Update on Drug-drug interactions in HIV-associated TB

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Rifampicin induction
Rifampicin induction

Co-repressor

Rifampicin

PXR

RXR

Response element

Target gene
Rifampicin induction

Co-activator

Response element

Target gene
Rifampicin induction

- **Co-activator**
  - **Rifampicin**
  - **PXR**
  - **RXR**
- **Response element**
- **Target gene**
- **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**

<table>
<thead>
<tr>
<th>Enzyme/transporter</th>
<th>ARV substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 (55.1-fold)</td>
<td>PIs, nevirapine, rilpivirine, etravirine, maraviroc</td>
</tr>
<tr>
<td>CYP2B6 (8.8-fold)</td>
<td>Efavirenz, nevirapine</td>
</tr>
<tr>
<td>UGT1A1 (2-fold)</td>
<td>INSTIs</td>
</tr>
<tr>
<td>P glycoprotein (4.2-fold)</td>
<td>PIs, TAF, maraviroc</td>
</tr>
<tr>
<td>BCRP</td>
<td>TAF, dolutegravir</td>
</tr>
</tbody>
</table>

*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

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>RBT alone</th>
<th>RBT with ritonavir-boosted PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy volunteers</td>
<td>TB/HIV patients</td>
</tr>
<tr>
<td>300 mg daily</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>150 mg daily</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>150 mg every 2 days</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Limited safety & efficacy data
Rifabutin not available in many resource-limited settings
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)
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 \textit{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 \textit{NAT2} slow metabolizer genotypes (isoniazid slow acetylators).
Dolutegravir & rifampicin

DTG 50 mg 12 hourly + rif

DTG 50 mg daily

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

**ART-naive pts with HIV-1 RNA ≥ 1000 c/mL and CD4+ cell count ≥ 50 cells/mm³ and RIF-sensitive TB coinfection (N = 113)**

- **Randomization (3:2)**
  - DTG 50 mg BID + 2 NRTIs (n = 69)
  - DTG 50 mg QD + 2 NRTIs (n = 69)
  - EFV 600 mg QD + 2 NRTIs (n = 44)

- **TB treatment (all pts)**
  - HRZE (2 mos)*
  - HR (4 mos)

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

Raltegravir $\text{AUC}_{0-\infty} \downarrow 40\%$ with rifampicin

Raltegravir 800 mg BID with rifampicin $\text{AUC}_{0-12} \uparrow 27\%$ 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 $19\times$ above IC$_{90}$)

Adjusted dosing problematic in high burden countries
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
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.
TAF-rifampicin Study Design

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

Day 1-28
TAF/FTC 25/200 mg OD

Day 29-56
TAF/FTC 25/200 mg + RIF 600 mg

Day 57-84
TDF 300 mg OD
Intracellular TFV-DP PK: TAF + RIF vs TAF

Mean PBMC Concentrations of TFV
By Treatment Group

Mean TFV concentration in PBMC (fmol/million-cells)
Time hr

TAF TAF+RIF
95% CI 95% CI

By Treatment Group
Mean PBMC Concentrations of TFV

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

GM (95% CI) | GMR (90% CI)
**Intracellular TFV-DP PK: TAF + RIF vs TDF**

**Mean PBMC Concentrations of TFV**

*By Treatment Group*

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<tr>
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<td>TDF</td>
<td>TAF/FTC + RIF</td>
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<tr>
<td>$C_{\text{max}}$ fmol*h/10^6</td>
<td>1135 (819 - 1572) 82%</td>
<td>4994 (3758 - 6635) 69%</td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td></td>
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<tr>
<td>$AUC_{0-24}$ fmol*h/10^6</td>
<td>19764 (14844 - 26316) 70%</td>
<td>83258 (60150 - 115243) 82%</td>
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<tr>
<td>CV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{24h}$ fmol*h/10^6</td>
<td>851 (637 - 1137) 71%</td>
<td>3529 (2507 - 4967) 87%</td>
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**n = 21**
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
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
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