Clinical pharmacology of new and upcoming ARV compounds

Marta Boffito

New/upcoming ARVs

- Bictegravir (BIC)
- Doravirine (DOR)
- Cabotegravir/rilpivirine (CAB/RPV)
- Other

BIC

BIC ADME

- Well absorbed (>70%)
- Highly bound to plasma proteins (>99%)
- Primarily circulates as parent drug (BIC accounted for 68% plasma radioactivity)
- Metabolism is the major clearance pathway for BIC with a similar contribution by oxidation (CYP3A4) and glucuronidation (UGT1A1)
  - Moderate hepatic impairment showed no clinically significant effect on PK
- Minimal renal clearance (~1% of unchanged parent drug excreted in urine)
  - No clinically significant effect with severe renal impairment (CrCl 15–30 mL/min) on PK

BIC

Metabolic pathways and transporters relevant to BIC/FTC/TAF

	Bictegravir	Emtricitabine	TAF
Enzymes			
Substrate	UGT1A1 CYP3A4	UGT (minimal)	CYP3A4 (minimal)
Inhibition	n/a	n/a	n/a
Induction	n/a	n/a	n/a
Transporters			
Substrate	?	n/a	P-gp BCRP
Inhibition	Limited OCT2 Limited MATE-1	MRP1-3 (*in vitro*)	n/a
Induction	n/a	n/a	n/a

BIC

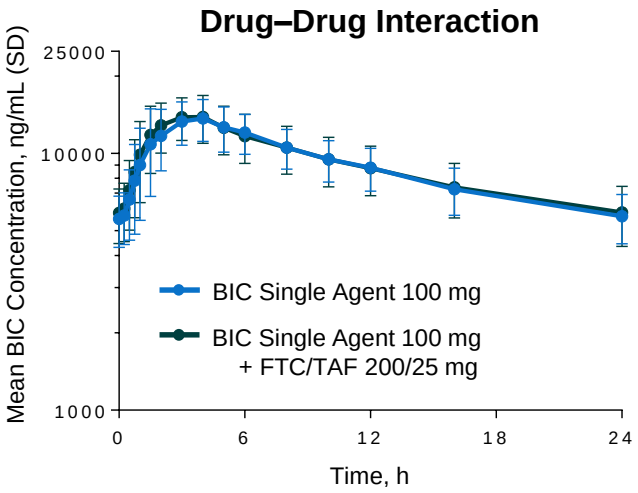
Clinical pharmacology profile of InSTI

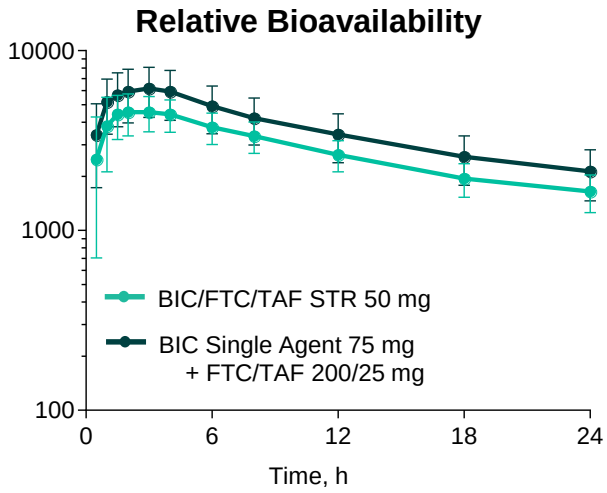
	RALTEGRAVIR	ELVITEGRAVIR	DOLUTEGRAVIR	BICTEGRAVIR
Clinical dose	400 mg BID OR 1200 mg QD	150 mg QD boosted with cobi and with FTC/TDF or FTC/TAF	50 mg QD (INI-naïve), 50 mg BID (INI-resistant)	50 mg QD with FTC/TAF
Metabolism and Excretion	**UGT1A1**, renal elimination ~ 9%	**CYP3A (major),** UGT1A1/3 (minor), renal elimination ~7%	**UGT1A1 (major),** CYP3A (minor), renal elimination <1%.	**UGT1A1 and CYP3A (equal)** renal elimination <1%.
Half Life $t_{1/2}$	~9 hours	~12.9 hours (boosted)	~14 hours	~18 hours
DDI Potential	Least	Highest	Slightly greater than RAL	**Moderate**

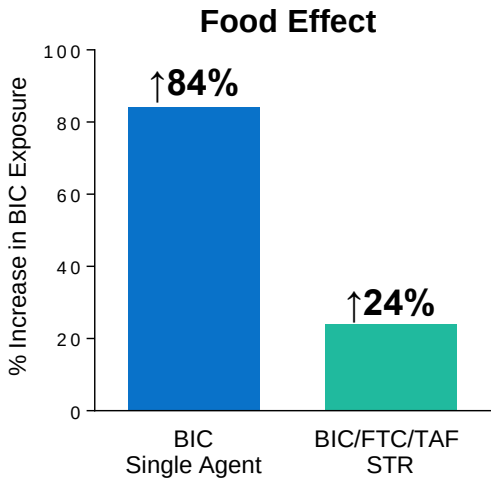
1. Tivicay SmPC updated October 2015. 2. Min S, et al. Antimicrob Agents Chemother 2010;54:254–8. 3. Min S, et al. AIDS 2011;25:1737–45.
4. Isentress SmPC July 2015; 5. Stribild SmPC updated June 2015); 6. Ramanathan S, et al. Clin Pharmacokinet 2011;50:229–44.

BIC

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 administered with or without food

Zhang H, et al, CROI, 2017

BIC

BIC DDI profile

- Perpetrator? Low potential (OCT2/metformin)

- Victim? Low or moderate potential?
  - 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

BIC DDI profile: perpetrator

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

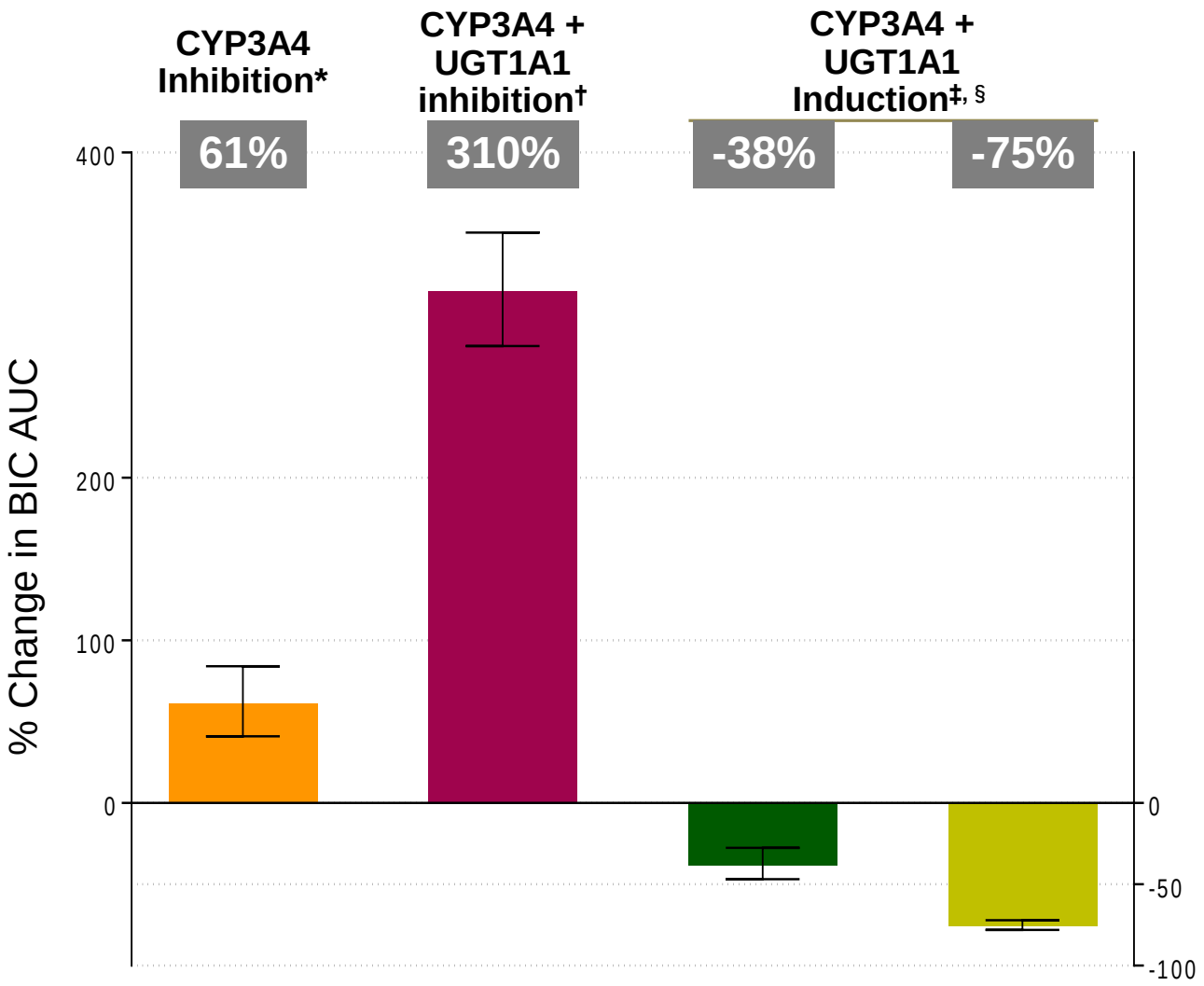
- **Low potential** to perpetrate DDIs
  - Not an inhibitor or inducer of CYP3A4 or UGT1A1
    - No effect on midazolam
  - No interaction with a representative oral contraceptive
    - No effect on norgestimate/ethinyl estradiol
  - No interaction with a representative HCV DAA
    - No effect on ledipasvir/sofosbuvir
  - 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.

BIC

BIC DDI profile: victim



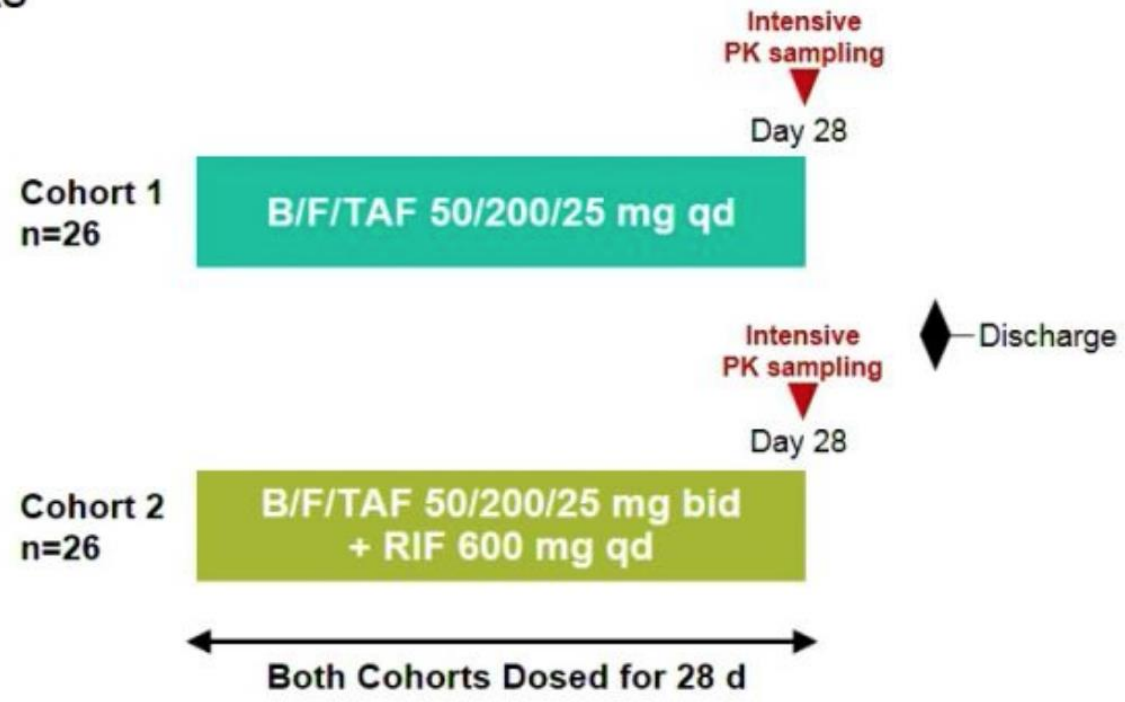
*Voriconazole; †atazanavir; ‡rifabutin; §rifampin.

Zhang, et al. CROI 2017

BIC

RIF + BIC BID: study design

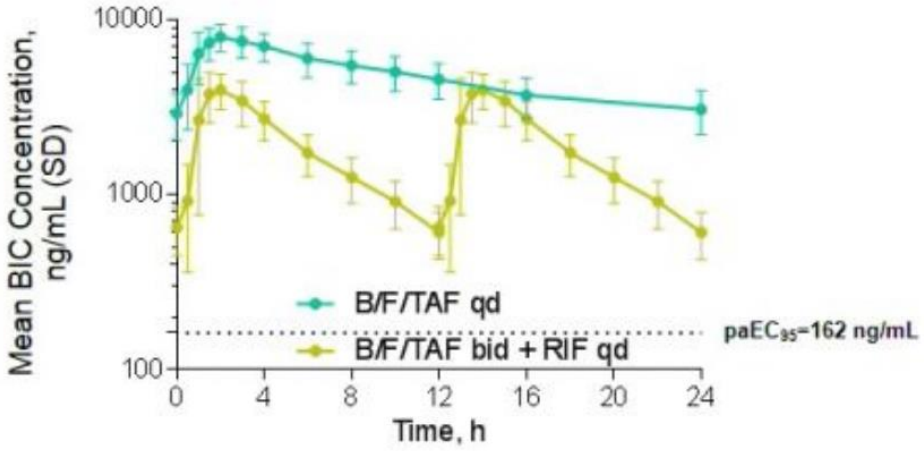
- Phase 1, open-label, parallel-design, multiple-dose, single-center study in healthy subjects



Custodio, et al. CROI 2018

BIC

RIF + BIC BID: results



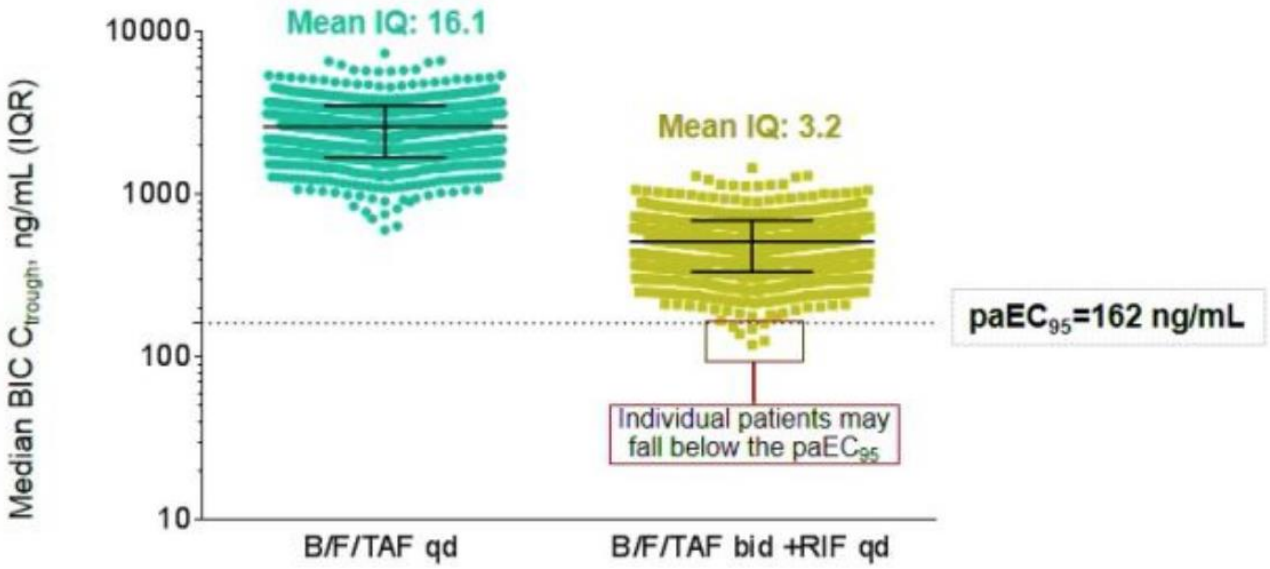
BIC PK Mean (%CV)	B/F/TAF qd n=26 (ref)	B/F/TAF bid + RIF qd n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24}, ng•h/mL	115,000 (21)	45,600 (23)	39.5 (35.7, 43.7)
C_{max}, ng/mL	8530 (16)	4560 (19)	53.2 (49.1, 57.6)
C_{trough}, ng/mL	3070 (28)	608 (30)	19.7 (17.2, 22.7)

- Daily BIC exposure (AUC_{0-24}) is expected to be ~60% lower following administration of B/F/TAF bid + RIF qd vs B/F/TAF qd
- Following administration of B/F/TAF bid + RIF qd, mean BIC C_T was reduced by ~80% vs B/F/TAF qd

Custodio, et al. CROI 2018

BIC

RIF + BIC BID: results



- Following administration of B/F/TAF in HIV-infected patients in Phase 3 studies (N=1193), mean IQ of BIC was 16.1[1]
  - After accounting for ~80% reduction in BIC C_{trough} following B/F/TAF bid + RIF qd vs B/F/TAF qd, individual patients may fall below the $paEC_{95}$

Custodio, et al. CROI 2018

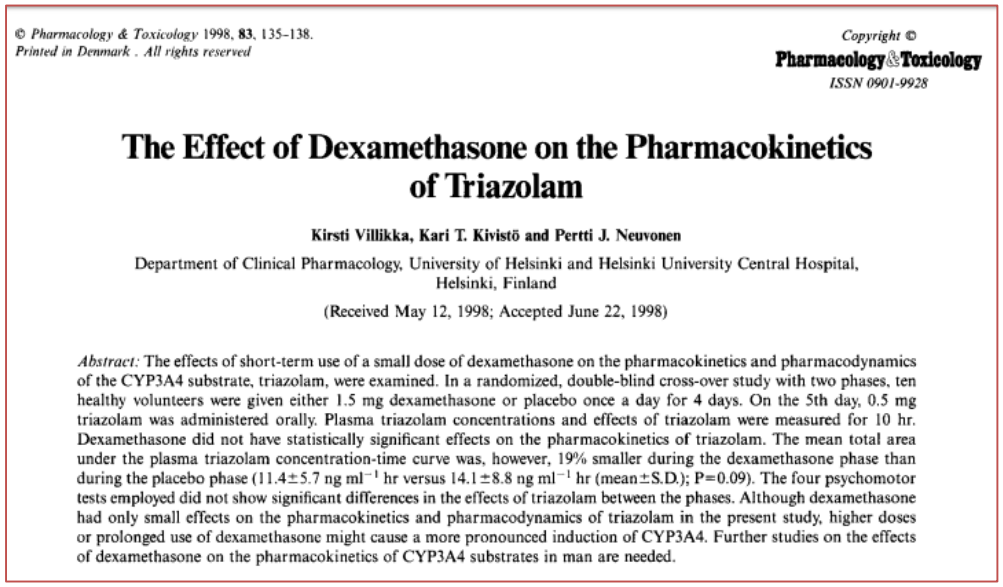
BIC

What about moderate inducers effect on BIC?

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers(2)	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort(3,4)
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe,(5) carbamazepine, phenytoin, rifampin, St. John's wort(3)	Bosentan, efavirenz, etravirine, modafinil, nafcillin dexamethasone	Amprenavir, aprepitant, armodafinil, clobazamechinacea,(4) pioglitazone, prednisone, rufinamide, vemurafenib
CYP2D6	None known	None known	None known

(1) Please note the following: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
(2) For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.
(3) The effect of St. John's wort varies widely and is preparation-dependent.
(4) Herbal product.
(5) Not a marketed drug.

BIC



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The Effect of Dexamethasone on the Pharmacokinetics of Triazolam

Kirsti Villikka, Kari T. Kivistö and Pertti J. Neuvonen

Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

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Abstract: The effects of short-term use of a small dose of dexamethasone on the pharmacokinetics and pharmacodynamics of the CYP3A4 substrate, triazolam, were examined. In a randomized, double-blind cross-over study with two phases, ten healthy volunteers were given either 1.5 mg dexamethasone or placebo once a day for 4 days. On the 5th day, 0.5 mg triazolam was administered orally. Plasma triazolam concentrations and effects of triazolam were measured for 10 hr. Dexamethasone did not have statistically significant effects on the pharmacokinetics of triazolam. The mean total area under the plasma triazolam concentration-time curve was, however, 19% smaller during the dexamethasone phase than during the placebo phase (11.4±5.7 ng ml^{-1} hr versus 14.1±8.8 ng ml^{-1} hr (mean±S.D.); P=0.09). The four psychomotor tests employed did not show significant differences in the effects of triazolam between the phases. Although dexamethasone had only small effects on the pharmacokinetics and pharmacodynamics of triazolam in the present study, higher doses or prolonged use of dexamethasone might cause a more pronounced induction of CYP3A4. Further studies on the effects of dexamethasone on the pharmacokinetics of CYP3A4 substrates in man are needed.

The Observer
Drugs

Students used to take drugs to get high. Now they take them to get higher grades

The use of so-called 'smart drugs', bought on the internet, to boost mental performance is rife in British universities. So can we all benefit from 'having an edge', or is it just a form of cheating that should be banned?

Modafinil: a prescription-only medication for narcolepsy that the NHS's website describes as "a central nervous system stimulant" that prevents "excessive sleepiness during daytime hours". Or, used off-label, bought via some off-shore pharmaceutical retailer, it's what's known as a "smart drug".

DOR ADME

- Well-absorbed (T_{max} 1-4 h)
- Moderate protein binding (86%)
- Extensively metabolized by CYP450 (CYP3A)
- Elimination half-life = 12–21 h
- Gender, age, moderate hepatic impairment, co-administration with food did not significantly alter DOR PK

DOR

DOR DDI I

Not a perpetrator of DDI

Victim of strong inducers

- AUC < 88% with rifampicin — Avoid
- AUC < 50% with rifabutin — Increase daily dose to 100 mg BD

PK affected by strong inhibitors

- AUC > 254% — No dose adjustment

DOR DDI II

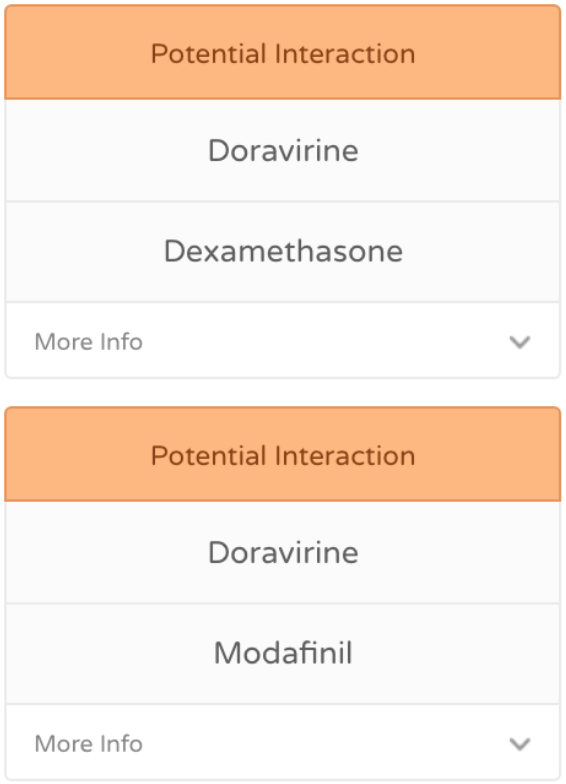
- No interactions with statins or DAAs

- No significant interactions noted between DOR and antacids (aluminum–magnesium) or pantoprazole

DOR

DOR DDI III

- What about moderate inducers?



Coadministration not been studied

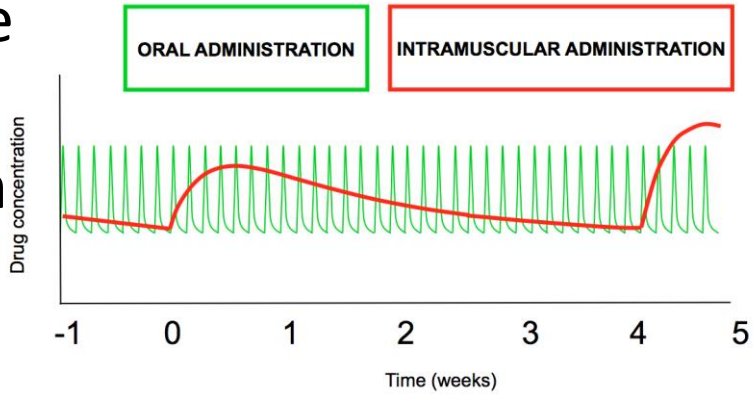
Could [DOR] decrease?

If co-administration cannot be avoided, DOR 100 mg BID (**based on the interaction study with rifabutin, another moderate inducer**) and maintained at this dose for at least another two weeks following cessation of moderate inducer.

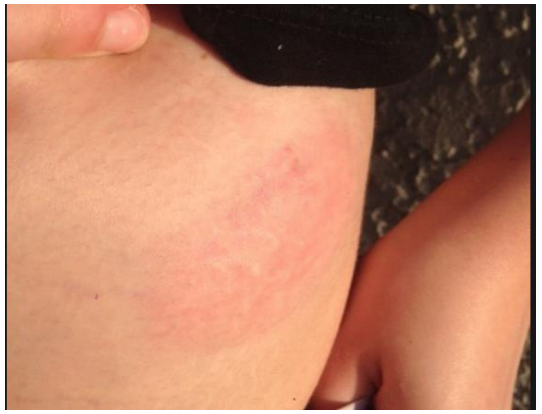
Intramuscular drug delivery

- **Advantages**
  - Drug is absorbed slowly, prolonged effect
  - Sustained exposure over time
  - Larger volume than SC
  - By-pass first pass metabolism

  LESS DRUG INTERACTIONS

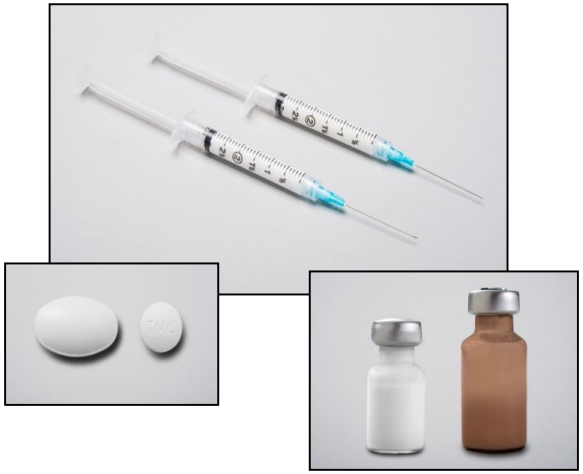


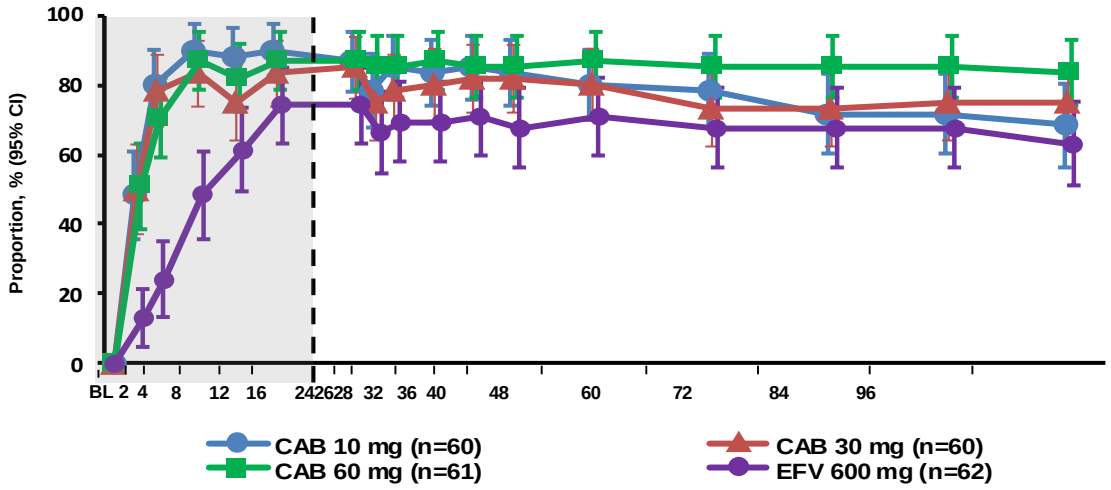
- **Disadvantages**
  - Invasive – patient discomfort
  - Irritation
  - Inflammation
  - My require <u>training</u>



CAB

- 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





BL, baseline; CI, confidence interval; LA, long-acting; $t_{½}$, half-life

Margolis et al. Lancet Infect Dis. 2015

CAB PK

- CAB primarily metabolized by UGT 1A1 with a minor contribution from UGT1A9
- Primarily eliminated in the feces (58.5% mean recovery) as unchanged drug [19]

- Low potential to be a significant perpetrator of clinically relevant drug interactions (no impact on CYP450)
- No DDI with midazolam or etravirine
- Inhibits OAT1/3
- Victim of strong inducers – rifampicin (both oral and IM)

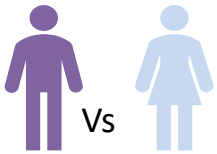
CAB/RPV

Factors influencing PK parameters: gender- and BMI-influenced absorption

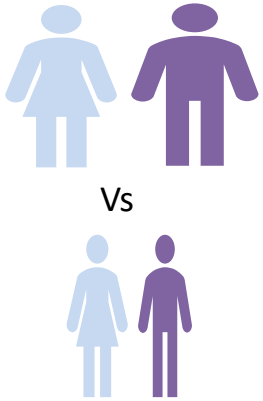
- 11,970 samples from 881 patients (56%) and healthy volunteers (44%) were analyzed

The majority of parameter (absorption rate) variability was influenced by female gender

BMI and split dosing were the remaining covariates that gave modest influence to absorption



A typical female has a slower absorption rate and a longer persistence of cabotegravir in the body

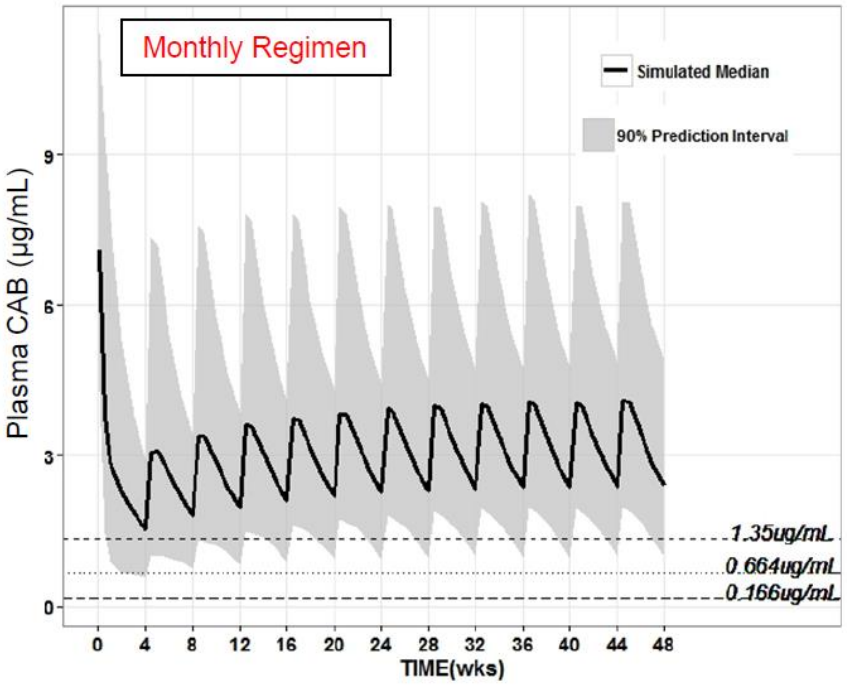


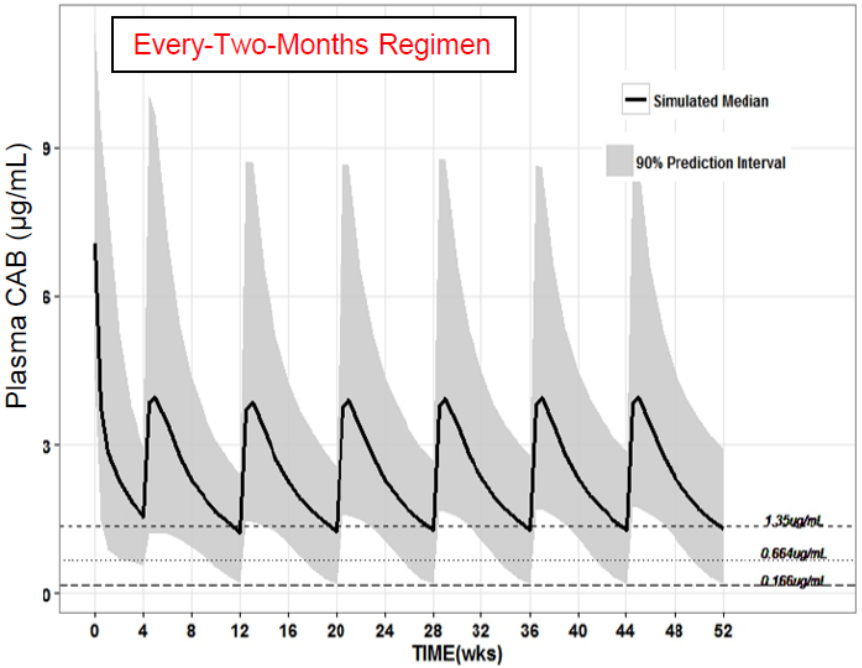
Accounting for gender, a larger BMI causes a modest decrease in absorption rate compared with smaller BMI

BUT… the magnitude of change in absorption did not alter trough levels to a clinically significant degree

Han et al. 22nd International AIDS Conference; Amsterdam, the Netherlands. Poster WEPDB0205.

Predicted median concentration-time profiles for CAB LA phase 3 regimens





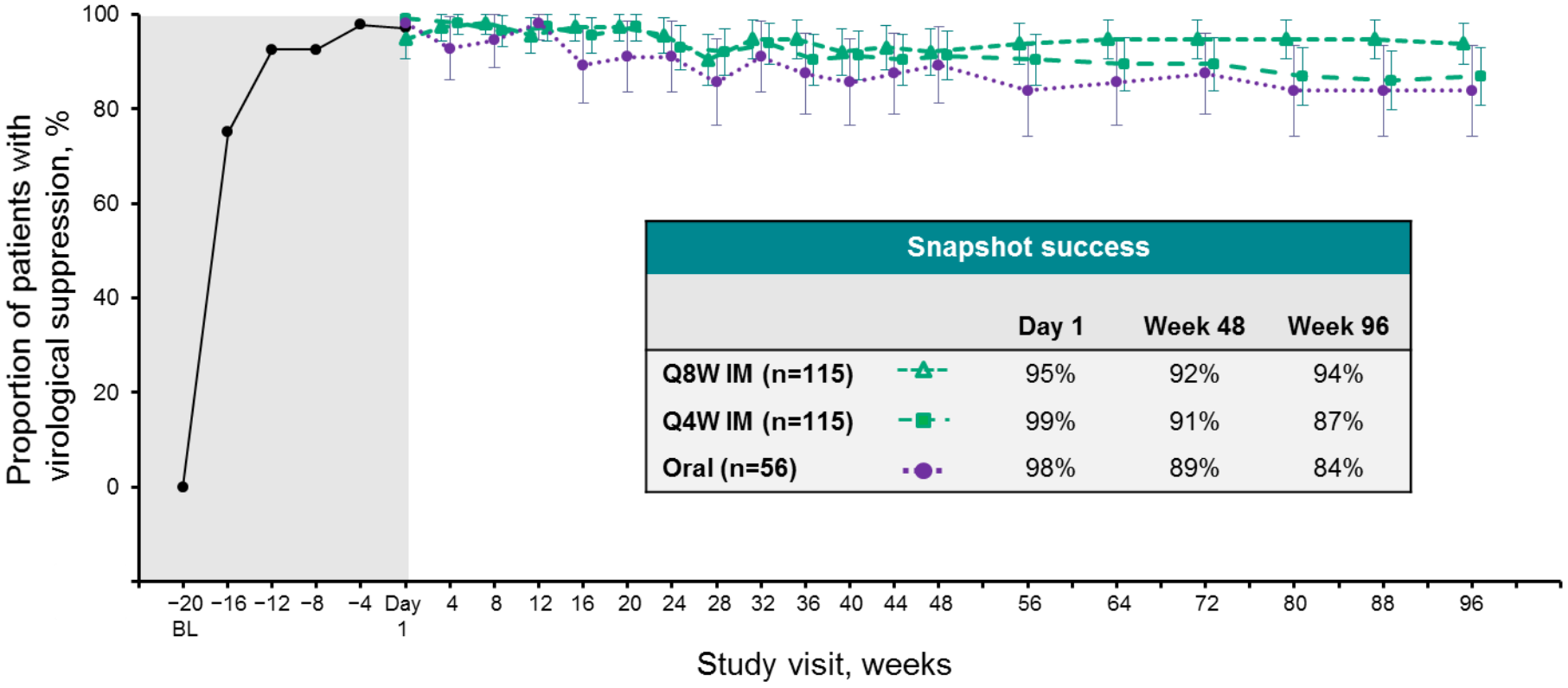
- CAB LA 600 mg (3 mL) IM is administered as the initial LA dose for both regimens
- 400 mg (2 mL) IM monthly injections start 1 month following the first injection (left panel)
- 600 mg (3 mL) IM every-two-month injections start 1 month following the first injection (right panel)
- 1.35 µg/mL = geometric mean C_{trough} following oral CAB 10 mg once daily (8x PA-IC90)
- 0.664 µg/mL = 4x PA-IC90
- 0.166 µg/mL = PA-IC90

Han K et al. IAC 2018; poster WEPDB0205

CAB/RPV

LATTE-2 Week 96 Results

HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



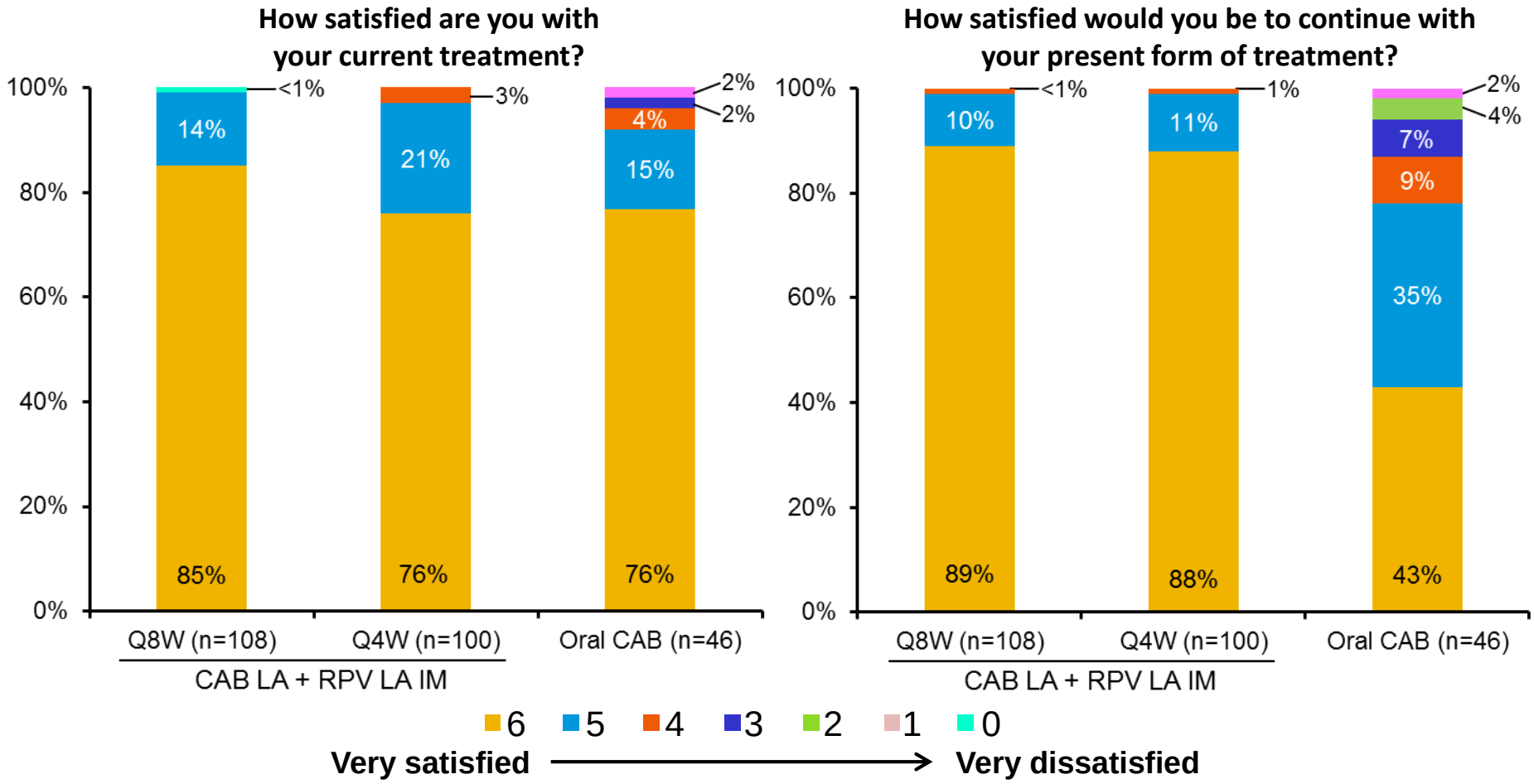
Snapshot success		Day 1	Week 48	Week 96
Q8W IM (n=115)		95%	92%	94%
Q4W IM (n=115)		99%	91%	87%
Oral (n=56)		98%	89%	84%

BL, baseline; CAB, cabotegravir; ITT-ME, intent-to-treat maintenance exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

CAB/RPV

Patient-Reported Outcomes at Week 96 Maintenance Treatment



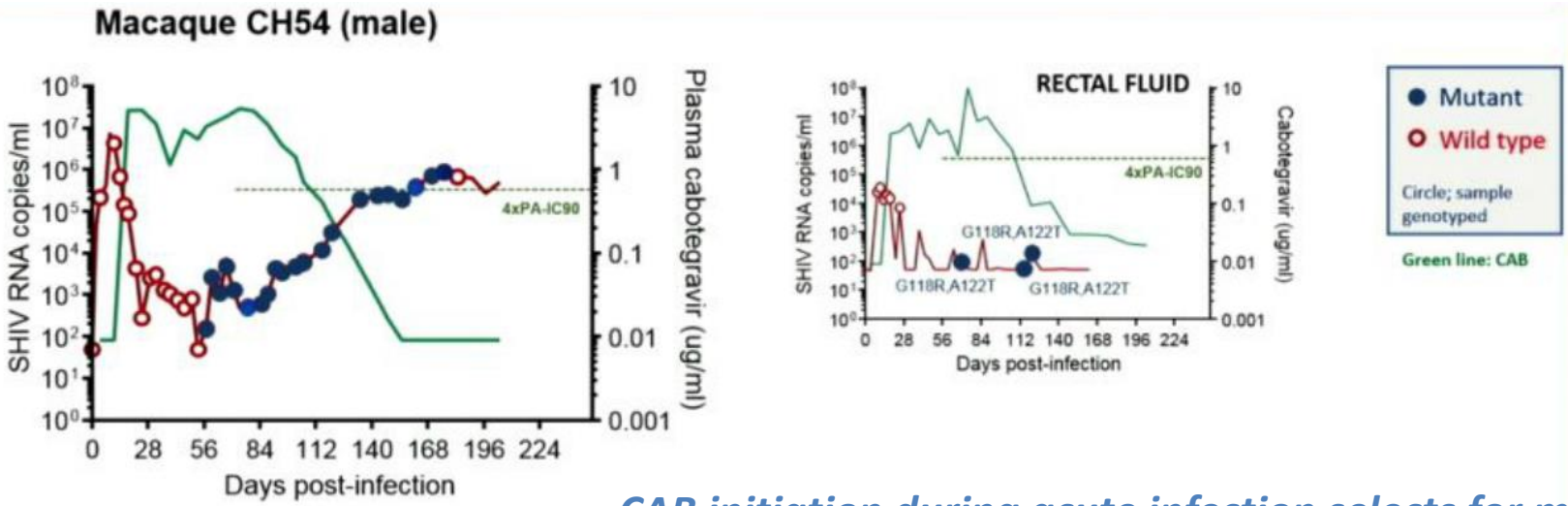
- CAB, cabotegravir; IM, intramuscular; LA, long acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

[a]Based on observed case data set of subjects who completed HIV Treatment Satisfaction Questionnaire status version at Week 96.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

CAB/RPV

Resistance emergence in macaques administered CAB LA during acute infection



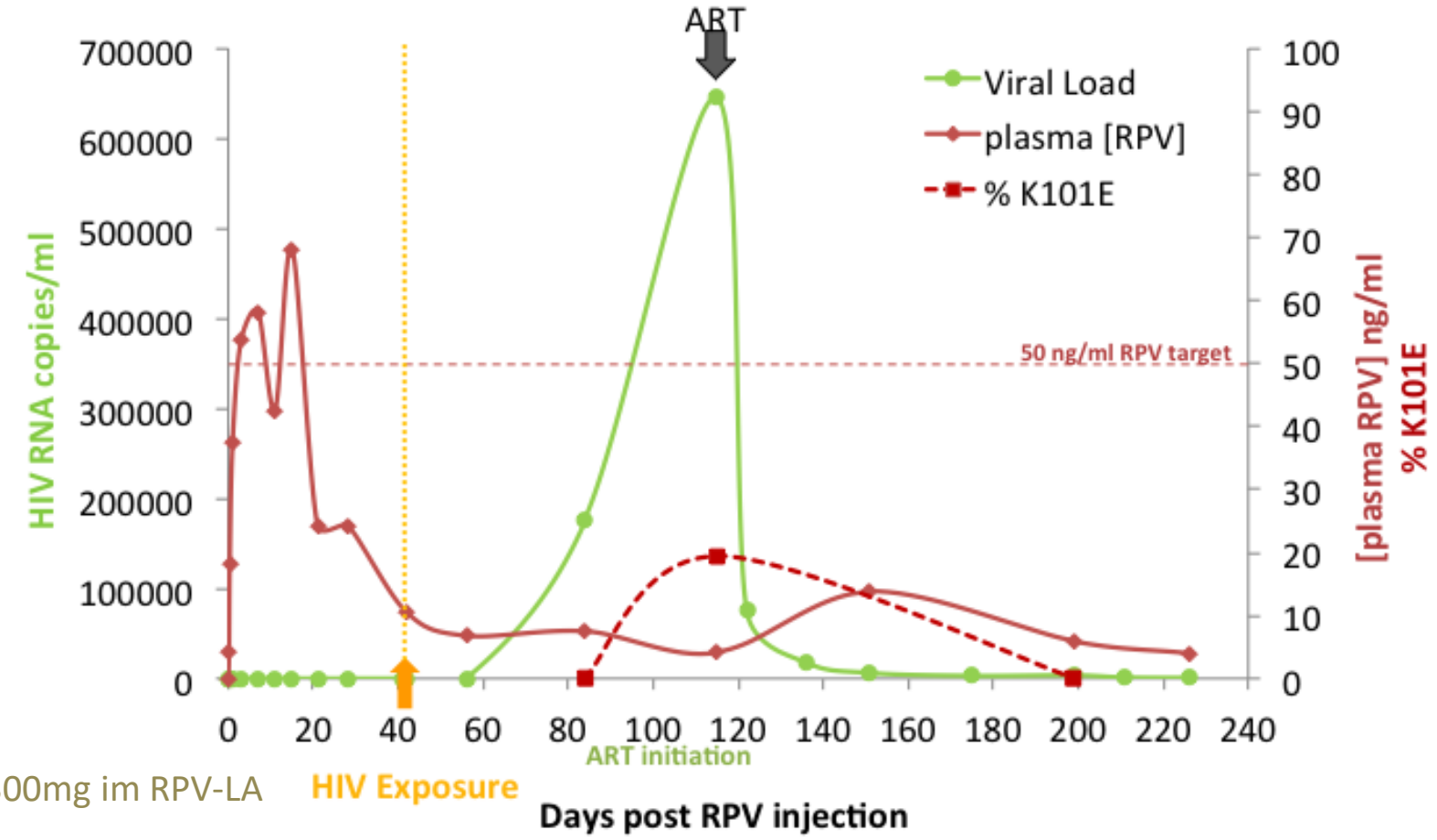
Day	Genotype
57-71	G118R, A122T
78	G118G/R, A122A/T
85-155	G118R, A122T
162	G118G/R, A122A/T
170-176	A122A/T

CAB initiation during acute infection selects for mutations in plasma and rectal/vaginal fluid associated with resistance to INI (G118R, E92Q, E92G), as early as 8 weeks and persisted during PK tail

Radzio et al. 2017

CAB/RPV

SSAT040: seroconversion and resistance development on study



First detectable VL (370 copies/mL) = day 57

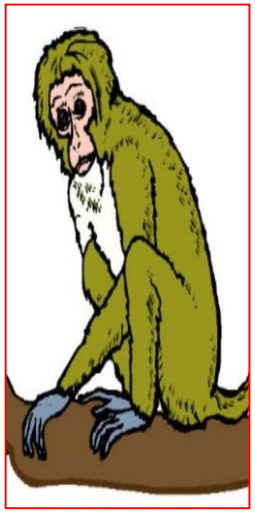
Seropositive = day 84

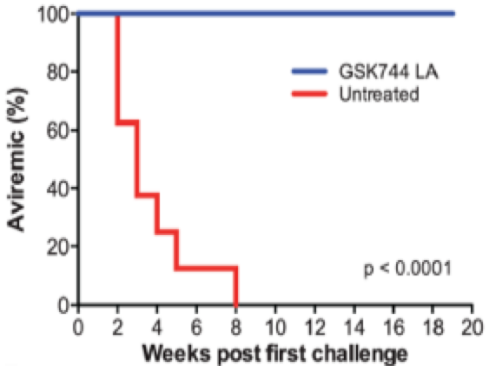
Penrose KJ et al. 2014

CAB/RPV

Cabotegravir LA

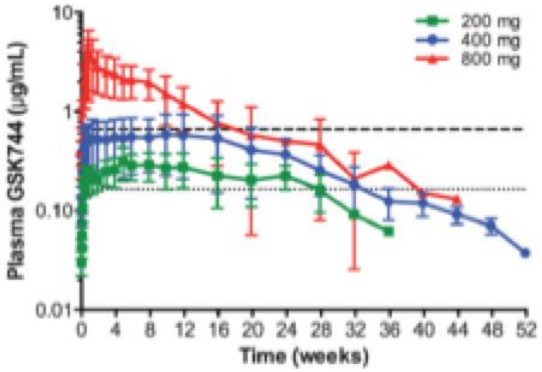
✓ ✗/✓ ✓ ?





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

Phase I



Concentrations in:

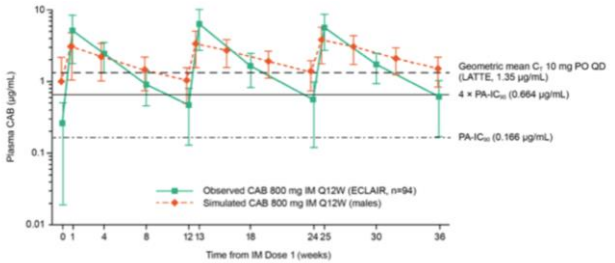
- *Female genital tract = 16%–28% of plasma*
- *Rectal tissue < 8% of plasma*

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

Global phase III study HPTN 083

CAB/RPV

Drawbacks of injectable cabotegravir and rilpivirine

1. High dosing volumes (≥3mL), IM in the buttocks

1. Extended PK tail, risk of resistance if lost to follow-up

2. Deliverability of injections is resource-intensive

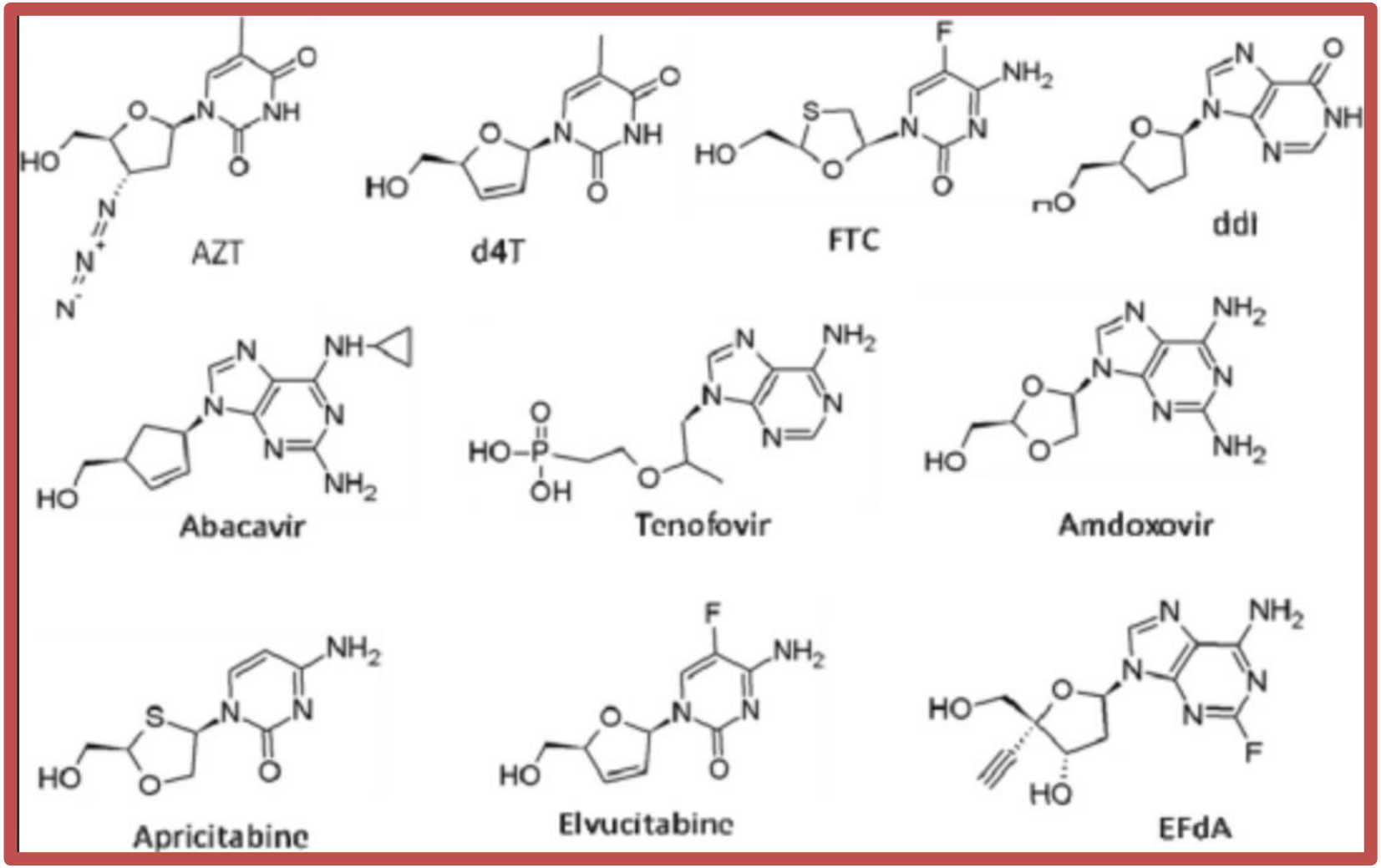
3. Oral lead-in period complicates implementation

4. DDI with rifampicin

5. Low genetic barrier

OTHER

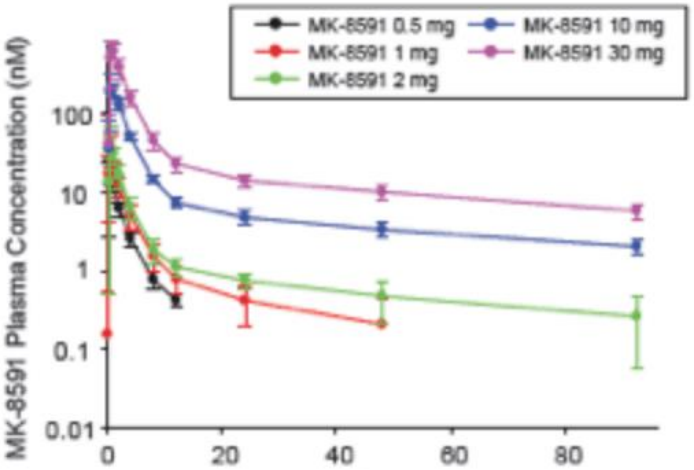
New NRTI or NtRTI

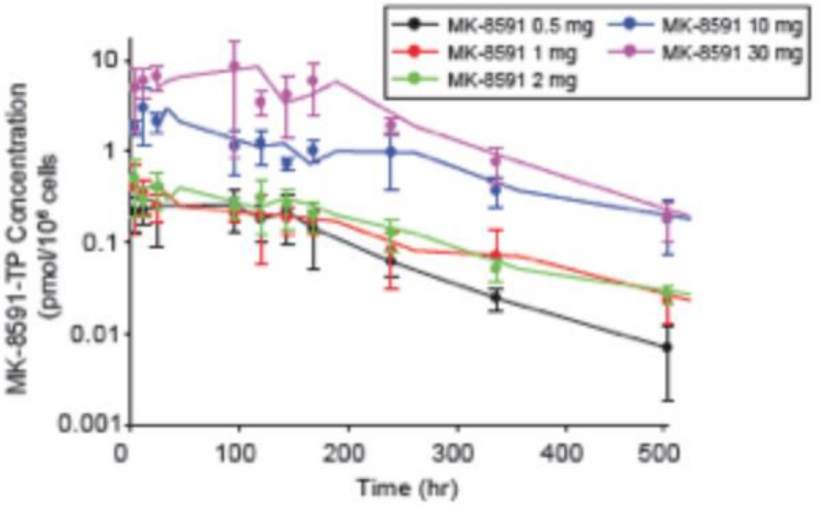


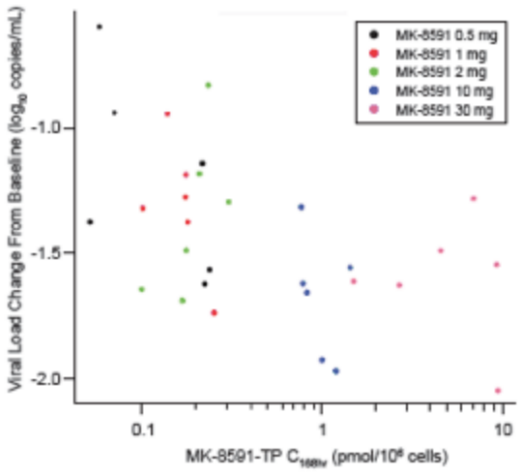
OTHER

Single doses as low as 0.5 mg of the NRTTI MK-8591 suppress HIV for at least 7 days

MK-8591 PHARMACOKINETICS







PK/PD relationship:
C168h versus VL decline

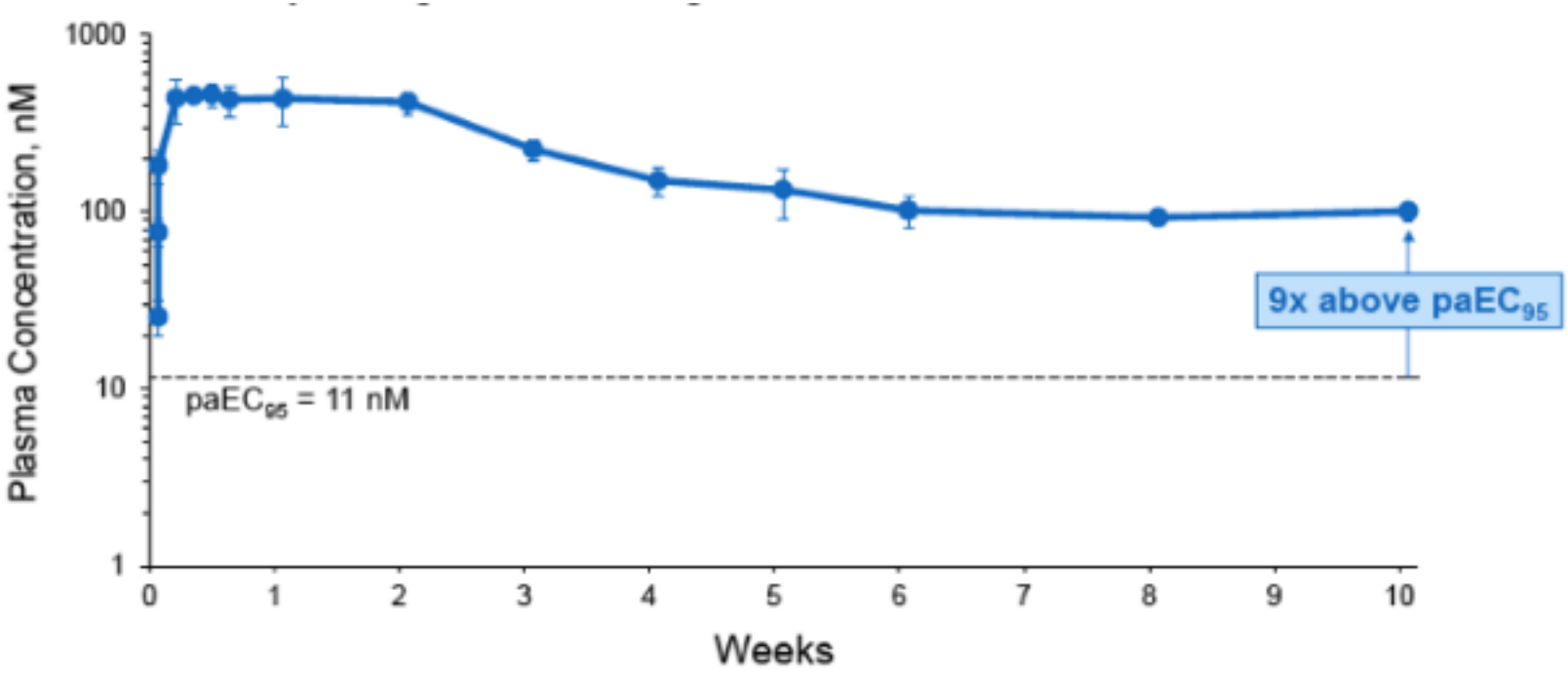
Matthews et al IAS 2017

OTHER

Novel class of HIV capsid inhibitors

- GS-CA1 PK in rats
- Extended release formulation

- Single SC injection maintains plasma concentrations well above the $paEC_{50}$ for > 10 weeks
- Potential for monthly or longer intervals



Tse et al. CROI 2017

Questions?