New antiretrovirals and TB drug interactions

Gary Maartens
First line TB regimens

• New TB regimens are being investigated for treatment shortening, but progress has been slow

• Rifampicin remains key 1\textsuperscript{st} line drug for TB for the medium term
Rifampicin induction

<table>
<thead>
<tr>
<th>Enzyme/transporter</th>
<th>ARV substrate</th>
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<tbody>
<tr>
<td>CYP3A4 (55.1-fold)</td>
<td>PIs, NVP</td>
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<tr>
<td>CYP2B6 (8.8-fold)</td>
<td>EFV, NVP</td>
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<td>P glycoprotein (3.5-fold)</td>
<td>PIs</td>
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<td></td>
<td>TAF</td>
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<td>BCRP</td>
<td>TAF</td>
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<td>UGT1A1</td>
<td>Raltegravir</td>
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<td>Dolutegravir</td>
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J Pharmacol Exp Ther 2001;299:849
Raltegravir & rifampicin

![Graph showing Raltegravir Plasma Concentration over time for 800 mg BID Raltegravir + Rifampin and 400 mg BID Raltegravir.](image-url)

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

Antiretroviral-naive pts initiating rifampin-containing therapy for TB coinfection (N = 154)

Wk 24 Primary endpoint

Wk 48

Raltegravir 400 mg BID + Tenofovir + Lamivudine (n = 51)

Raltegravir 800 mg BID + Tenofovir + Lamivudine (n = 51)

Efavirenz + Tenofovir + Lamivudine (n = 51)

Lancet Infect Dis 2014;14:459
REFLATE – VL outcomes
Dolutegravir & rifampicin

\[ \text{AUC}_{0-24} \]

- DTG 50 mg/d  32.1
- DTG 50 mg 12 hly + rif  42.6
Dolutegravir adjusted doses in TB

• Absorption is saturable, so doubling the daily dose is not an option

• Clearance is increased and estimated $C_{\text{min}}$ 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-
Double dose LPV/r with rifampicin: HIV+ adults on 2\(^{nd}\) line ART, VL <400

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

Plasma TFV

Intracellular TFV-DP

Mean TFV Concentration, ng/mL (SD)

Time (h)

E/C/F/TDF (n=29)
E/C/F/TAF (n=36)

Geometric mean (95% CI)

TFV Exposure (µM*h)

E/C/F/TDF (n=14)
E/C/F/TAF (n=21)

4.1 X

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