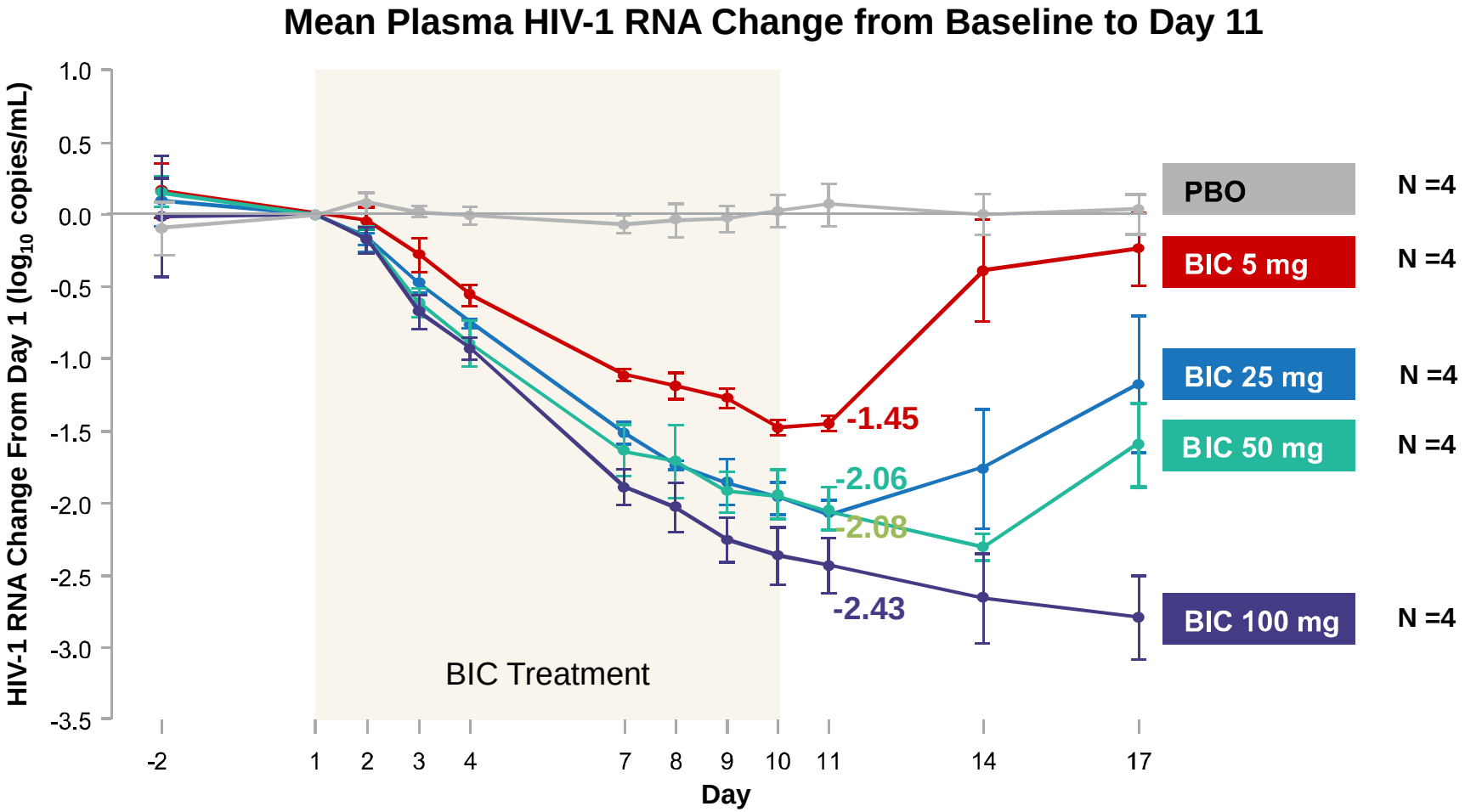
- Bictegravir/TAF/emtricitabine (evidence rating AIa)[b]
- Dolutegravir/abacavir/lamivudine (evidence rating AIa)[c,d]
- Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[c,e]

INSTIs – based Triple Regimens
No TDF
No RAL

BICTEGRAVIR



BIC Multiple-Dose: Viral Dynamics

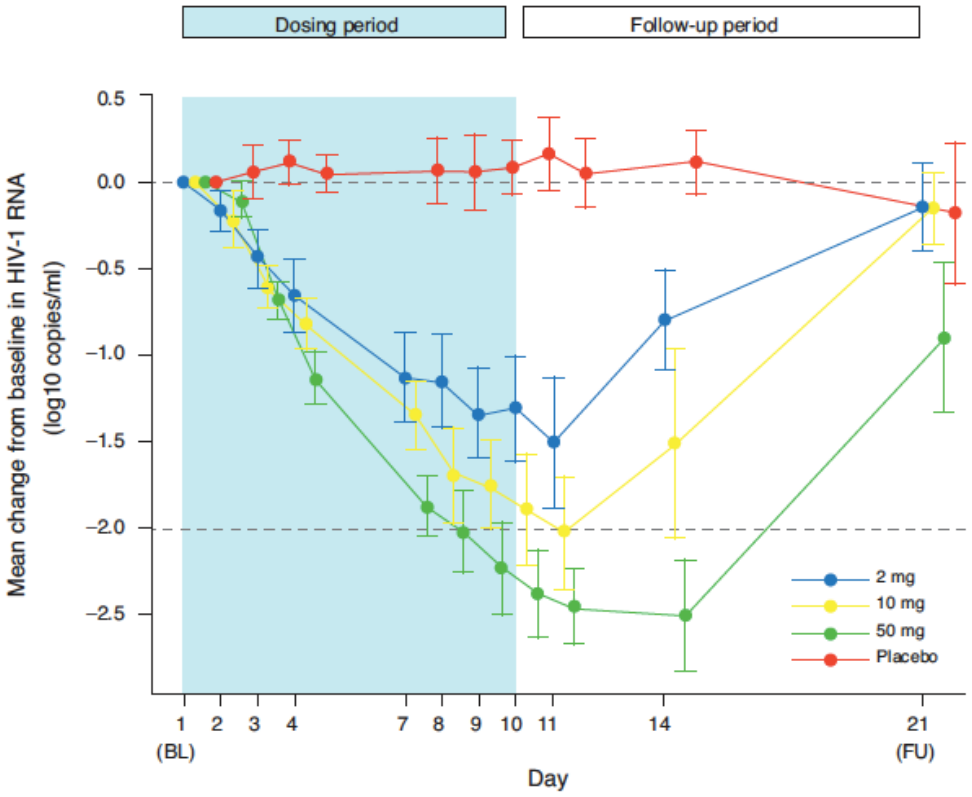


- **BIC has a rapid, dose–response antiviral effect with no emergent resistance**
- **Three participants achieved HIV-1 <50 copies/mL (1 on BIC 50 mg, 2 on BIC 100 mg)**

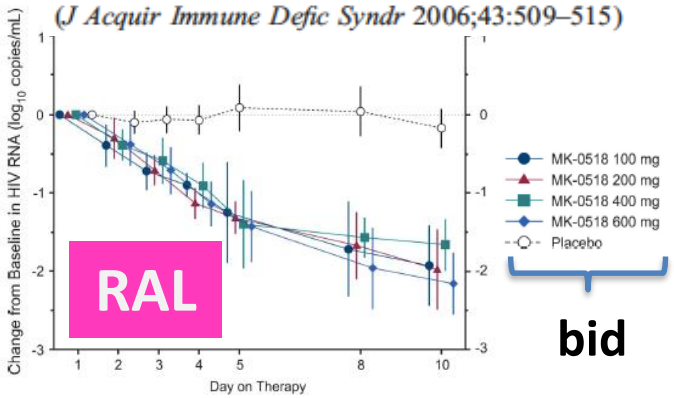
Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults

Min S, et al.

AIDS 2011, 25:1737–1745

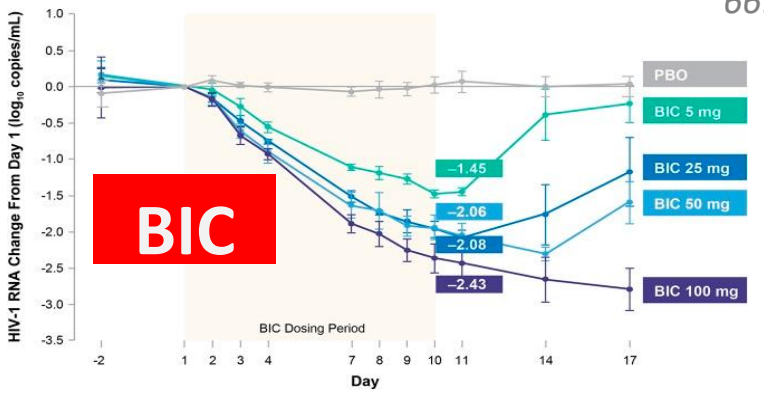


Markowitz M, et al.



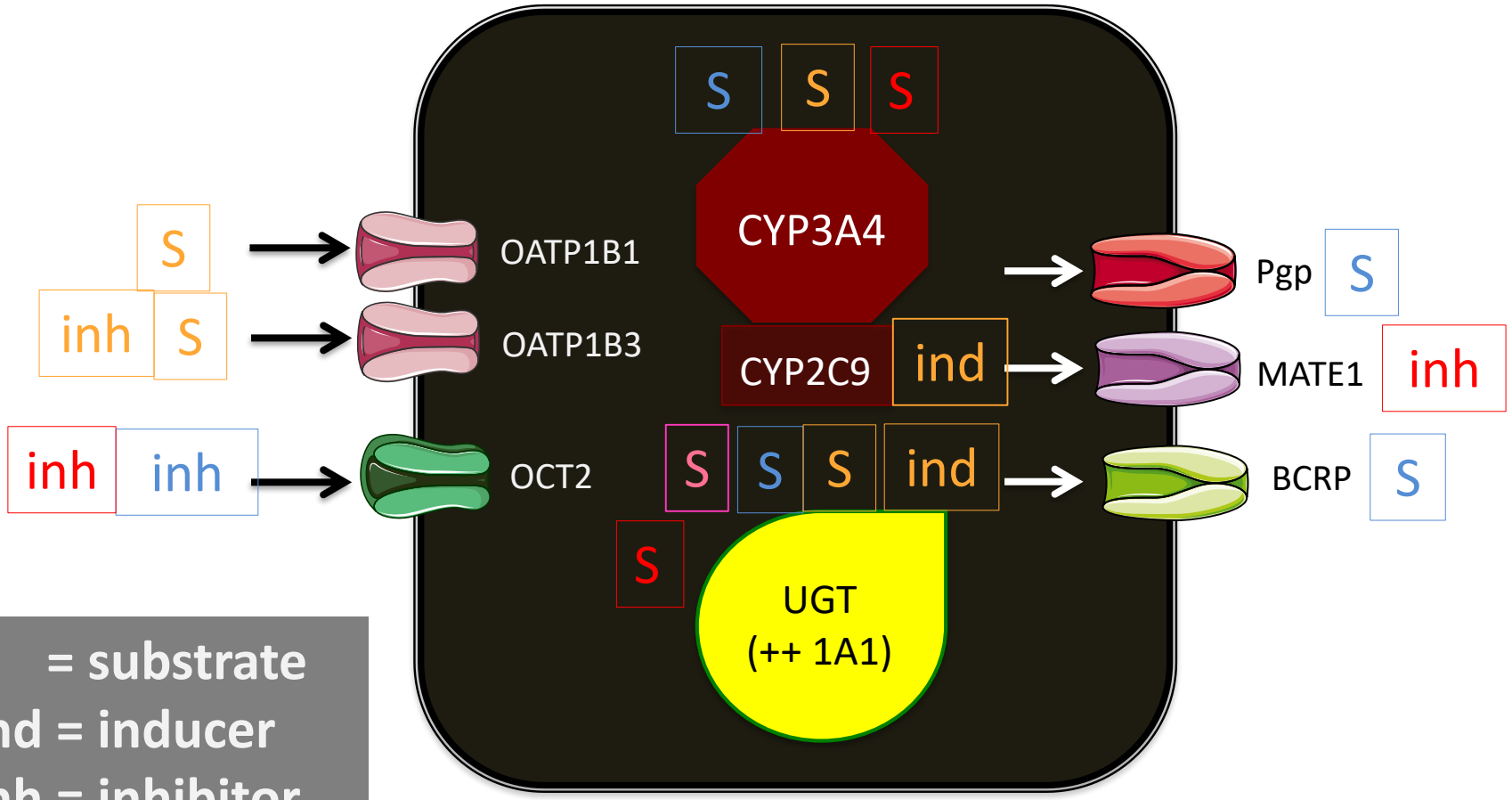
Gallant JE, et al.

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



Raltegravir | Dolutegravir | Elvitegravir | Bictegravir

METABOLISM OF INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)



S = substrate
ind = inducer
inh = inhibitor

BICTEGRAVIR Comparative Basic Clinical Pharmacology (1)

	MW	T/2 (h)	Protein binding	Substrate	Inhibitor	Inducer
RAL	482.51	9	83%	UGT1A1	-	-
ELV/COBI	447.9	12.9	98-99%	CYP3A, UGT1A1-3, OATP1B1-3	OATP1B3	CYP2C9 (±), UGT
DTG	441.36	14	98.9%	UGT1A1-3-9, CYP3A, Pgp, BCRP	OCT2	-
BIC	471.4	17.3	> 99%	CYP3A, UGT1A1, Pgp, BCRP	OCT2, MATE1	-

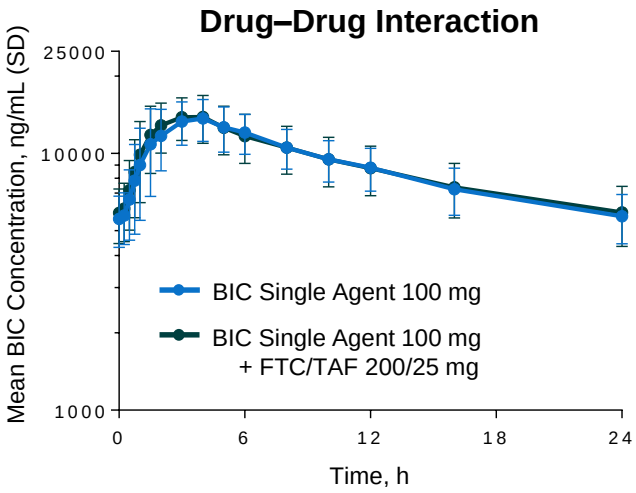
BICTEGRAVIR Comparative Basic Clinical Pharmacology (2)

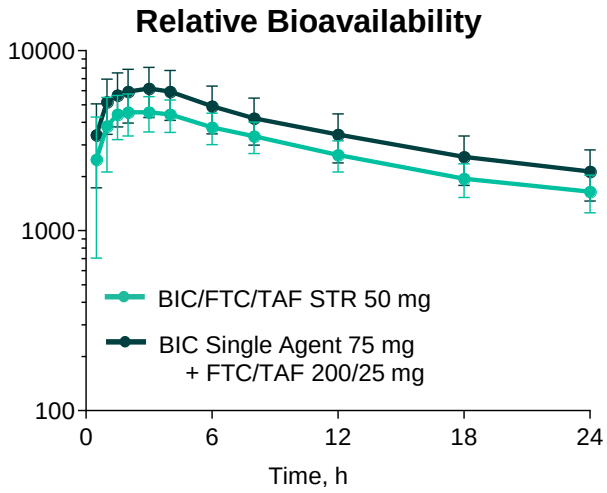
	Food Effect Low-Fat	Food Effect High-Fat	Pk CV (%)	Urinary Clearance
RAL	+ 13%	+ 200%	122 - 212	32% (u 9%)
ELV/COBI	+ 36%	+ 91%	25.5	6.7%
DTG	+ 33%	+ 66%	20 - 40	31% (u <1%)
BIC	+ 24%	+ 24%	22.9 – 35.2	35% (u <1%)

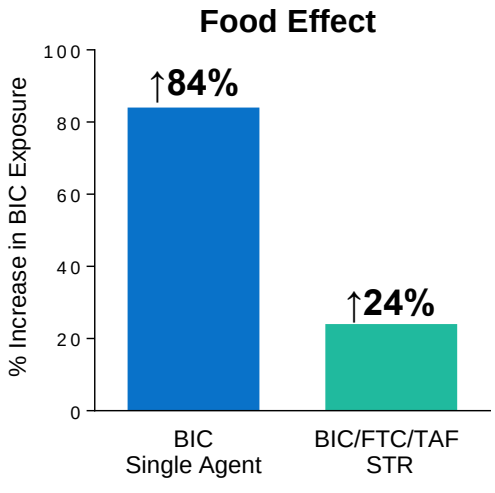
Dissociation Time of Strand-Transfer Integrase Inhibitors (INSTIs)

	WT	G140S + Q148H ± other INSTIs RAMs
RAL	5.2	nm
EVG/COBI	1.5	nm
DTG	16	0.65
BIC	38	2.5

Co-formulation of BIC + FTC/TAF Into STR & Food Effect







- Lack of DDI between BIC and FTC/TAF established
  - FTC/TAF 200/25 mg dose
- STR formulation development
  - Improved BIC bioavailability vs single-agent Phase 2 formulation
  - Reduced food effect vs single-agent Phase 2 formulation
  - STR with 50 mg BIC dose selected for Phase 3; administered with or without food

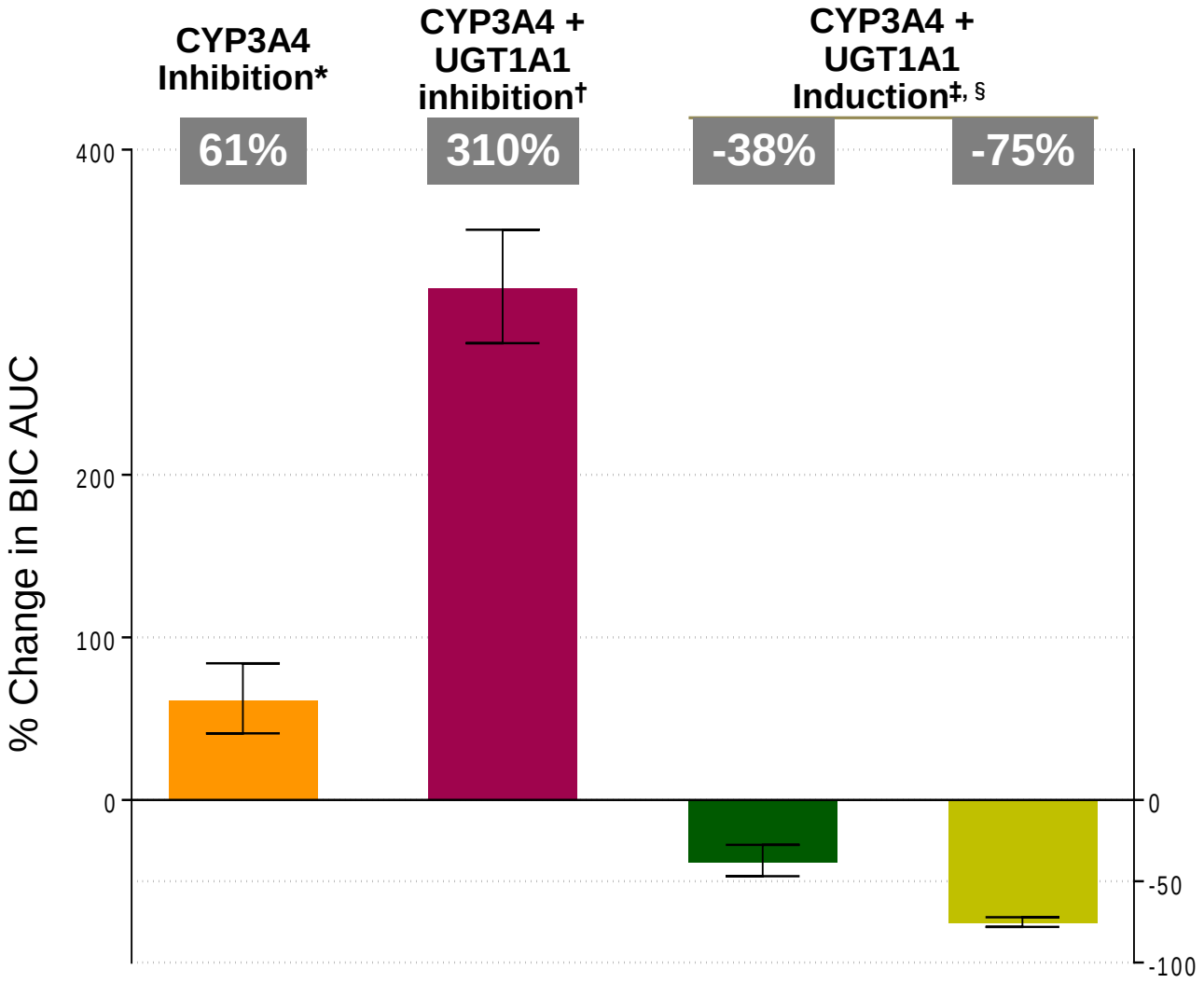
Zhang H, et al, CROI, 2017.

BIC Drug–Drug Interaction Profile

- Perpetrator? Low potential (OCT2/metformin)
- Victim? Low potential (or moderate?)
  - INSTIs are affected by cation-containing antacids
    - BIC administration with antacids should be staggered (± 2 hours)
    - Fasted administration 2 hours before or 2 hours after antacid resulted in a decrease in BIC exposures of 13% and 52%, respectively
  - BIC is a substrate of CYP3A4 and UGT1A1
    - Inhibition of both CYP3A4 and UGT1A1 needed for substantial increase in exposure
    - Potent induction reduces exposure to a clinically significant extent

Zhang, et al. CROI 2017

BIC Drug–Drug Interaction Profile. Clinical Study Probing Effect of Inhibitors or Inducers



*Voriconazole; †atazanavir; ‡rifabutin; §rifampin.

Zhang, et al. CROI 2017

BIC Drug–Drug Interaction Profile

Effect of BIC on the PK of Coadministered Drugs

		Change in AUC
CYP3A4 Probe Substrate	Midazolam	↔
Representative Oral Contraceptive	Norelgestromin*	↔
	Ethinyl estradiol	↔
Representative HCV DAA	Ledipasvir	↔
	Sofosbuvir	↔
OCT2/MATE1 Probe Substrate	Metformin	↑ 39%

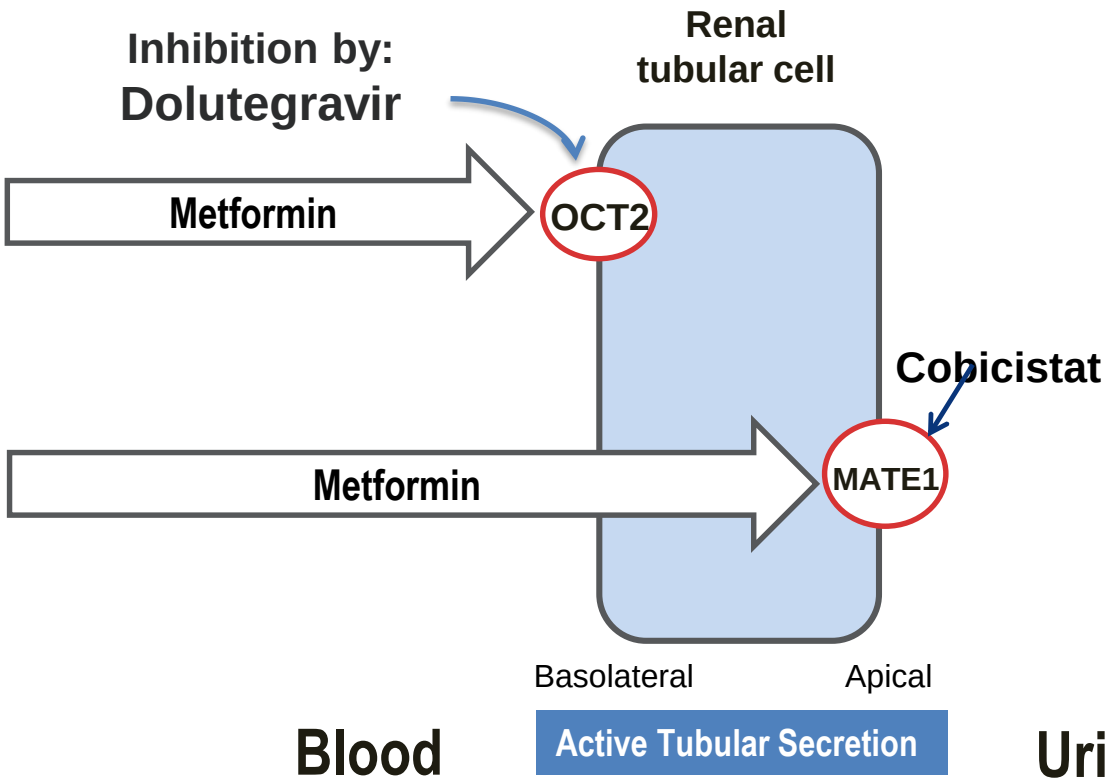
- Low potential to perpetrate DDIs
  - Not an inhibitor or inducer of CYP3A4 or UGT1A1
    - No effect on midazolam
  - No interaction with a representative oral contraceptive
    - No effect on norgestimate/ethinyl estradiol
  - No interaction with a representative HCV DAA
    - No effect on ledipasvir/sofosbuvir
  - Limited liability for inhibition of renal transporters (OCT2 and MATE1)
    - Modest increase in metformin exposure

*Norelgestromin is circulating pharmacologically active progestin from norgestimate.
90% CI of GMR were within (↔) or extended above (↑) the predetermined protocol defined equivalence boundaries of 70 143%.

Zhang, et al. CROI 2017, Oral 40.

Integrase Inhibitors and Metformin

- Metformin used in type-2 diabetes requires titration to optimize dosing[1]



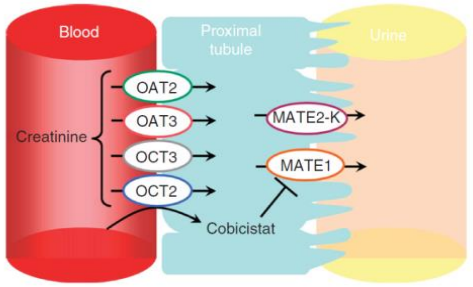
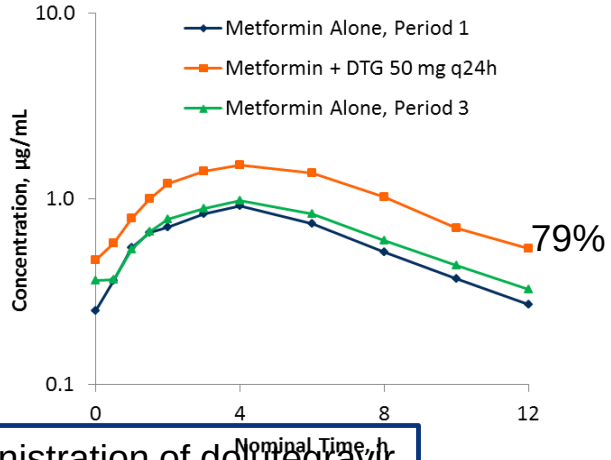


Figure 4 | Proposed mechanism for serum creatinine elevations observed clinically with cobicistat. The active tubular secretion of creatinine is mediated by basolateral uptake by organic anion transporters OAT2 and OAT3, and organic cation transporters OCT2 and OCT3, and apical efflux by multidrug and toxin extrusion transporters MATE1 and MATE2-K. Although no transport was



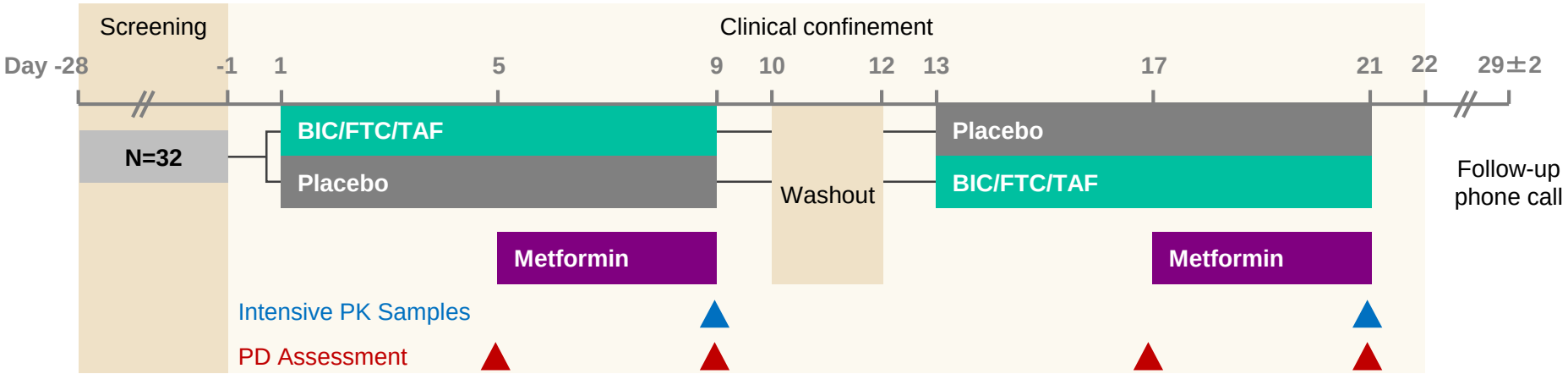
Consider dose-adjusting metformin when starting and stopping administration of dolutegravir with metformin. Also, dose-adjust in moderate renal impairment on coadministration (lactic acidosis).

1. GLUCOPHAGE [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2008. 2. Christensen MM, et al. Pharmacogenet Genomics. 2013;23:526-534.

Zhong, et al. Glasgow HIV Congress 2014

PK/PD Study (HIV-, Non-Diabetic): BIC/FTC/TAF vs Placebo + Metformin

Study Design

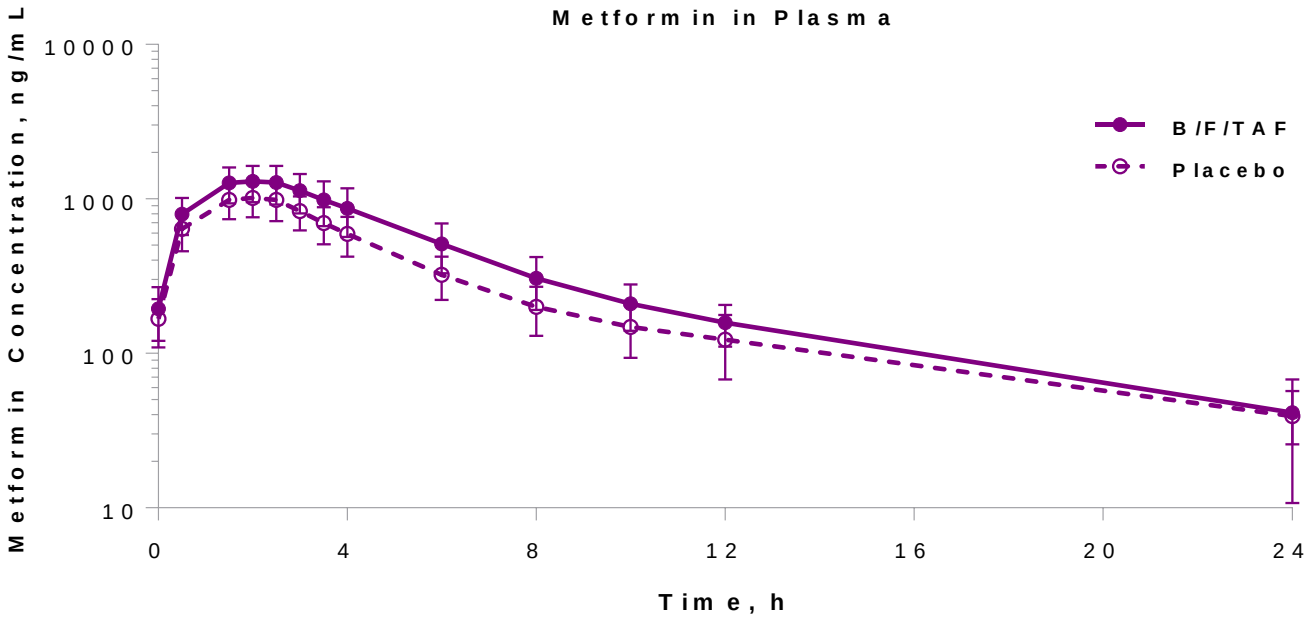


- Phase 1, blinded, placebo-controlled, multiple-dose, 2-period,crossover study in healthy subjects
- 32 subjects were randomised 1:1 to receive either BIC/FTC/TAF or placebo OD for 9 days, followed by a 3-day washout
- Study drug treatment
  - BIC/FTC/TAF 50/200/25 mg or placebo 1 tab PO OD on Days 1–9 or 13–21
  - Metformin:
    - 850 mg 1 tab PO OD on Day 5 or 17 (with BIC/FTC/TAF or placebo 1 tab PO OD)
    - 500 mg 1 tab PO BID on Days 6–8 and 18–20 (with BIC/FTC/TAF or placebo tab 1 PO OD)
    - 500 mg 1 tab PO OD on Day 9 or 21 (with BIC/FTC/TAF or placebo 1 tab PO OD)
- Oral glucose tolerance test was performed before and after last dose of metformin

Objectives: To assess changes in metformin levels and the clinical impact when metformin is coadministered with BIC/FTC/TAF

Zhang H, et al. IWCPT 2017. Chicago, IL. Poster #50.

Metformin PK Following Coadministration with BIC/FTC/TAF or Placebo



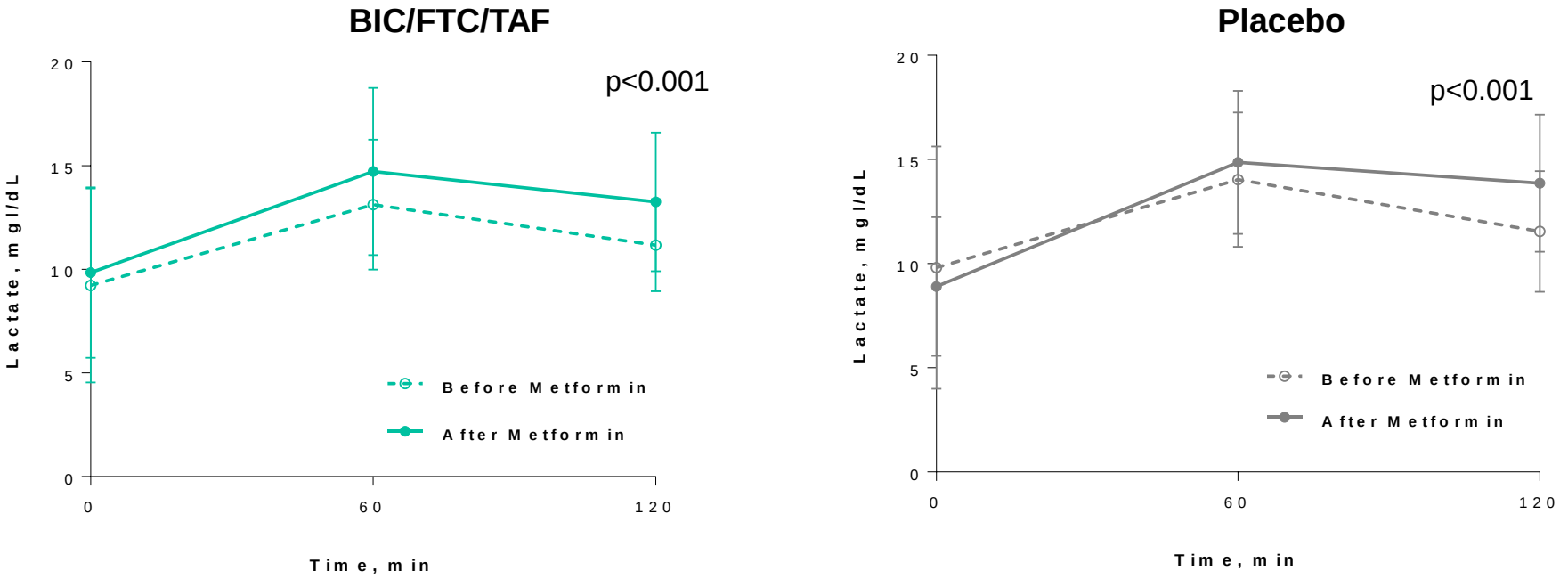
Metformin Mean (%CV)	BIC/FTC/TAF n=32	Placebo n=30	% GLSM Ratio (90% CI)
AUC_{τ}, h·ng/mL	7180 (27.3)	5180 (24.8)	139 (131, 148)
C_{max}, ng/mL	1353 (27.1)	1059 (25.4)	128 (121, 136)

AUC_{τ}, area under curve for doing interval; C_{max}, maximal concentration; Q, quartile; GLSM, geometric least-squares mean.

Following coadministration with BIC/FTC/TAF vs placebo, metformin plasma exposure increased ~39% (due to BIC's inhibition of renal transporters OCT-2 and/or MATE-1)

Zhang H, et al. IWCPT 2017. Chicago, IL. Poster #50.

Plasma Lactate Concentrations Over Time Before and After Metformin with BIC/FTC/TAF or Placebo Coadministration



Lactate Increase	Mean (90% CI) Difference (Before vs After Metformin)		p value
	BIC/FTC/TAF (n=32)	Placebo (n=30)	BIC/FTC/TAF vs Placebo
60 min post-glucose, pmol/L	1.6 (0.5, 2.6); *p=0.01	0.8 (–0.3, 1.9); *p=0.18	0.37
120 min post-glucose, pmol/L	2.1 (1.1, 3.0); *p<0.001	2.2 (1.2, 3.2); *p<0.001	0.73

*p value compares the difference between post-baseline vs baseline.

Metformin-induced increases in plasma lactate were comparable between BIC/FTC/TAF and placebo Metformin given with BIC/FTC/TAF is not expected to increase the risk of lactic acidosis

Zhang H, et al. IWCPT 2017. Chicago, IL. Poster #50.

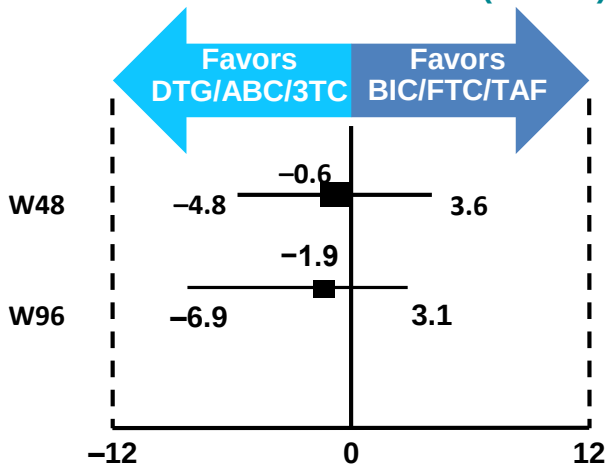
BIC clinical data in treatment-naïve and -experienced patients

- Study 1489: BIC/FTC/TAF vs DTG/ABC/3TC in treatment-naïve participants
- Study 1490: BIC/FTC/TAF vs DTG + FTC/TAF in treatment-naïve participants
- Study 1878: Switch to BIC/FTC/TAF vs remaining on PI-based regimens
- Study 1844: Switch to BIC/FTC/TAF vs remaining on DTG/ABC/3TC
- Study 1961: Switch to BIC/FTC/TAF in virologically suppressed women
- Study 1474: BIC/FTC/TAF study in children and adolescents

TREATMENT-NAÏVE Patients

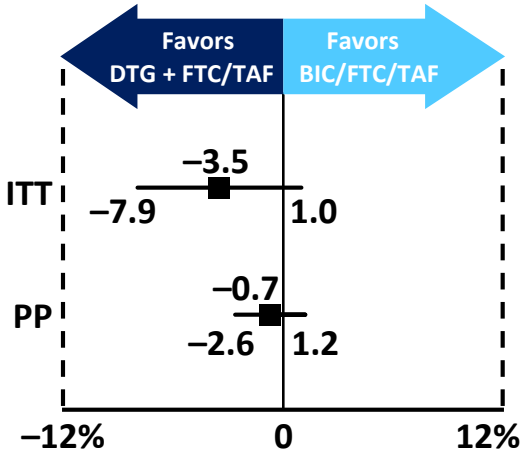
Study 1489

BIC/FTC/TAF vs DTG/ABC/3TC



Study 1490

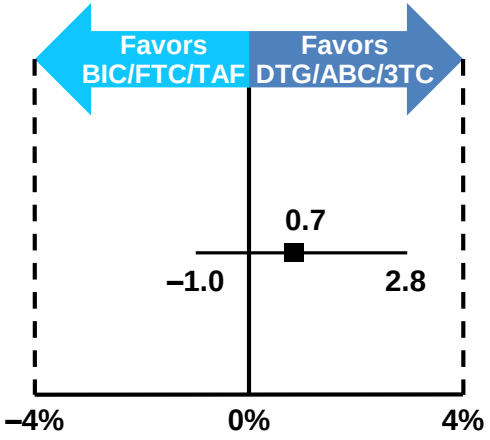
BIC/FTC/TAF vs DTG + FTC/TAF



TREATMENT-EXPERIENCED Patients

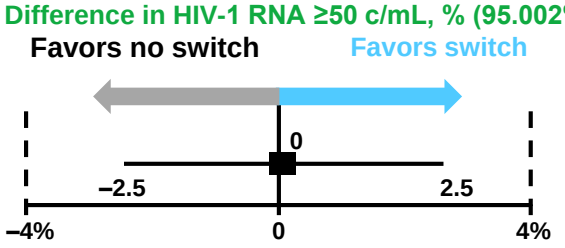
Study 1844

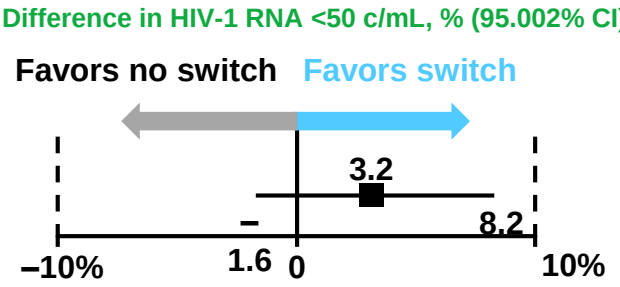
Switch to BIC/FTC/TAF vs rem. on DTG/ABC/3TC



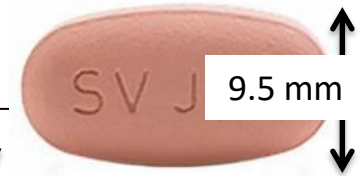
Study 1878

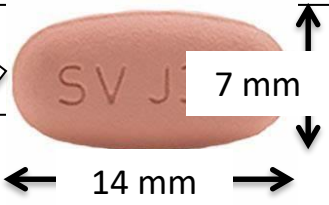
Switch to BIC/FTC/TAF vs remaining on PI



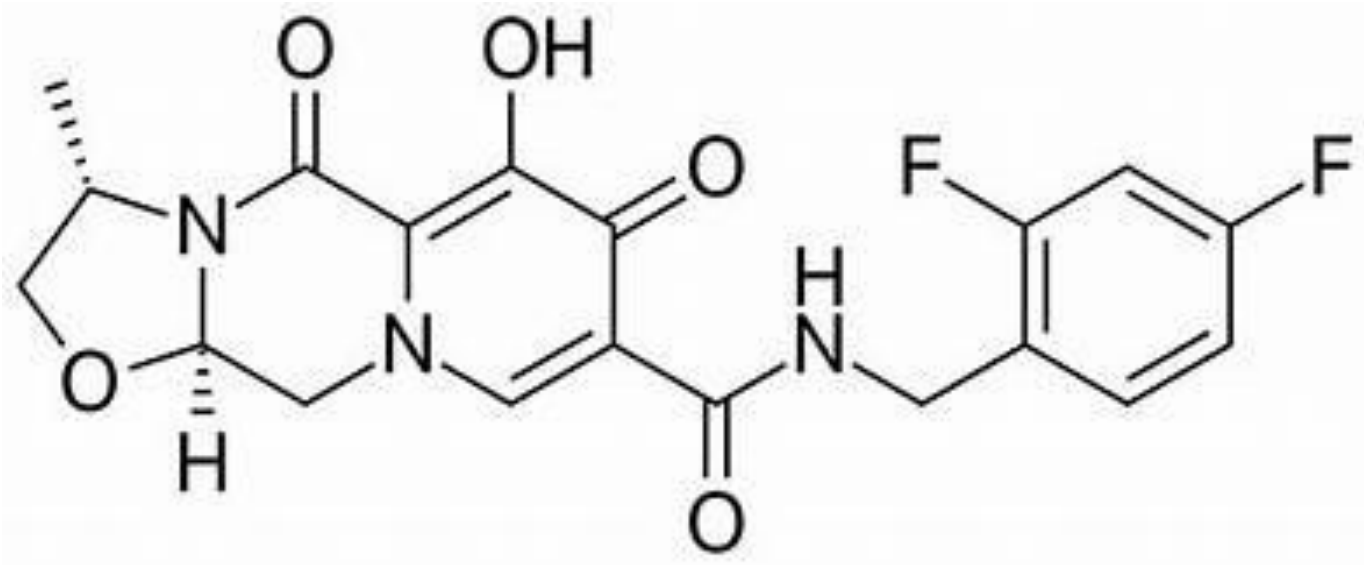


n. of pills https://www.hiv-druginteractions.org/		Regimen total weight (mg)
BIC/FTC/TAF	1	**275** (50 + 200 + 25)
DTG/3TC/ABV	1	**950** (50 + 300 + 600)
DTG + FTC/TDF	1	**495** (50 + 200 + 245)
DTG + FTC/TAF	1	**275** (50 + 200 + 25)
RAL + FTC/TDF	1	**1645** (1200 + 200 + 245)
RAL + FTC/TAF	1	**1425** (1200 + 200 + 25)
RPV/FTC/TAF	3	**250** (25 + 200 + 25)
DRV/COBI/FTC/TAF	4	**1175** (800 + 150 + 200 + 25)
DTG/3TC	1	**350** (50 + 300)
DTG/RPV	1	**75** (50 + 25)

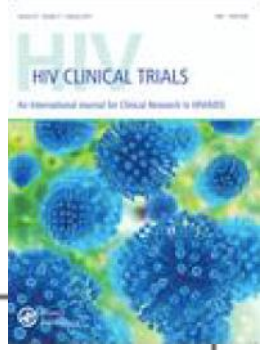


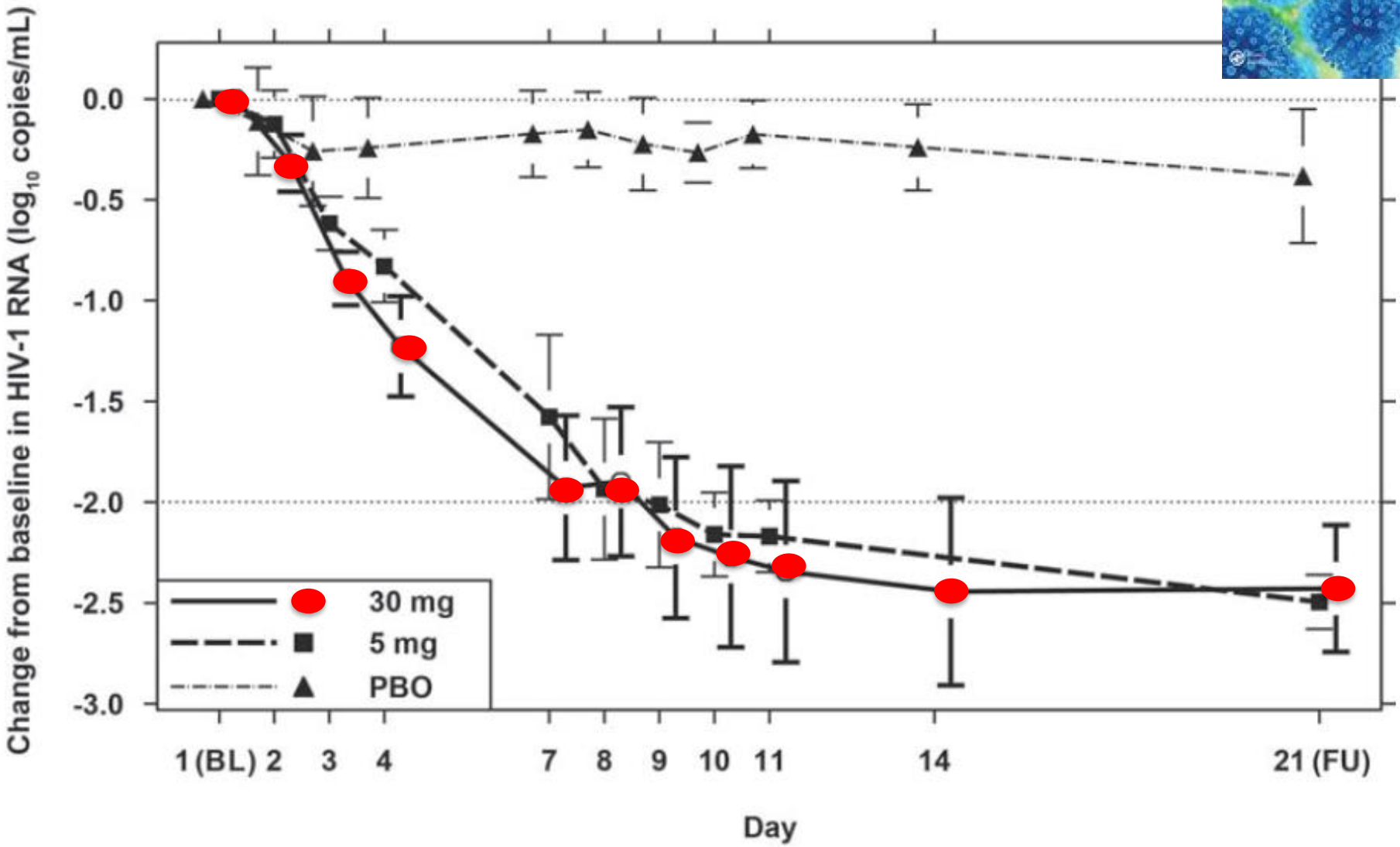


CABOTEGRAVIR



Pharmacokinetics, Safety, and Monotherapy Antiviral Activity of GSK1265744, an HIV Integrase Strand Transfer Inhibitor





Spreen W, et al. HIV Clinical Trials 2013; 14: 192-203

CABOTEGRAVIR Comparative Basic Clinical Pharmacology

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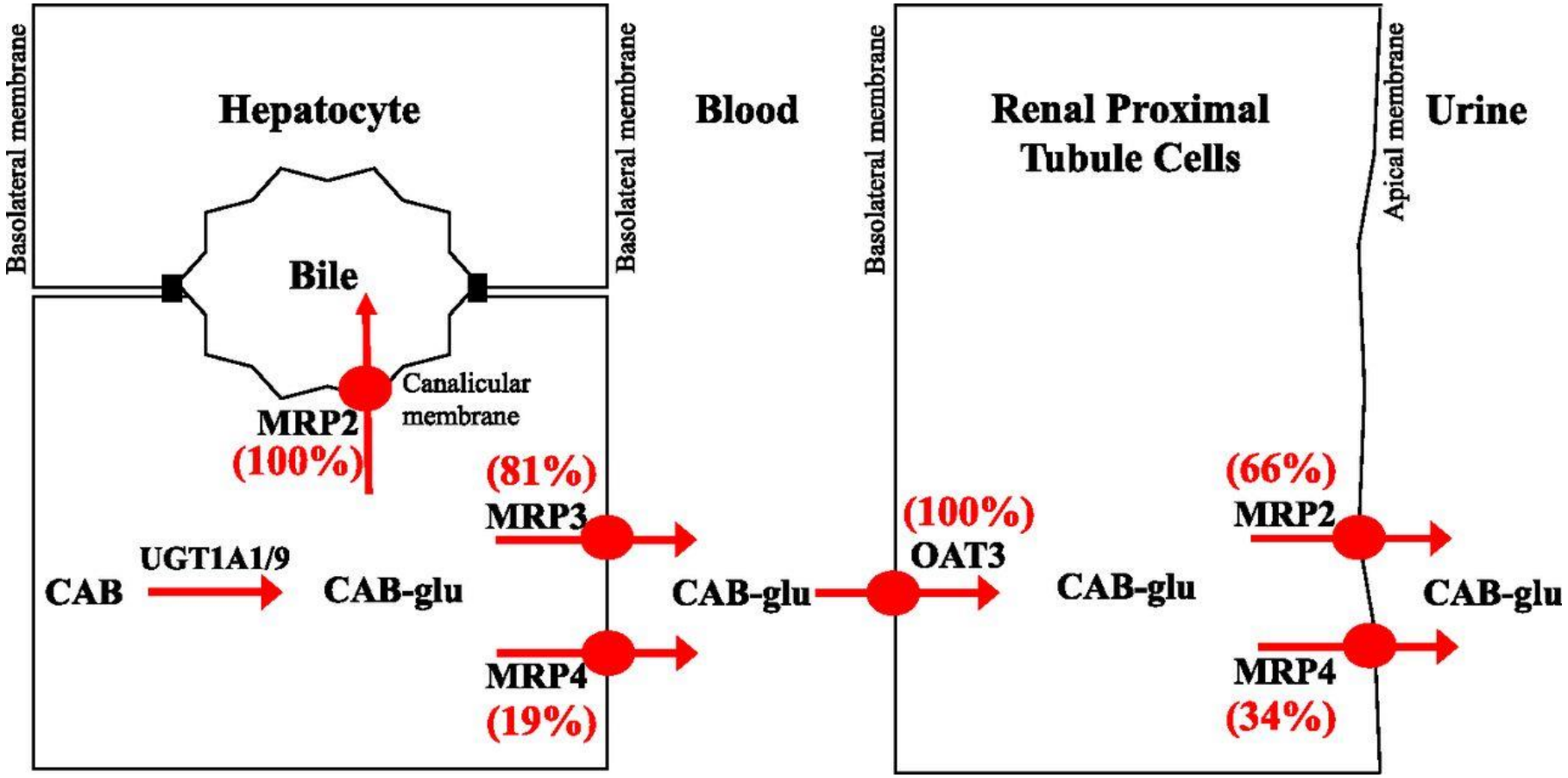
DTG	441.36	14	98.9%	UGT1A1-3-9, CYP3A, Pgp, BCRP	OCT2	-	31%	20 - 40
BIC	471.4	17.3	> 99%	CYP3A, UGT1A1, Pgp, BCRP	OCT2, MATE1	-	35%	22.9 – 35.2
CABO	405.4	31.5 (oral) 25 -53 days (IM)	> 99%	UGT1A1/9 Pgp, BCRP	OAT1 OAT3	-	27%	13 -34

Transporter mechanisms mediating the disposition of cabotegravir–glucuronide (CAB-glu) in humans.

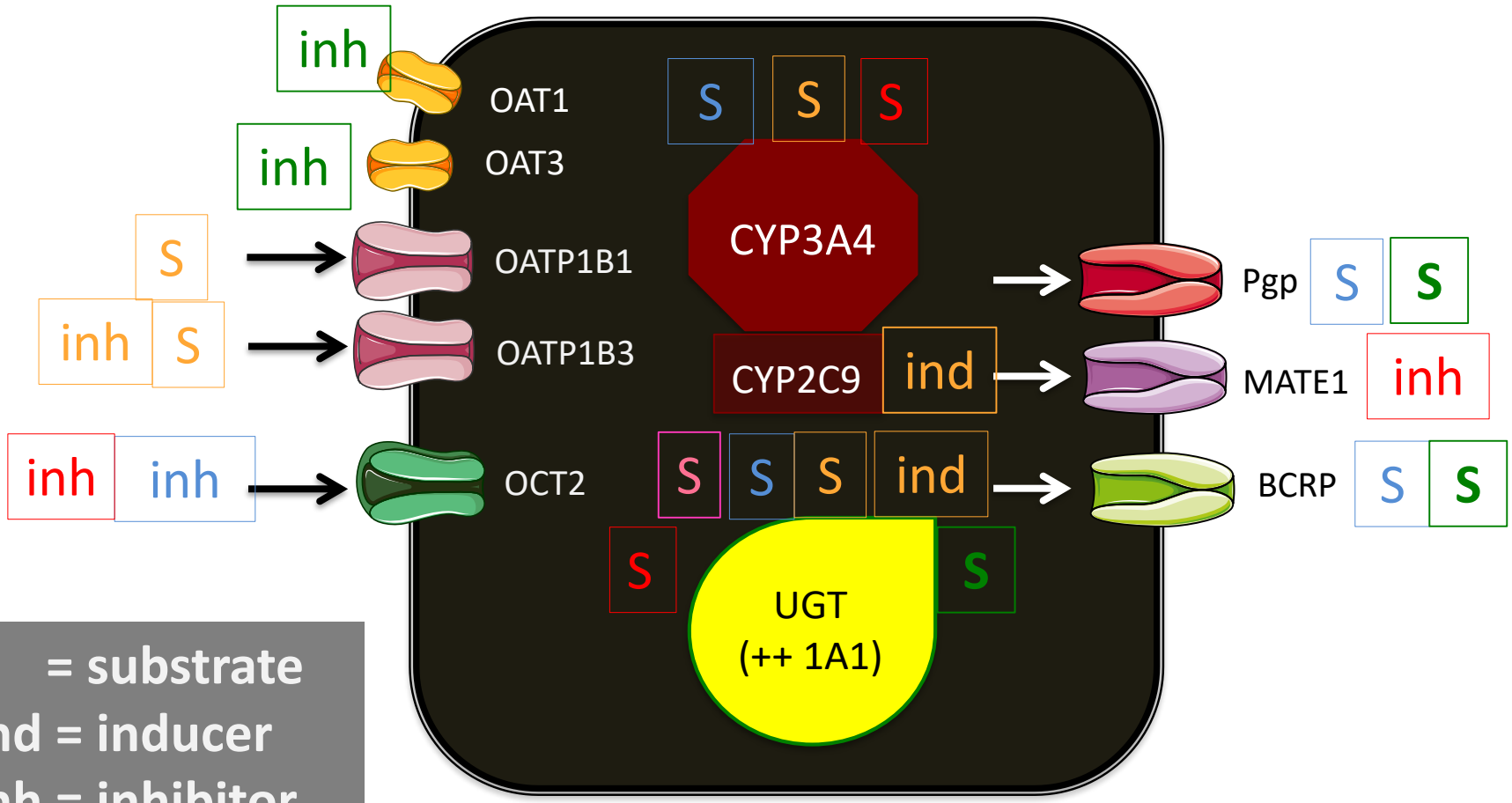


Mitesh Patel et al. J Pharmacol Exp Ther 2019;370:269-277

ASPET THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Raltegravir | Dolutegravir | Elvitegravir | Bictegravir | Cabotegravir

METABOLISM OF INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)



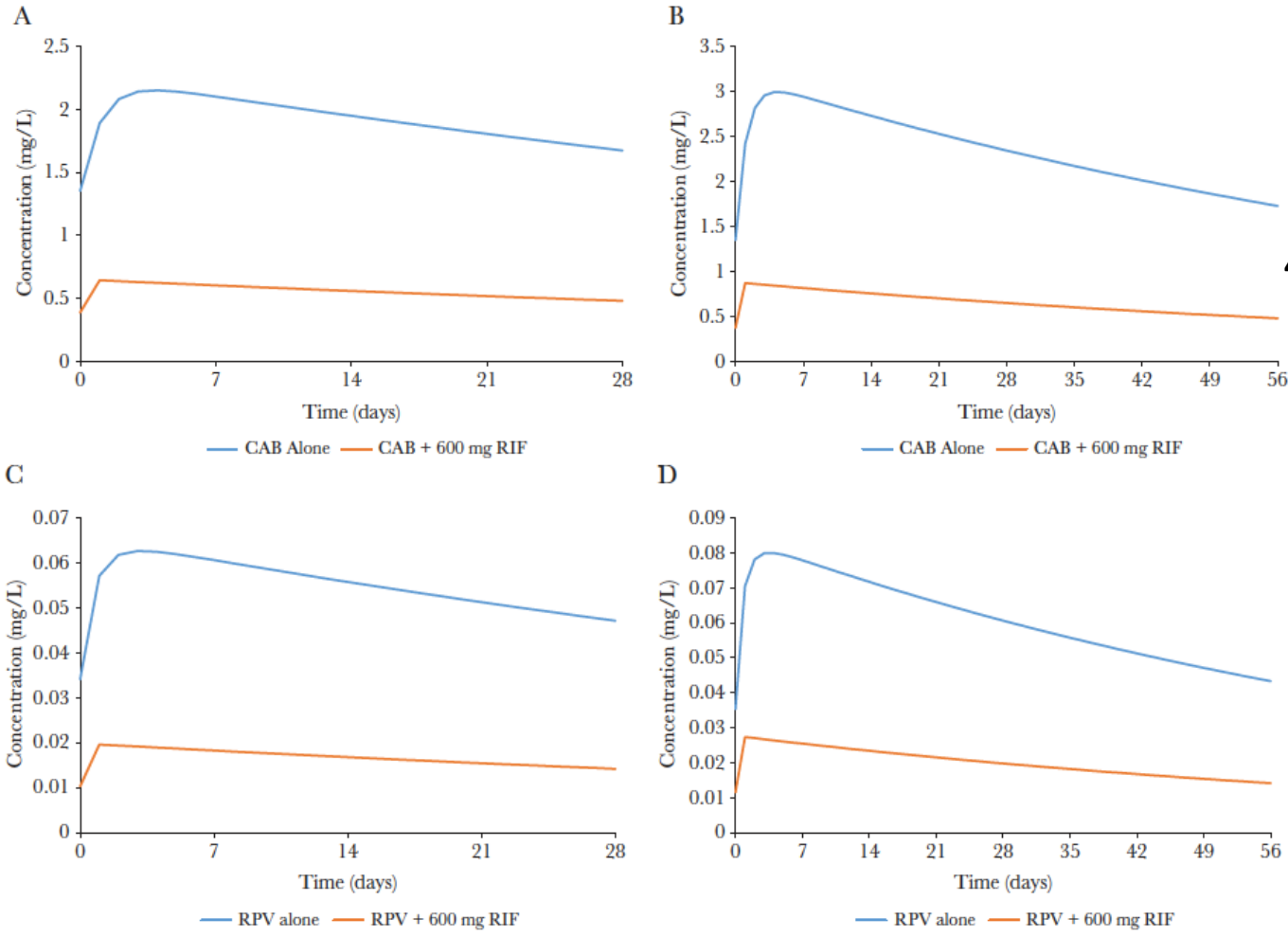
S = substrate
ind = inducer
inh = inhibitor

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

The Journal of Infectious Diseases

MAJOR ARTICLE

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

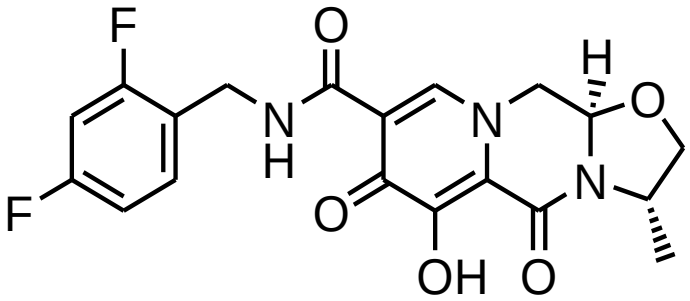


400 mg CAB / 4 weeks

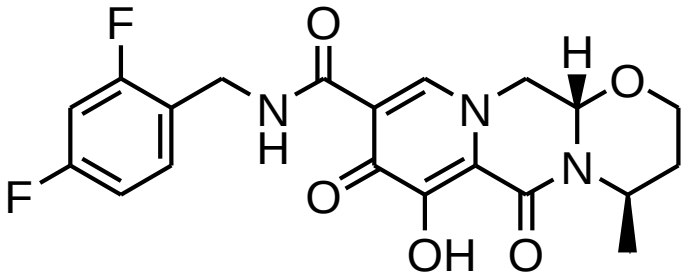
600 mg CAB / 8 weeks

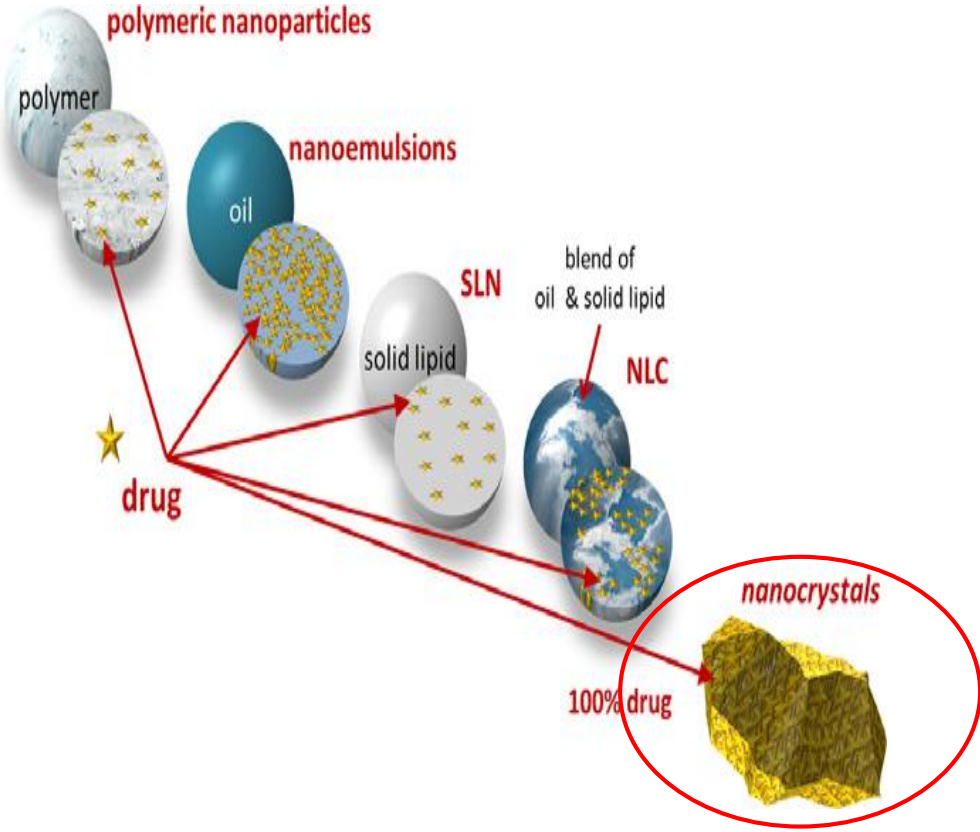
GSK744 LA is Formulated as a 200 mg/mL Nanosuspension

GSK1265744
(GSK744)



Dolutegravir





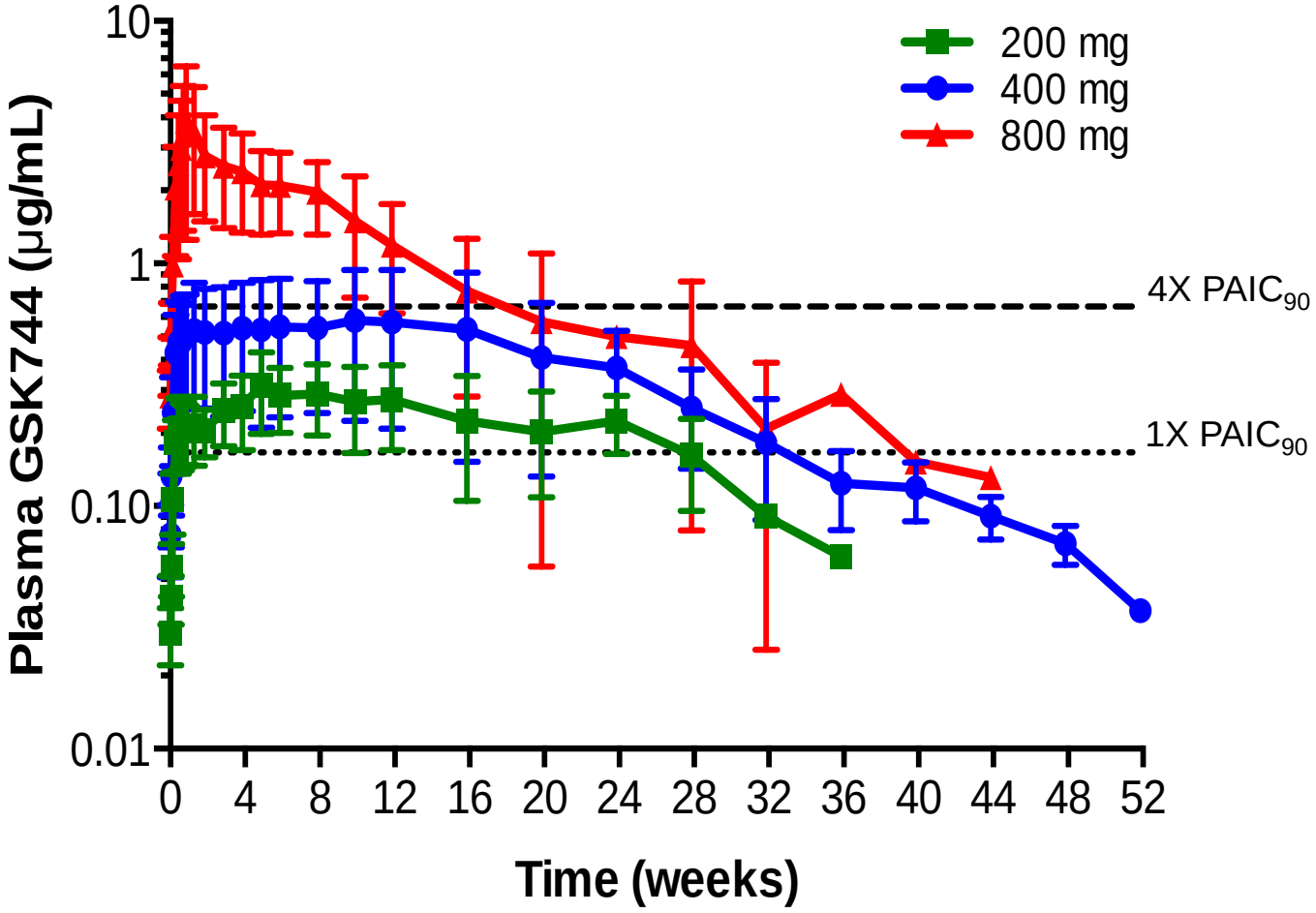
R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

W. Spreen,7th IAS, Jun 2013.

S. Min, et al, 49th ICAAC, Sept 2009. Abstract H-1228

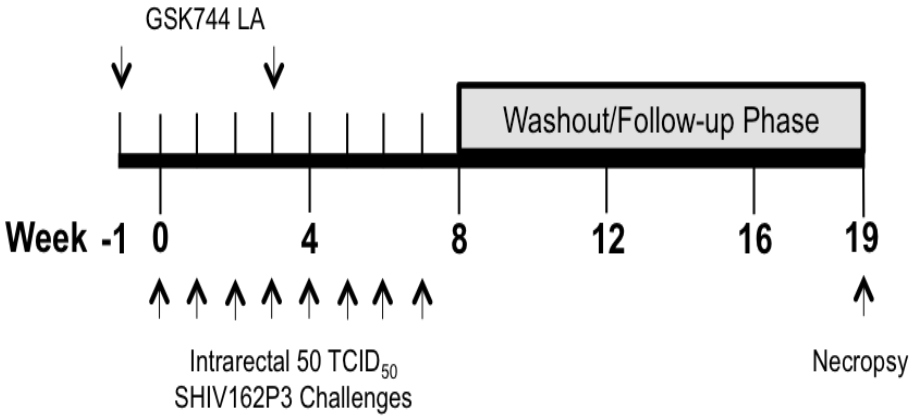
Y. Taoda, et al, 11th International Congress on Drug Therapy in HIV Infection, Nov 2012. Abstract P206

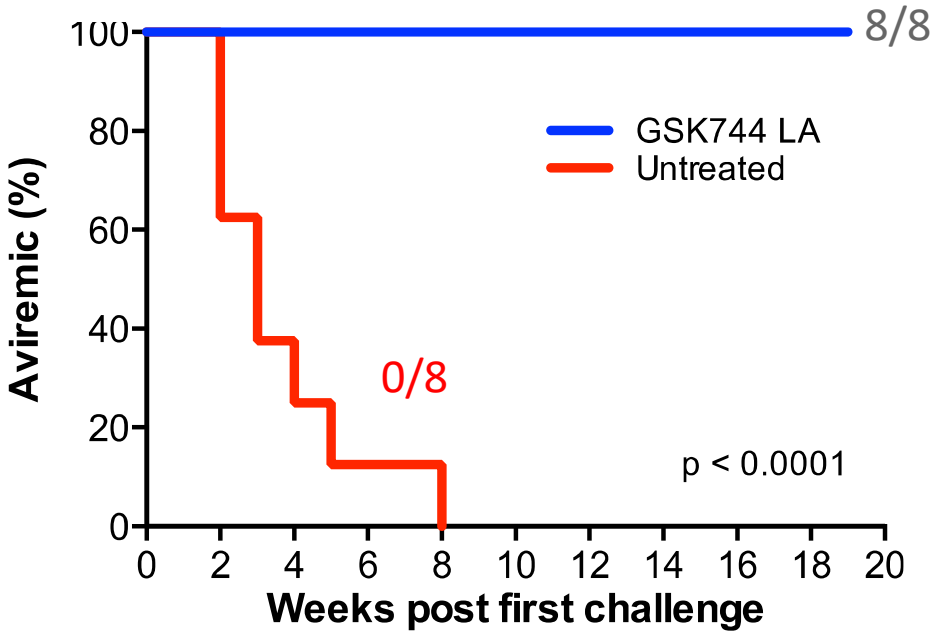
Pharmacokinetic Evaluation of a Single Intramuscular GSK744 LA Injection in Human Volunteers



Adapted from W. Spreen, et al, 19th IAC, July 2012. Abstract TUPE040

GSK744 LA is an Effective PrEP Agent in Rhesus Macaques

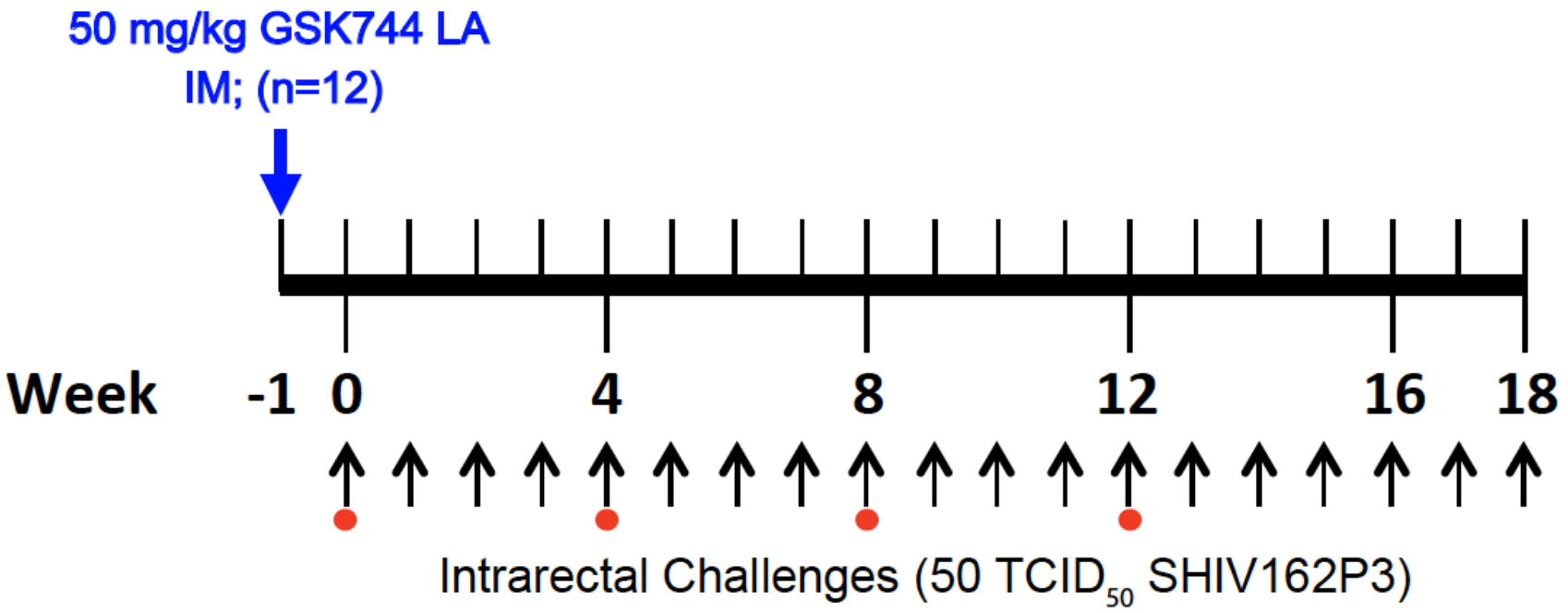




C. Andrews, et al, 20th CROI, Mar 2013

Andrews, C. D. et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 343, 1151–1154 (2014).

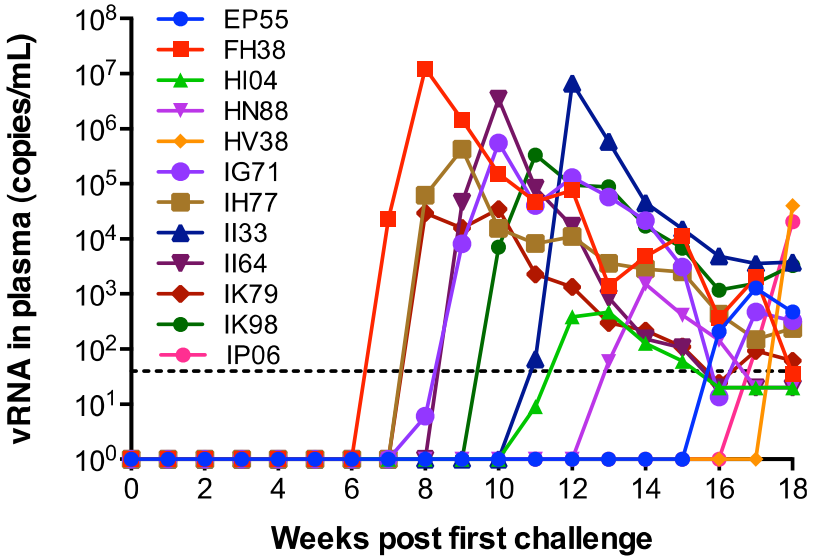
Repeated Low-Dose IR Challenges to Evaluate Threshold GSK744 LA Concentrations for Protection in 16 Macaques

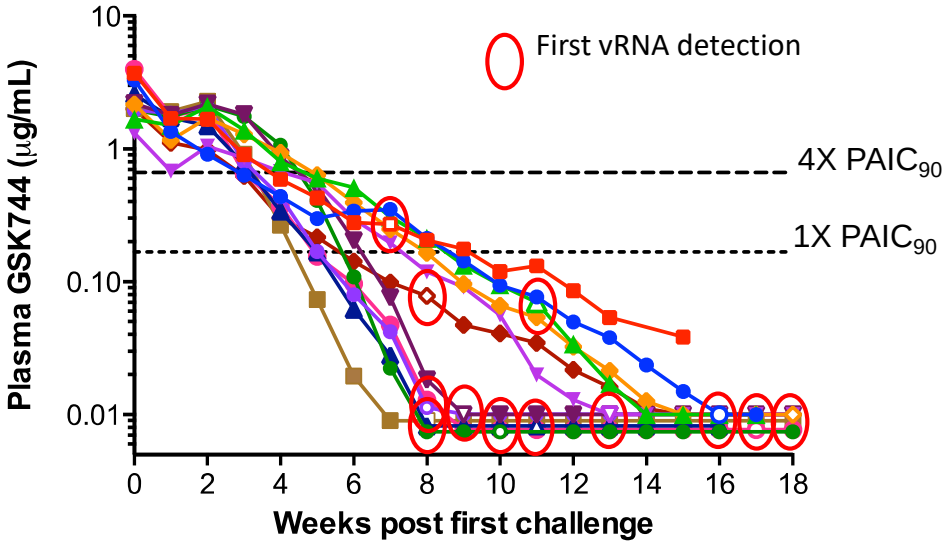


Andrews, C. D. et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 343, 1151–1154 (2014).

One 50 mg/kg Dose of GSK744 LA Protects Macaques for at least Five Challenges

CD Andrews CD, et al. , CROI 2014. Boston, March 3-6. Abstract 39.

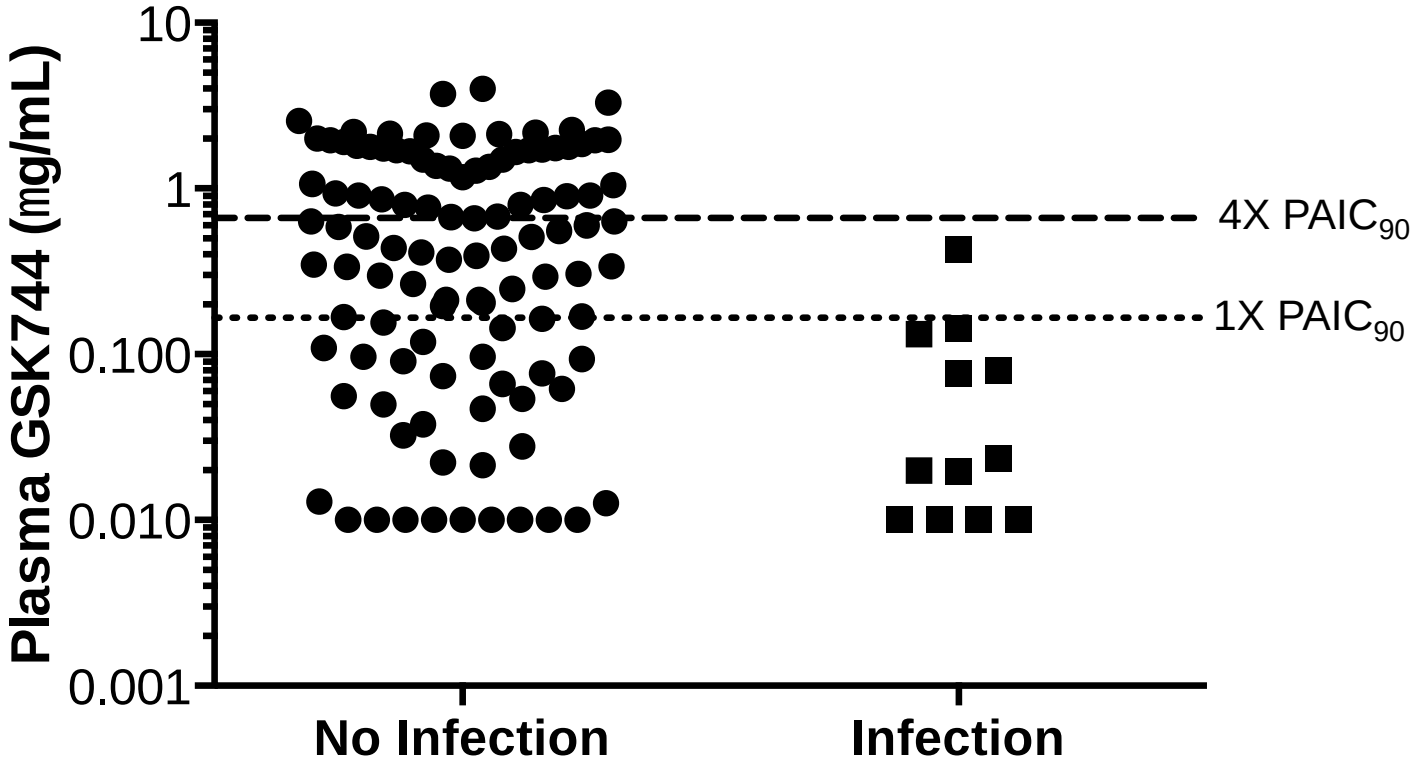




Andrews, C. D. et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 343, 1151–1154 (2014).

GSK744 Plasma Concentrations Resulting in Infection During Repeated Low-Dose IR Challenges are <3X $PAIC_{90}$

CD Andrews CD, et al. , CROI 2014. Boston, March 3-6. Abstract 39.

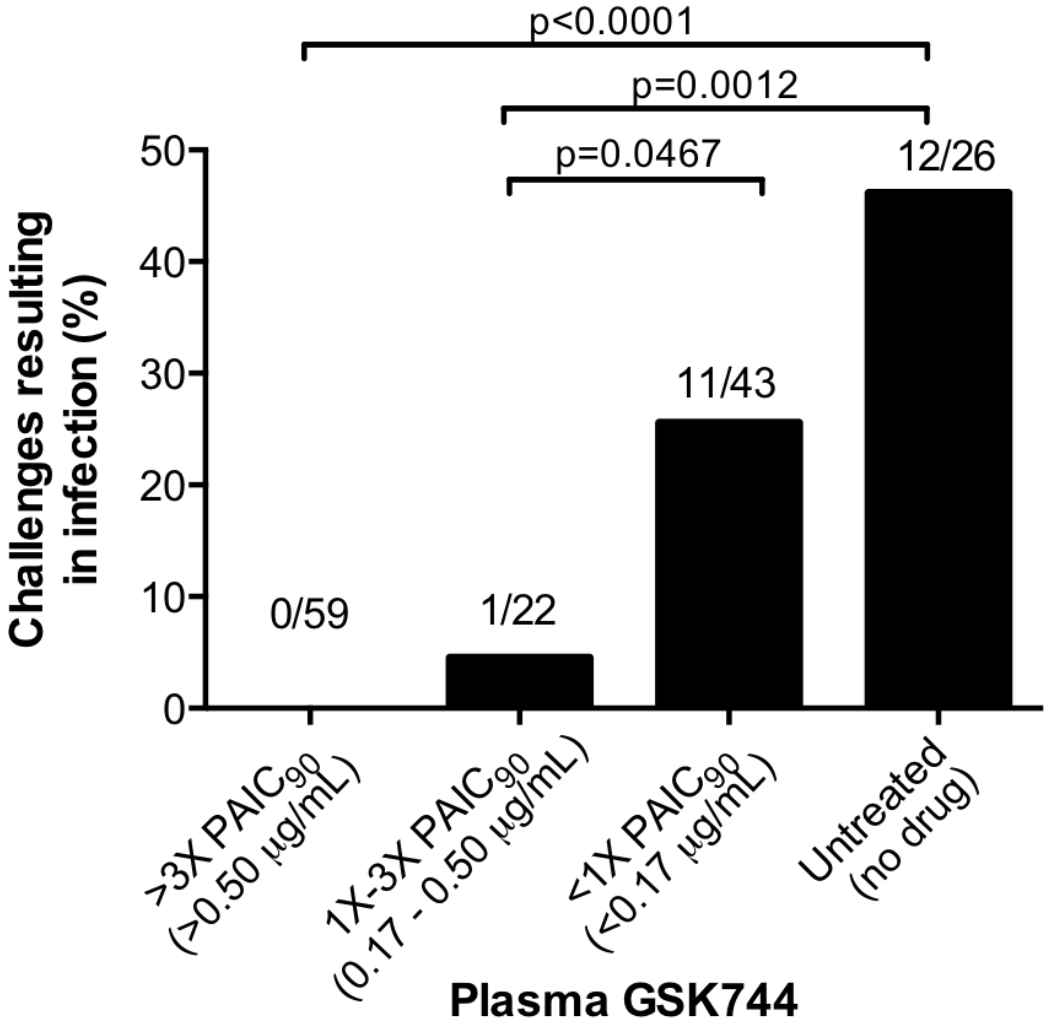


- GSK744 plasma concentrations >3X $PAIC_{90}$ result in 100% protection, while levels ≥1X $PAIC_{90}$ provide ~97% protection
- GSK744 plasma levels corresponding to protection can be readily achieved in man with quarterly 800 mg intramuscular injections

Andrews, C. D. et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 343, 1151–1154 (2014).

GSK744 Plasma Concentrations >3X $PAIC_{90}$ Result in 100% Protection, while ≥1X$PAIC_{90}$ are 97% Effective

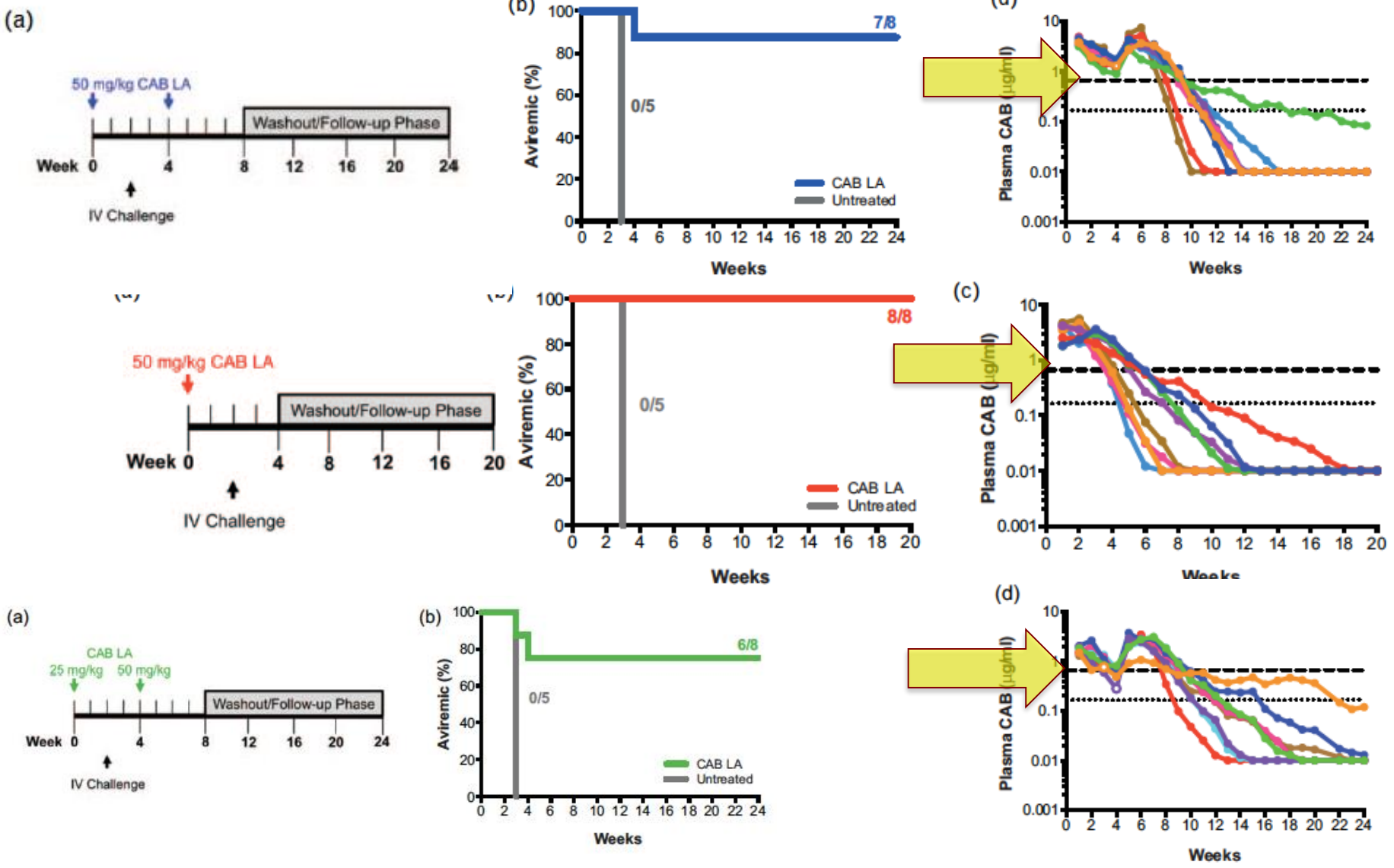
CD Andrews CD, et al. , CROI 2014. Boston, March 3-6. Abstract 39.



Andrews, C. D. et al. Long-acting integrase inhibitor protects macaques from intrarectal simian/human immunodeficiency virus. Science 343, 1151–1154 (2014).

Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251

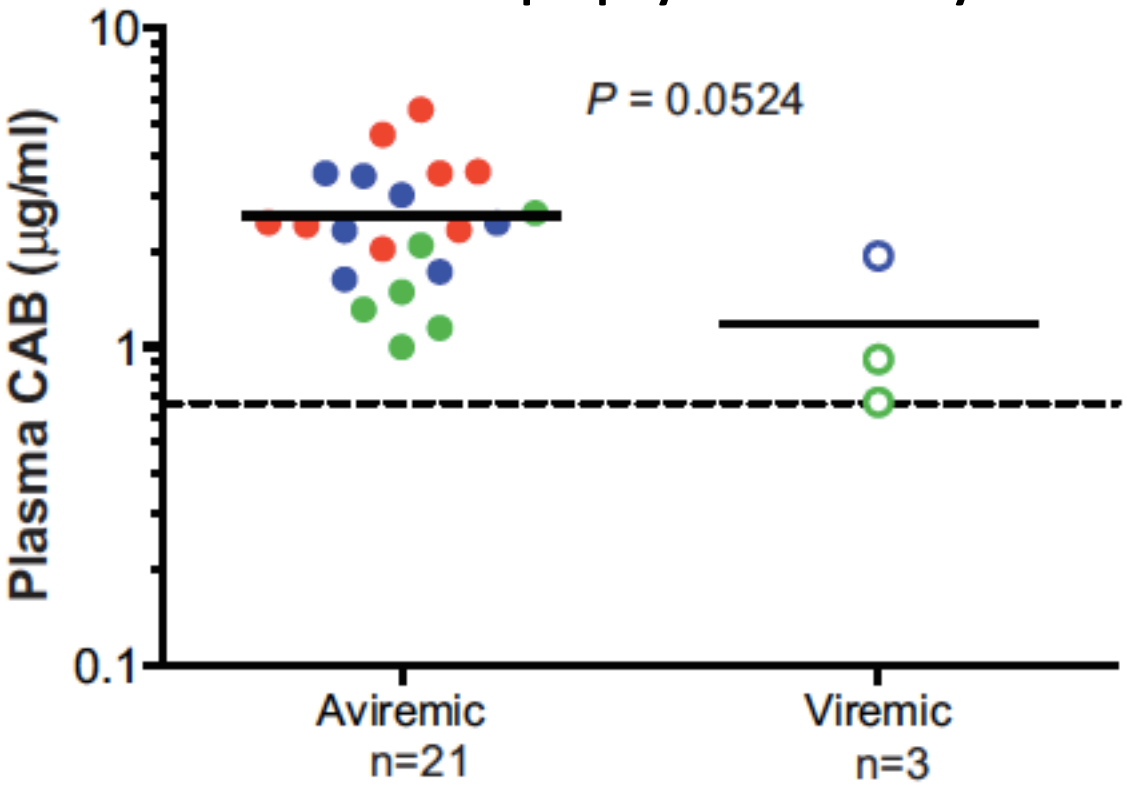
Andrews CD, et al. *AIDS* 2017, 31:461–467



Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251

Andrews CD, et al
AIDS 2017, 31:461–467

Impact of plasma CAB concentration at time of intravenous challenge on prophylactic efficacy



4 protein-adjusted IC90

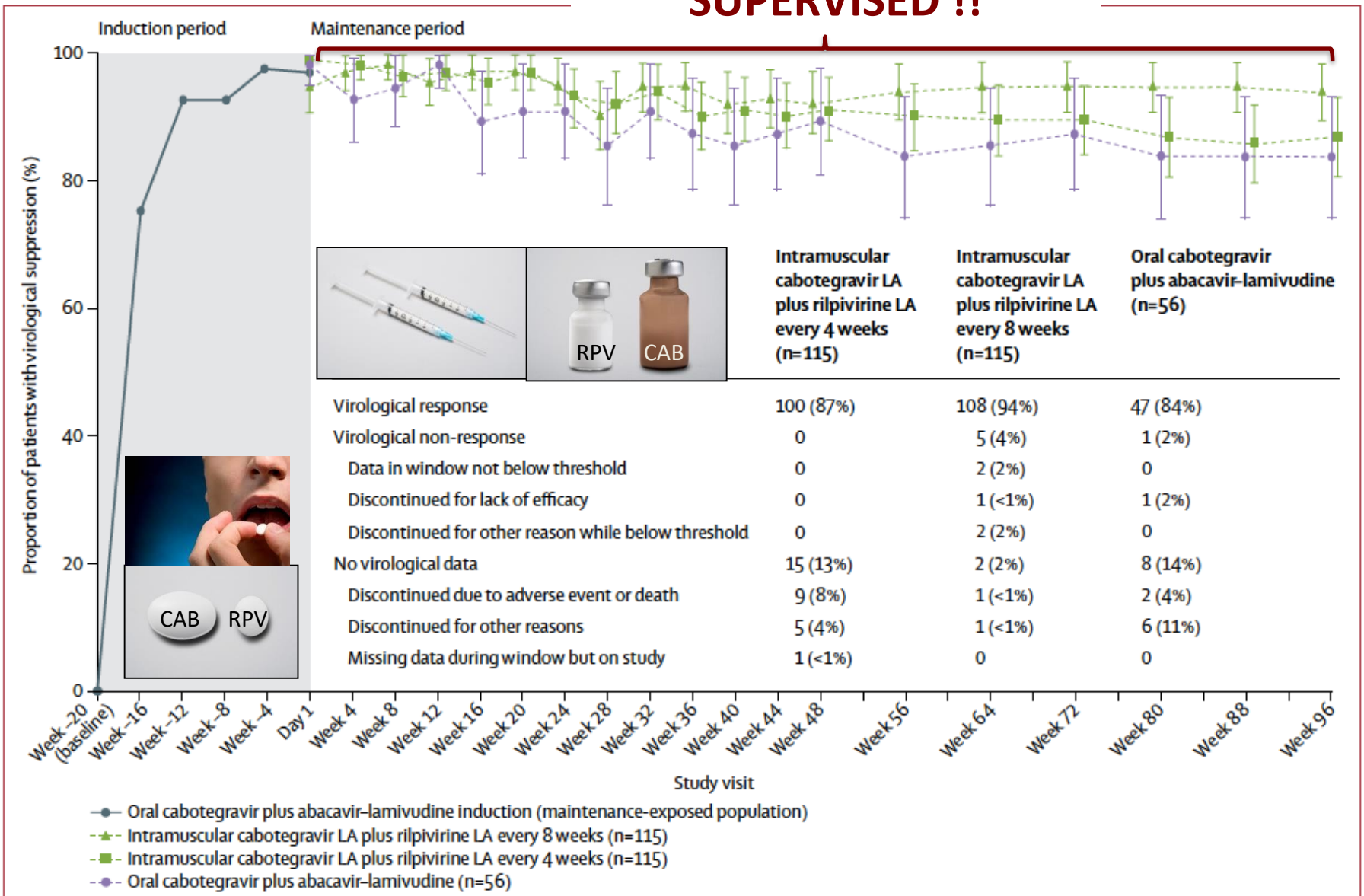
- 50 mg/kg on week 0 and 4
- 50 mg/kg on week 0
- 25 mg/kg on week 0 and 50 mg/kg on week 4

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al

Lancet 2017; 390: 1499–510

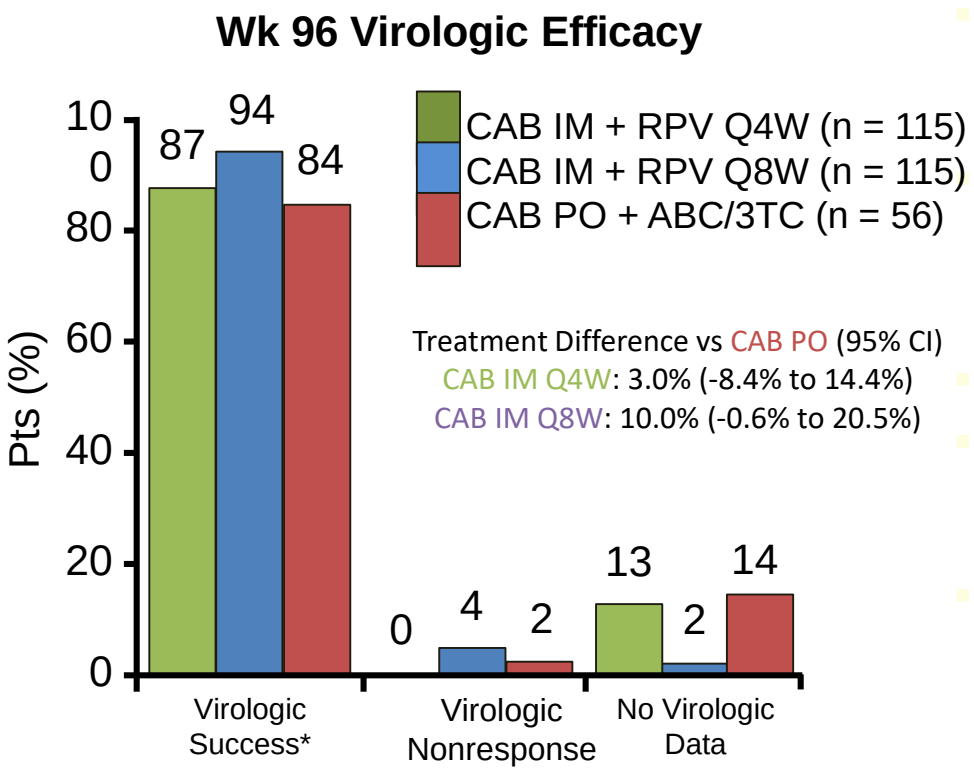
SUPERVISED !!



	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir-lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART

- **Cabotegravir:** INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to **CAB 400 mg IM + RPV 600 mg Q4W, CAB 600 mg IM + RPV 900 mg Q8W**, or **CAB 30 mg PO + ABC/3TC 600/300 mg QD** after induction/ virologic suppression with oral CAB + ABC/3TC (N = 309)[1,2]



*HIV-1 RNA < 50 copies/mL.

- At 96 wks, ~ 30% of pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving CAB IM very satisfied to continue present treatment at Wk 96 vs 43% receiving CAB PO
- Phase III maintenance trials (ATLAS and FLAIR) moving forward with Q4W dose[3,4]

1. Eron J, et al. IAS 2017. Abstract MOAX0205LB.
2. Margolis DA, et al. Lancet. 2017;[Epub ahead of print].
2. ClinicalTrials.gov. NCT02951052.
3. ClinicalTrials.gov. NCT02938520.

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et Lancet 2017; 390: 1499–510

At week 96:

4-week arm
CAB 400 mg + RPV 600 mg Qmonth

0 virological non-response

8-week arm
CAB 600 mg + RPV 900 mg Q2months

5 virological non-response

2 protocol-defined virologic failures

Controls
CAB 30 mg + ABV/3TC QD

1 virological non -response

1 protocol-defined virologic failure

Virological non-response = HIV-RNA > 50 c./mL (50< HIV-RNA <200 c/mL)
Protocol-defined virological failure = HIV-RNA > 200 c/mL

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

Margolis DA, et al Lancet 2017; 390: 1499–510

At week **48**:

4-week arm
CAB 400 mg + RPV 600 mg Qmonth

8-week arm
CAB 600 mg + RPV 900 mg Q2months

Controls
CAB 30 mg + ABV/3TC QD

All had RPV [c] in the lowest 25th quartile

1 virological non-response

8 virological non-response

1 virological non -response

4 patients were resuppressed (HIV-RNA < 50 c./mL) at week 96 without any change in therapy

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

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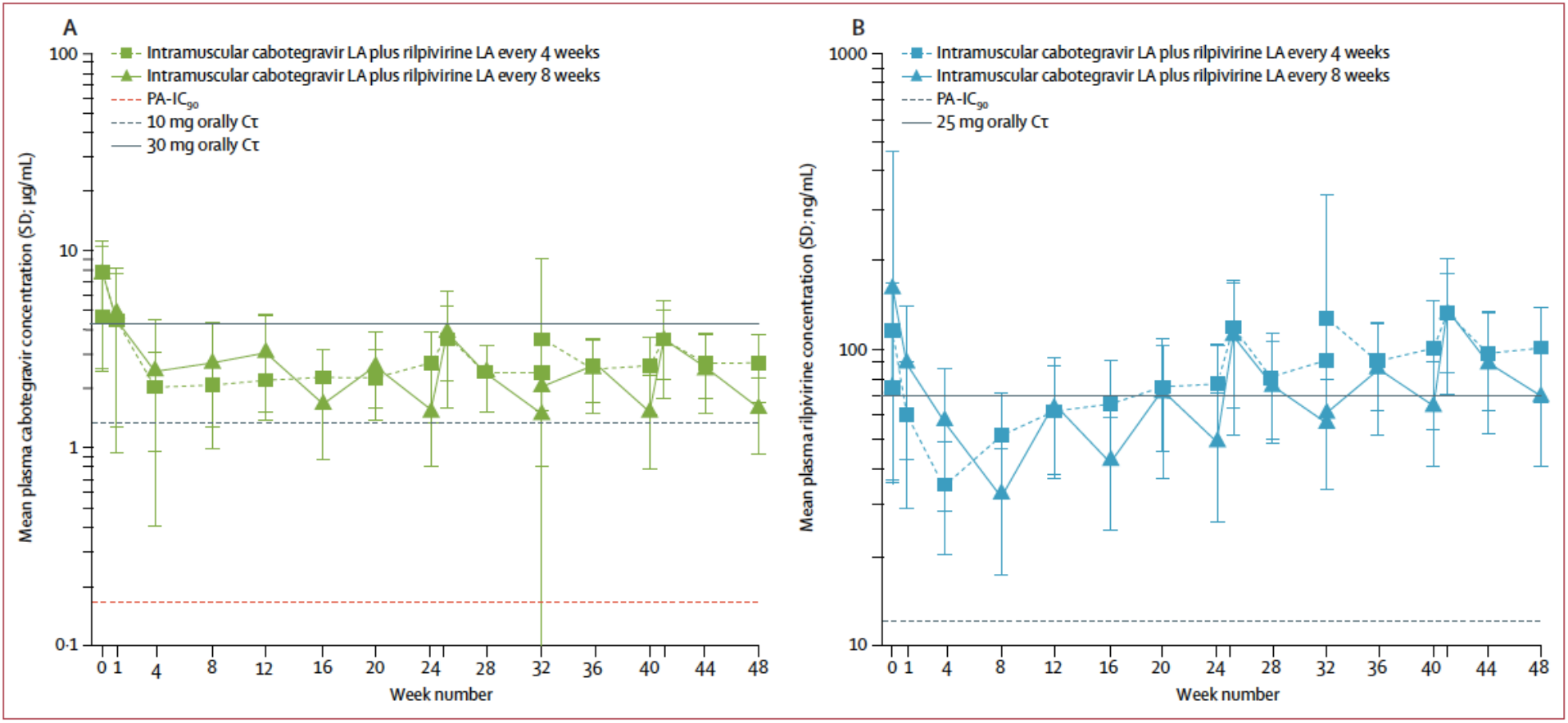

***Figure 3*: Arithmetic mean (SD) plasma concentration–time profiles following every 4 weeks and every 8 weeks administration of (A) cabotegravir LA and (B) rilpivirine LA through week 48**

Cτ=concentration at the end of dosing interval. LA=long-acting. PA-IC_{90}=protein-adjusted 90% inhibitory concentration.

Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial

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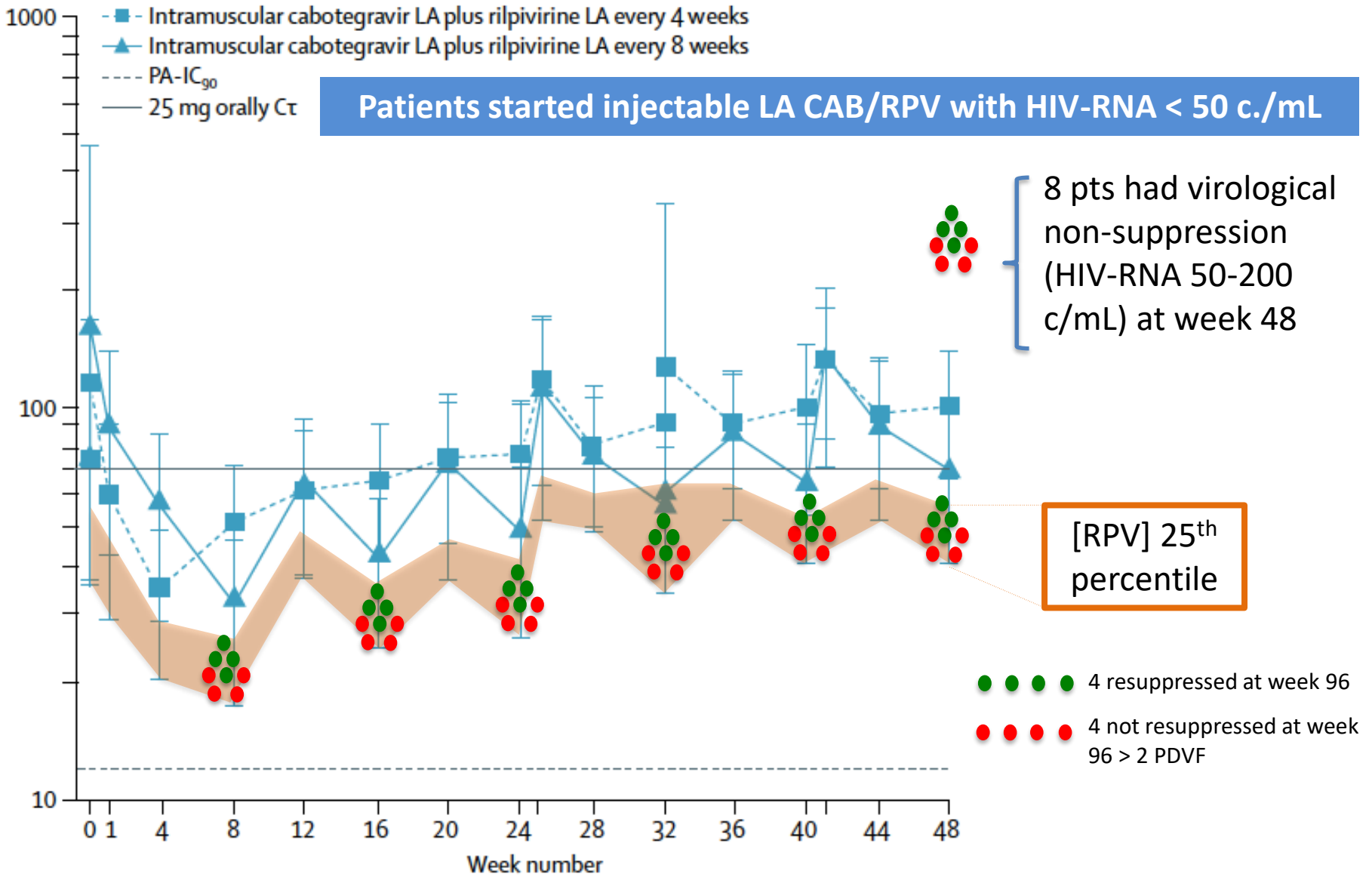
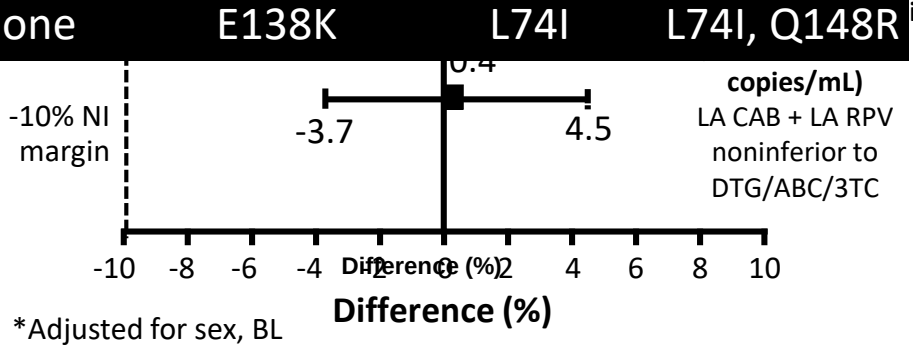


FLAIR: Efficacy at Wk 48 in ITT-E Population

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

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



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

Orkin. CROI 2019. Abstr 140LB.

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