Update on Drug-drug interactions in HIV-associated TB

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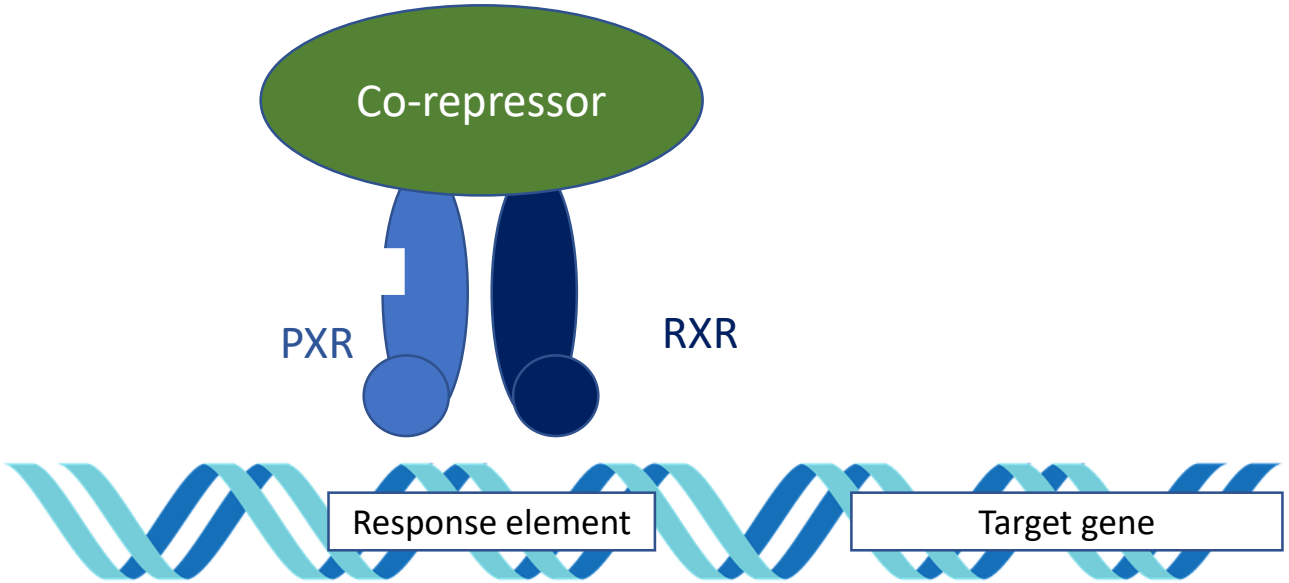
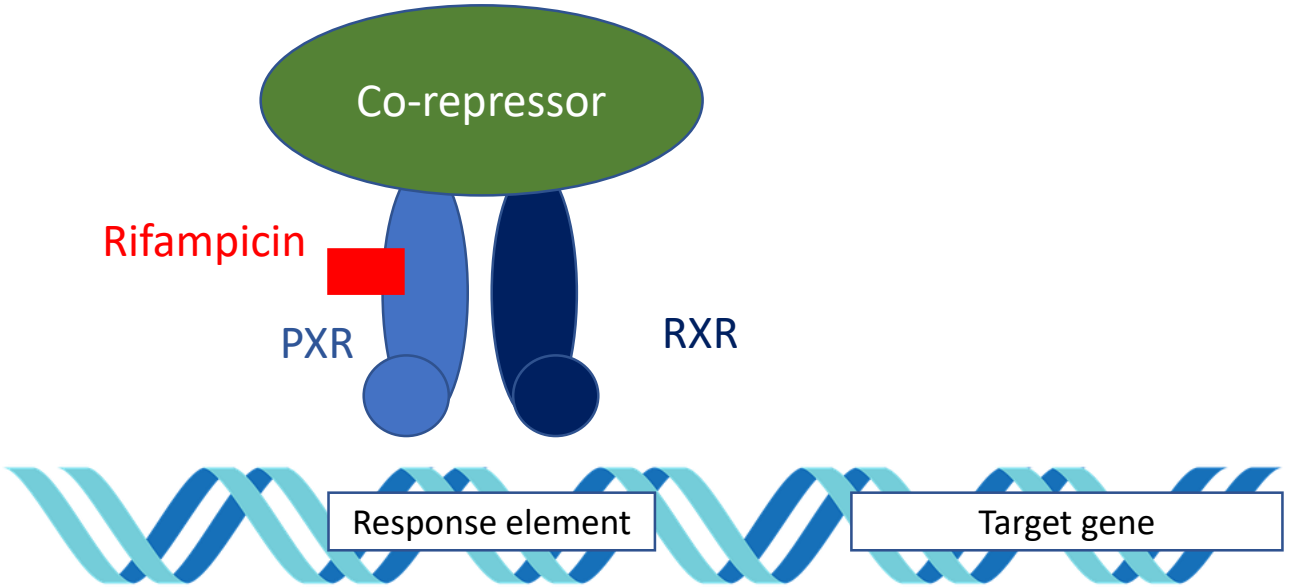
Rifampicin induction

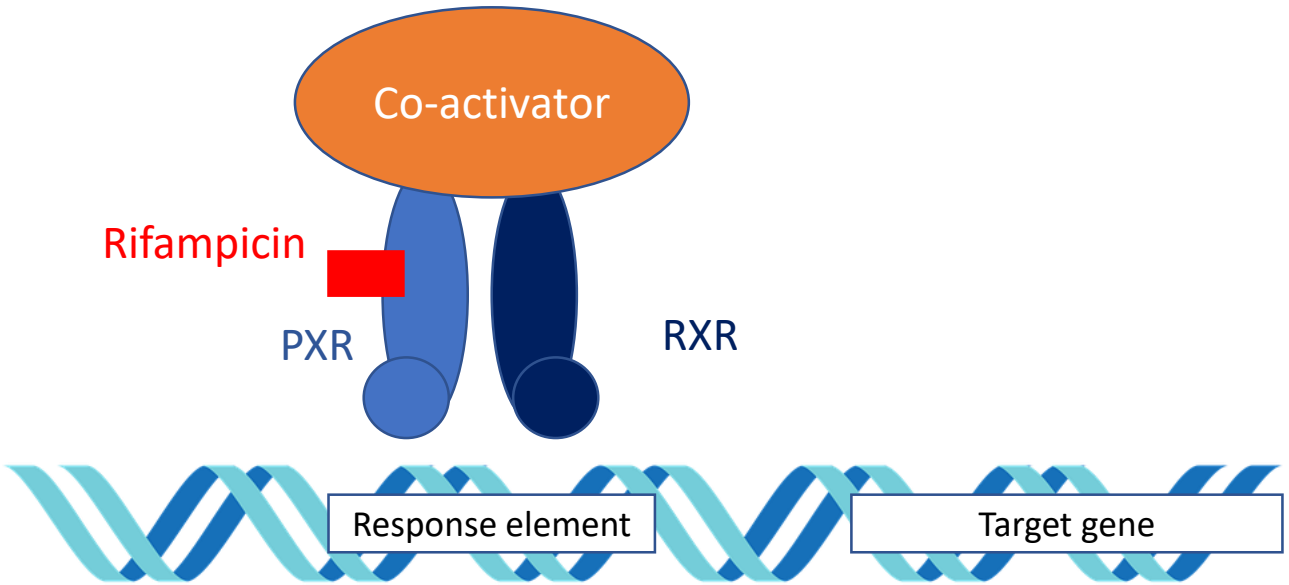


Slide courtesy Graeme Meintjes

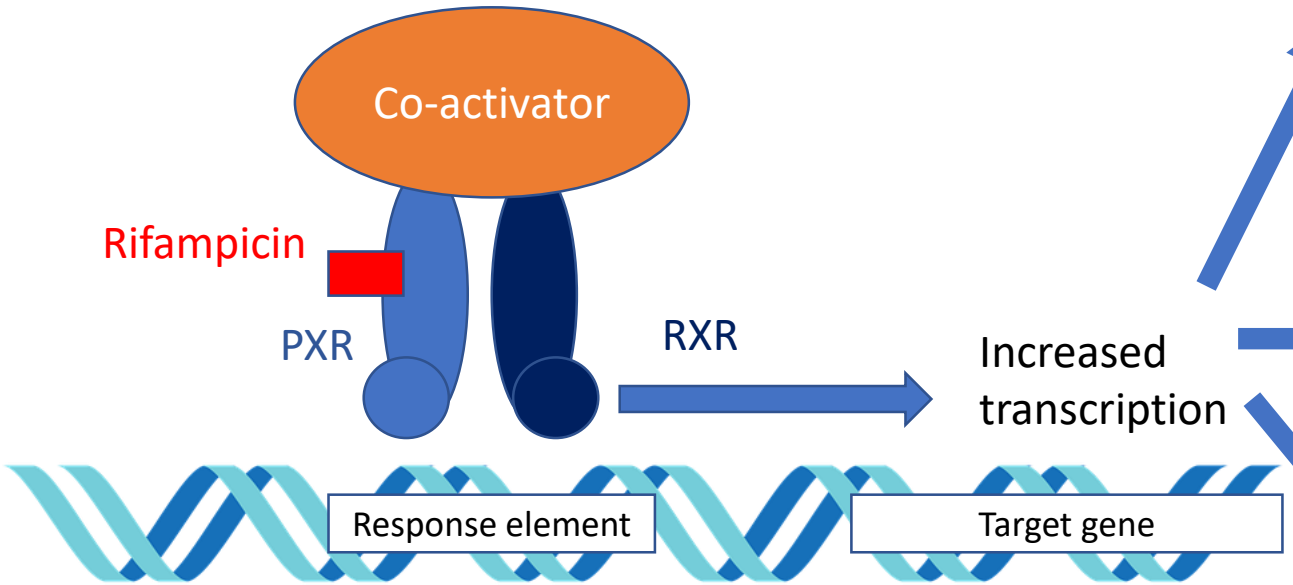
Rifampicin induction



Rifampicin induction



Rifampicin induction



Increased transcription

Phase 1 metabolizing enzymes
eg. CYP3A4 (PI, rilpivirine, nevirapine are substrates)

Phase 2 metabolizing enzymes
eg. UGT1A1 (Integrase inhibitors are substrates)

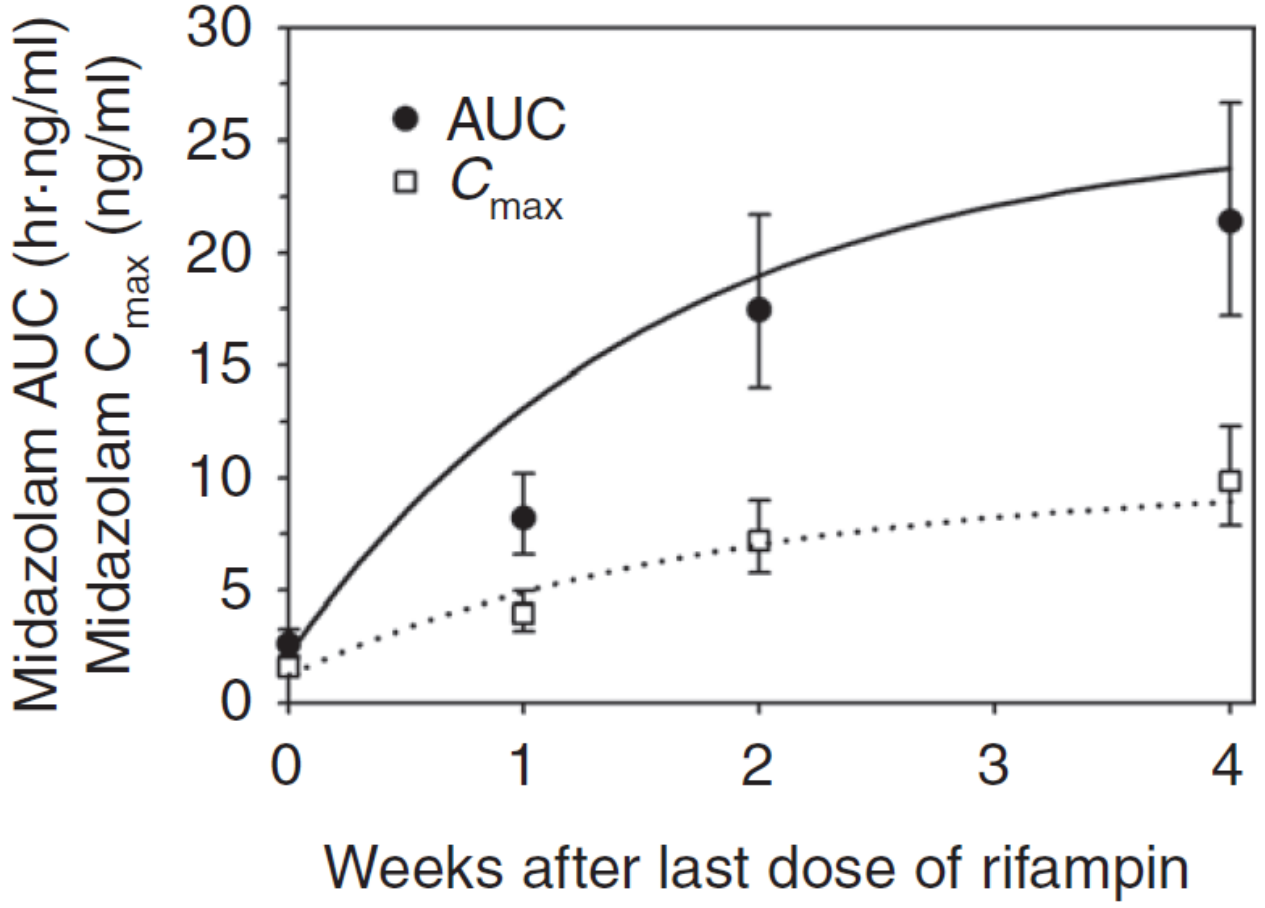
Efflux transporters
eg. P-glycoprotein (protease inhibitors, TAF are substrates)

Effect of pregnane X receptor activation by rifampicin

Enzyme/transporter	ARV substrate
CYP3A4 (55.1-fold)	PIs, nevirapine, rilpivirine, etravirine, maraviroc
CYP2B6 (8.8-fold)	Efavirenz, nevirapine
UGT1A1 (2-fold)	INSTIs
P glycoprotein (4.2-fold)	PIs, TAF, maraviroc
BCRP	TAF, dolutegravir

Clin Pharmacol Ther 2000;68:345
J Pharmacol Exp Ther 2001;299:849
Ann Clin Microbiol Antimicrob 2006; 5:3
Gastroenterology 2005;129:476
Biochem Pharmacol 2005;70:949

Time course of rifampicin induction waning



Clin Pharmacol Ther. 2011;89(2):234-42

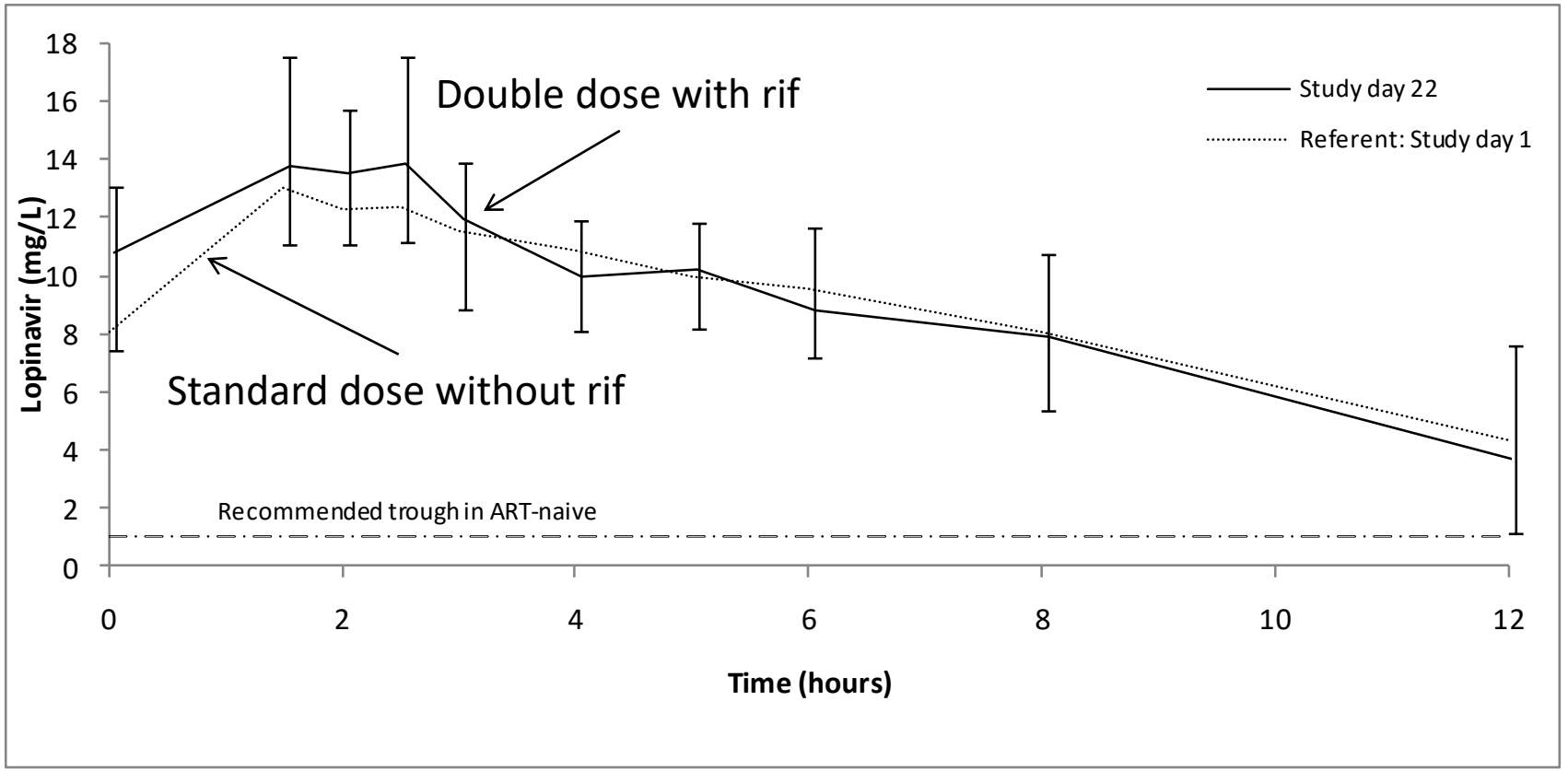
PIs & rifampicin: healthy volunteers

Very high rates of clinical hepatitis reported in 3 healthy volunteer studies of adjusted dose PIs (Saquinavir, Atazanavir, Lopinavir) - all stopped early

Is this relevant to HIV+ patients? e.g. rif + pyrazinamide for TB prevention fairly well tolerated in HIV+, but high rates of hepatotoxicity in HIV-

Arch Drug Inf. 2009 Mar;2(1):8-16
AIDS 2008;22:931-5
JAIDS 2009;50:290-3
CID 2004;39:561

Double dose lopinavir/r with rifampicin in HIV+ adults



2/21 asymptomatic grade 3/4 ALT
Adjusted doses of darunavir-r & atazanavir-r starting soon

Decloedt AAC 2011;55:3195

Rifabutin average steady state (mg/L) with PIs: Population PK pooled analysis

Dose	RBT alone		RBT with ritonavir-boosted PI	
	Healthy volunteers	TB/HIV patients	Healthy volunteers	TB/HIV patients
300 mg daily	0.17	0.17	0.80	0.48
150 mg daily	0.08	0.08	0.40	0.24
150 mg every 2 days	0.04	0.04	0.20	0.12

Limited safety & efficacy data

Rifabutin not available in many resource-limited settings

JAC 2016;71:1330

Dolutegravir & rifapentine

Drug-drug interaction study of dolutegravir and weekly rifapentine + isoniazid in healthy volunteers

Two of first four developed systemic hypersensitivity reactions (‘flu-like symptoms, hepatitis, fever, & pro-inflammatory cytokine release)

Study stopped early

Study in HIV+ patients recently started (PI Gavin Churchyard)

Brooks CID 2018 Feb 3 doi: 10.1093/cid/ciy082
ClinicalTrials.gov Identifier: NCT03435146

Efavirenz & rifampicin-based TB therapy

Many studies in patients with HIV-associated TB show no significant effect on efavirenz concentrations

Rifampicin adds little to efavirenz auto-induction of CYP2B6

- Will this also be true with efavirenz 400 mg?

International guidelines recommend standard dose efavirenz in patients with HIV-associated TB

Regulators still recommend dose increase of efavirenz to 800 mg based on company study of 12 healthy volunteers

Clin Pharmacokinet 2002;41:681
JAC 2006;58:1299
Antivir Ther 2009;14;687
JAIDS 2009;50:439
AAC 2009;53:863
Clin Infect Dis 2013;57(4):586

Efavirenz & rifampicin-based TB therapy: Pharmacogenomics

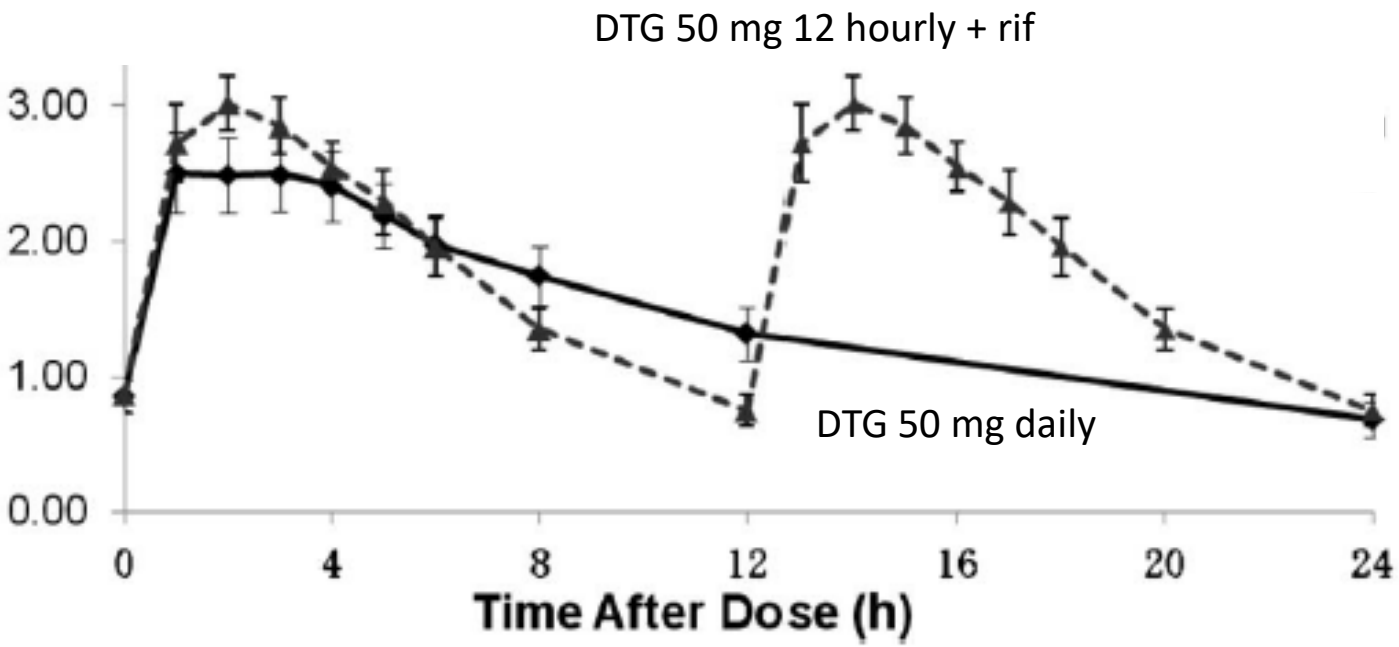
Patients with *CYP2B6* slow metabolizer genotypes (15-25% in Africa, India, & Thailand) have **higher** efavirenz concentrations on TB therapy

Isoniazid inhibits CYP2A6, accessory metabolizing enzyme of efavirenz

Effect exacerbated in *NAT2* slow metabolizer genotypes (isoniazid slow acetylators)

AIDS 2013;27:1933
J Infect Dis 2015; 211:197
Clin Infect Dis 2015;60:1860

Dolutegravir & rifampicin

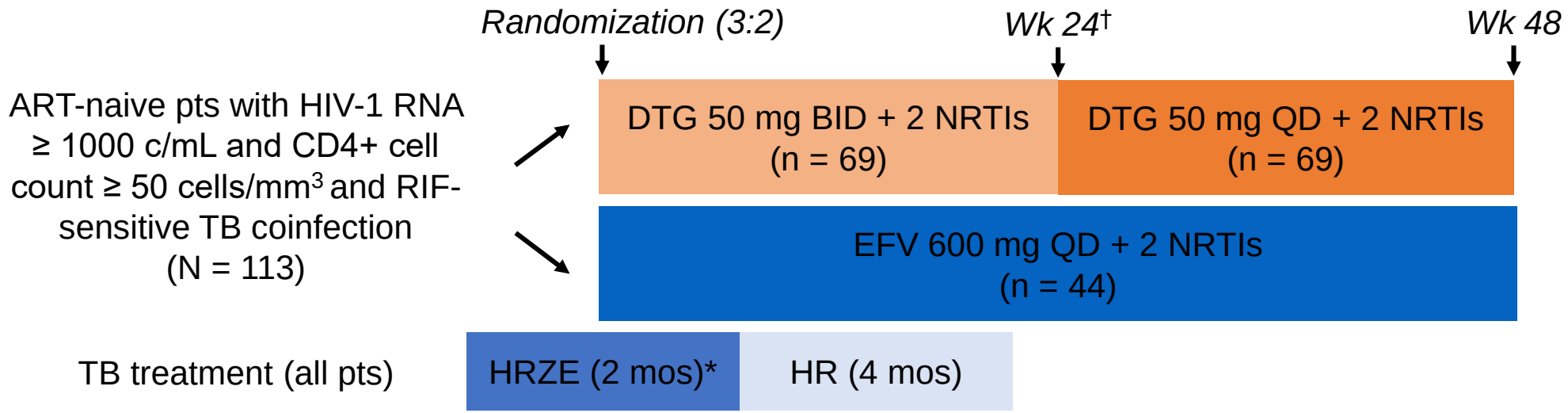


AUC_{0-24} DTG 50 mg/d 32.1
DTG 50 mg 12 hly + rif 42.6

JAIDS 2013;62:21

INSPIRING: DTG BID + 2 NRTIs For ART-Naive Pts Receiving Rifampicin-Based TB Therapy

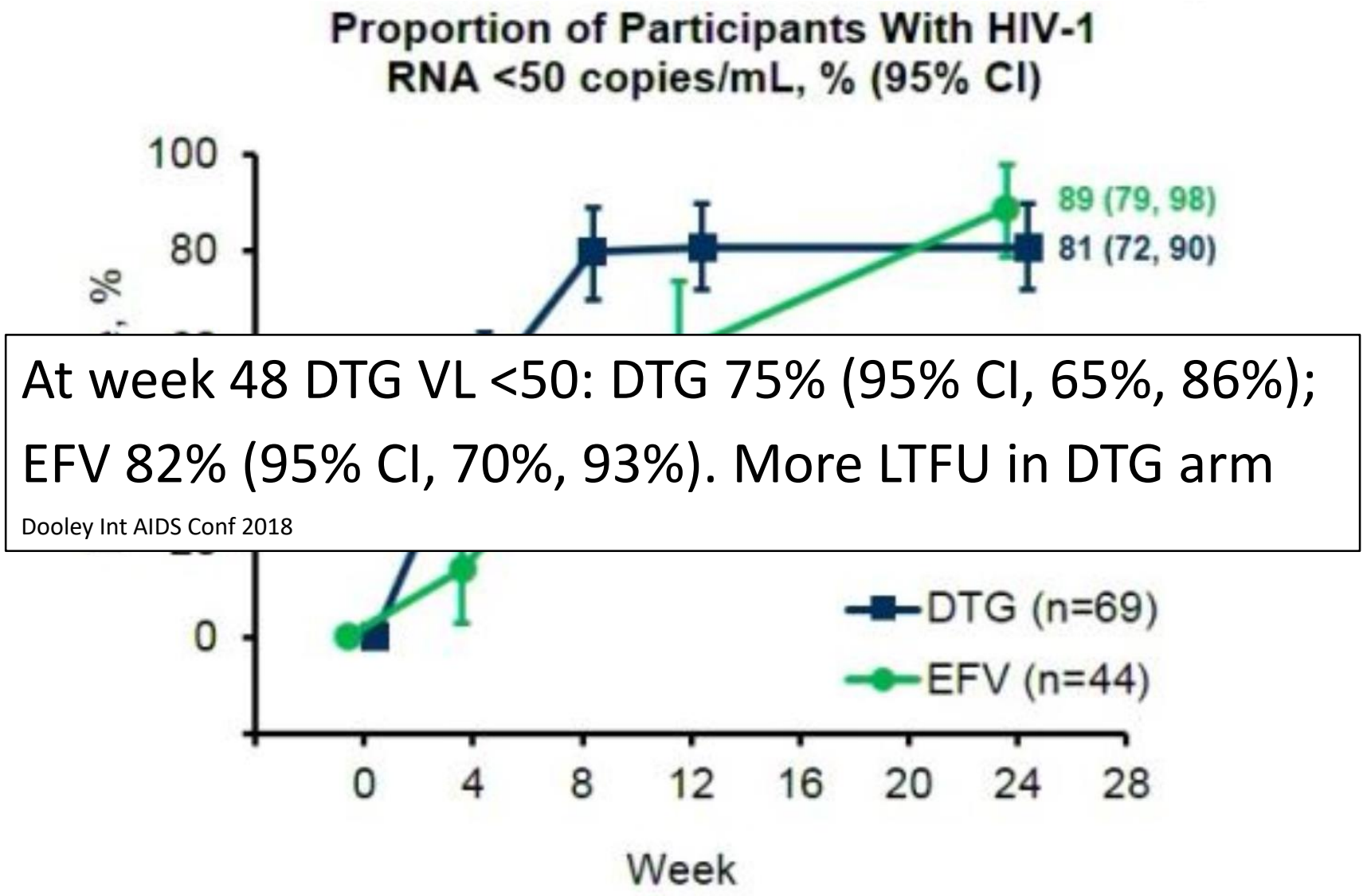
- Interim analysis of open-label, randomized, noncomparative, active-controlled phase IIIb study
  - Primary endpoint: Wk 48 HIV-1 RNA < 50 c/mL (modified FDA snapshot, ITT-E)
  - Pts from South Africa, Brazil, Peru, Mexico, Russia, Argentina, and Thailand



*TB treatment containing RIF could be started up to 8 wks before randomization and no later than screening (28 to 14 days prior to randomization). †DTG dose switch to occur 2 wks after TB treatment completed.

Dooley KE, et al. CROI 2018. Abstract 33.

Slide credit: clinicaloptions.com



At week 48 DTG VL <50: DTG 75% (95% CI, 65%, 86%); EFV 82% (95% CI, 70%, 93%). More LTFU in DTG arm

Dooley Int AIDS Conf 2018

Dooley KE, et al. CROI 2018. Abstract 33.

Slide credit: clinicaloptions.com

Do we always need to dose adjust to match exposure of ARVs induced by rifampicin?

Raltegravir $AUC_{0-\infty}$ ↓40% with rifampicin

Raltegravir 800 mg BID with rifampicin AUC_{0-12} ↑27% compared with raltegravir 400 mg BID without rifampicin

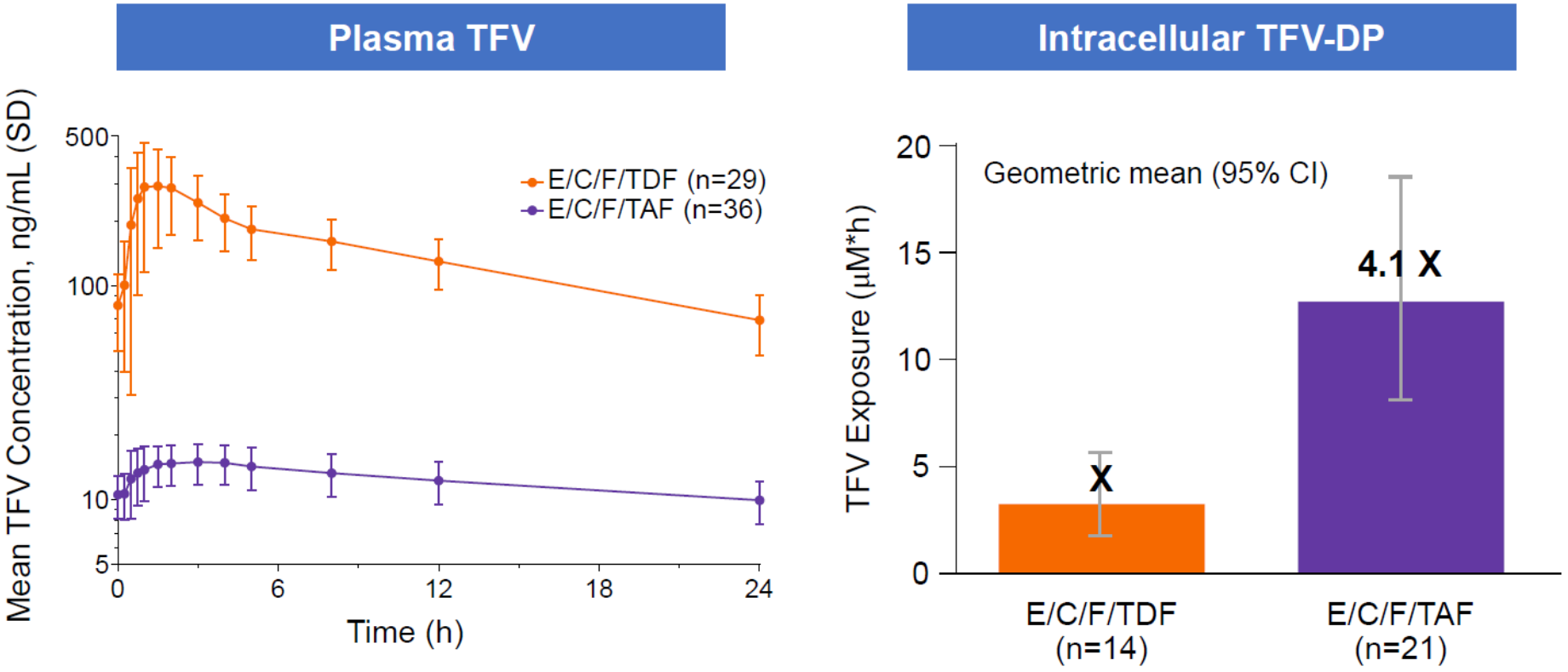
REFLATE phase 2 study showed similar virologic suppression with raltegravir 400 mg BID & 800 mg BID in patients with HIV-TB

Many ARVs have a lot of “forgiveness” (e.g. dolutegravir trough concentrations 19× above IC_{90})

Adjusted dosing problematic in high burden countries

AAC 2009;53:2852
Lancet ID 2014;14:459

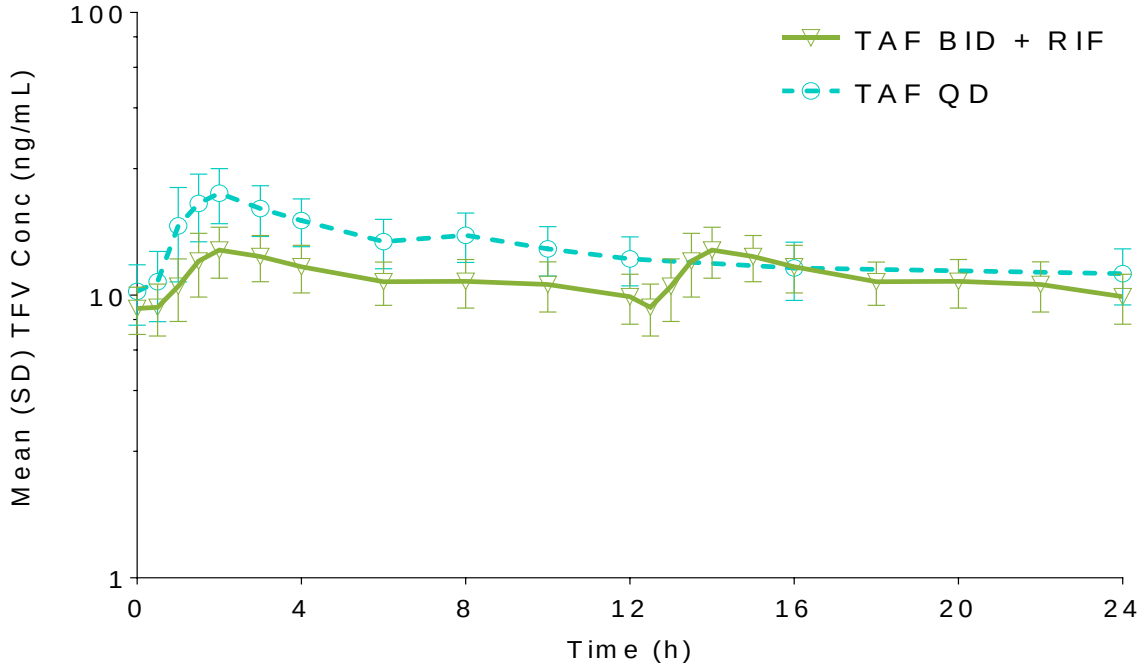
Tenofovir Alafenamide vs TDF: Pharmacokinetics



TAF much more likely victim of drug-drug interactions than TDF

Wohl DA, et al. CROI 2015. Abstract 113LB. CCO

Plasma TFV PK Following TAF BID + RIF vs TAF QD



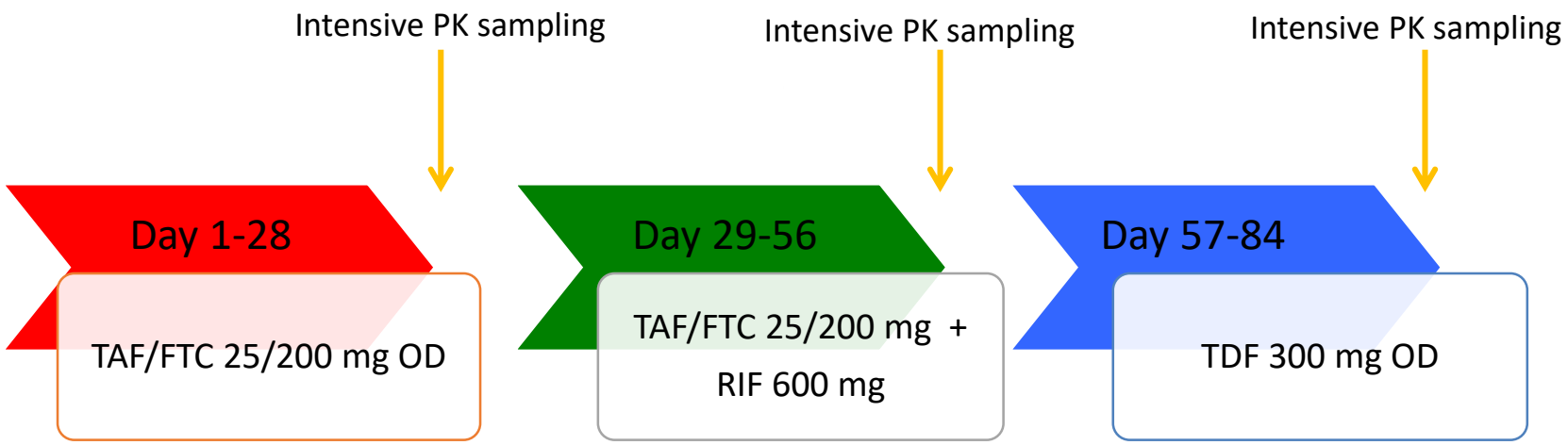
TFV PK Mean (%CV)	TAF QD n=26 (ref)	TAF BID + RIF n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24} (ng•h/mL)	348 (20)	277 (19)	79.9 (73.1, 87.3)

The total overall systemic plasma TFV exposure over 24 hours is expected to be ~20% lower following BID administration of TAF + RIF, versus TAF QD

Custodio et al. 16° EACS, 2017, PS13/4.

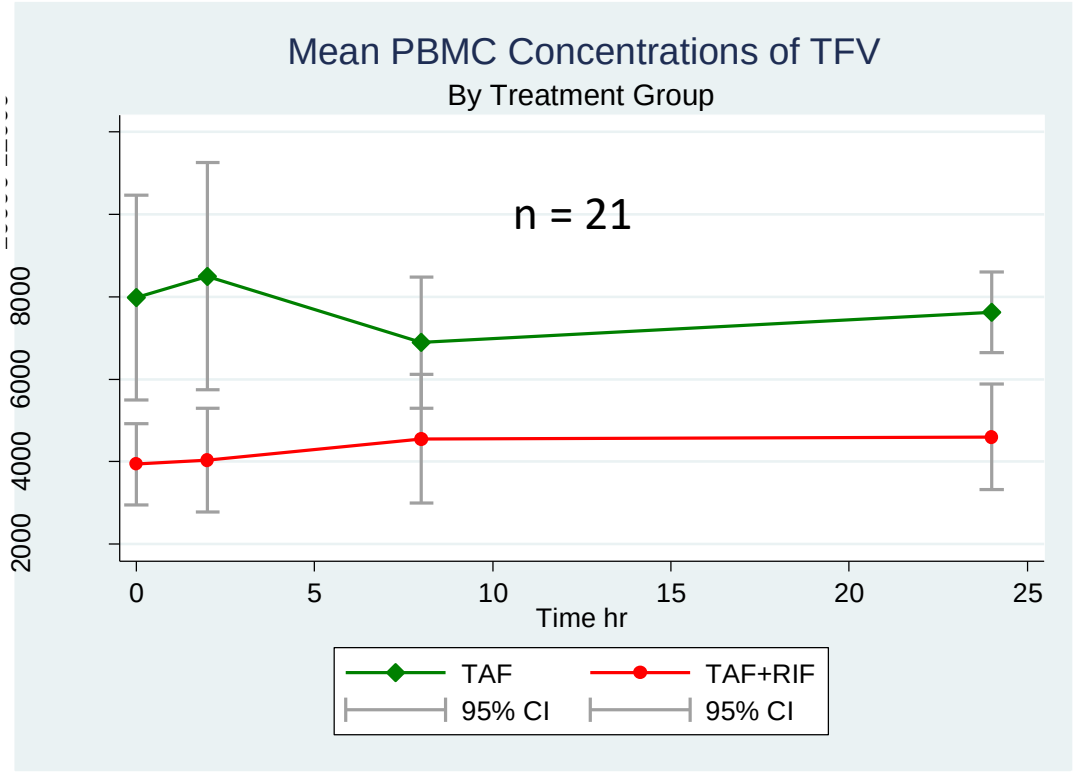
TAF-rifampicin Study Design

Phase I, open-label, single arm, single centre study in 23 healthy volunteers (21 completed)



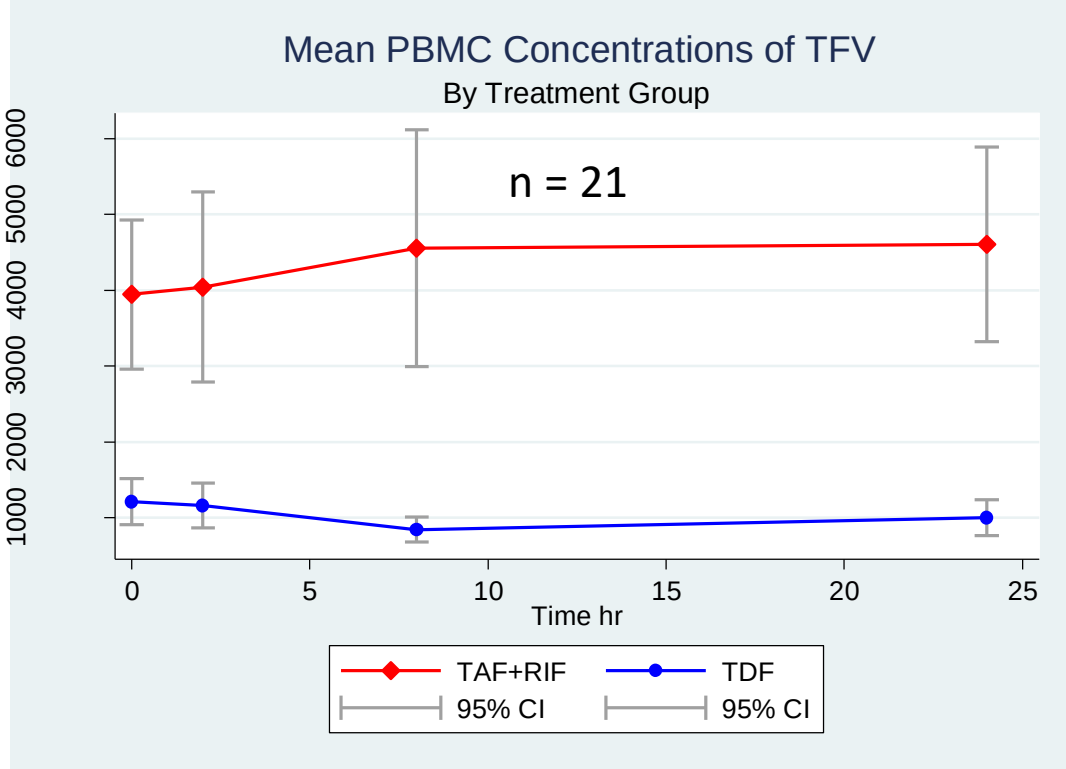
Cerrone CROI 2018

Intracellular TFV-DP PK: TAF + RIF vs TAF



	GM (95% CI)		GMR (90% CI)
IC TFV-DP PK parameter	TAF/FTC + RIF	TAF/FTC	TAF/FTC+RIF vs TAF
C_{max} fmol*h/10^6 CV	4994 (3758 6635) 69%	8082 (6184 10564) 64%	0.62 (0.52 0.74)
AUC_{0-24} fmol*h/10^6 CV	83258 (60150 115243) 82%	130526 (88648 192188) 102%	0.64 (0.54 0.75)
C_{24h} fmol*h/10^6 CV	3529 (2507 4967) 87%	6138 (4811 7831) 58%	0.57 (0.47 0.71)

Intracellular TFV-DP PK: TAF + RIF vs TDF



	GM (95% CI)		GMR (90% CI)
IC TFV-DP PK parameter	TDF	TAF/FTC + RIF	TDF vs TAF/FTC+RIF
C_{max} fmol*h/10^6 CV	1135 (819 1572) 82%	4994 (3758 6635) 69%	0.23 (0.17 0.30)
AUC_{0-24} fmol*h/10^6 CV	19764 (14844 26316) 70%	83258 (60150 115243) 82%	0.24 (0.18 0.32)
C_{24h} fmol*h/10^6 CV	851 (637 1137) 71%	3529 (2507 4967) 87%	0.24 (0.18 0.32)

TAF and rifampicin – bottom line:

No need for dose adjustment (pending confirmation in patients)

FDA et al won’t accept this

Bedaquiline and ARVs

New anti-TB drug with novel mechanism of action (inhibits ATP synthase)

Substrate of CYP3A4, terminal half-life of 5.5 months

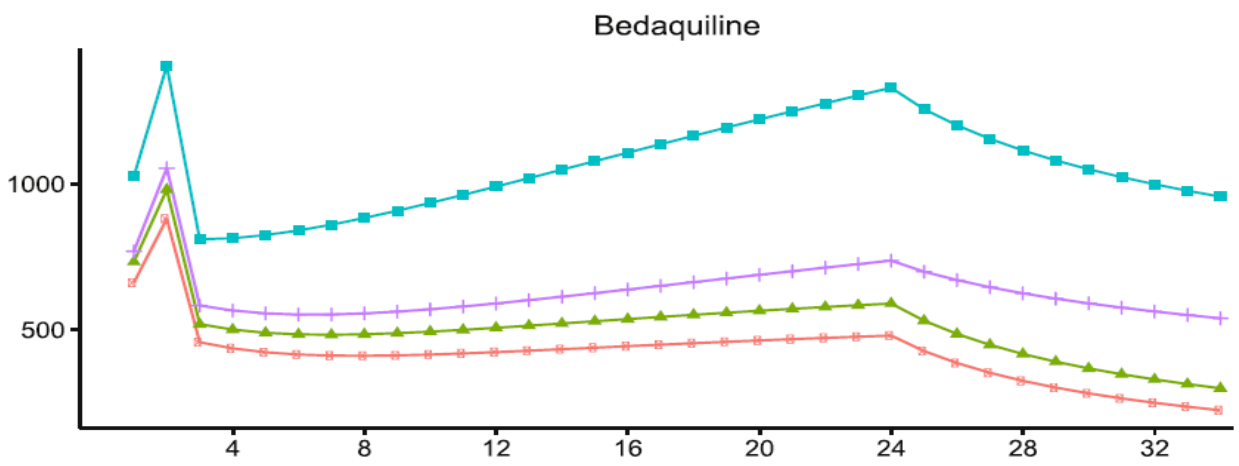
Non-compartmental analysis (NCA) of single dose drug-drug interaction studies showed bedaquiline AUC increased 22% by lopinavir/r & reduced 18% by efavirenz

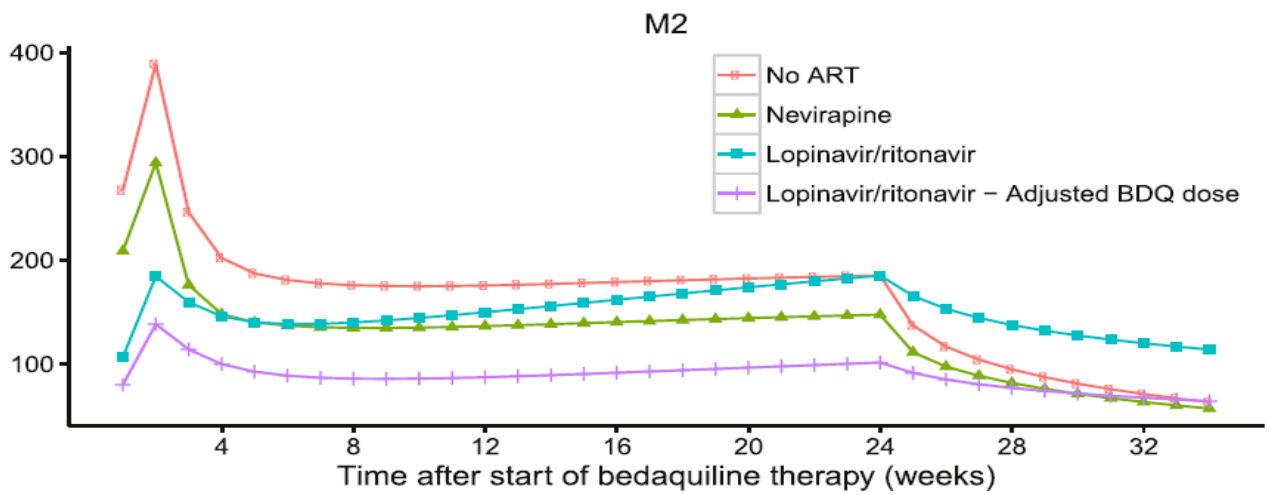
Simulations using non-linear mixed effects modelling showed bedaquiline AUC ↓52% by efavirenz and ↑288% by lopinavir/r

NCA of study in patients with drug-resistant TB showed lopinavir/r increased bedaquiline AUC 62%, but we could not assess time effect

AAC 2014;58:6406
AAC 2013;57:2780
JAC 2016;71:1037

Population PK analysis of bedaquiline with LPV/r confirming model predictions





Lower M2 concentrations on LPV-r implies interaction won't cause harm as M2 drives toxicity

Int J Antimicrob Agents 2017;49:212

Acknowledgements

- PIs/supervisors
  - Lubbe Wiesner (UCT Clinical Pharmacology lab)
  - Pharmacometrics: Paolo Denti (UCT) & Elin Svensson (Uppsala)
  - Helen McIlleron (UCT)
  - Marta Boffito (Chelsea & Westminster)
- Funders
  - EDCTP
  - SA MRC
  - FIDSSA
  - St Stephen’s AIDS trust