Using new antiretroviral agents and dosing with TB treatment

Sean Wasserman
University of Cape Town
HIV drives TB incidence
High burden of HIV-associated TB

WHO Global Report 2016

1.2m cases (260k in SA) 390k deaths (73k in SA)

HIV prevalence in TB cases, 2015
HIV-associated TB has worse outcomes

Outcomes of TB treatment by HIV status, 2013

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>
Improved outcomes on ART

- Observational studies: 64 - 95% reduced mortality
- SAPIT: 56% reduced mortality when ART started during TB Rx (median CD4 ~150)
All HIV-infected people should start ART

**Recommendation 1: When to start ART among people living with HIV**

<table>
<thead>
<tr>
<th>Target population</th>
<th>Specific recommendation</th>
<th>Strength of the recommendation</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults&lt;sup&gt;a&lt;/sup&gt; (&gt;19 years)</td>
<td>ART should be initiated in all adults living with HIV at any CD4 cell count</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
ART coverage associated with reduced TB incidence
ART not fully protective

Risk of TB > 4-fold higher than HIV-uninfected even when on suppressive ART and CD4 count > 700
Many people will be 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
Bioavailability influenced by drug transporters and metabolising enzymes

Induced by rifampicin
Inhibited by ritonavir
Drug transporters P-gp

Phase 1 enzymes CYPs

Phase 2 enzymes UGTs

Drug X

OH

O

IR

Hydrophobic

Hydrophilic
CYPs major metabolic pathway for TB drugs and ARVs

Source of PK and PD variability and DDIs

Zanger Pharmacology and Therapeutics 2013
Treatment for DS-TB same in HIV on ART

- Rifampicin
- Isoniazid
- Ethambutol
- Pyrazinamide

2 months

- Rifampicin
- Isoniazid

4 months

Weight-based dosing

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 37 kg</td>
<td>2 RHZE</td>
</tr>
<tr>
<td>38 - 54 kg</td>
<td>3 RHZE</td>
</tr>
<tr>
<td>55 - 70 kg</td>
<td>4 RHZE</td>
</tr>
<tr>
<td>&gt; 70 kg</td>
<td>5 RHZE</td>
</tr>
</tbody>
</table>

Give daily

30 - 37 kg: 2 RH (150/75)
38 - 54 kg: 3 RH (150/75)
55 - 70 kg: 2 RH (300/150)
> 70 kg: 2 RH (300/150)
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</td>
</tr>
<tr>
<td></td>
<td>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

Cohen Antivir Ther 2009
Friedland JAC 2006
Manosuthi AIDS 2005
Paradoxically EFV exposure increased in some patients on TB treatment

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

49% incr in EFV concentrations
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.

Variava E¹, Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, Maartens G, Martinson NA.
Rifampicin and LPV/r

- PIs substrates of CTP3A4 and P-gp
- Rifampicin reduces LPV/r exposure by 75%

Decloedt AAC 2011
Double dose of LPV/r overcomes induction by rifampicin

- Although limited hepatotoxicity and few discontinuations in study, poorly-tolerated in practice
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 AUC$_{0-24}$ (90% CI)</th>
<th>Mean reduction in 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
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
  - Powered to compare to historical average: not efficacy comparison
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)
RIF reduces DTG exposure: (over)compensated by BD dosing

- Healthy volunteers:
  - Increased clearance with rif, but Cmin still above IC50 threshold with BD dosing
  - DTG 50 mg BD + RIF has higher exposures (33%) than DTG 50 mg OD alone

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**DTG concentrations**

**AUC**
- 50 mg OD: 32.1
- 50 mg BD + RIF: 42.6
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)
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:</td>
<td>92% decrease</td>
<td>34% decrease</td>
</tr>
<tr>
<td>effect on indinavir AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in AUC when given with</td>
<td>No effect</td>
<td>293% increase</td>
</tr>
<tr>
<td>a CYP3A inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rifabutin and ARVs

• Dosing with PIs:
  – **RBT 150 mg daily results in similar exposure to standard dose (300 mg daily) without PI: new recommendation**
  – But increased des-rifabutin metabolite and risk of toxicity: monitor ALT, neutrophils, and vision

• Dosing with NNRTIs
  – EFV induces RBT (38% reduction in AUC): increase RBT dose to 450 mg daily
  – RPV exposure reduced by 42% with RBT: increase RPV dose 50 mg daily (US guidelines: avoid)
## 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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Incr dose with RBT</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</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>
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)
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
DR-TB is a big problem

- Incidence of MDR-TB unchanged or declining less slowly
- Around 600,000 cases of MDR in 2015
- Quarter of a million deaths
- 9.5% of MDR have XDR-TB
DR-TB is a big problem

- < 50% treatment success in high burden countries
- XDR mortality in 2013: 27%
- XDR treatment success: 28%

74% 5-year mortality for XDR-TB
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)
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</td>
<td>Open-label RCT of an injection-free regimen including <em>linezolid</em> and <em>bedaquiline</em> (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</td>
<td>Open-label, single-arm evaluation of <em>bedaquiline</em> and <em>pretomanid</em> plus <em>linezolid</em> 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</td>
<td>Open-label RCT of five all-oral experimental regimens compared with standard of care. Experimental regimens contain <em>bedaquiline</em> and/or <em>delamanid</em> together with four companion drugs, including <em>linezolid</em></td>
<td>Favorable outcome at 18 months</td>
</tr>
<tr>
<td>TB-PRACTECAL (NCT02589782)</td>
<td>Phase 2 to 3</td>
<td>MDR-TB, adults</td>
<td>Open-label RCT comparing three novel regimens including <em>bedaquiline</em>, <em>pretomanid</em>, and <em>linezolid</em>, plus <em>moxifloxacin</em> or <em>clofazimine</em> 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</td>
<td>Open-label RCT comparing a 9–12-month regimen of <em>delamanid</em>, <em>linezolid</em>, 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
- Metabolised 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

Pandie JAC 2016
Svensson AAC 2013
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

Pandie JAC 2016
Svensson AAC 2014
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?

Mallikaarjun AAC 2016
Sasahara Drug Metab Dispos 2015
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></td>
<td>• Increased DLM exposure: clinical relevance?</td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>• Increases BDQ exposure: may lead to toxicity?</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

FQs, BDQ, DLM, CFZ

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

INH, TZD, LZD
d4T, ddI

SLIs, Rif
TDF

INH, TZD
EFV, DTG

LZD
AZT

QT interval

psychosis
Conclusions

• Many people on HIV and TB treatment
• Clinical consequences of DDIs and shared toxicity
• Many potential DDIs, particularly with rifampicin
• Key new HIV and TB drugs have important DDIs