Long-acting injectables for TB prevention in people living with HIV: prospects and challenges

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Tuberculosis (TB) in people living with HIV (PLWH)

- Among the estimated 37 million PLWH, the risk of developing active TB is 20 (range 17-23) times higher than among people without HIV.
- TB is the leading cause of hospital admission and mortality among PLWH.
- Among people with latent TB infection (LTBI), HIV-co-infection is the highest risk factor for disease progression.
- TB preventive therapy is effective, including in PLWH.


UNAIDS. Global AIDS Update 2018.
**TB preventive therapy**

**WHO-recommended regimens for TB preventive therapy**
1) 6-9 months of daily isoniazid (isoniazid preventive therapy, IPT)
2) 3 months of weekly high-dose isoniazid plus rifapentine
3) 3-4 months of daily isoniazid plus rifampin
4) 3-4 months of daily rifampin

**Newly evaluated regimen**
1 month of daily isoniazid plus rifapentine
(Swindells et al. 2018)

Compared to IPT, the shorter regimens have non-inferior efficacy but have higher completion rates.

**Special considerations in PLWH**
- At least 36 months of IPT, if living in a high-burden setting
- Rifampin and rifapentine: drug-drug interactions with antiretrovirals (ARVs)

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Long-acting injectable (LAI) drug formulations

LAI formulations can improve adherence to long-term and perpetual drug administration.
  o Hormone therapy
  o Schizophrenia

For HIV therapy and PreP:
  o Cabotegravir and rilpivirine phase 3 randomized clinical trial, NCT02951052
  o High level of user interest and acceptance

Additional potential benefits of LAI formulations:
  o Mitigate drug-drug interactions
  o Reduce toxicity
  o Overcome oral bioavailability problems
  o Reduce pharmacokinetic variability
  o Ease administration to children

For TB preventive therapy:
  o Completion of treatment for LTBI may be improved with LAI formulations.
  o If infrequent enough, an LAI could be useful for continuous TB preventive therapy for PLWH in settings with high TB burden.

## LAI formulations for TB preventive therapy: Target product profile

Prepared by the Working Group on Long-Acting/Extended Release Formulations for the Prevention and Treatment of TB (LEAP-TB)

<table>
<thead>
<tr>
<th></th>
<th>Minimal regimen</th>
<th>Ideal regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of compounds</strong></td>
<td>Monotherapy</td>
<td>Monotherapy</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Presumed DS-TB exposure</td>
<td>Any TB exposure</td>
</tr>
<tr>
<td><strong>Target populations</strong></td>
<td>Adults and other age groups with approval, irrespective of HIV status</td>
<td>All age groups, irrespective of HIV status</td>
</tr>
<tr>
<td><strong>Product presentation</strong></td>
<td>Injections, or implant</td>
<td>Single injection, or implant</td>
</tr>
<tr>
<td><strong>Dosage form/schedule</strong></td>
<td>Weekly or less frequently</td>
<td>Monthly or less frequently</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Non-inferior to SOC</td>
<td>Superior to SOC</td>
</tr>
<tr>
<td><strong>Contraindications, precautions, interactions</strong></td>
<td>No additional monitoring required; drug-drug interactions no worse than SOC</td>
<td>No contraindications or warnings; no significant drug-drug interactions</td>
</tr>
<tr>
<td><strong>Shelf-life/storage</strong></td>
<td>2 years at 4°C</td>
<td>3 years at 40°C and 75% humidity</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>No greater than SOC</td>
<td>Less than SOC</td>
</tr>
</tbody>
</table>

DS: drug-susceptible  
DST: drug susceptibility testing  
IM: intramuscular  
IV: intravenous  
SC: subcutaneous  
SOC: standard-of-care

Potential drawbacks of LAI formulations:

- **Cost.** Proprietary LAI formulations will not be available for generic manufacturing.

- **Safety.** Drug safety will need to be understood before testing as an LAI formulation.

- **Resistance.** Prolonged sub-inhibitory drug concentrations could select resistant organisms **IF** an individual actually has active TB.
  - Theoretical
  - Prolonged sub-inhibitory concentrations should not pose greater risk – and may actually pose less risk – than higher concentrations produced by oral drug treatment, which could cause greater selective pressure.
Key physiochemical and PK/PD characteristics informing choice of agents for LAI formulations

- Water solubility
  - Compatibility with strategy
  - Range of existing LAI agents
- Surrogate for rate of clearance
  - Derived from oral $C_{min}$ values
- PK half-life (oral)
- Target concentration

Figure courtesy of Andrew Owen, University of Liverpool
Compatibility of existing TB drugs for LAI formulations

Isoniazid

Rifampin

Pyrazinamide

Ethambutol

Water solubility

PK half-life

Target concentration

Figures courtesy of Andrew Owen, University of Liverpool
Compatibility of newer TB drugs for LAI formulations

- Rifabutin
- Rifapentine
- Delamanid
- Bedaquiline

Water solubility
PK half-life
Target concentration

Figures courtesy of Andrew Owen, University of Liverpool
Preclinical testing: example bedaquiline

**Physiologically-based pharmacokinetic (PBPK) models** are compartmental PK models in which basic biological knowledge is considered; the compartments are real anatomical spaces.

- Information on organs (interconnectivity, composition, volume, blood flow perfusions)
- Absorption, distribution, metabolism, and elimination
- Allometric data

![Plasma [bedaquiline] following a single, 2000 mg intramuscular injection (Rajoli et al. 2018)](image)

### PK prediction of a single intramuscular injection at release rate of 0.0015 h⁻¹. (Rajoli et al. 2018)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>(C_{\text{max}}) mg/l</th>
<th>(C_{\text{trough}}) mg/l</th>
<th>AUC mg × h/l</th>
<th>Target concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>2000</td>
<td>0.39 ± 0.08</td>
<td>0.16 ± 0.03</td>
<td>177 ± 36</td>
<td>1.6 (ECOFF)³²</td>
</tr>
<tr>
<td>Delamanid</td>
<td>1500</td>
<td>0.11 ± 0.03</td>
<td>0.044 ± 0.011</td>
<td>50 ± 12</td>
<td>0.04 (ECOFF)²⁵</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>2000</td>
<td>0.39 ± 0.13</td>
<td>0.15 ± 0.05</td>
<td>170 ± 56</td>
<td>0.125 (CC)³³</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>250</td>
<td>0.50 ± 0.06</td>
<td>0.21 ± 0.02</td>
<td>232 ± 21</td>
<td>0.18 (MIC*3)³⁴</td>
</tr>
</tbody>
</table>

**PBPK** = physiologically based pharmacokinetic; \(C_{\text{max}}\) = maximum plasma concentration; \(C_{\text{trough}}\) = trough plasma concentration 24 h after administration; AUC = area under the concentration-time curve; ECOFF = epidemiological cut-off, CC = critical concentration, MIC = minimum inhibitory concentration.

Janssen developed an aqueous bedaquiline microsuspension for LAI use.

Plasma bedaquiline and M2 metabolite concentrations after intramuscular injection of long-acting bedaquiline formulation at 160 mg/kg in male Swiss mice

Preclinical testing: example bedaquiline PK of LAI formulation in mice

Based on PK modeling, a 1 g single intramuscular injection of B\textsubscript{LAI} in humans is predicted to maintain plasma bedaquiline concentrations > 0.1 µg/mL for > 1 month. (Vermeulen et al. 2018)

Figure adapted from Kaushik et al. Antimicrob Agents Chemother 2019; pii: AAC.00007-19.
Preclinical testing: example bedaquiline

*In vivo* activity in a mouse model of LTBI

Model: Generate a stable, low-level *M. tuberculosis* lung infection in BALB/c mice
- Immunize by aerosol infection with *M. bovis* rBCG30
- 6 weeks later, challenge by aerosol infection with *M. tuberculosis* H37Rv
- ≥6 week later, start treatment

Lung bacterial counts after 1 month of treatment

Duration of treatment to prevent 50% relapse

- **R**, rifampin; **P**, rifapentine; **H**, isoniazid; **B**, bedaquiline

Adapted from Zhang *et al.* AJRCCM 2011;184:732.
Our objective was to evaluate the in vivo activity of the bedaquiline LAI in a mouse model of LTBI treatment.

<table>
<thead>
<tr>
<th>Control regimens</th>
<th>Untreated</th>
<th>Negative control</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_{10}</td>
<td>Positive control; oral rifampin 10 mg/kg, 5 days/week</td>
<td></td>
</tr>
<tr>
<td>H_{50}P_{15}</td>
<td>Positive control; oral rifapentine 15 mg/kg and isoniazid 50 mg/kg, 1 day/week</td>
<td></td>
</tr>
<tr>
<td>B_{25}</td>
<td>Positive control; oral bedaquiline 25 mg/kg, 5 days/week</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test regimens</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B_{2.67}</td>
<td>Oral bedaquiline 2.67 mg/kg, 5 days/week = 160 mg/kg in 12 weeks</td>
<td></td>
</tr>
<tr>
<td>B_{5.33}</td>
<td>Oral bedaquiline 5.33 mg/kg, 5 days/week = 320 mg/kg in 12 weeks</td>
<td></td>
</tr>
<tr>
<td>B_{8}</td>
<td>Oral bedaquiline 8 mg/kg, 5 days/week = 480 mg/kg in 12 weeks</td>
<td></td>
</tr>
<tr>
<td>B_{LAI-160 \times 1}</td>
<td>LAI bedaquiline 160 mg/kg, 1 intramuscular injection = 160 mg/kg in 12 weeks</td>
<td></td>
</tr>
<tr>
<td>B_{LAI-160 \times 2}</td>
<td>LAI bedaquiline 160 mg/kg, 2 intramuscular injections, 4 weeks apart = 320 mg/kg in 12 weeks</td>
<td></td>
</tr>
<tr>
<td>B_{LAI-160 \times 3}</td>
<td>LAI bedaquiline 160 mg/kg, 3 intramuscular injections, 4 weeks apart = 480 mg/kg in 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

R, rifampin; P, rifapentine; H, isoniazid; B, bedaquiline
Bedaquiline LAI in a mouse model of LTBI

Results: control regimens

R, rifampin; P, rifapentine; H, isoniazid; B, bedaquiline

Figure adapted from Kaushik et al. *Antimicrob Agents Chemother* 2019; pii: AAC.00007-19.
Results: daily bedaquiline regimens

Figure adapted from Kaushik et al. Antimicrob Agents Chemother 2019; pii: AAC.00007-19.
Results: LAI bedaquiline regimens

Figure adapted from Kaushik et al. *Antimicrob Agents Chemother* 2019; pii: AAC.00007-19.
Bedaquiline LAI in a mouse model of LTBI

Results: daily versus LAI bedaquiline regimens

Total bedaquiline dose: 160 mg/kg

Total bedaquiline dose: 320 mg/kg

Total bedaquiline dose: 480 mg/kg

Figure adapted from Kaushik et al. Antimicrob Agents Chemother 2019; pii: AAC.00007-19.
Preclinical testing: Bedaquiline LAI in a mouse model of LTBI

In this mouse model of LTBI treatment:

• Over 12 weeks, once-monthly dosing with $B_{LAI-160}$ demonstrated superior or equivalent activity to daily oral administration of rifampin or the same total bedaquiline dose.

• A single dose of $B_{LAI-160}$ demonstrated bactericidal activity for up to 12 weeks post-administration.

• Bactericidal activity was observed at plasma concentrations above the MIC (7H11) for *M. tuberculosis*.
Conclusions

- LAI formulations could significantly, positively impact the implementation of TB preventive therapy, including continuous therapy in PLWH.

- Bedaquiline LAI formulation has promise for TB preventive therapy.

- The paucibacillary mouse model of LTBI is a validated model for testing regimens that
  - can provide key PK/PD data, including estimation of treatment duration;
  - cannot precisely predict the magnitude of drug-drug interactions (e.g., ARVs).

- Development and optimization of LAI therapies will be an iterative process involving PK/PD modeling, formulation development, in vivo testing, and clinical PK studies, in addition to safety/tolerability assessments, prior to clinical efficacy trials.
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