Elisa H Ignatius Johns Hopkins University School of Medicine (presented by Eric Nuermberger)
Role of LA drugs: Where are we now, where would we like to be?

"We have a good bit to learn, but a lot to be inspired by."

## Why we need LA TB formulations

Improve uptake and completion of lifesaving TPT.

- Global uptake and access to SOC regimens remain low.
  - 5-year WHO targets were not met, except PLHIV.
  - Duration correlates with completion rate (Shorter is better: 1HP>3HR>4R>6H>9H).
- **A one-shot regimen at index case diagnosis could improve WHO targets**.
  - Service delivery could leverage established public health and clinical infrastructure.
  - A single injection ensures completion.

Improve completion and outcomes of TBD treatment.

- Current regimens have little forgiveness.
  - Non-adherence drives unfavorable outcomes (HR 5.7 if >10% of doses are missed).
  - ***The continuation phase carries high risk of non-adherence and discontinuation.*** The bulk of rapidly replicating bacteria have been cleared, and patients are feeling better.
- **LA formulations could improve adherence and completion rates for better individual and population health.**

Provide person-centered care.

- Understand all aspects of acceptability through research.
  - Diverse stakeholder perspectives (communities, at-risk populations, and providers).
  - Potential impact of DDIs of interest (e.g., ART, contraception, and opioid replacement).
  - Build treatment literacy around LAIs (i.e., Dissociate new LAIs from injectable aminoglycosides).
- Provide choice, as with HIV.

## Considerations for initial LA targets

| TPT | Continuation Phase |
|---|---|
| One drug likely sufficient (unlikely to promote future resistance).<br>Pan-TB regimen is ideal (cannot reliably assess susceptibility).<br>Focus on sterilizing drugs for shortest possible duration. *Diarylquinolines (DARQs) and Rifamycins.*<br>Early inclusion of children in safety and efficacy trials. *TPT is particulalrly effective among HHC<5y.* | Two drugs sufficient (≥3 drugs needed for induction phase).<br>Need for repeat dosing (goal is ≤2)<br>Should we focus only on the continuation phase? *Sterilizing LTBI candidates can likley be used.*<br>Should we advance candidates for DS and DR-TB separately or Pan-TB only? |

*Compatible with pregnancy and lactation; No cold chain requirement.

## Where we are now

| Diarylquinolines | |
|---|---|
| BDQ | • **TPT frontrunner.**<br>• Single injection of BDQ-LAI (160 mg/kg) in a TPT mouse model.<br>Bactericidal activity for 8w, then bacteriostatic for an additional 4 to 8w.<br>• Promising regimens.<br>BDQ/RPT(2w) + $BDQ_{LAI-160}$x1 or BDQ(4w) + $BDQ_{LAI-160}$ x2 suppressed Mtb growth at 6m. |
| TBAJ-876 | • **More potent potential pan-TB regimen** (CROI 2024).<br>• Dose-ranging study of a single IM injection.<br>62.5, 125, 250 mg/kg doses sustained target (>36ng/mL) for 4, 6, and >6w, respectively.<br>• Single injection of 3 formulations rendered mice culture-negative for 8 to 12w.<br>**More bactericidal than QD oral BDQ x 4w and 1HP.** |

| Rifamycins | |
|---|---|
| RPT | • Single injection of RPT-LAI can sustain antibacterial conc >14d.<br>• Dose-ranging study (0.6, 2, 3.5) of single and divided-doses.<br>$RPT_{LAI-3.5}$ has similar bactericidal activity as 1HP in a treatment model. |
| RBT | • Single injection of RBT-LAI has similar early bactericidal activity as 1HP.<br>• RBT-LAI delivery via an in-situ forming implant (UNC).<br>Increased the drug load and sustained antibacterial conc for >16w.<br>A single injection eliminated Mtb in a pre- and post-exposure LTBI model. |

## Where we are going

PK challenges for LA TB formulations.

- PK targets are lower for LTBI vs TBD.
- What is the target exposure for LAIs?
  - AUC/MIC as in oral dosing; Trough concentration; 2- to 4-fold above MIC; Intermittently or consistently; Err on the side of well above the target due to resistance concerns?
  - Target exposures will be different for different agents. Validate target exposures from mouse models; Need modeling and simulation approaches.
- Is a long PK tail a concern? The paradigm (i.e., cure/eradication) is different than HIV.

Pharmaceutics considerations & types for diverse LATs.

- Potency, loading, physiochemistry, logP, Ke, prodrug approaches, volume, amphiphiles to alter solubility.
- How to best match API, technology platform, and use context?

| Injectable | MAP | Implant |
|---|---|---|
| • Solid drug particles<br>• Microspheres<br>• Polymer approaches for controlled release of potent water-soluble drugs<br>• Hyaluronidase to allow larger injection volumes. | • Minimally invasive.<br>• More acceptable.<br>• Patch size?<br>• Need to push through proof of concept. | • Biodegradable, ISFI, biodurable.<br>• Surgically implanted.<br>• Worth it for short-duration TPT?<br>• Need tunability for TBD treatment. |

  - Does hyaluronidase impact PK? Data suggest kinetics are affected, yet exposures are comparable.
  - Is the cold chain issue easier to address via a solid or liquid product?

Inclusion of priority populations early in development.

- Pregnancy and postpartum. Exposure during pregnancy is inevitable given that LA formulations are detectable for weeks to months post administration.
- Adolescents. Current care models are not sufficient – LA could provide a bridge to enhance TPT and TBD treatment and help mitigate: Increased TB incidence; Higher likelihood of severe disease at presentation; Higher loss to follow; Partial adherence; and Potential long-term consequences of absenteeism from school or work.
- Need to generate pre-emptive PK and safety data. Model-based predictions are helpful, but not sufficient; Dedicated trials are often delayed, contributing to delayed access; Spinoff trials are an opportunity to test successful regimens in priority populations (sample size based on expected AE rate).

Patient-centered data collection to understand preferences and inform product development.

- Preemptive community engagement and assessment. Focus Groups and Discrete Choice Experiments.
- Prospective qualitative studies embedded in clinical trials. FACIT (TB); WHOQOL-BREF (Culturally specific); PRO-CTCAE (Cancer trials).

## Where we want to be

- Widespread access to affordable & acceptable LA drugs (for TPT & DS-/DR-TB) with excellent safety & efficacy and predicatble PK, which can be administered without advanced medical training and are compatible with various life states and concomitant medications.