TB vaccine roadmap for people with HIV

Gavin J. Churchyard: Aurum Institute
Maurine Miner: Fred Hutchinson Cancer Research Center
Amita Gupta: Johns Hopkins University
James Kublin: Fred Hutchinson Cancer Research Center
On behalf of the Cross-Network TB Vaccine Working Group

Global Forum on TB vaccines
24th February 2022
Overview

- Background
- Methods
- Consensus statements
- Conclusion

(Harris, Science Translational Medicine, 2020)
Background
Why include PWHIV in TB vaccine trials

- PWHIV:
  - are a large subpopulation at high risk of TB infection and disease
  - have historically been excluded from TB vaccine clinical trials
- Trials of TB vaccines among PWHIV are required to demonstrate safety, immunogenicity and efficacy
- Modeling suggests exclusion of PWHIV from mass TB vaccination campaigns reduces ability to control transmission in populations most affected

(Harris, Sci. Transl. Med. 2020)
Global roadmap for research and development of TB vaccines

(Cobelens, EDCTP / aighd, 2021)
Purpose & methods
Purpose

To accelerate development of TB vaccines for PWHIV by identifying gaps that need addressing with respect to:

- Basic & translational studies
- Pre-clinical models
- Selection of vaccine candidates
- Clinical trial designs
Methods

- DAIDS/NIH Cross-network TB Vaccine Working Group recognized the need to develop a roadmap for TB vaccines in PWHIV

- Framing questions developed to guide consensus statements for the roadmap

- In January 2021, the ACTG, IMPAACT and HVTN convened symposiums to discuss framing questions and identify consensus statements to guide research and policy on TB vaccines for PWHIV

- Experts in TB and HIV immunology, vaccinology, ethics, regulatory, epidemiology, and modeling participated in a series of presentations followed by discussion sessions based on the six framing questions developed by the symposium organizers and experts
TB vaccine roadmap for PWHIV

Themes
- Landscape
- Use case
- Prioritisation

Strategic recommendations
- Translational science
  - Evaluate Immunogenicity
  - Identify COP
- Preclinical models
  - Develop NHP SIV/SHIV models
  - Evaluate novel platforms
- Clinical trials
  - Who?
  - Eligibility criteria
  - Endpoints
  - Trial design
  - SOC
  - Ethics & regulatory
  - Community
Consensus statements
TB vaccine roadmap for PWHIV

Themes

Landscape

Use case

Prioritisation

Strategic recommendations

Translational science
- Evaluate Immunogenicity
- Identify COP

Preclinical models
- Develop NHP SIV/SHIV models
- Evaluate novel platforms

Clinical trials
- Who?
- Eligibility criteria
- Endpoints
- Trial design
- SOC
- Ethics & regulatory
- Community
Q1: What is the landscape of TB vaccines?

• Trials of subunit/adjuvanted, mycobacterial inactivated, fragmented and live attenuated, and viral vectored TB vaccine candidates should include PWHIV.

Adapted from: https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/2021
Q2: What is the use case or rationale for developing TB vaccines for PWHIV?

- The potential individual and population level impact of novel TB vaccines targeting PWHIV should be modelled.

- Mathematical modelling should be used to:
  - Develop preferred vaccine characteristics for TB vaccines for PWHIV & sub-populations (CD4 count, age, TB preventive treatment, ART-treated)
  - Estimate cost effectiveness and budget impact

- PWHIV across the disease spectrum should be studied to inform vaccine strategies.
Q3. Which vaccine candidates should be prioritized for study in PWHIV on ART?

- **Adults/adolescents living with HIV**
  - Subunit and viral vectored vaccines should be prioritized
  - Inactivated mycobacterial vaccines may also be evaluated
  - The evaluation of live attenuated vaccines early in development is encouraged, considering possible risks and benefits
  - mRNA and DNA vaccines should be prioritized for evaluation

- **Infants and children living with HIV**
  - Subunit and viral vectored vaccines should be evaluated
  - Inactivated TB vaccines may also be evaluated
  - As live attenuated vaccines are being developed for infants, it is important to know the safety, immunogenicity, and efficacy in HIV-infected infants on ART
Q3. Which vaccine candidates should be prioritized for study in PWHIV on ART?

- **Adults/adolescents living with HIV**
  - Subunit and viral vectored vaccines should be prioritized
  - Inactivated mycobacterial vaccines may also be evaluated
  - The evaluation of live attenuated vaccines early in development is encouraged, considering possible risks and benefits
  - mRNA and DNA vaccines should be prioritized for evaluation

- **Infants and children living with HIV**
  - Subunit and viral vectored vaccines should be evaluated
  - Inactivated TB vaccines may also be evaluated
  - As live attenuated vaccines are being developed for infants, it is important to know the safety, immunogenicity, and efficacy in HIV-infected infants on ART
Q3. Which vaccine candidates should be prioritized for study in PWHIV on ART?

- **Adults/adolescents living with HIV**
  - Subunit and viral vectored vaccines should be prioritized
  - Inactivated mycobacterial vaccines may also be evaluated
  - The evaluation of live attenuated vaccines early in development is encouraged, considering possible risks and benefits
  - mRNA and DNA vaccines should be prioritized for evaluation

- **Infants and children living with HIV**
  - Subunit and viral vectored vaccines should be evaluated
  - Inactivated TB vaccines may also be evaluated
  - As live attenuated vaccines are being developed for infants, it is important to know the safety, immunogenicity, and efficacy in HIV-infected infants on ART
Q3. Which vaccine candidates should be prioritized for study in PWHIV on ART?

- **Adults/adolescents living with HIV**
  - Subunit and viral vectored vaccines should be prioritized
  - Inactivated mycobacterial vaccines may also be evaluated
  - The evaluation of live attenuated vaccines early in development is encouraged, considering possible risks and benefits
  - mRNA and DNA vaccines should be prioritized for evaluation

- **Infants and children living with HIV**
  - Subunit and viral vectored vaccines should be evaluated
  - Inactivated TB vaccines may also be evaluated
  - As live attenuated vaccines are being developed for infants, it is important to know the safety, immunogenicity, and efficacy in HIV-infected infants on ART
TB vaccine roadmap for PWHIV

- **Translational science**
  - Evaluate Immunogenicity
  - Identify COP

- **Preclinical models**
  - Develop NHP SIV/SHIV models
  - Evaluate novel platforms

- **Clinical trials**
  - Who?
  - Eligibility criteria
  - Endpoints
  - Trial design
  - SOC
  - Ethics & regulatory
  - Community
Q4.1. When should PWHIV be included in TB vaccine trials?

Among adults, adolescents, infants, and children with HIV

- Subunit/adjuvant, viral vectored, and inactivated candidate vaccines may be evaluated in phase Ib trials, depending on the preclinical safety profile of the candidate vaccine, and phase II, III and post licensure trials.

- BCG and live attenuated vaccines may be evaluated in phase II, III, & post licensure trials if on balance, there is prospect of more benefit than harm.

Pregnant women with HIV

- Pregnant women with HIV on ART should be included in phase II / III trials of subunit, viral vectored and inactivated TB vaccines.

- Should not be considered for trials of BCG and new live attenuated vaccines.
Q4.2. What should the SOC be for PWHIV in TB vaccine trials?

- All PWHIV participating in TB vaccine trials should be on ART
- TPT should be offered to PWHIV according to WHO 2020 guidelines as the SOC either prior to or post enrolment
- In trials of live attenuated TB vaccines, TPT should not be provided in the trial, as TPT may reduce the activity of live attenuated TB vaccines
Q4.3. What are the HIV specific eligibility criteria?

**PWHIV with CD4+ T-cell counts <100 cells/µl or HIV RNA >200 copies/mL**
- Should be excluded from BCG and live attenuated vaccine trials
- May be included in phase Ib/II trials of subunit, viral vectored and inactivated TB vaccines
- May be included in phase III trials, if vaccines shown to be safe and immunogenic in phase II

**PWHIV with CD4+ T-cell counts ≥100 cells/µl and HIV RNA <200 copies/mL may be included in**
- Phase Ib/II trials of subunit, viral vectored, inactivated and live attenuated TB vaccines
- Phase III trials of subunit, viral vectored, inactivated and live attenuated TB vaccines, if shown to be safe and immunogenic in phase II
Q4.4. What are the HIV specific efficacy endpoints for PWHIV?

- Efficacy endpoints for PWHIV should be the same as for HIV-uninfected participants in POI, POD, POR/therapeutic TB vaccine trials.
- Consider including subclinical (asymptomatic) TB as an efficacy endpoint, ideally at the end of follow-up, so as not to compromise evaluation of efficacy in preventing clinical (symptomatic) TB disease.
- The risk of TB among PWHIV with sustained TB infection should be established.
Q4.5. What are the trial design and statistical considerations?

- Placebo is the preferred choice for the comparator arm
  - Except in trials enrolling BCG-naïve infants, where BCG should be the comparator
- The comparator arms for testing safety and efficacy of live attenuated vaccines in older children, adolescents and adults who are well controlled on ART should include BCG revaccination, in addition to placebo
- Immune-bridging studies are recommended if a correlate of protection has been identified and PWHIV are underrepresented in phase III trials
- Clinical trial simulation models should inform sample size estimations for trials including PWHIV, to maximize the likelihood of showing efficacy

(Source: R Mogg, GMRI, 2021)
Q4.6. What are the ethical considerations?

- An equity-oriented research agenda that seeks to reduce disparities between PWHIV and the general population should be adopted.
- The timing of when to include PWHIV in TB vaccine trials should be based on consideration of risks (safety) versus the need to reduce the “time-to-evidence” for people with HIV.
Q4.7. What are the regulatory considerations?

- Communication with regulatory authorities should occur early and throughout the development process.
Q4.8. How should community be involved?

- Community stakeholders of PWHIV should be engaged early in the process to ensure best outcomes and to provide input into study design, trial conduct, and results dissemination.
TB vaccine roadmap for PWHIV

## Strategic recommendations

<table>
<thead>
<tr>
<th>Translational science</th>
<th>Preclinical models</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate Immunogenicity</td>
<td>Develop NHP SIV/SHIV models</td>
<td>Who?</td>
</tr>
<tr>
<td>Identify COP</td>
<td>Evaluate novel platforms</td>
<td>Eligibility criteria</td>
</tr>
</tbody>
</table>

- **Clinical trials**
  - Who?
  - Eligibility criteria
  - Endpoints
  - Trial design
  - SOC
  - Ethics & regulatory
  - Community
Q5. What is the role of immunological correlates of protection in PLWH?

- Identified CoP should be validated in PWHIV to enable immuno-bridging studies.
- Standardized collection of samples across trials is encouraged to enable immune-bridging studies.
- Enrolling limited numbers of people with HIV who are not virally suppressed into immune-bridging studies should be considered.
TB vaccine roadmap for PWHIV

Themes
- Landscape
- Use case
- Prioritisation

Strategic recommendations
- Translational science
  - Evaluate Immunogenicity
  - Identify COP
- Preclinical models
  - Develop NHP SIV/SHIV models
  - Evaluate novel platforms
- Clinical trials
  - Who?
  - Eligibility criteria
  - Endpoints
  - Trial design
  - SOC
  - Ethics & regulatory
  - Community
Q6. What are the gaps in preclinical models for studying TB vaccines in PLWH?

- NHP models have not yet been validated as predictive of protection from TB in humans.
- Investment in NHP SIV/SHIV models (with and without ART) for TB vaccine studies is required.
- Novel vaccine platforms, such as mRNA and DNA TB vaccines, should be evaluated in NHP SIV/SHIV models.

(Scriba, Nemes, Nature Med. 2019)
Conclusion

- PWHIV are at high risk of TB disease & would benefit from TB vaccines
- TB vaccines in PWHIV may have some safety concerns and induce less robust responses
- The efficacy of TB vaccines in PWHIV needs to be optimised to maximise individual benefit and population level impact
- The roadmap identifies priorities for developing TB vaccines in PWHIV
Acknowledgements

“Roadmap” was led and written by Gavin Churchyard (ACTG), James Kublin (HVTN), Amita Gupta (IMPAACT) and Maurine Miner (HVTN), with support from Austin Van Grack (Social & Scientific Systems) under the overall direction of Judith Currier and Joseph Eron (ACTG), Glenda Gray (HVTN), Sharon Nachman (IMPAACT) and Peter Kim and Sarah Read (NIAID DAIDS). The ACTG, HVTN and IMPAACT provided support for developing the Roadmap.

The following presenters are gratefully acknowledged. Session 1: Gavin Churchyard (Aurum Institute), Amita Gupta (Johns Hopkins University), James Kublin (Fred Hutchinson Cancer Research Center), Sarah Read (NIAID DAIDS), Joseph Eron (University of North Carolina), Glenda Gray (South African Medical Research Council), Sharon Nachman (Stony Brook University), Richard White (London School of Hygiene and Tropical Medicine), Anneke Hessling (Desmond Tutu TB Centre – Stellenbosch University); Session 2: Gavin Churchyard (Aurum Institute), Mark Hatheril (SATVI, University of Cape Town, Amsterdam Institute for Global health & Development), Sheral Patel (U.S. Food and Drug Administration), Mike Frick (Treatment Action Group), Theodore Bailey (Greater Baltimore Medical Center); Session 3: James Kublin (Fred Hutchinson Cancer Research Center), Robert Seder (NIAID Vaccine Research Center), Joanne Flynn (University of Pittsburgh Center for Vaccine Research), Jyothi Rengarajan (Emory University), Deepak Kaushal (Texas Biomedical Research Institute), Willem Hanekom (African Health Research Institute), Alexander Schmidt (Gates Medical Research Institute); Session 4: Amita Gupta (Johns Hopkins University), Thomas Scriba (South African Tuberculosis Vaccine Initiative), Elisa Nemes (South African Tuberculosis Vaccine Initiative), Erica Andersen-Nissen (Fred Hutchinson Cancer Research Center), Alan Landay (Rush University), Susan Dorman (Medical University of South Carolina), Grace Aldrovandi (UCLA Mattel Children's Hospital), Lisa Cranmer (Emory University), Cheryl Day (Emory University); Session 5: Gavin Churchyard (Aurum Institute), Lele Rangaka (University College London), Alberto Garcia-Basteiro (ISGlobal), Andrew Fiore-Gartland (Fred Hutchinson Cancer Research Center), Robin Mogge (Gates Medical Research Institute); Vidya Mave (Byramjee Jeejeebhoy Government Medical College).

The contribution of the following people is acknowledged: Abdou Fofana (Boston University), Adrienne Shapiro (University of Washington), Alison Augustine (NIAID Division of Allergy, Immunology, and Transplantation), Ana Weinberg (EDCTP), Anchalee Avihingsanon (Thai Red Cross AIDS Research Centre), Ann Ginsberg (Gates Foundation), Catherine Yen (NIAID DAIDS), Chandler Church (University of Washington), César Boggiano (NIAID DAIDS), Chetan Seshadri (University of Washington), Corey Casper (IDRI), Dale Hu (NIAID DAIDS), Debra Benator (Washington DC Veterans Affairs Affairs Medical Center), Deepak Kaushal (Texas Biomedical Research Institute), Dereck Tait (IAVI), Richard Chaisson (Johns Hopkins University), Emily Douglass (Rutgers University), Fadzi Kasambira (NIAID DAIDS), Georgia Tomaras (Duke University Medical Center), Gerald Voss (TuBerculosis Vaccine Initiative), Hans Spiegel (NIAID DAIDS), Judith Currier (University of California), Julia Hutter (NIAID DAIDS), Justin Shenje (South African Tuberculosis Vaccine Initiative), Katrin Eichelberg (NIAID Division of Microbiology and Infectious Diseases).