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Long-acting injectable agents as tools to end TB: The future is now.

"We see this meeting as a call to action."

The unmet need

Significant progress has been made over the past 30 years, but we need to do better.

- We are still missing 3.1M of the estimated 10.6M TB cases.
- Overall treatment success has been stagnant at 85% for years.
- 60% of the estimated TB cases are successfully treated.
- The economic toll of TB on patients is devastating.

LAI as a complement to the Gates MRI holistic TB strategy

Vaccine + LAI to prevent TB progression among the vast TBI reservoir.

- M72 vaccine is in P3 and enrolling rapidly (Q12024).
- ***50% protection over 3y (P2) leaves 50% who might not benefit.***

Simpler, safer, shorter oral TB regimens + LAI to reduce TB transmission.

- A pan-TB regimen using novel oral agents is in P2b/c treatment shortening trials (First trial launched July 2023; NCT05971602).
  - Target regimen profile: Simple "test and treat" paradigm (DS- and DR-TB); Shorter than SOC (≤3m); No baseline or ongoing safety monitoring required; All oral QD dosing; non-inferior to DS- and DR-TB SOC regimens; Affordable.
- ***Oral regimen delivery remains a struggle, even if reduced to 2-3m.***

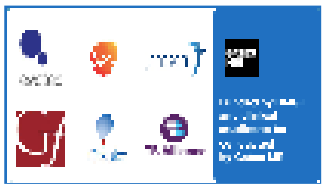
Leveraging oral therapeutic development for LAI

The opportunity is unprecedented.

- There are many promising oral agents in the global new TB drug pipeline (2024) that could be assessed for reformulation as LAIs.
- Shelved oral agents could potentially be revisited for use as LAIs.

Collaborations for complex, resource-laden development.

- PAN-TB collaboration for a novel oral TB regimen as a model:
  - Seven organizations agreed to work together to plan, implement, execute, and govern trials.
  - Development is focused on the PAN-TB target oral regimen profile is the focus.
  - Process is collaborative and cyclical: **Candidate selection** from PAN-TB partner and the Gates MRI accessible agents; **Selection of regimen combinations and down-selection** via Evotec's preclinical platform (BALB/c and kramnik relapsing mouse models); **Regimen prioritization and clinical trials** based on the PAN-TB target regimen profile.



Target LAI regimen profile

Draft target profile for pulmonary TB (priority use case).

- Ideal is a single curative injection containing ≤ 4 drugs.
  - One-time LAI (no OLI); Single SC injection <3mL containing 3-4 drugs; Coverage ≥4m.
- Minimally acceptable is OLI + maintenance LAIs x 2 with ≤ 4 drugs.
  - OLI (≤2m) + LAIs of 2-4 drugs; ≤4 separate agent IM or SC injections (<3mL) with effective PK coverage >2m; ≤2 LAI doses (e.g., at 1m and 2m).
- Additional use cases.
  - LTBI: Single curative injection containing 2 drugs.
  - Sub-clinical TB: Single curative injection containing ≤ 4 drugs.

Proactive assessment of core attributes with stakeholders and end users to hone target profile.

- Survey among payers, providers, and patients in HBCs.
  - South Africa, India, and Philippines.
  - Philippines was selected for pilot testing due to resource constraints (4th highest TB burden; Integrated TB services; VDOT use; High diabetes mellitus prevalence).
- Partnered with Family Health International (FHI).
  - Staff located in numerous HBCs and have translatable experience assessing the acceptability of LAIs for HIV prevention in LMICs.
- Collaborative development of survey tools.
  - FHI, MMV, UNITAID/CELT, PAN-TB partners, etc.
  - Surveys include discrete choice experiment and case scenarios.
- Enlist additional implementation partners to expand the countries.
  - USAID, SMART4TB, TAG, etc. and possibly WHO.

Technical considerations for LAI development

Candidate drug selection.

- TBD09 (MK-7762; P1) and CLB-073 (Early stage preclinical).
  - Agents in the Gates MRI portfolio are being prioritized for reformulation as LAIs based on compatible solubility, clearance, and potency (as per LEAP consortium guidance).

Long-acting technology selection**.**

- Micronized aqueous suspensions of crystalline drug is the initial focus.
  - High drug loading and simple, low-cost manufacturing.
  - Same strategy was used to generate proof-of-concept preclinical data for LA BDQ.
- Will consider prodrug strategy or more sophisticated LATs (e.g., polymeric microspheres or ISFI) as needed to tune drug release kinetics.

We can do better to accelerate TB decline

- **LAIs have a strategic role in interrupting TB transmission & progression.** Can increase efficiency by leveraging oral therapeutics and experience from other indications (HIV, mental health, contraception, malaria).
- **LAIs are game-changer tools for patients and allow more resources for case-finding and field support.** Reduced DOT & stigma burden; Improved outcomes.
- **Harness collaboration models and community engagement** to advance and optimize LAI regimen development for maximum impact.
- **Prioritize funding and resources for LAI,** but not at the cost of prevention tools & oral therapy.