Developing tuberculosis vaccines for people with HIV: consensus statements from an international expert panel

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New tuberculosis vaccine candidates that are in the development pipeline need to be studied in people with HIV, who are at high risk of acquiring *Mycobacterium tuberculosis* infection and tuberculosis disease and tend to develop less robust vaccine-induced immune responses. To address the gaps in developing tuberculosis vaccines for people with HIV, a series of symposia was held that posed six framing questions to a panel of international experts: What is the use case or rationale for developing tuberculosis vaccines? What is the landscape of tuberculosis vaccines? Which vaccine candidates should be prioritised? What are the tuberculosis vaccine trial design considerations? What is the role of immunological correlates of protection? What are the gaps in preclinical models for studying tuberculosis vaccines? The international expert panel formulated consensus statements to each of the framing questions, with the intention of informing tuberculosis vaccine development and the prioritisation of clinical trials for inclusion of people with HIV.

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Introduction

Tuberculosis, caused by *Mycobacterium tuberculosis*, was responsible for 1·5 million deaths in 2020, and continues to pose a threat to global health, particularly to people who live in nations with a high tuberculosis burden. WHO estimated that 9·9 million people developed tuberculosis in 2020, 8% of whom were co-infected with HIV.[1] Almost 800 000 people with HIV were diagnosed with tuberculosis in 2020, leading to 214 000 deaths.[1]

People with HIV have a 15–21 times higher risk of developing tuberculosis disease and succumbing to death than do people without HIV.[1–3] HIV infection results in T-cell immune dysfunction, including in the lungs.[4–6] Although the risk of tuberculosis in people with HIV might be substantially reduced by antiretroviral therapy (ART) and tuberculosis preventive treatment (TPT),[7,8] ART does not fully reconstitute HIV-induced immune suppression, which could compromise immune-dependent tuberculosis clearance.[9]

A comprehensive roadmap, including short-term and long-term goals for tuberculosis vaccine research and development, was developed by the Amsterdam Institute for Global Health & Development in cooperation with the European & Developing Countries Clinical Trials Partnership, but it does not specifically address tuberculosis vaccines for people with HIV.[10] We therefore convened an international panel of experts to make strategic recommendations to address key gaps and priorities in the development of tuberculosis vaccines for people with HIV, with respect to basic and translational studies, preclinical models, vaccine candidate selection, and clinical trial design considerations.

Tuberculosis vaccines

BCG, a live-attenuated vaccine first used in 1921, remains the only vaccine for the prevention of tuberculosis. BCG is effective in preventing severe forms of tuberculosis in children, particularly tuberculosis meningitis and miliary tuberculosis, and in 2004, WHO recommended a single dose of BCG be given to infants at birth in countries with high tuberculosis burden. In 2007, WHO provided additional guidance that infants and children with HIV who are not on ART should not be given BCG due to an increased risk of disseminated BCG disease.[11] A 2011 study, however, suggests that infants and children with HIV who initiate ART early, before immunological or clinical progression, have a reduced risk of developing regional lymphadenitis associated with BCG immune reconstitution inflammatory syndrome.[12] WHO's Strategic Advisory Group of Experts working group on BCG recommended in 2017 that BCG administration can be considered in people with HIV who are clinically well and immunologically stable, especially those living in high-burden countries.[13]

Ten vaccine candidates are currently in phase 1 to phase 3 clinical trials and several more are in various stages of planning (figure).[14–17] Vaccine candidates in development include live-attenuated (n=3), viral-vector (n=1), protein subunit (n=4), and whole-cell and inactivated vaccines (n=2) that could be used for the prevention of infection, prevention of disease, prevention of recurrence, and adjunctively with tuberculosis treatment as therapeutic vaccines. So far, no DNA or mRNA-based tuberculosis vaccines are being tested in humans, although an mRNA-based vaccine is in the planning stages.[18]

Tuberculosis vaccine trials in people with HIV

Because of HIV-associated immunosuppression, tuberculosis vaccines might have lower immunogenicity and efficacy in people with HIV than in people without HIV.[19] People with HIV have historically been excluded from tuberculosis vaccine trials to maximise the ability to

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show immunogenicity and efficacy. There have been concerns about the use of live-attenuated vaccines, such as BCG, in people with HIV, particularly those not on ART, due to possible dissemination of live bacteria.

Modelling suggests that exclusion of people with HIV from mass disease prevention vaccination campaigns that target adolescents and adults in high-HIV-prevalence communities reduces the ability to control tuberculosis transmission at a population level.[20] As people with HIV are a large subpopulation of people at high risk of tuberculosis infection and disease, it is crucial that tuberculosis vaccine trials include them. Additional evidence is required to optimise vaccine safety, immunogenicity, and efficacy in people with HIV. Additionally, a substantial population of people with HIV do not know they are seropositive, a majority of whom live in tuberculosis-endemic regions and would be recipients of any mass vaccination roll-out. It is therefore imperative to include people with HIV in trials of any potential vaccine for widespread use.

To date, nine completed studies, involving six tuberculosis vaccine candidates, have included people with HIV: two viral-vectored (MVA85A [IDT Biologika, Germany] and Aeras-402 [Aeras, MA, USA]), two subunit (H1:IC31 [Statens Serum Institut, Denmark] and M72/AS01E [GSK, UK]), and two whole-cell inactivated bacterial vaccines (RUTI [Archivel Farma, Spain] and *Mycobacterium obuense* [Aeras, MD, USA]).[19,21–32] Overall, tuberculosis vaccines in people with HIV are safe, induce cellular immunity, and have variable durability (table, appendix pp 1–2). Several trials are in the planning and development stages, and a subset of these will include people with HIV (figure).

Methods

In 2019, the US National Institute of Allergy and Infectious Diseases (NIAID) established a cross-network tuberculosis vaccine working group comprised of members from the AIDS Clinical Trials Group, HIV Vaccine Trials Network (HVTN), International Maternal Paediatric Adolescent AIDS Clinical Trials Network, and NIAID. The working group was tasked to develop consensus statements to help guide the prioritisation of candidate vaccines for study in people with HIV. Between Jan 22 and Feb 24, 2021, the cross-network working group convened an international panel of recognised experts in tuberculosis and HIV epidemiology, modelling, clinical care, immunology, vaccinology, ethics, community engagement, and regulatory affairs to participate in a virtually held workshop. We also invited members of the tuberculosis vaccine working groups from the three networks, opinion leaders, representatives from the global community of people with HIV and tuberculosis, vaccine developers, funders, and other tuberculosis research networks. Subject matter experts were identified on the basis of a review of their published work and those known to be working in the field of tuberculosis vaccines. Organisers and panellists were tasked with generating consensus statements supporting priorities and pathways for inclusion of people with HIV in trials of novel tuberculosis vaccine candidates and strategies. Discussions were framed by six guiding questions developed a priori by the organising members (GC, AG, and JGK), with input from participating experts. A series of presentations by subject matter experts was followed by discussion sessions based on the six framing questions developed by the symposium organisers and experts. The workshop was conducted virtually, comprising a total of six sessions (appendix pp 3–10). A written draft of the summary discussions of the framing questions and consensus statements was developed by a core group (GC, AG, JGK, and MDM) and additional comments on the context and consensus statements were then sought by participating subject matter experts.

What is the use case or rationale for developing tuberculosis vaccines for people with HIV?

Tuberculosis remains the leading cause of morbidity and mortality in people with HIV, and people with advanced HIV have the highest risk for tuberculosis disease.[1] Despite ART lowering the viral load to undetectable levels and effective TPT reducing the risk of tuberculosis, people with HIV remain at higher risk of developing tuberculosis and having poorer outcomes than the general population.[33,34] As HIV results in innate and adaptive immune response dysfunction, both safety and immunogenicity findings from studies conducted in people without HIV cannot be assumed to be replicated in people with HIV. Reduced immunogenicity has been observed in virologically suppressed and unsuppressed people, including those with in utero HIV exposure.[35] Therefore, it is imperative to include people with HIV in upcoming vaccine trials to identify potential differences in safety and immunogenicity. Models clearly show the importance of vaccines to reduce tuberculosis incidence, but these models require refinement as they have not included all the relevant variables specific to people with HIV or people exposed to HIV.[36] As we have seen with SARS-CoV-2, having data from people with HIV in vaccine trials is necessary to make any real-world recommendations for this population. As the proportion people with HIV exceeds 20% of some African populations, being able to vaccinate this group has not only local but global ramifications.[37] Delaying the inclusion of people with HIV in tuberculosis vaccine trials results in unnecessary morbidity and mortality.

There is a higher burden of tuberculosis among people with HIV and infants exposed to HIV than among the general population. Potentially different risk–benefit profiles for people with HIV and infants exposed to HIV, compared to the general population, must be carefully studied to generate relevant evidence for vaccine strategies across the tuberculosis disease and HIV

spectrum. The potential individual-level and population-level effects of novel tuberculosis vaccines targeting people with HIV should be further modelled. Mathematical modelling should also be used to develop a target product profile for tuberculosis vaccines for people with HIV and particular subpopulations (eg, by CD4 T-cell count, age group, and TPT and ART history), and to estimate cost-effectiveness and budget impact.

What is the landscape of tuberculosis vaccine candidates for people with HIV?

A variety of tuberculosis vaccines are being tested in early and late phase clinical trials. However, assessments to date have not focused specifically on people with HIV. Some vaccine candidates, such as live or vectored vaccines, need special assessment of safety profiles in people with HIV. Including people with HIV early in clinical development avoids unnecessary delays for this population in accessing vaccine products. All vaccine approaches, including prevention of infection, disease, recurrence, and therapeutic vaccines, should include people with HIV given their higher tuberculosis incidence, higher recurrence, and poorer treatment outcomes than people without HIV. People with HIV can be categorised by age group into adults (18 years and older) and adolescents (aged 12–17 years), and infants (aged 0–1 year) and children (aged 1–11 years), and the strategies for tuberculosis vaccines might differ for each population. As most adolescents and adults living with HIV in tuberculosis-endemic countries will have received BCG at birth, a new vaccine would be considered a booster to the BCG prime. For example, pre-exposure vaccines to prevent infection could target infants and children as a prime, whereas pre-exposure and post-exposure strategies to prevent disease might be more appropriate for adolescents and adults as a booster strategy in tuberculosis endemic countries. According to WHO's preferred product characteristics, a tuberculosis vaccine for adolescents and adults should show at least 50% efficacy in preventing confirmed pulmonary tuberculosis, protect participants with or without past *M tuberculosis* infection, and be protective in many geographical regions.[38] For infants and children, the efficacy of a pre-exposure tuberculosis vaccine should be 80% or higher than baseline incidence, or superior to BCG with equal or improved safety. Additionally, reduction of injection site swelling, pain, drainage, scarring, and local lymphadenopathy would be improvements on BCG. Trials of tuberculosis vaccine candidates should include people with HIV with careful assessment of safety, immunogenicity, and efficacy, specific to this group.

Which vaccine candidates should be prioritised for study in people with HIV on ART?

As only a fraction of *M tuberculosis* infected people go on to develop clinical disease, there are two crucial timepoints for prevention of disease with vaccines: preinfection or postinfection. Preinfection vaccine strategies are appropriate for use in infants in endemic settings or adolescents in low-burden regions. Postinfection vaccine strategies include disease prevention in *M tuberculosis* infected people, therapeutic vaccination in those with tuberculosis disease to reduce the proportion of tuberculosis patients with unfavourable treatment outcomes, and prevention of recurrence in tuberculosis patients who have been successfully treated.[39] Tuberculosis vaccine candidates have been evaluated in people with HIV (table; appendix pp 1–2). Viral-vectored, subunit protein adjuvanted, and whole-cell (killed) tuberculosis vaccines induce variable humoral and cellular immunity in people with HIV, although responses in ART-naive people tend to be poorer.

For adolescents and adults with HIV, balancing potential safety, immunogenicity and efficacy, subunit protein adjuvanted tuberculosis vaccines, and inactivated mycobacterial vaccines should be prioritised for development in people with HIV, followed by non-replicating viral-vectored vaccines. Similarly, for infants and children

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See **Online** for appendix

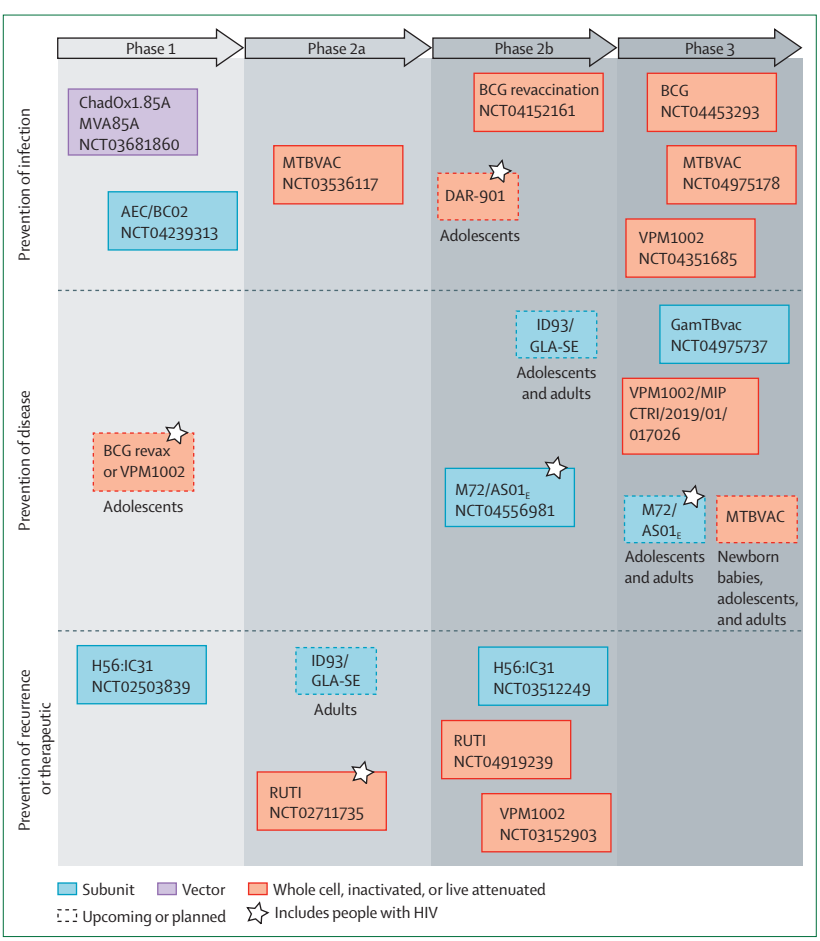

Figure: **Tuberculosis vaccine pipeline in 2021**
Ongoing trials were identified through ClinicalTrials.gov, WHO International Clinical Trials Registry, and Clinical Trials Registry of India. Upcoming or planned trials were identified via International AIDS Vaccine Initiative,[14] Suliman and colleagues,[15] and Treatment Action Group.[16] Adapted from TuBerculosis Vaccine Initiative.[17]

	MVA85A (TB011)[19,23]	MVA85A (Aeras-485)[21]	Ad35/85A85BTB10.4 (Aeras-402)[26]	M72/AS01E[27,28]	M72/AS01E[32]	H1:IC31[31]	RUTI[22]	*Mycobacterium obuense* (DARDAR)*[25,29]	*M obuense* (DAR901)[24]
Product type	Viral vector	Viral vector	Viral vector	Subunit plus adjuvant	Subunit or adjuvant	Subunit or adjuvant	FCMtb	Whole-cell inactivated	Whole-cell inactivated
Phase	2a	2	2	2	1/2	2	2	3	1
Participants									
With HIV, not receiving ART (n)	12	136	26	80	..	48	47	2000	..
With HIV and receiving ART (n)	12	513	..	80	37	..	..	..	6
With tuberculosis but without HIV (n)	12	..	..	..	..	..	..	..	..
With HIV and tuberculosis (n)	12	..	..	..	..	..	..	..	..
Without HIV or tuberculosis (n)	..	..	..	80	..	..	48	..	53
Safety	Safe in all	Safe in all	Safe in all	Safe in all	Safe in all	Safe in all	Mild local nodules and abscesses in 6–46% of vaccine recipients	Safe in all	Safe in all
T-cell responses	Participants with HIV receiving ART similar to HIV-negative participants with 85A-specific CD4 durable to 3 years; no CD4 durable responses for participants with HIV	Mostly monofunctional 85A-specific CD4 and low CD8; no difference between participants with HIV whether receiving ART or not	Mixed CD4 and CD8 to 85A and 85B, which decreased by 6 months; mostly bifunctional and polyfunctional	Participants with HIV receiving ART had higher M72-specific CD4 than HIV-negative participants or participants with HIV not receiving ART up to 3 years; mostly polyfunctional; no CD8 detected	M72-specific CD4 peaked 1 month after second dose but durable to 7 months; mostly polyfunctional; no CD8 detected	H1-specific CD4 peaked 1 month after second dose but durable to 6 months; mostly bifunctional and polyfunctional; no CD8 detected	Polyantigenic IFN-γ highest with 25 μg; HIV-negative participants higher than for participants with HIV	Polyantigenic IFN-γ and proliferation increased at 2 months after last dose	No difference between HIV-negative participants and participants with HIV receiving ART
Humoral responses	Not measured	Not measured	Binding antibody to 85A and 85B	Binding antibody to M72 peaked 1 month after second dose but durable to 3 years; HIV-negative and HIV with ART were greater than HIV without ART	Binding antibody to M72 peaked 1 month after second dose but durable to 7 months	Not measured	Not measured	Binding antibody to lipoarabinomannan increased at 2 months after last dose	No difference between HIV-negative participants and participants with HIV receiving ART

ART=antiretroviral therapy. FCMtb=fragmented, detoxified, heat inactivated, and liposomed *Mycobacterium tuberculosis*. IFN-γ=interferon-γ. *39% efficacy for secondary endpoint of definite tuberculosis.

Table: **Tuberculosis vaccine trials in people with HIV**

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with HIV, subunit protein adjuvanted, inactivated, and viral-vectored vaccines should be evaluated in this population. As live-attenuated vaccines are being developed for infants, it will be important to know the safety, immunogenicity, and efficacy of these vaccines in infants with HIV on ART. We encourage the evaluation of immunogenicity and safety of novel live-attenuated vaccines early in development, considering possible risks and benefits for each candidate vaccine (in each age group) in people with HIV on ART. Novel vaccine platforms, such as mRNA and DNA, should be prioritised for evaluation among people with HIV, including infants and children.

What are the design considerations of tuberculosis vaccine trials that include people with HIV?

When should people with HIV be included in tuberculosis vaccine trials?

People with HIV are at high risk of tuberculosis disease and would benefit from participating in tuberculosis vaccine trials as soon as safely possible to minimise the time to accessing effective tuberculosis vaccines that come to market.

Among adolescents and adults, and infants and children with HIV, subunit, viral-vectored, inactivated, and novel mRNA or DNA tuberculosis vaccines, once developed, can be evaluated in phase 1b trials, depending on the preclinical safety profile of the candidate vaccine, and then in phase 2, phase 3, and post-licensure trials. BCG and new live-attenuated vaccines could be evaluated in phase 2, phase 3, and post-licensure trials, depending on CD4 count, viral load, and if there is potential for more benefit than harm. That is, the safety and efficacy signal in people with HIV supports further development. Pregnant women with HIV on ART could be included in phase 2, phase 3, and post-licensure trials of subunit, viral-vectored, and inactivated vaccines. However, they should not be considered for planned trials of BCG and new live-attenuated vaccines because WHO does not recommend BCG for pregnant women.

What should the standard of care be for people with HIV in tuberculosis vaccine trials?

An effective tuberculosis vaccine for people with HIV would complement existing tools for tuberculosis prevention in people with HIV, which includes early disease detection, prompt diagnosis and treatment, infection prevention and control, and TPT. TPT is the WHO standard of prevention for people with HIV.[1] Isoniazid preventive treatment in conjunction with ART is more effective in reducing the risk of tuberculosis than ART alone.[40] An extended duration of isoniazid TPT was found to be equally effective as short-term rifamycin and isoniazid-based therapy in reducing tuberculosis risk in people with HIV.[41] As the combined effect of TPT with immune modulation is greater than either intervention alone, it is reasonable to assume that TPT with tuberculosis vaccines might have a synergistic effect on reducing the risk of developing tuberculosis disease. However, offering TPT to eligible participants with HIV in tuberculosis vaccine trials could reduce the apparent effectiveness of tuberculosis vaccines. This confounder is not unlike offering pre-exposure prophylaxis (PrEP) to participants in HIV vaccine clinical trials; ethically, it is the right thing to do, but does reduce the power to observe potential vaccine efficacy. Thus, next-generation HIV vaccine and other preventive trials are being designed to allow for a lower incidence due to PrEP uptake.[42]

All people with HIV participating in tuberculosis vaccine trials should be receiving ART. Because WHO recommends TPT as standard of care for people with HIV regardless of *M tuberculosis* infection status, tuberculosis vaccine-trial participants with HIV (on ART), regardless of age, *M tuberculosis* infection status, phase of trial (1–3), or mechanism of action (prevention of infection, disease, or recurrence), should either have previously completed a course of TPT before enrolment, or be offered TPT during the study if they have no evidence of active tuberculosis disease. TPT should not be provided in trials of live-attenuated tuberculosis vaccines because it could reduce the activity of live-attenuated tuberculosis vaccines. People eligible for TPT who have not previously taken TPT should be advised to complete a course of TPT before enrolling in the trial.

What are the HIV-specific eligibility criteria?

As CD4 T-cell count and viral load are predictive of developing opportunistic infections, survival, and vaccine responses, these clinical characteristics should be included as eligibility criteria in tuberculosis vaccine trials that include participants with HIV. People with HIV receiving ART should therefore only be considered for inclusion in tuberculosis vaccine trials if viraemia and CD4 T-cell counts meet prespecified thresholds.

The eligibility criteria for inclusion in tuberculosis vaccine trials for people with HIV on ART should differ depending on CD4 T-cell count. Participants with HIV with CD4 T-cell counts of less than 100 cells per µL or HIV RNA greater than 200 copies per mL should be excluded from trials of BCG and live-attenuated vaccines; could be included in phase 1b/2 trials of subunit, viral-vectored, and inactivated tuberculosis vaccines; and could be included in phase 3 trials if vaccines are shown to be safe and immunogenic in phase 2 trials.

Participants with HIV with CD4 T-cell counts of at least 100 cells per µL or HIV RNA less than 200 copies per mL could be included in phase 1b/2 trials of subunit, viral-vectored, and inactivated tuberculosis vaccines; phase 2 trials of live-attenuated tuberculosis vaccines; and phase 3 trials of subunit, viral-vectored, inactivated, and live-attenuated tuberculosis vaccines, if vaccines are shown to be safe and immunogenic in phase 2 trials.

What are the HIV-specific efficacy endpoints for people with HIV?

Tuberculosis among people with HIV is often paucibacillary, extrapulmonary, or subclinical, particularly among individuals with marked immunosuppression.[43,44] Prevention of infection vaccine trials in infants, uninfected adolescents, or adults evaluate *M tuberculosis* infection as the endpoint. The gold standard diagnostic for *M tuberculosis* infection is the interferon-γ release assay (IGRA), which measures cytokine production from *M tuberculosis* antigen-stimulated blood cells. Also, it has been shown that increased IGRA concentrations or sustained conversion predicts an increase in risk of tuberculosis disease progression. Whether this association holds true for people with HIV is currently unknown, as is how accurate use of IGRA is in this population. Prevention of disease vaccine trials typically evaluate clinical, bacteriologically confirmed, pulmonary tuberculosis disease as a highly specific endpoint using solid and liquid culture methods and nucleic acid amplification assays.

Subclinical tuberculosis occurs frequently in people with HIV and could have a role in *M tuberculosis* transmission. A benefit of including subclinical tuberculosis as an endpoint in prevention of disease, recurrence, or therapeutic vaccine studies is that it could decrease the sample size and reduce the duration of follow-up, as subclinical tuberculosis would contribute to the number of endpoints and occurs earlier than clinical tuberculosis disease. However, the decrease in sample size assumes that the vaccine will be equally efficacious at preventing clinical and subclinical tuberculosis. Whether prevention of subclinical tuberculosis should be a priority for prevention of disease, prevention of recurrence, and therapeutic tuberculosis vaccines is unclear: preventing subclinical tuberculosis would be more difficult for the vaccine to achieve; the evidence that subclinical tuberculosis substantially contributes to tuberculosis transmission is still circumstantial; and identifying and treating subclinical tuberculosis disease might compromise the ability to show efficacy against clinical tuberculosis.

Both prevention of recurrence and therapeutic tuberculosis vaccine trials evaluate clinical, bacteriologically confirmed, recurrent, pulmonary tuberculosis disease as a highly specific endpoint using solid or liquid sputum culture; therapeutic trials additionally consider treatment failure and tuberculosis-related deaths as unfavourable outcomes in a trial. Isolates of *M tuberculosis* should undergo whole-genome sequencing to characterise recurrent tuberculosis as relapse or reinfection tuberculosis.

Efficacy endpoints for participants with HIV should be the same as for people without HIV in prevention of infection, prevention of disease, prevention of recurrence, and therapeutic tuberculosis vaccine trials. Because paucibacillary, extrapulmonary, or subclinical tuberculosis occurs more commonly in people with HIV than the general population, consideration should be given to also include them as endpoints in tuberculosis vaccine trials among people with HIV. Subclinical tuberculosis should ideally only be assessed at the end of follow-up to not compromise evaluation of efficacy in preventing clinical (symptomatic) tuberculosis disease. As sustained *M tuberculosis* infection is used as an endpoint in prevention of infection trials, the risk of tuberculosis among people with HIV with sustained tuberculosis infection should be established.

What are the trial design and statistical considerations?

Statistical considerations for tuberculosis vaccine trials involving people with HIV include comparator arms, immune bridging, and sample size. TPT history, participant preferences and values, and local policy should also be considered when designing prevention of disease tuberculosis vaccine efficacy trials.

As a comparator arm, placebo gives the best chance of minimising bias and is the preferred choice, except in infants for whom BCG is licensed and has shown efficacy. Therefore, a placebo should not be used in BCG-naive infants with virological control on ART; rather, BCG should serve as the standard of care comparator. Similarly, the comparator arms for testing safety and efficacy of live-attenuated vaccines in older children, adolescents, and adults with virological control on ART could include BCG revaccination in addition to placebo to enable comparison with BCG, if a new vaccine is shown to be efficacious in these age groups.

We recommend the use of immune-bridging studies, which measure participant immune responses to vaccines rather than waiting for efficacy endpoints, for people with HIV if a correlate of protection has been identified and people with HIV are not a sufficiently large subgroup in phase 3 trials to permit precise estimation of efficacy. Even without an established correlate of protection, immunogenicity endpoints will be beneficial.

What are the ethical considerations?

People with HIV have a more urgent need for tuberculosis vaccines than the general population, given their substantially higher risks of developing tuberculosis disease, drug–drug interactions, and poorer tuberculosis treatment outcomes.[1–3] Consequently, delays in developing an effective tuberculosis vaccine for people with HIV would have greater individual-level consequences than for the general population. Excluding people with HIV from tuberculosis vaccine trials would also worsen existing health disparities. The differentially higher burden of tuberculosis among people with HIV justifies their inclusion in tuberculosis vaccine trials, with some degree of greater in-trial risk compared with participants from the general population.

An equity-oriented research agenda that seeks to reduce disparities between people with HIV and the

general population should be adopted. The timing of when to include people with HIV in tuberculosis vaccine trials should be based on the consideration of risks (safety) versus the need to reduce the time-to-evidence for people with HIV.

What are the regulatory considerations?

To increase enrolment of under-represented populations, including people with HIV in later phase clinical trials, sponsors can follow the US Food and Drug Administration (FDA) guidance for industry.[45] Sponsors developing a tuberculosis vaccine are encouraged to submit an investigational new drug application, even if there is no US market for that vaccine and the primary target population is outside the USA.[46,47] Expedited programme designations are available to facilitate development of qualifying tuberculosis vaccines for people with HIV.[48] Tuberculosis is on the list of qualifying tropical diseases eligible for a tropical disease priority review voucher (which expedites FDA review), which includes tuberculosis vaccines developed for people with HIV.[49] Furthermore, sponsors can use the EU-Medicines for all procedure[50] that aims to facilitate prequalification by WHO and registration by national regulatory authorities by providing a scientific opinion of the benefit–risk balance of the product, and the African Vaccine Regulatory Forum. Communication with regulatory authorities should occur early and throughout the development process.

How should community be involved?

Since 2016, HIV vaccine-efficacy trial design has been modified to account for volunteer willingness to take PrEP.[42,51] This new trial design was implemented after extensive community engagement and deliberations with community advisory boards and other local leaders.[52] This type of creative, next-generation trial design can be applied to the tuberculosis vaccine field to ensure people with HIV are included safely. Additionally, community advisory boards and other community stakeholders substantially enhance enrolment and retention of participants in clinical trials, especially in underserved populations.[53,54] Community stakeholders of people with HIV should be engaged early in the process to ensure best outcomes and to provide input into study design, trial conduct, and results dissemination.

What is the role of immunological correlates of protection in people with HIV?

Currently, there are no correlates of protection accepted by regulatory authorities for tuberculosis vaccines. Concerted efforts are being made to analyse immune responses from tuberculosis vaccine clinical trials that have shown some efficacy.[55,56] Correlates of protection identified in these trials will require validation in larger phase 3 or implementation studies. Ultimately, establishing correlates of protection for specific classes of vaccines could enable immune bridging of vaccines to more inclusive populations, such as people with HIV. This type of study could help accelerate licensure and broaden indication for these populations, even if they are not adequately represented in the efficacy trials. Another avenue for tuberculosis vaccine trials is the human infection challenge platform, in which volunteers are vaccinated and challenged with either BCG or another attenuated mycobacterial strain. With strict regulatory and safety oversight, these studies could help identify potential immune correlates and help inform future studies in people with HIV. A more detailed immunological characterisation of people with HIV at baseline might be required, as the quality and quantity of innate and adaptive immune responses of virally suppressed individuals might vary.[57–59]

Correlates of protection and other immunogenicity endpoints identified in people with HIV should be applied to, and evaluated in, people with HIV by use of immune-bridging studies. The collection of standardised sets of samples across trials is essential to enable such immune-bridging studies. Immunogenicity trials (phase 1b/2) should include people with HIV to maximise the chance of identifying a correlate of protection that could enable immune bridging.

What are the gaps in preclinical models for studying tuberculosis vaccines in people with HIV?

The non-human primate model of simian immunodeficiency virus (SIV) and simian HIV (SHIV) infection recapitulates many aspects of HIV acquisition and pathogenesis. As such, it remains a valuable research tool to aid in assessing the immunogenicity and efficacy of candidate tuberculosis vaccines to model what happens in people with HIV.[60] SIV and SHIV non-human primate models can help tailor preclinical studies to be relevant to people with HIV. SIV and SHIV non-human primate models provide an opportunity to look at possible effects of ART and TPT coadministration, to study correlates in an unbiased fashion, and to further understand the effect of HIV acquisition on memory immune responses from infant BCG vaccination. This platform would also be ideal for testing new vaccine regimens before doing phase 1 studies with participants with HIV, although non-human primate models have not yet been shown to be predictive of protection from tuberculosis in humans. The non-human primate model can also help identify tissue-specific correlates that can then be measured in human trials and subsequently modify the tissue-specific assays to assays that can use plasma or sputum samples. The US National Institutes of Health has funded several centres to focus on preclinical models for identifying vaccine correlates of protection.[61]

It is necessary to invest in non-human primate SIV and SHIV models (with and without ART) for tuberculosis

Panel: Key consensus points

- To inform vaccine strategies among people with HIV across the tuberculosis disease and HIV spectrum, the potential individual-level and population-level effect of novel tuberculosis vaccines targeting people with HIV should be modelled.
- Trials of tuberculosis vaccine candidates should include people with HIV with careful consideration of safety, immunogenicity, and efficacy specific to people with HIV. For people of all ages with HIV, subunit protein or adjuvanted tuberculosis vaccines and inactivated mycobacterial vaccines should be prioritised, followed by non-replicating viral-vectored vaccines.
- As live-attenuated vaccines are being developed for infants, it will be important to know the safety, immunogenicity, and efficacy of these vaccines in infants with HIV on antiretroviral therapy (ART). The evaluation of immunogenicity and safety of novel live-attenuated vaccines early in development, considering the possible risks and benefits for each candidate vaccine (in each age group) in people with HIV on ART, is encouraged. Novel vaccine platforms such as mRNA and DNA should be prioritised for evaluation among people with HIV, including infants and children.
- All people with HIV participating in tuberculosis vaccine trials must be on ART. Eligibility criteria for people with HIV on ART differ depending on CD4 T-cell count and viral load. Tuberculosis vaccine trial participants with HIV should either previously have completed a course of tuberculosis preventive treatment (TPT) before enrolment or be offered TPT during the study. Community stakeholders of people with HIV should be engaged early in the process to provide input into study design, trial conduct, and results dissemination.
- Correlates of protection and other immunogenicity endpoints identified in people without HIV should be applied to and evaluated in people with HIV with immune-bridging studies.
- Non-human primate simian immunodeficiency virus and simian HIV models (with and without ART) should be invested in for tuberculosis vaccine studies.

vaccine studies. Novel vaccine platforms, such as mRNA and DNA tuberculosis vaccines, should be evaluated in non-human primate SIV and SHIV models, keeping in mind that non-human primate models have not yet been validated as predictive of protection from tuberculosis in humans.

Conclusions

We developed consensus statements to accelerate the development of tuberculosis vaccines for people with HIV. The consensus statements address several strategic questions that make the case for including people with HIV as early as possible in clinical development of tuberculosis vaccines, and address gaps in preclinical models that could portend challenges in the future development of a variety of vaccine candidates (panel). The safety and efficacy of tuberculosis vaccines in people with HIV need to be optimised to maximise individual benefit and population-level effect.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "tuberculosis/tuberculosis/*Mycobacterium tuberculosis*", "vaccine", "people with HIV/PWH/PLWH", "HIV", and "clinical trial" from database inception up until Nov 1, 2021. We also identified ongoing tuberculosis vaccine clinical trials involving people with HIV by searching ClinicalTrials.gov, WHO International Clinical Trials Registry, and Clinical Trials Registry of India. Studies related to tuberculosis vaccine clinical trials among the general public and people with HIV were included if they were peer-reviewed and written in English. The final reference list was generated on the basis of relevance to this Review.

Contributors

AG, JGK, and GC organised the goals and the content of the expert consensus meeting. All authors participated in the preparation of the manuscript with contributions to draft statements in preparation for consensus, contributing to final consensus statements as panel members, drafting the manuscript, or providing revisions to content.

Declaration of interests

We declare no competing interests.

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