New antiretrovirals and TB drug interactions

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First line TB regimens

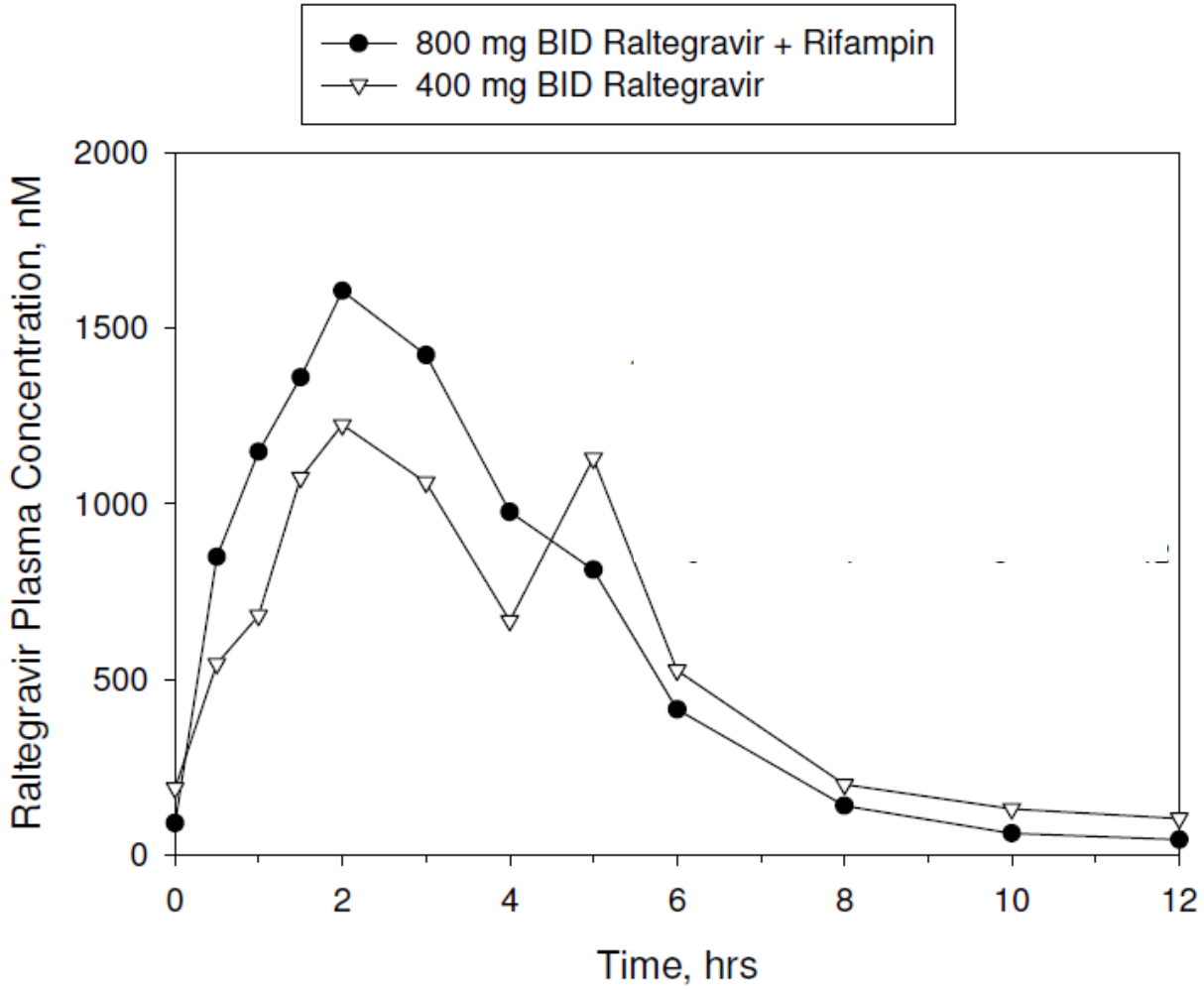
- New TB regimens are being investigated for treatment shortening, but progress has been slow
- Rifampicin remains key 1st line drug for TB for the medium term

Rifampicin induction

Enzyme/transporter	ARV substrate
CYP3A4 (55.1-fold)	PIs, NVP
CYP2B6 (8.8-fold)	EFV, NVP
P glycoprotein (3.5-fold)	PIs TAF
BCRP	TAF
UGT1A1	Raltegravir Dolutegravir

J Pharmacol Exp Ther 2001;299:849
Pharmacol Rev 2013;65:944–966

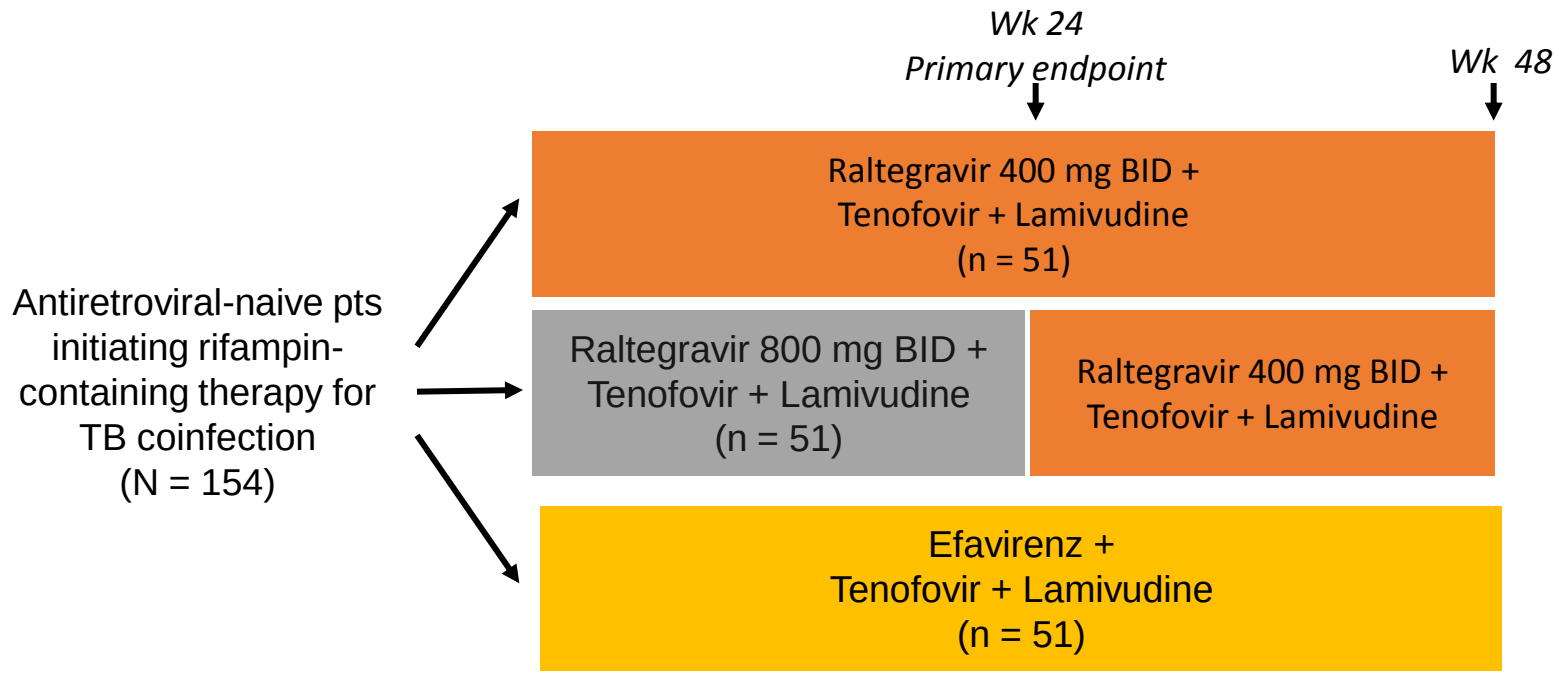
Raltegravir & rifampicin



Wenning AAC 2009

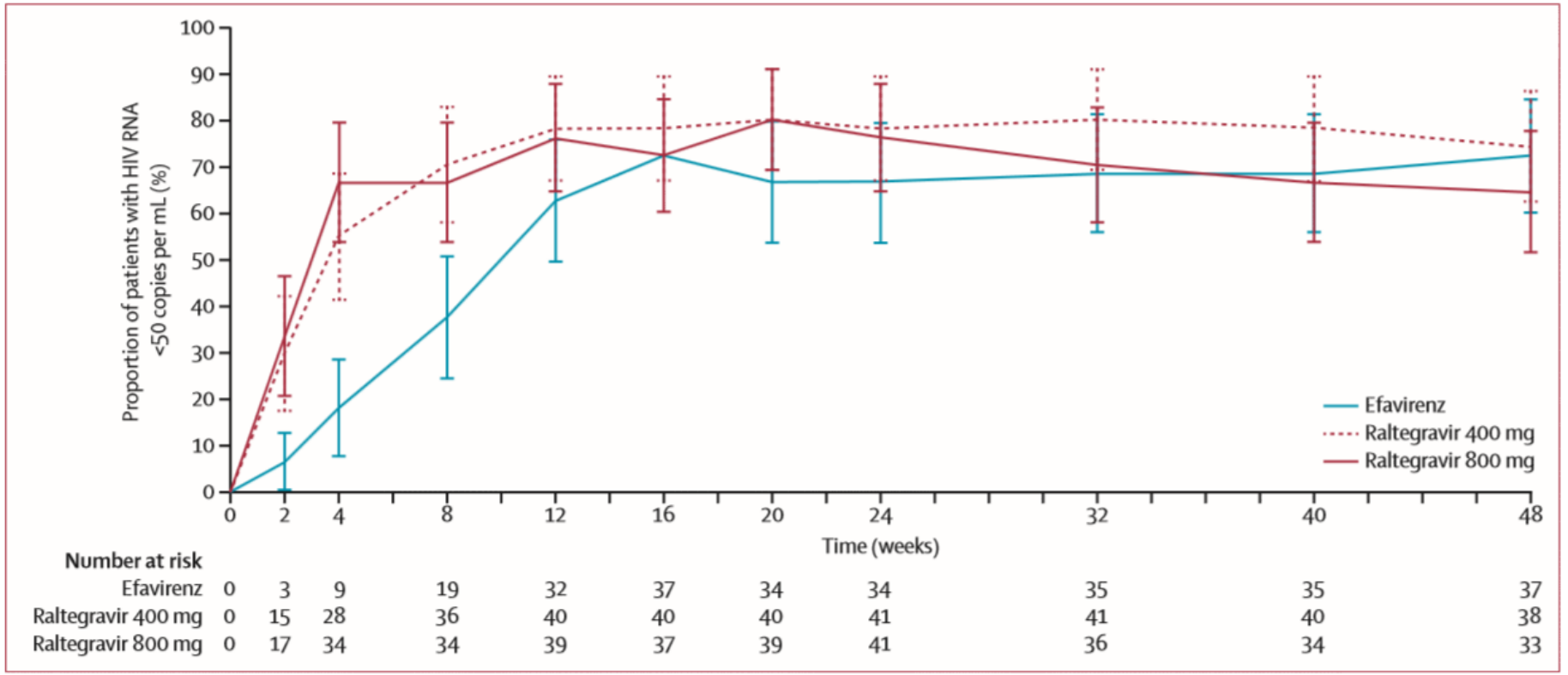
ANRS REFLATE: EFV- vs RAL-based ART in TB

- Multicenter, randomized, open-label phase II trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

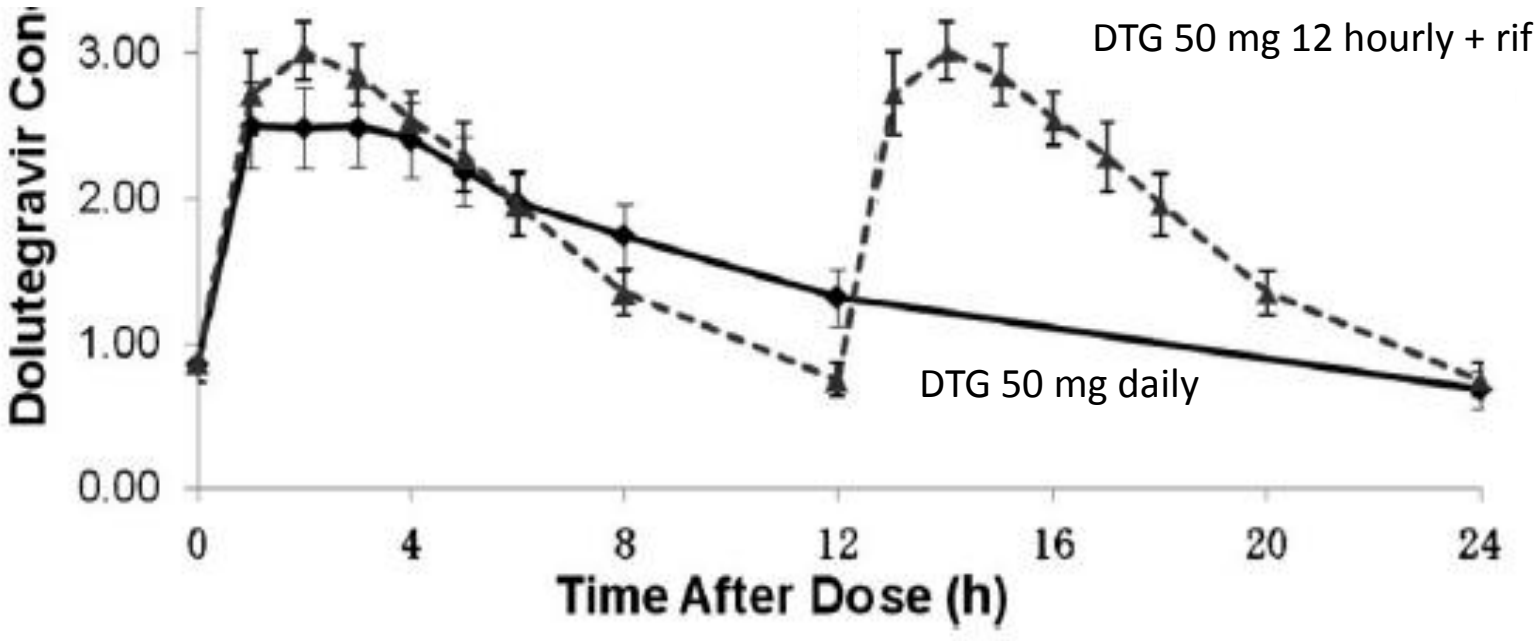


Lancet Infect Dis 2014;14:459

REFLATE – VL outcomes



Dolutegravir & rifampicin



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

JAIDS 2013;62:21

Dolutegravir adjusted doses in TB

- Absorption is saturable, so doubling the daily dose is not an option
- Clearance is increased and estimated C_{min} is about the same as IC90
- Therefore 12 hourly dosing is likely to be necessary
- INSPIRING study will assess PK of DTG 12 hourly in patients with TB & evaluate efficacy (not powered versus comparator though)
- Need an adequately powered RCT of virologic efficacy of DTG 12 hourly (plus 2 NRTI) against the current standard of care (EFV, TDF, FTC) in patients with TB

Cobicistat

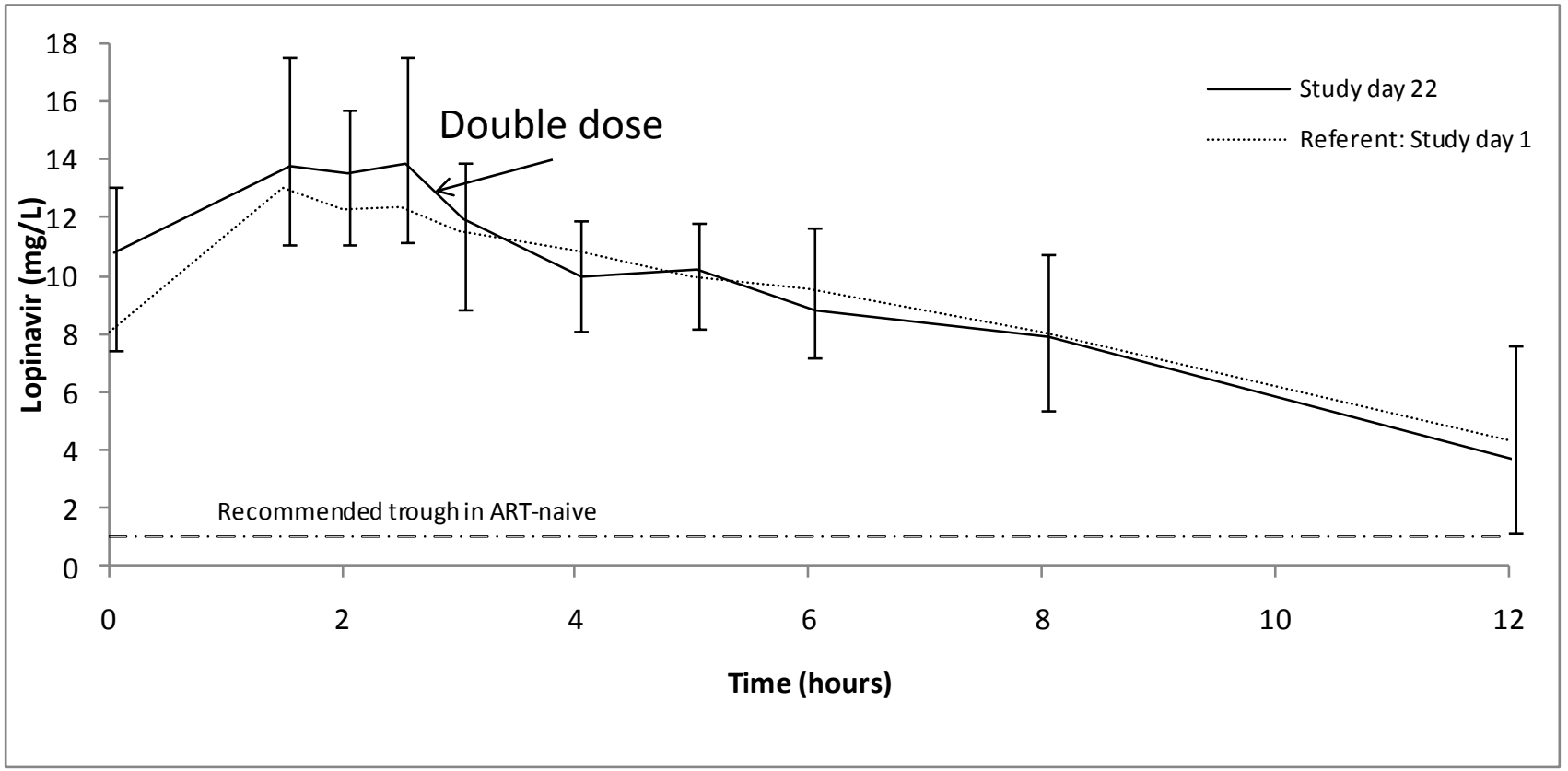
- CYP3A4 inhibitor used as a pharmacoenhancer for PIs & elvitegravir
- Compared with ritonavir:
  - Not an antiretroviral
  - No inducing effect
  - Relatively more specific for CYP3A4
  - Easier to co-formulate with PIs
- Cobicistat is a substrate of CYP3A4, so its metabolism can be induced by rifampicin
- Need to investigate whether increased doses of cobicistat-boosted PIs can overcome induction by rifampicin

Adjusted dose PIs & rifampicin: healthy volunteers

- Very high rates of hepatitis reported in 3 healthy volunteer studies (Saquinavir, Atazanavir, Lopinavir); all stopped early due to toxicity
- ?relevant to HIV+ patients: e.g. rif + PZA for LTBI well tolerated in HIV+, but not 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 LPV/r with rifampicin: HIV+ adults on 2nd line ART, VL <400



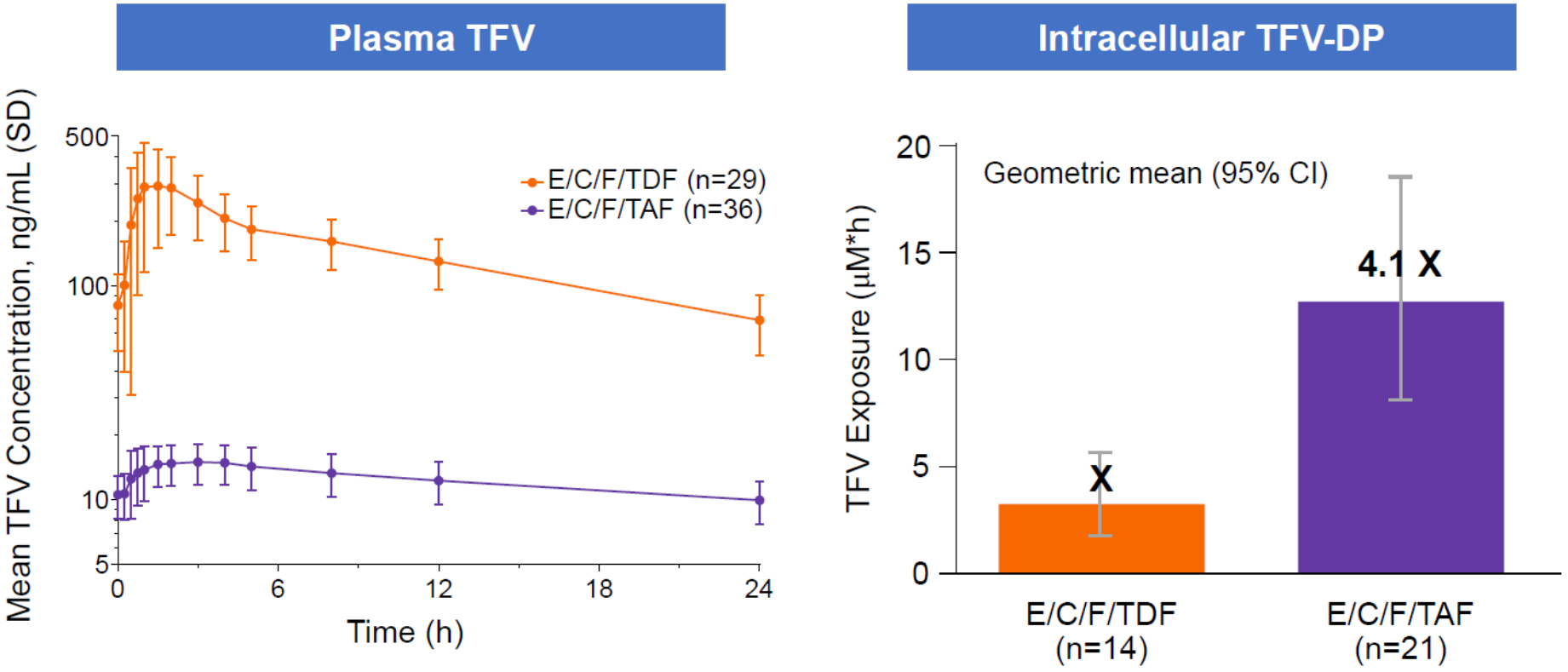
2/21 asymptomatic grade 3/4 ALT
0/18 grade 3/4 ALT in TB patients

Decloedt AAC 2011;55:3195
Decloedt PLoS ONE 7(3): e32173

PIs and rifampicin-based ART

- Need to investigate adjusted doses of boosted atazanavir & darunavir in patients
- Assess PK effects when boosted with cobicistat & ritonavir
- Need data in young children

Tenofovir Alafenamide vs TDF: Pharmacokinetics



Lancet 2015; 385: 2606–15 (suppl app)

Tenofovir Alafenamide

- TAF is a substrate of the drug transporters P-glycoprotein, OATP1B1, OATP1B3 and BCRP; and also (minimal) CYP3A4
- When co-administered with cobicistat (an inhibitor of P-gp, OATP1B1, OATP1B3, BCRP and CYP3A4) the dose of TAF is reduced from 25 mg to 10 mg (versus modest 23% ↑AUC for TDF, requiring no dose adjustment).
- Rifampicin induces CYP3A4, P-gp, and BRCP; and inhibits (!) OATP1B1 and OATP1B3 – the nett effect is unknown (package insert: co-administration not recommended)
- Urgent need for a PK study with rifampicin, endpoint intracellular tenofovir-DP