Using new antiretroviral agents and dosing with TB treatment

Samantha Potgieter
Sean Wasserman University of Cape Town
HIV drives TB incidence

Kwan CMR 2011
High burden of HIV-associated TB

HIV prevalence in TB cases, 2015

WHO Global Report 2016

1.2m cases (260k in SA)
390k deaths (73k in SA)
HIV-associated TB has worse outcomes

Outcomes of TB treatment by HIV status, 2013

Treatment success: HIV+ (80), HIV- (80)
Failed: HIV+ (0), HIV- (0)
Died: HIV+ (10), HIV- (10)
Lost to follow-up: HIV+ (20), HIV- (20)
Not evaluated: HIV+ (10), HIV- (10)

WHO Global report 2015
Improved outcomes on ART

• Observational studies: 64 - 95% reduced mortality
• SAPIT: 56% reduced mortality when ART started during TB Rx (median CD4 ~150)

Abdool Kariem NEJM 2010
All HIV-infected people should start ART

<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(^a) (&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>Adults(^a) (&gt;19 years)</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(^3)</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

Gupta PloS ONE 2012
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 metabolizing enzymes

Induced by rifampicin
Inhibited by ritonavir

Bailey CMAJ 2004
CYPs major metabolic pathway for TB drugs and ARVs

Source of PK and PD variability and DDIs

Rifampicin (I)
Rifabutin (S, I)
Ritonavir (S)
Lopinavir (S)
Other PIs (S)
NVP (S, I)
EFV (I)
Rilpivirine (S, I)
Etravirine (S, I)
BDQ (S)
DLM (S)

INH (I)

CYP2J2 (3%)
CYP3A4/5 (30.2%)
CYP2E1 (3%)
CYP2D6 (20%)
CYP2C19 (6.8%)
CYP1A2 (8.9%) Ritonavir (I)
CYP2A6 (3.4%) Rifampicin (I)
CYP2B6 (7.2%) EFV (S, I)
CYP2C8 (4.7%) Rifampicin (I)
CYP2C9 (12.8%) Ritonavir (I)
EFV (S, I)
INH (I)
Treatment for DS-TB same in HIV on ART

- Rifampicin
- Isoniazid
- Ethambutol
- Pyrazinamide

2 months

- Rifampicin
- Isoniazid

4 months

- Rifampicin
- Isoniazid

Give daily

Weight-based dosing

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</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>

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 37 kg</td>
<td>2 RH (150/75)</td>
</tr>
<tr>
<td>38 - 54 kg</td>
<td>3 RH (150/75)</td>
</tr>
<tr>
<td>55 - 70 kg</td>
<td>2 RH (300/150)</td>
</tr>
<tr>
<td>&gt; 70 kg</td>
<td>2 RH (300/150)</td>
</tr>
</tbody>
</table>
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</td>
</tr>
<tr>
<td></td>
<td>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
• Conclusion: No dose adjustment for regimen 1 ART on standard TB treatment
Paradoxically EFV exposure increased in some patients on TB treatment

- SAPIT study: 30% reduction in EFV clearance during TB treatment (‘slow metabolizers')
- EFV concentrations higher in patients with slow metabolizer 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.

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

- PIs substrates of CYP3A4 and P-gp
- Rifampicin reduces LPV/r exposure by 75%

![Graph showing LPV/r levels with and without rifampicin](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>
Rifampicin reduces RAL exposure in healthy volunteers

RAL AUC reduced by 40%
Cmin reduced by 60%

Wenning AAC 2009
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
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 IC50 threshold with BD dosing
  - DTG 50 mg BD + RIF has higher exposures (33%) than DTG 50 mg OD alone

<table>
<thead>
<tr>
<th>Dosage</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (μg·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG 50 mg OD</td>
<td>32.1</td>
</tr>
<tr>
<td>DTG 50 mg BD + RIF</td>
<td>42.6</td>
</tr>
</tbody>
</table>

Dooley JAIDS 2013
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 compared to EFV
• UGT1A1 polymorphisms
  – Higher exposures and toxicity?
• Higher pill burden than FDC
  – Adherence?
• More potent than EFV
  – More IRIS?
• Pregnant women?

van den Berk CROI 2016
De Boer AIDS 2016
Menard AIDS 2017
Viswanathan CROI 2017
Rifampicin and TAF

• Much higher intracellular concentration of active drug than TDF, and much lower plasma concentration of tenofovir
  – Less toxicity
  – Lower doses required
• TAF substrate of P-gp and other transporters: levels reduced by rifampicin
• No PK studies with rifampicin, 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 metabolism, thus increasing exposure and necessitating dose reduction of the rifabutin
Rifabutin and PIs

• Dosing with PIs:
  – RBT 150 mg daily with PIs results in similar exposure to standard dose (300 mg daily) without PI
  – Recommendation: Halve the dose in the setting of PI co-administration
In Practise…

• Lopinavir based ART
  – Continue rifampicin based TB regimen
  – Double the dose of LPV/r
• Patients requiring Atazanavir because of LPV intolerance
• OR patients requiring Darunavir because of resistance (ie Regimen 3)
  – Use a Rifabutin based regimen
  – Dose adjust to 150mg Rifabutin daily
Rifabutin and NNRTIs

- Rilpivirine
  - 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>INH in slow metabolizers may increase EFV toxicity</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>• Do not coadminister</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>
</tbody>
</table>
| Lopinavir/ritonavir | • Requires double dose with 4 tablets (800/200 mg) BD  
   • Increase the dose gradually | • Can use with RBT (adjust RBT dose to half)     |
| Atazanavir/ritonavir| • Do not coadminister                           |                                                   |
| Darunavir/ritonavir | • Do not coadminister                           |                                                   |
| Raltegravir         | • Standard dose                                 | • No adjustment with RBT                         |
| Dolutegravir        | • Double dose 50 mg BD                           |                                                   |
| TAF                 | • Do not coadminister                           |                                                   |
Preferred regimens in TB co-infection

• First Line ART
  – WHO and NDoH: TDF + 3TC/FTC + EFV (600)

• For Second line
  – AZT/3TC or TDF/FTC + double dose LPV/r
  – ATV/r use rifabutin

• For Third line
  – DRV/r use rifabutin instead of rifampicin

• (IAS-USA: EFV, DTG, RTG (boosted PI only if INSTI not an option)

Bonnet LID 2013
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

WHO Global Report 2016
DR-TB is a big problem

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

5-year mortality for XDR-TB = 74%

WHO Global Report 2015/6
Pietersen Lancet 2014
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>NEoT (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 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 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 together with four companion drugs, including linezolid</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, 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, levofloxacin, and pyrazinamide with WHO standard or care</td>
<td>Treatment success at 24 months</td>
</tr>
</tbody>
</table>
Key New MDR Drugs

- Bedaquiline
- Delamanid/Pretomanid
- Linezolid
- Clofazimine
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 reduces steady state concentrations of bedaquiline (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
- We are using this combination at standard doses
Delamanid

- Nitroimidazole
- Metabolised by albumin, smaller contribution by CYP3A4
- Associated QT prolongation
- Delamanid has No impact on EFV or LPV/r exposure
- Higher DLM concentrations with LPV/r: clinical impact?
- We are using it at standard doses
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

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

FQs, BDQ, DLM, CFZ

INH, TZD, LZD
d4T, ddi

SLIs, Rif
TDF

INH, TZD
EFV, DTG

LZD
AZT
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