TB/HIV Drug-Drug Interaction Studies: Issues

- Timing in drug development
- Population/setting
- Overlapping toxicities
- Drug/metabolite contributions to efficacy/toxicity
- Lack of PK/PD targets
- Pharmacogenomics
- Average value vs. variability
- Combined effects of >1 inducer/inhibitor
- Timing of TB vs. HIV treatment
- Special populations (children, pregnant women)
### TB drug pipeline: Drugs in Phase 2 or 3 development

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug name</th>
<th>Pharmacology issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP synthase inhibitors</td>
<td>Bedaquiline**</td>
<td>Metabolized by CYP3A Long terminal half-life QT prolongation</td>
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<tr>
<td></td>
<td>(TMC207)</td>
<td></td>
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<tr>
<td>Nitroimidazoles</td>
<td>PA824</td>
<td>Partially metabolized by CYP3A</td>
</tr>
<tr>
<td></td>
<td>Delamanid</td>
<td>Low metabolic drug interaction risk</td>
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<tr>
<td></td>
<td>(OPC67683)</td>
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<tr>
<td>Oxazolidinones</td>
<td>Sutezolid</td>
<td>30% metabolized by CYP3A, but metabolites may be more active than parent drug</td>
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<tr>
<td></td>
<td>(PNU100480)</td>
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<tr>
<td>Ethylenediamines</td>
<td>SQ109</td>
<td>Metabolized by 2D6 and 2C19</td>
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<tr>
<td></td>
<td>AZD5847</td>
<td><strong>Licensed by FDA in December of 2012 for treatment of MDR-TB</strong></td>
</tr>
</tbody>
</table>
Bedaquiline

- Registered for use in patients for whom there are no other good options (MDR- or XDR-TB)
- Bedaquiline is a substrate of cytochrome P450 3A4 (CYP3A4)
- Bedaquiline terminal half-life is about 5 months
- QTc prolongation
- M2 and M3 metabolites are less active in vitro against M. tuberculosis; in vitro studies suggest M2 may be more toxic than parent drug

Effects of EFV on Bedaquiline PK: ACTG5267

• Healthy volunteers were enrolled in AIDS Clinical Trials Group Study 5267
  • TMC207 400 mg on Days 1 and 29
  • EFV 600 mg once daily on Days 14-42

Bedaquiline and M2 metabolite (log scale)

**Bedaquiline**

**M2 metabolite**

*Values shown represent means with SE.*

n.b. Note triphasic elimination

*Values shown represent means with SE.*
Modeling Results: Impact of EFV on steady state exposure of BDQ

\[ C_{ss,av} = \frac{F\cdot Dose}{CL\cdot \tau} \Rightarrow Rel_{C_{ss,av}} = \frac{C_{ss,av(EFV)}}{C_{ss,av}} = \frac{CL}{CL(EFV)} \]

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline</th>
<th>M2</th>
<th>M3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rel ( C_{ss,av} ) (SE)</strong></td>
<td>48 (1.9)%</td>
<td>48 (1.9)%</td>
<td>88 (3.7)%</td>
</tr>
<tr>
<td><strong>Inter individual variability [CV] in Rel ( C_{ss,av} ) (SE)</strong></td>
<td>21 (2.7)%</td>
<td>29 (7.7)%</td>
<td>35 (9.8)%</td>
</tr>
</tbody>
</table>

Calculated from simulated (n=10000) individual CL values from each of 93 sets of parameter estimates obtained in a bootstrap of the primary model.

Possible dose adjustments

![Graph showing exposure to bedaquiline during the last treatment week for different EFV regimens.](image)
Other DDI studies involving *single-dose* bedaquiline

- **Lopinavir/ritonavir** (400/100 BID) increases single-dose BDQ AUC 22% -- “use with caution”

- **Nevirapine** (200 mg BID for 4 weeks)(n=16) did not change BDQ PK appreciably – “no dosage adjustment required”

- **Standard-dose Rifampin** reduces bedaquiline AUC by ~50%, **rifabutin** likely less so

Sirturo™ package insert; van Heeswijk *et al.* IAS 2011 MOPE172; Good *et al.* Clinical Pharmacology of TB Drugs (2012)
Additive toxicities: QT prolongation

- “...concurrent use with SIRTURO resulted in additive QT prolongation, proportional to the number of QT prolonging drugs in the treatment regimen.”
  - SIRTURO alone → mean QTcF increase over baseline of 23.7 ms (none > 480 ms)
  - SIRTURO with >2 other QT prolonging drugs → mean increase of 30.7 ms

“QT increases from baseline in the SIRTURO group persisted even after SIRTURO treatment was stopped. “

- “Mean increases in QTc were larger in the 17 subjects who were using clofazimine with bedaquiline”
Nitroimidazoles: Delamanid and ARVs

- Co-administration of **delamanid** and **EFV** had no effects on the PK of either (no change in delamanid $C_{\text{max}}$, 3% decrease in AUC; 6% decrease in EFV $C_{\text{max}}$ and AUC)

- Lopinavir/ritonavir associated with 20% increase in **delamanid** exposure (but delamanid 100 mg **twice daily** did not affect **TDF**, **LPV**, or **RTV** concentrations)

Nitroimidazoles: PA-824 with ART

- PA-824, moxifloxacin, pyrazinamide (PaMZ) currently being tested in 2-month Phase 2B clinical trial

- PA-824 is extensively metabolized, 20% of metabolism catalyzed by 3A4
Study Schema: ACTG Study 5306

**Design:** Phase I, three-arm, open label crossover trial in healthy HIV-seronegative participants*

- Arm 1: EFV (600 mg qd) and PA-824 200 mg
- Arm 2: LPV/r (400/100 bid) and PA-824
- Arm 3: Rifampin (600 mg qd) and PA-824

**Duration:** 49 days (Arms 1 and 2); 29 days (Arm 3)

**Sample size:** 48 volunteers (16 per arm)

*Men and women 18-65, HIV-, Hep B & C neg, CrCl>50, nl ALT, QTc≤450
Effect of EFV on PA-824

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Co-administration (Mean ±SD)</th>
<th>Administered alone (Mean ±SD)</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA-824</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (ug*h/mL)</td>
<td>26,830 ±10,089</td>
<td>41,227 ±15,443</td>
<td>0.65 (0.56, 0.76)</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>695 ±337</td>
<td>1,227 ±493</td>
<td>0.54 (0.45, 0.64)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1,622.2 ±539.0</td>
<td>2,290 ±799</td>
<td>0.71 (0.62, 0.83)</td>
</tr>
<tr>
<td>CL/F (L/hour)</td>
<td>8.6 ±3.6</td>
<td>5.7 ±2.8</td>
<td>1.53 (1.31, 1.78)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hour)</td>
<td>17.5 ±5.4</td>
<td>23.4 ±5.2</td>
<td>0.73 (0.67, 0.80)</td>
</tr>
<tr>
<td>EFV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24h&lt;/sub&gt; (ug*h/mL)</td>
<td>57,280 ±17,531</td>
<td>59,357 ±16,648</td>
<td>0.96 (0.90, 1.02)</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (ng/mL)</td>
<td>1,773 ±695</td>
<td>1,818 ±645</td>
<td>0.96 (0.89, 1.04)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>3,801 ±1,282</td>
<td>4,283 ±942</td>
<td>0.86 (0.72, 1.02)</td>
</tr>
<tr>
<td>CL/F (L/hour)</td>
<td>3.9 ±1.4</td>
<td>3.7 ±1.3</td>
<td>1.04 (0.98, 1.11)</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hour)</td>
<td>26.7 ±18.5</td>
<td>21.3 ±7.5</td>
<td>1.14 (0.93, 1.40)</td>
</tr>
</tbody>
</table>
Sutezolid

**PK issues:**
- Oxidized to two active metabolites
- CYP3A4 contributes 20-30% of metabolism (to which metabolite?)

**Activity:**
- Time-dependent
- **Parent** drug
  - Intracellular activity
- PNU101603 metabolite
  - Extracellular activity

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Wallis et al IAS 2012; Louie et al. ICAAC 2012
How much is enough?

Bedaquiline pharmacodynamics

PA-824 pharmacodynamics

Is rifapentine as potent an inducer of metabolizing enzymes as rifampin?

*Midazolam is a CYP3A4 probe drug*

TBTC Study 29B: Dooley et al. (2012) CPT
In Vitro Induction of Cytochrome P450 3A4 in Human Hepatocytes by Rifampicin, Rifabutin and Rifapentine

N.B. Data should be interpreted in the context of differences in plasma concentrations seen clinically among the rifamycins. At standard doses, RIF, RBT, and RPT average concentrations are about 2.3 µM, 0.3 µM and 15.7 µM, respectively.
Rifapentine for ultrashort LTBI treatment

**ACTG 5279 EFV PK Study:**
Does concomitant dosing of EFV and RPT result in adequate EFV exposure (>1mg/L)

1\textsuperscript{st} EFV PK assessment @ N=31 evaluable\* subjects\**

- >20 of 31 subjects have acceptable EFV levels (>1mg/L) at both Weeks 2 & 4
  - PASS
- ≤ 20 of 31 subjects have acceptable EFV levels (>1mg/L) at both weeks 2 & 4
  - FAIL

2\textsuperscript{nd} EFV PK assessment @ N=90 subjects\**

- Lower 95\% CI on the proportion of subjects that have acceptable EFV levels at both weeks 2 & 4 is > 80\%
  - PASS
- Lower 95\% CI on the proportion of subjects that have acceptable EFV levels at both weeks 2 & 4 is ≤ 80\%
  - FAIL

\*Evaluable = Measurable Baseline, Week 2 and 4 EFV levels, subjects ≥ 18 yrs

**Any participant with baseline, week 2 or 4 BLQ concentrations will be deemed non-adherent & the PK data will not be evaluable.

Slide courtesy of Courtney Fletcher
Pharmacogenomics: we do not all metabolize drugs the same

Mean EFV concentrations (SE), by CYP2B6 genotype

Change in Bedaquiline AUC by EFV AUC

*Chromosome 19, CYP2B6 rs3745274 (exon 4, 516G>T), rs28399499 (exon 9, 983T>C)

Courtesy of David Haas and Jeong-Gun Park
## Drug interaction: typical value vs. variability

### Maternal EFV trough estimates

<table>
<thead>
<tr>
<th></th>
<th>Pre/intrapartum (n=59)</th>
<th>6 weeks Post-partum (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{min}}$ (mg/L)*</td>
<td>1.4 (0.99, 1.89)</td>
<td>1.68 (1.22, 2.78)</td>
</tr>
<tr>
<td>% with $C_{\text{min}}&lt;1$ mg/L</td>
<td>25.4%</td>
<td>20.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Taking rifampin for TB treatment (n=30)</th>
<th>Not taking rifampin (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{min}}$ (mg/L)*</td>
<td>1.76 (0.89, 3.13)</td>
<td>1.52 (1.14, 2.02)</td>
</tr>
<tr>
<td>% with $C_{\text{min}}&lt;1$ mg/L</td>
<td>29.6%</td>
<td>17.1%</td>
</tr>
</tbody>
</table>
Summary points (specific)

• **EFV** reduces **bedaquiline** concentrations by at least 20%, likely closer to 50%
• **EFV** reduces **PA-824** concentrations by about 30%
• **Delamanid** appears to have lower metabolic drug interaction risk, but must be taken twice a day
• **Sutezolid** hasn’t been tested in PK studies with ARVs, results might be hard to interpret
• Can’t assume magnitude of induction of metabolizing enzymes by **high-dose rifampin or rifapentine** will be similar to that of standard-dose rifampin
Summary points (general)

• All TB treatment trials must have well-designed pharmacology components else we will never know PK/PD targets (& can’t interpret DDI)

• There is no one-size-fits-all PK drug interaction study design

• Once dose(s) going forward is known, nested vs. stand-alone drug interaction studies with ARVs are needed if drug interaction is likely

• Strong inducers (or inhibitors) can affect companion drug PK even if contribution of P450 metabolism is “minor”

• DDI trials in healthy subjects should be considered pilot studies

• If pharmacogenomics matter, make sure all relevant genotypes are represented in DDI studies
Thanks to:

- ACTG Study Teams
  - A5267
  - A5306
- TBTC Study 29B Team
- TSHEPISO Study Team
- Uppsala University
  - Mats Karlsson, Elin Svensson
- University of Liverpool
  - Andrew Owen & Beth Williamson
- TB Alliance, Sanofi
- Johns Hopkins
  - Center for TB Research
  - Division of Clinical Pharmacology
- HIV/TB Research Frontiers Planning Committee, for the invitation
Extra slides
### Bedaquiline and M2 PK summary

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Alone*</th>
<th>With efavirenz*</th>
<th>GMR**</th>
<th>90% CI</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-336}) (ng*h/mL)</td>
<td>58155 (42222, 78249)</td>
<td>52135 (39868, 62528)</td>
<td>0.82</td>
<td>(0.75-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>3390 (2420, 4290)</td>
<td>3708 (2716, 4529)</td>
<td>1.00</td>
<td>(0.88, 1.13)</td>
<td>0.88</td>
</tr>
<tr>
<td>T(_{1/2}) (h)</td>
<td>51.1 (48.7, 55.3)</td>
<td>47.5 (43.5, 53.0)</td>
<td>0.92</td>
<td>(0.88, 0.97)</td>
<td>0.006</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>M2 metabolite</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>AUC(_{0-336}) (ng*h/mL)</td>
<td>7432 (6189, 9753)</td>
<td>8542 (6274, 10589)</td>
<td>1.07</td>
<td>(0.97, 1.19)</td>
<td>0.295</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>42.4 (34.9, 50.3)</td>
<td>83.3 (56.2, 107.9)</td>
<td>1.89</td>
<td>(1.66, 2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T(_{1/2}) (h)</td>
<td>231.3 (207.6, 321.1)</td>
<td>100.44 (87.8, 142.8)</td>
<td>0.50</td>
<td>(0.38, 0.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Predicting effect of EFV on steady state bedaquiline
Nitroimidazoles: PA-824 with ART

ARM 1: Volunteers will be randomized to Treatment 1A or Treatment 1B.

TREATMENT 1A

Period 1
PA-824 Days 1-7

No treatment
Washout Period Days 8-21

Period 2
EFV Days 22-35
EFV plus PA-824 Days 36-42

Intensive 24 hr PA-824 PK (day 7)
Intensive 24 hr EFV PK (day 34)
Intensive 24 hr EFV (day 41) and PA-824 PK (day 42)

TREATMENT 1B

Period 1
EFV Days 1-14

EFV plus PA-824 Days 15-21

No treatment
Washout Period Days 22-35

Period 3
PA-824 Days 36-42

Intensive 24 hr EFV PK (day 13)
Intensive 24 hr EFV (day 20) and PA-824 PK (day 21)
Intensive 24 hr PA-824 PK (day 42)

PA-824 is administered at a dose of 200 mg once daily.
EFV is administered at a dose of 600 mg once daily.
Effect of PA-824 on EFV

See Poster 188LB