Using new antiretroviral agents and dosing with TB treatment

John Black

With many acknowledgments
### TABLE 3.3
Estimated epidemiological burden of TB in 2015 for 30 high TB burden countries, WHO regions and globally. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Rates per 100 000 population except where indicated.

<table>
<thead>
<tr>
<th></th>
<th>HIV-NEGATIVE TB MORTALITY</th>
<th>HIV-POSITIVE TB MORTALITY</th>
<th>TOTAL TB INCIDENCE</th>
<th>HIV PREVALENCE IN INCIDENT TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
</tr>
<tr>
<td>Angola</td>
<td>45</td>
<td>27-67</td>
<td>29</td>
<td>6.5-67</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>45</td>
<td>27-68</td>
<td>0.14</td>
<td>0.12-0.18</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.7</td>
<td>2.5-2.8</td>
<td>1.1</td>
<td>0.96-1.7</td>
</tr>
<tr>
<td>Cambodia</td>
<td>55</td>
<td>39-74</td>
<td>2.8</td>
<td>1.2-6.0</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>45</td>
<td>26-70</td>
<td>55</td>
<td>20-107</td>
</tr>
<tr>
<td>China</td>
<td>2.6</td>
<td>2.5-2.7</td>
<td>0.19</td>
<td>0.09-0.33</td>
</tr>
<tr>
<td>Congo</td>
<td>49</td>
<td>29-75</td>
<td>53</td>
<td>44-63</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>61</td>
<td>40-87</td>
<td>0.15</td>
<td>0.07-0.26</td>
</tr>
<tr>
<td>DR Congo</td>
<td>66</td>
<td>39-99</td>
<td>21</td>
<td>17-26</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>26</td>
<td>15-38</td>
<td>4.0</td>
<td>1.6-7.4</td>
</tr>
<tr>
<td>India</td>
<td>32</td>
<td>20-35</td>
<td>2.8</td>
<td>1.6-4.3</td>
</tr>
<tr>
<td>Indonesia</td>
<td>40</td>
<td>26-57</td>
<td>10</td>
<td>7.6-13</td>
</tr>
<tr>
<td>Kenya</td>
<td>20</td>
<td>13-27</td>
<td>16</td>
<td>1.5-45</td>
</tr>
<tr>
<td>Lesotho</td>
<td>55</td>
<td>29-89</td>
<td>223</td>
<td>139-328</td>
</tr>
<tr>
<td>Liberia</td>
<td>70</td>
<td>41-107</td>
<td>19</td>
<td>16-22</td>
</tr>
<tr>
<td>Mozambique</td>
<td>74</td>
<td>43-115</td>
<td>120</td>
<td>73-178</td>
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<tr>
<td>Myanmar</td>
<td>49</td>
<td>30-74</td>
<td>9.0</td>
<td>6.4-12</td>
</tr>
<tr>
<td>Namibia</td>
<td>32</td>
<td>21-45</td>
<td>36</td>
<td>2.5-112</td>
</tr>
<tr>
<td>Nigeria</td>
<td>99</td>
<td>53-160</td>
<td>31</td>
<td>24-40</td>
</tr>
<tr>
<td>Pakistan</td>
<td>23</td>
<td>4.9-56</td>
<td>0.83</td>
<td>0.60-1.1</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>41</td>
<td>24-61</td>
<td>8.8</td>
<td>5.2-13</td>
</tr>
<tr>
<td>Philippines</td>
<td>13</td>
<td>8.7-19</td>
<td>0.44</td>
<td>0.24-0.70</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>11</td>
<td>10-11</td>
<td>1.0</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>51</td>
<td>30-76</td>
<td>13</td>
<td>6.2-21</td>
</tr>
<tr>
<td><strong>South Africa</strong></td>
<td><strong>44</strong></td>
<td><strong>39-50</strong></td>
<td><strong>133</strong></td>
<td><strong>50-256</strong></td>
</tr>
<tr>
<td>Thailand</td>
<td>12</td>
<td>10-15</td>
<td>8.0</td>
<td>4.9-12</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>56</td>
<td>25-99</td>
<td>47</td>
<td>31-66</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>17</td>
<td>12-23</td>
<td>1.1</td>
<td>0.21-2.8</td>
</tr>
<tr>
<td>Zambia</td>
<td>31</td>
<td>18-47</td>
<td>77</td>
<td>42-121</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>11</td>
<td>6.3-16</td>
<td>40</td>
<td>14-81</td>
</tr>
</tbody>
</table>
HIV-associated TB has worse outcomes

Estimated case fatality ratios (CFRs) in the absence of treatment

<table>
<thead>
<tr>
<th>CATEGORY OF TB CASE</th>
<th>CFR (95% UNCERTAINTY INTERVAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative, not on TB treatment</td>
<td>0.43 (0.28–0.53)</td>
</tr>
<tr>
<td>HIV-positive, not on TB treatment or ART</td>
<td>0.78 (0.65–0.94)</td>
</tr>
</tbody>
</table>

WHO Global report 2015
Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

Table 2. Death Rates and Hazard Ratios, Stratified According to CD4+ Cell Count.

<table>
<thead>
<tr>
<th>CD4+ Count</th>
<th>Integrated Therapy</th>
<th>Sequential Therapy</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Person-Yr</td>
<td>No. of Deaths</td>
<td>No. of Person-Yr</td>
</tr>
<tr>
<td>All patients</td>
<td>429</td>
<td>467</td>
<td>25</td>
<td>5.4 (3.5–7.9)</td>
</tr>
<tr>
<td>≤200 cells/mm³</td>
<td>273</td>
<td>281</td>
<td>23</td>
<td>8.2 (5.2–12.3)</td>
</tr>
<tr>
<td>&gt;200 cells/mm³</td>
<td>156</td>
<td>186</td>
<td>2</td>
<td>1.1 (0.1–3.9)</td>
</tr>
</tbody>
</table>

* Hazard ratios are for the integrated-therapy group, as compared with the sequential-therapy group.

Figure 2. Kaplan–Meier Survival Curves.
Intervention of Antiretroviral Therapy with Tuberculosis Treatment

Abdool Karim et al

(incidence-rate ratio, 0.32; 95% CI, 0.07 to 1.13; P = 0.06).

Vs CAMELIA (median CD4 = 25)
• Mortality 18% vs 27%
HR 0.62 95% CI; 0.44 to 0.86; P = 0.006

Vs ACTG (CD4 <50 subgroup)
• Mortality 15.5% vs 26.6%
(95% CI, 1.5 to 20.5; P = 0.02)

Regardless of disease 25% of those with CD4<50 die if delay ART by 2/12
Use of Anti-Retroviral Therapy in Tuberculosis Patients on Second-Line Anti-TB Regimens: A Systematic Review

Matthew Arentz¹*, Patricia Pavlinac¹, Michael E. Kimerling², David J. Horne¹, Dennis Falzon³, Holger J. Schünemann⁴, Sarah Royce⁵, Keertan Dheda⁶,⁷,⁸, Judd L. Walson¹, for the ART/DR-TB study group¹

PLoS ONE 7(11): e47370. doi:10.1371/journal.pone.0047370

**Probability of Survival by ART Use**

- No ART (N=56 deaths)
- ART (N=35 deaths)

(HR 0.4, 95% CI 0.3–0.6)

**Probability of Cure by ART Use**

- No ART (N=7 cured)
- ART (N=33 cured)

(HR 3.4, 95% CI 1.6–7.4)
### 10.4.2 TB treatment in HIV

#### Table 36: ART for adults with concomitant TB

<table>
<thead>
<tr>
<th>TB develops while on ART</th>
<th>TB diagnosed before starting ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue ARV therapy throughout TB treatment</td>
<td>In TB/HIV co-infection not on ART</td>
</tr>
<tr>
<td>First-line regimen:</td>
<td>Start with TB treatment first, followed by ART as soon as possible and within 8 weeks</td>
</tr>
<tr>
<td>Patient can remain on the regimen they are taking (unless they are on NVP)</td>
<td>If CD4 &lt;50 cells/μl initiate ART within 2 weeks of starting TB treatment, when the patient’s symptoms are improving and TB treatment is tolerated</td>
</tr>
<tr>
<td>Second-line regimen:</td>
<td>If CD4 &gt;50 cells/μl initiate ART within 2-8 weeks of starting TB treatment</td>
</tr>
<tr>
<td>The Lopinavir/Ritonavir (LPv/r) dose should be doubled (increase gradually from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on Rifampicin-based TB treatment</td>
<td>First line ART regimen:</td>
</tr>
<tr>
<td>Monitor ALT monthly</td>
<td>» Tenofovir 300mg daily</td>
</tr>
<tr>
<td>Reduce Lopinavir/Ritonavir to standard dose 2 weeks after TB treatment is completed</td>
<td>» Lamivudine 300mg or Emtricitabine 200mg daily</td>
</tr>
<tr>
<td></td>
<td>» Efavirenz 600mg at night</td>
</tr>
</tbody>
</table>

**NOTE:** HIV positive TB patients qualify for lifelong ART regardless of CD4 cell count.

Complete 2 to 8 weeks maximum, of TB therapy before commencing ART (and as soon as possible if CD4 count is less than 50 cells/μl). In general, ART should be initiated as soon as the patient is tolerating their TB therapy; this is usually within 2-4 weeks.

EFV-based regimens are generally preferred in patients with active TB; however, other regimens are also effective. Dose adjustment of PI may be required. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Monitor and investigate appropriately for hepatotoxicity symptoms. Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment.
High Co-Infection Rate- Many patients on TB treatment and ART

• Important to understand co-prescribing in HIV/TB
• Consequences of DDIs:
  • Reduced treatment efficacy due to low exposures (in both directions)
  • Increased risk of toxicity due to increased concentrations
• Identify and manage shared toxicities
SA guidelines

First line:
• Tenofovir
  – Low barrier
  – Renal and bone
  – Hep b cover
• Emtricitabine
  – Low barrier
  – Low toxicity
• Efavirenz
  – Low barrier
  – Neuropsych and liver toxicity
  – Drug interactions
• FDC and good potency

Second line:
• Zidovudine
  – High barrier
  – Significant toxicity
• Lamivudine
  – Crippling effect
• Lopinavir/ritonavir
  – High barrier
  – Significant toxicity
  – Significant drug interactions
• No FDC
Prospective Sentinel Surveillance of Tuberculosis and Human Immunodeficiency Virus in South Africa and Related Drug Resistance: Study design

• Sentinel site surveillance using the GERMS platform
  – 1 clinic per province
• To measure levels of HIV + TB DR at initiation of therapy
• MP, NW, EC, GP, KZN (Nov ‘14 – May ‘17)
Preliminary Data

Demographics:

• To date, n=1,139 specimens collected and tested for HIVDR
• 340 questionnaires were captured:
  – 71% of enrolled participants were female
  – median age of all participants is 32 years (IQR 26 - 40 years)
  – median recent CD4 count at time of cART initiation was 257 cells/µl (IQR 160 – 389 cells/µl).
• Prior exposure to ART (as PMTCT and/or previous cART) was reported in 80/326 (24.5%) participants
  – 14 (17.5%) reported receiving PMTCT
  – 47 (58.8%) had previously received standardized cART for clinical management
  – 19 (23.7%) participants reported receiving both PMTCT and cART.
Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study according to self-reported prior ART exposure

**NNRTI resistance:**
- 37.5% in ART starters with prior exposure to ARVs
- 13.4% in ARV-naive
Levels of NNRTI and dual-class resistance detected amongst patients enrolled into study in 8 clinics across SA (N=1,032)
• SA will need to change first and second line regimens
• Ideal drugs:
  – High barrier to resistance
  – High potency/efficacy
  – Low toxicity
  – Low DDI potential
  – Fixed dose combination
  – Once a day dosing
# Recommended ART Regimens for Treatment-Naive Pts

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DHHS(^{[1]})</th>
<th>IAS-USA(^{[2]})</th>
<th>BHIVA(^{[3]})</th>
<th>EACS(^{[4]})</th>
<th>GeSIDA(^{[5]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/3TC/ABC</td>
<td>Green</td>
<td></td>
<td>Yellow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG + FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>DTG + FTC/TAF</td>
<td>Green</td>
<td></td>
<td>Yellow</td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>EVG/COBI/FTC/TDF</td>
<td>Green</td>
<td>Yellow</td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TAF</td>
<td>Green</td>
<td></td>
<td>Yellow</td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>RAL + FTC/TDF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>RAL + FTC/TAF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>ATV/RTV + FTC/TDF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>ATV/RTV + FTC/TAF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>DRV/RTV* + FTC/TDF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>DRV/RTV* + FTC/TAF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td></td>
</tr>
<tr>
<td>RPV/FTC/TDF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td>Yellow</td>
</tr>
<tr>
<td>RPV/FTC/TAF</td>
<td>Yellow</td>
<td></td>
<td>Green</td>
<td>Green</td>
<td></td>
</tr>
</tbody>
</table>

- **Recommended**
- **Alternative**
- **Not included**

References in slide notes.

Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
# Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential for interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td>Substrate/Inhibitor: CYP3A4, P-gp; Inducer: 2C9</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Substrate: CYP3A4, 2D6, P-gp; Inhibitor: CYP3A4, 2D6, P-gp; Inducer: CYP1A2, 2C8, 2C9, 2C19</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Substrate/Inhibitor: CYP3A4, 2D6, P-gp (inhibit)</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Substrate: CYP3A4; Inducer: CYP2C9</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Substrate: P-gp</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Substrate: CYP3A4, P-gp</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No involvement in P-gp or CYP450</td>
</tr>
</tbody>
</table>

P-gp: P- glycoprotein.
## Drugs That Should Not Be Used With Antiretroviral Agents

<table>
<thead>
<tr>
<th>ARV</th>
<th>Drugs That Should Not Be Used Concomitantly</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG[^1]</td>
<td>Dofetilide, rifapentine, St John’s wort</td>
</tr>
<tr>
<td>EFV[^1]</td>
<td>St John’s wort, dasabuvir, ombitasvir, paritaprevir, simeprevir, elbasvir/grazoprevir</td>
</tr>
<tr>
<td>EVG/COBI[^1]</td>
<td>Ranolazine, eplerenone, ivabradine, lovastatin, simvastatin, rifampin, rifapentine, carbamazepine, phenobarbital, phenytoin, lurasidone, pimozide, midazolam, triazolam, St John’s wort, dasabuvir, elbasvir/grazoprevir, ledipasvir, ombitasvir, paritaprevir, simeprevir, alfuzosin, cisapride, ergot derivatives, flibanserin, salmeterol, sildenafil for PAH</td>
</tr>
<tr>
<td>RPV[^1]</td>
<td>Rifampin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St John’s wort, dasabuvir, ombitasvir, paritaprevir, PPIs (eg, omeprazole)</td>
</tr>
<tr>
<td>TAF/FTC[^1,2]</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John’s wort</td>
</tr>
<tr>
<td>TDF/FTC[^2]</td>
<td>Nephrotoxic drugs</td>
</tr>
</tbody>
</table>

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Slide credit: [clinicaloptions.com](http://clinicaloptions.com)
Bioavailability influenced by drug transporters and metabolising enzymes

Induced by rifampicin
Inhibited by ritonovir

Bailey CMAJ 2004
Metabolism: CYP450 drug interactions

Substrates (lipid soluble)
- Inducers
  - Rifampicin
  - Efavirenz
  - Phenytoin
  - Carbamazepine
- Increase levels of substrate, may cause toxic concentration

Cytochrome P450

Metabolites (water soluble)
- Inhibitors
  - Ritonavir
  - Macrolides
  - Cimetidine
  - Azoles
- Reduce levels of substrate, may cause sub-therapeutic concentrations
CYPs major metabolic pathway for TB drugs and ARVs

Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013
CYPs major metabolic pathway for TB drugs and ARVs

- CYP3A4/5 (30.2%)
  - Rifampicin (I)
  - Rifabutin (S, I)
  - Ritonavir (In)
  - Lopinavir (S)
  - Other PIs (S)
  - NVP (S, I)
  - EFV (I)
  - Rilpivirine (S, I)
  - Etravirine (S, I)
  - BDQ (S)
  - DLM (S)

- CYP2D6 (20%)
  - Polymorphism (↑↑)
  - Inflammation (↑)

- CYP2C9 (12.8%)
  - Rifampicin (I)
  - Ritonavir (I)
  - Etravirine (S)

- CYP2C19 (6.8%)
  - Rifampicin (I)
  - EFV (I)
  - Etravirine (S)

- CYP2J2 (3%)
  - Polymorphism (↓)

- CYP2E1 (3%)
  - INH (I)

Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013
Inhibition of CYP450

- Inhibition may be reversible or irreversible
- Irreversible inhibitors (e.g. ritonavir):
  - Reactive intermediate metabolite binds irreversibly to enzyme causing inactivation
  - More potent inhibition than reversible
  - Duration of inhibition is longer (5-10 days compared with about 48 hours after stopping) as new enzyme needs to be synthesised
- Severe toxicity may occur if a P450 substrate is co-administered
Induction of metabolism

- Many drugs & exogenous substances (e.g., smoking, grilled food, garlic) can induce
- Several (2 main) pathways to turn on regulatory gene that affects MANY downstream genes that have the net effect of reducing exposure to a xenobiotic/drug
PXR-RXR mechanism of enzyme induction

- Rifampin
- Phenobarbital
- Ritonavir
- St. John’s wort

- Calcium-channel blockers
- Cyclosporine
- Triazolam
- Lovastatin
- Erythromycin
- HIV- protease inhibitors
- Sildenafil

- Increased CYP3A4 activity

- OTHERS
  - Phase I
    - CYP2B6
    - CYP2C8/9
  - Phase II
    - UGT
    - GST
  - Transporters
    - P-glycoprotein

- NEJM 2005;352:2211
- Chen 2006
Time course of induction

Max at about 2 weeks - wanes in 2 weeks
Rifampicin leads to increased transcription of CYP3A4
Rifampicin is a potent inducer of multiple enzyme/transporters: DDIs

<table>
<thead>
<tr>
<th>Enzyme/transporter</th>
<th>ARV substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>PIs, NVP</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>EFV, NVP</td>
</tr>
<tr>
<td>P-glycoprotein</td>
<td>PIs, TAF</td>
</tr>
<tr>
<td>BCRP</td>
<td>TAF</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Raltegravir, Dolutegravir</td>
</tr>
</tbody>
</table>
Rifampicin and EFV

- Package insert reports reduced EFV exposure and recommends dose increase to 800 mg daily with rifampicin if weight > 60kg
- But no difference in exposure or impact on clinical outcomes when EFV 600 mg used with rifampicin
Paradoxically EFV exposure increased in some patients on TB treatment

STRIDE study

SAPIT study: 30% reduction in EFV clearance during TB treatment (20% ‘slow metabolisers’)
EFV concentrations higher in patients with slow metaboliser CYP2B6 genotypes on TB Rx

Prevalence of slow metaboliser genotypes
~20% in black South Africans
Increased EFV concentrations during TB treatment in patients with slow metaboliser genotypes may be explained by INH inhibition of CYP2A6.

This may lead to increased risk of EFV-neurotoxicity.

Consider EFV toxicity in all HIV/TB patients with unexplained encephalopathy.
Letter to the Editors

Severe efavirenz-induced vacuolar axonopathy complicated by fatal aspiration pneumonia

Chris Kenyon,1 Sipho Mfolozi,2 Roland Croxford,3 Robert Colebunders5 & Karen Cohen4


Late efavirenz-induced ataxia and encephalopathy: a case series.

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

• Irrelevant to HIV+ patients: e.g. rif + PZA for LTBI well tolerated in HIV+, but not in HIV-
Rifampicin and LPV/r

- PIs substrates of CYP3A4 and P-gp
- Rifampicin reduces LPV/r exposure by 75%
Double dose of LPV/r overcomes induction by rifampicin
Rifampicin reduces exposure of all PIs

- ATV 95%: don’t co-administer
- DRV 57%: don’t co-administer
  - Modelling study found potential doses to overcome induction:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean DRV $\text{AUC}_{0-24}$ (90% CI)</th>
<th>Mean reduction in $\text{AUC}_{0-24}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>800/100 OD</td>
<td>69.4 (68.0–70.8)</td>
<td>Ref</td>
</tr>
<tr>
<td>800/100 OD + RIF</td>
<td>29.7 (29.0–30.4)</td>
<td>57%</td>
</tr>
<tr>
<td>1200/200 OD + RIF</td>
<td>51.4 (50.3–52.6)</td>
<td>26%</td>
</tr>
<tr>
<td>1600/200 OD + RIF</td>
<td>68.5 (67.0–70.1)</td>
<td>1.3%</td>
</tr>
<tr>
<td>800/100 BD + RIF</td>
<td>58.7 (57.6–59.8)</td>
<td>15%</td>
</tr>
</tbody>
</table>

Dickinson JAC 2016
Rifabutin and ARVs

• Rifabutin is a weak inducer and a substrate of CYP3A4
  – Minimal effect on PI exposure: used in TB treatment with PIs
  – PIs inhibit RBT increasing exposure and necessitating dose reduction

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Rifampicin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major metabolic pathway</td>
<td>Deacetylation, hydrolysis to formyl derivatives</td>
<td>CYP3A-mediated hydroxylation, deacetylation</td>
</tr>
<tr>
<td>Serum half-life (h)</td>
<td>2-5</td>
<td>32-67</td>
</tr>
<tr>
<td>Effect on CYP3A</td>
<td>Pronounced</td>
<td>Weak</td>
</tr>
<tr>
<td>Auto-induction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Example of CYP3A induction: effect on indinavir AUC</td>
<td>92% decrease</td>
<td>34% decrease</td>
</tr>
<tr>
<td>Change in AUC when given with a CYP3A inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No effect</td>
<td>293% increase</td>
</tr>
</tbody>
</table>
# Complications of Antiretroviral Therapy in Patients with Tuberculosis: Drug Interactions, Toxicity, and Immune Reconstitution Inflammatory Syndrome

**Helen McIlanner, Graeme Meintjes, William J. Burman, and Gary Maartens**

1Division of Clinical Pharmacology, and 2Department of Medicine, University of Cape Town, Cape Town, South Africa; 3Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver

## Table 1. Pharmacokinetic drug interactions between rifampin (RIF), rifabutin (RIB), protease inhibitors (PIs), and nonnucleoside reverse-trancriptase inhibitors (NNRTIs).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction with RIF</th>
<th>Recommendation for concurrent ARV use with RIF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Interaction with RIB</th>
<th>Recommendation for concurrent ARV use with RIB</th>
<th>RIB dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTV</td>
<td>RTV ↓ 35%</td>
<td>No dose adjustment</td>
<td>RIB ↑ 435%</td>
<td>No dose adjustment</td>
<td>150 mg 3× per week</td>
</tr>
<tr>
<td>IDV</td>
<td>IDV ↓ 89%</td>
<td>Avoid</td>
<td>IDV ↓ 32%; RIB ↑ 204%</td>
<td>IDV 1000 mg t.i.d.;</td>
<td>150 mg daily or 300 mg 3× per week</td>
</tr>
<tr>
<td>SQV</td>
<td>SQV ↓ 84%</td>
<td>Avoid SQV (400 mg) + RTV (400 mg) b.i.d.; may be effective but is hepatotoxic in healthy volunteers; monitor liver function closely</td>
<td>SQV ↓ 40%</td>
<td>Avoid unboosted SQV</td>
<td></td>
</tr>
<tr>
<td>NFV</td>
<td>NFV ↓ 82%</td>
<td>Avoid</td>
<td>NFV (1250 mg b.i.d.)&lt;sup&gt;b&lt;/sup&gt; ---; RIB ↑ 207%</td>
<td>NFV 1250 mg b.i.d.</td>
<td>150 mg daily or 300 mg 3× per week</td>
</tr>
<tr>
<td>APV</td>
<td>APV ↓ 82%</td>
<td>Avoid</td>
<td>APV ↓ 15%; RIB ↑ 193%</td>
<td>No dose adjustment</td>
<td>150 mg daily or 300 mg 3× per week</td>
</tr>
<tr>
<td>ATV</td>
<td>Predicted significant ATV ↓</td>
<td>Avoid</td>
<td>RIB ↑ 250%</td>
<td>No dose adjustment</td>
<td>150 mg daily or 150 mg 3× per week</td>
</tr>
<tr>
<td>RTV-boosted&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Avoid</td>
<td></td>
<td></td>
<td>No dose adjustment</td>
<td>150 mg 3× per week</td>
</tr>
<tr>
<td>RTV-boosted LPV (Kaletra)</td>
<td>LPV ↓ 75%</td>
<td>Avoid LPV+rtv + RTV (300 mg b.i.d.); monitor liver function closely</td>
<td>RIB ↑ 303%</td>
<td>No dose adjustment</td>
<td>150 mg 3× per week</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>NVP ↓ 20%–55%</td>
<td>No dose adjustment; safety and efficacy not established; monitor liver function closely</td>
<td>NVP ↓ 16%</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>EFV</td>
<td>EFV ↓ 25%</td>
<td>Consider EFV ↑ to 800 mg daily in patients &gt;60 kg</td>
<td>EFV ↑; RIB ↓ 35%</td>
<td>No dose adjustment</td>
<td>450-600 mg daily or 600 mg 3× per week</td>
</tr>
<tr>
<td>DLV</td>
<td>DLV ↓ 96%</td>
<td>Avoid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from [10]. Percentage values are changes in area under the concentration-time curve: ↑, increase; ↓, decrease; ---, no change. APV, amprenavir; ARV, antiretroviral; ATV, atazanavir; b.i.d., twice daily; Dlv, delavirdine; EFV, etravirine; F-APV, fosamprenavir; IDV, indinavir; LPV, lopinavir; LPV/rtv, ritonavir-boosted LPV; NFV, nevirapine; RTV, ritonavir; SQV, saquinavir, t.i.d., 3 times daily.

<sup>a</sup> Rifampin levels are not significantly affected by PI or NNRTI coadministration; therefore, no rifampin dose adjustment is required.

<sup>b</sup> NFV (750 mg t.i.d.) should not be used with RIB.

<sup>c</sup> SQV, APV/APX, IDV, or ATV.
Rifabutin recommendations:
- 300mg od with no interacting drugs
- 150mg od preferred with PI based regimens
  - Concerns about failure risk with intermittent dosing and poor PI adherence
- 600mg od with EFV
- Monitor for toxicity (WCC, eyes)
NOW TO THE NEW:
Rifampicin reduces RAL exposure in healthy volunteers

RAL AUC reduced by 40%  
*Cmin reduced by 60%

Effect on AUC overcome by RAL 800 (but not Cmin)
But what is the PK and clinical impact in HIV/TB patients?

- ANRS-REFLATE trial: Phase II open label RCT
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24
Lower trough with RAL 400 + RIF but not significant

GMR AUC ~1
GMR Cmin 0.69 (0.42 – 1.13)

Only a single Cmin < 14 ng/L (IC_{50} for RAL)

RAL 800 resulted in 68% higher Cmin
Clinical impact of standard RAL dose in HIV/TB: similar rates of virological suppression

Requires Phase III trial, but based on these limited PK and clinical data RAL 400 recommended for patients on TB treatment (IAS-USA)

Grinsztejn LID 2014
Günthard JAMA 2016
RIF reduces DTG exposure: (over)compensated by BD dosing

- Healthy volunteers:
  - Increased clearance with rif, but Cmin still above IC\textsubscript{50} threshold with BD dosing
  - DTG 50 mg BD + RIF has higher exposures (33%) than DTG 50 mg OD alone

\text{AUC}_{0-24}

50 mg OD: 32.1
50 mg BD + RIF: 42.6

Dooley JAIDS 2013
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
Recommended dose 50 mg BD with TB Rx, but important questions:

- Does it translate into similar efficacy compared with EFV?
- Emerging concerns about neuropsychiatric AEs on DTG
  - Meta-analysis of clinical trials: uncommon but similar frequency to EFV
  - Discontinuation due to intolerability ~14% in European cohorts (NP-AEs most common reason)
- UGT1A1 polymorphisms
  - Higher exposures and toxicity?
- Higher pill burden than FDC
  - Adherence?
- More potent than EFV
  - More IRIS?
Rifampicin and TAF

- Much higher intracellular concentration of active drug than TDF, and much lower plasma concentration of TFV
  - Less toxicity
  - Lower doses required
- TAF substrate of P-gp and other transporters: inhibited by RTV, cobicistat, induced by rifampicin
- No PK studies with rif, but co-administration not recommended (package insert)
Preferred regimens in TB co-infection

- WHO and NDoH: TDF + 3TC/FTC + EFV (600)
- IAS-USA: EFV, DTG, RTG (boosted PI only if INSTI not an option)

NVP failed to demonstrate non-inferiority to EFV in patients with TB (CARINEMO trial)
# Summary of important DDIs in DS-TB

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Rifampicin</th>
<th>Other DS-TB Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>• Does not require dose adjustment</td>
<td>• Caution with INH • Incr RBT dose</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>• Omit 200 mg daily lead-in dose</td>
<td>• Worse outcomes with TB Rx</td>
</tr>
<tr>
<td>Rilpivirine/etravirine</td>
<td>• Do not coadminister</td>
<td>• Incr RVP dose with RBT</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>• Requires double dose with 4 tablets (800/200 mg) BD • Increase the dose gradually</td>
<td>• Can use with RBT (adjust RBT dose)</td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>• Do not coadminister</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>• Do not coadminister</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>• Standard dose</td>
<td>• No adjustment with RBT</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>• Double dose 50 mg BD</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>• Do not coadminister</td>
<td></td>
</tr>
<tr>
<td>TAF</td>
<td>• Do not coadminister</td>
<td></td>
</tr>
</tbody>
</table>
Definitions of TB Drug Resistance

Drug Sensitive
- Rifampicin
- Isoniazid

Multi drug resistant
- Rifampicin
- Isoniazid

Pre-XDR
- Rifampicin
- Isoniazid
- Fluoroquinolone
- Or
- Amikacin or kanamycin or capreomycin

Extensively drug resistant
- Rifampicin
- Isoniazid
- Fluoroquinolone
- Or
- Amikacin or kanamycin or capreomycin
Standard Rx for MDR-TB: no major DDIs with ART

Conventional
Mfx/Km/Eto/Tzd/PZA +- hdINH/Emb
18 – 24 months

Shortened
Mfx/Km/Cfz/PZA/Emb/Eto /hdINH)
9-12 Months
BDQ and DLM are being rolled out

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

The use of delamanid in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

WHO Global Report 2016
# Multiple trials of new DR-TB regimens

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Patients</th>
<th>Design</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NExT (NCT02454205)</td>
<td>Phase 2 to 3</td>
<td>MDR-TB, adults $n = 300$</td>
<td>Open-label RCT of an injection-free regimen including linezolid$^1$ and bedaquiline (plus standard drugs without kanamycin) for 6–9 months compared with WHO standard regimen</td>
<td>Favorable outcome at 24 months</td>
</tr>
<tr>
<td>Nix-TB (NCT02333799)</td>
<td>Phase 3</td>
<td>MDR- and XDR-TB, adults $n = 200$</td>
<td>Open-label, single-arm evaluation of bedaquiline and pretomanid plus linezolid$^2$ for 6–9 months</td>
<td>Bacteriologic or clinical failure at 24 months</td>
</tr>
<tr>
<td>endTB (NCT02754765)</td>
<td>Phase 3</td>
<td>MDR-TB, adults $n = 750$</td>
<td>Open-label RCT of five all-oral experimental regimens compared with standard of care. Experimental regimens contain bedaquiline and/or delamanid$^3$ together with four companion drugs, including linezolid$^4$</td>
<td>Favorable outcome at 18 months</td>
</tr>
<tr>
<td>TB-PRACTICAL (NCT02589782)</td>
<td>Phase 2 to 3</td>
<td>MDR-TB, adults $n = 630$</td>
<td>Open-label RCT comparing three novel regimens including bedaquiline, pretomanid, and linezolid$^5$, plus moxifloxacin or clofazimine for 6 months with WHO standard of care</td>
<td>Culture conversion and discontinuation/death at 8 weeks, unfavorable outcome at 72 weeks</td>
</tr>
<tr>
<td>MDR-END (NCT02619994)</td>
<td>Phase 3</td>
<td>MDR-TB, adults $n = 238$</td>
<td>Open-label RCT comparing a 9–12-month regimen of delamanid, linezolid$^6$, levofloxacin, and pyrazinamide with WHO standard or care</td>
<td>Treatment success at 24 months</td>
</tr>
</tbody>
</table>
Bedaquiline

- Diarylquinoline, novel MoA: potent against MTB
- Accumulates in tissues: extremely long half life ~6 months
- Metabolized by CYP3A4 to M2 metabolite (less active, more toxic); no influence on CYP or transporters

AEs include QT prolongation and hepatitis: related to dose?
BDQ DDIs: NNRTIs

- EFV steady state concentrations reduced by 52% (modelling study): do not coadminister

- NVP has no significant effect on BDQ bioavailability in models and clinical study
  - Can be used

- Rilpivirine: not studied, unlikely to have an effect on BDQ concentrations
BDQ DDIs: Aluvia

- Model: reduces BDQ clearance by 35%, M2 clearance by 58% (2- and 3-fold increase in steady state concentrations)
- Patients: 62% increase in AUC
- Clinical consequences unclear: monitor ECG closely
Delamanid

- Nitroimidazole
- Metabolised by albumin, smaller contribution by CYP3A4
- Associated QT prolongation
- No impact on EFV or LPV/r exposure
- Higher DLM concentrations with LPV/r: clinical impact?
Other new/repurposed drugs

- Pretomanid (PA-824)
  - Metabolised by CYP3A4
  - Phase I study: reduced exposure with EFV - avoid
- Clofazimine
  - Substrate of P-gp: effect of PIs?
- Linezolid
  - May be a P-gp and/or CYP substrate: effect of PIs?
### Summary of important DDIs in DR-TB

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Bedaquiline</th>
<th>Delaminid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>• Do not coadminister</td>
<td>• No interaction</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>• No dose adjustment</td>
<td>• Not expected</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>• Not expected</td>
<td>• Not expected</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>• Increases BDQ exposure: may lead to toxicity?</td>
<td>• Increased DLM exposure: clinical relevance?</td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>• No interaction expected</td>
<td>• Not studied, no interaction expected</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Shared toxicities

- All TB drugs
- NNRTIs
- Cotrimoxazole

- RHZ, RBT, FQs, BDQ, PMD, DLM
- NNRTIs, PIs
- Cotrimoxazole

- SLIs, Rif
- TDF

- LZD
- AZT

- FQs, BDQ, DLM, CFZ

- INH, TZD, LZD
- d4T, ddi

- INH, TZD
- EFV, DTG

psychosis
Conclusions

• Many co-infected patients on HIV and TB treatment
• TB is a real and present danger in South Africa
• Rifampicin remains a core drug for DS TB
• Many potential DDIs particularly with rifampicin
• Key new HIV and TB drugs also have important DDIs
• Ongoing PCV and close monitoring required