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Developing TB Vaccines for People with HIV: consensus statements from an international expert panel

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AG, JGK, and GC organised the meeting. All authors have 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.

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SEARCH STRATEGY AND SELECTION CRITERIA

References for this Review were identified through searches of PubMed with the search terms “TB/tuberculosis/Mycobacterium tuberculosis,” “vaccine,” “people with HIV/PWH/PLWH,” “HIV,” and “clinical trial” up until November 1, 2021. We also identified ongoing TB 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 TB 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.

SUPPLEMENTARY APPENDIX

Summary of TB vaccines evaluated in people with HIV.

Symposium Agenda. Agenda for Developing a TB Vaccine Roadmap for People with HIV.

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SUMMARY

New tuberculosis (TB) vaccine candidates in the development pipeline need to be studied in people with HIV, who are at high risk of developing *Mycobacterium tuberculosis* (Mtb) infection and TB disease and tend to develop less robust vaccine induced immune responses. Many questions in the development of a TB vaccine for people with HIV remain unanswered. To address the gaps in developing TB vaccines for people with HIV, a series of symposia was held that posed framing questions to a panel of international experts. Framing questions specific to developing TB vaccines for people with HIV included: 1) What is the use case or rationale for developing TB vaccines? 2) What is the landscape of TB vaccines? 3) Which vaccine candidates

should be prioritized? 4) What are the TB vaccine trial design considerations? 5) What is the role of immunological correlates of protection? and 6) What are the gaps in preclinical models for studying TB vaccines? The international expert panel formulated consensus statements to each of the framing questions, with the intention of informing TB vaccine development and the prioritization of clinical trials for inclusion of people with HIV.

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), was responsible for 1·5 million deaths in 2020 and continues to pose a threat to global health, particularly to those who live in high TB burden nations. The World Health Organisation (WHO) estimated that 9·9 million people developed TB in 2020, 8% of whom were coinfected with HIV (1). Almost 800,000 people with HIV (PWHIV) were diagnosed with TB in 2020 leading to 214,000 deaths (1).

PWHIV have a 15-21-fold higher risk of developing TB disease and succumbing to death compared to their uninfected counterparts (1–3). HIV infection results in T-cell immune dysfunction, including in the lung (4–6). Although the risk of TB in PWHIV may be substantially reduced by antiretroviral therapy (ART) and TB preventive treatment (TPT) (7, 8), ART does not fully reconstitute HIV-induced immune suppression, which may compromise immune-dependent TB clearance (9).

Developing TB vaccines for people with HIV

A comprehensive roadmap including short and long term goals for TB vaccine research and development (Global Roadmap for Research and Development of Tuberculosis Vaccines) was recently 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 TB vaccines in PWHIV (10). We therefore convened an international panel of experts to make strategic recommendations to address key gaps and priorities in the development of TB vaccines for PWHIV with respect to 1) basic and translational studies, 2) pre-clinical models, 3) vaccine candidate selection, and 4) clinical trial design considerations.

TB vaccines

Bacillus Calmette-Guérin (BCG)

BCG, a live attenuated vaccine first used in 1921, remains the only vaccine for the prevention of TB. BCG is effective in preventing severe forms of TB in children, particularly TB meningitis and miliary TB, and in 2004 the WHO recommended a single dose of BCG be given to infants at birth in high TB burden countries. In 2007, WHO provided additional guidance that infants and children with HIV not on ART should not be given BCG due to an increased risk of disseminated BCG disease (11). More recent evidence, however, suggests that HIV-infected infants and children who initiate ART early prior to immunological or clinical progression have a reduced risk of developing BCG-IRIS (immune reconstitution inflammatory syndrome) regional lymphadenitis (12). The WHO SAGE Working Group on BCG vaccination in 2017 therefore recommended that BCG administration can be

considered in PWHIV that are clinically well and immunologically stable, especially those living in high burden countries (13).

TB vaccine pipeline

There are 10 vaccine candidates currently in Phase 1-Phase 3 clinical trials and several more in various stages of planning (Figure 1) (14–17). Vaccine candidates in development include live attenuated (n=3), viral vector (n=1), protein subunit (n=4), and whole cell/inactivated (n=2) that may be used for the prevention of infection (POI), prevention of disease (POD), prevention of recurrence (POR), and adjunctively with TB treatment (therapeutic vaccines). So far, no DNA or mRNA-based TB vaccines are being tested in humans, although an mRNA based vaccine is in the planning stages (18).

TB vaccine trials in people with HIV

Justification

Due to HIV-associated immunosuppression, TB vaccines in PWHIV may have lower immunogenicity and efficacy (19). PWHIV have historically been excluded from TB vaccine trials to maximize the ability to demonstrate immunogenicity and efficacy. There have been concerns with using live attenuated vaccines, such as BCG, in PWHIV, particularly those not on ART, due to possible dissemination of live bacteria.

Modelling suggests that exclusion of PWHIV from mass POD vaccination campaigns targeting adolescents and adults in high HIV prevalence communities reduces the ability to control TB transmission at a population level (20). As PWHIV are a large subpopulation of persons at high risk of TB infection and disease, it is crucial that TB vaccine trials include them. Additional evidence is required to optimize vaccine safety, immunogenicity and efficacy in PWHIV. Additionally, there is a substantial population of PWHIV who do not know they are seropositive, a majority of whom live in TB endemic regions, and would be recipients of any mass vaccination rollout. It is therefore imperative PWHIV are included in trials of any potential vaccine for widespread use.

Experience

To date, nine completed studies involving six TB vaccine candidates have included PWHIV: two viral vectored (MVA85A, Aeras-402), two subunit (H1:IC31, M72/AS01E), and two whole cell inactivated bacterial vaccines (RUTI, *M. obuense*) (19, 21–32). Overall, TB vaccines in PWHIV are safe, induce cellular immunity, and have variable durability. Key findings from these trials are summarised in Table 1 and Supplementary Appendix pg 1–2. Several trials are in the planning and development stages, and a subset of these will include PWHIV (Figure 1).

METHODS

In 2019, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) established a Cross-Network TB Vaccine Working Group comprised of members from the AIDS Clinical Trials Group (ACTG), HIV Vaccine Trials Network (HVTN), International

Maternal Paediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, and NIAID. The Working Group was tasked to develop consensus statements to help guide the prioritization of candidate vaccines for study in PWHIV. Between January and March 2021, the Cross-Network Working Group convened an international panel of recognized experts in TB 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 TB vaccine working groups from the three networks, opinion leaders, representatives from the global community of HIV and TB, vaccine developers, funders, and other TB research networks. Subject matter experts were identified based on review of published work as well as those known to be working in the field of TB vaccines. Organizers and panellists were tasked with generating consensus statements supporting priorities and pathways for inclusion of PWHIV in trials of novel TB vaccine candidates and strategies. Discussions were framed by six guiding questions (Box 1) developed a priori by the organizing members (GC, AG, JGK) with input from participating experts (see Acknowledgements). A series of presentations by subject matter experts was followed by discussion sessions based on the six framing questions developed by the symposium organizers and experts. The workshop was conducted virtually comprising a total of six sessions (see Supplementary Appendix pg 3–10 for full agenda). A written draft of the summary discussions of the framing questions and consensus statements was developed by a core group (GC, AG, JGK, MDM) and additional comments to the context and consensus statements were then sought by participating subject matter experts.

RESULTS

Framing questions and consensus statements

For each framing question, the context for each question is provided followed by the consensus statement.

1. What is the use case or rationale for developing TB vaccines for PWHIV?

—Context: TB remains the leading cause of morbidity and mortality in PWHIV, and persons with advanced HIV have the highest risk for TB disease (1). Despite ART lowering viral load to undetectable levels and effective TPT reducing the risk of TB, PWHIV remain at significantly higher risk of developing TB 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 persons without HIV cannot be assumed to be replicated in PWHIV. Reduced immunogenicity has been observed in virologically suppressed and unsuppressed persons including those with in utero HIV exposure (35). Therefore, it is imperative to include PWHIV in upcoming vaccine trials to determine potential differences in safety and immunogenicity. Models clearly show the importance of vaccines to reduce TB incidence, but these models require refinement as they have not included all the relevant parameters specific to PWHIV or those exposed (36). As we have seen with SARS-CoV-2, having data from PWHIV in vaccine trials is necessary to make any real-world recommendations for that population. As this population exceeds 20% of some African populations, being able to vaccinate this group has not only local but global

ramifications (37). Delaying inclusion of PWHIV in TB vaccine trials results in unnecessary morbidity and mortality.

Consensus statements: There is a higher burden of TB among PWHIV and infants exposed to HIV than the general population. There are also potentially different risk-benefit profiles that must be carefully studied to generate relevant evidence for vaccine strategies among PWHIV across the TB disease and HIV spectrum. The potential individual and population level impact of novel TB vaccines targeting PWHIV should be further modelled. Mathematical modelling should also be used to develop a target product profile for TB vaccines for PWHIV and particular sub-populations (e.g., by CD4 T-cell count, age group, and TPT and ART history), and to estimate cost effectiveness and budget impact.

2. What is the landscape of TB vaccine candidates for people with HIV?— Context: A variety of TB vaccines are being tested in early and late phase clinical trials. However, landscape assessments to date have not focused specifically on PWHIV. Certain vaccine candidates, such as live or vectored vaccines, need special assessment of safety profiles in PWHIV. Including PWHIV beginning early in clinical development avoids unnecessary delays for this population accessing vaccine products. All vaccine approaches, including POI, POD, POR and therapeutic vaccines, should include PWHIV given their higher TB incidence, higher recurrence, and poorer treatment outcomes. PWHIV can be categorized by age group into adults/adolescents and infants/children and the strategies for TB vaccines may differ for each population. As most adolescents/adults living with HIV in TB endemic countries will have received BCG at birth, a new vaccine would be considered a booster to the BCG ‘prime.’ For example, pre-exposure/POI vaccines could target newborns/infants/children as a prime while pre- and post-exposure/POD strategies may be more appropriate for adolescents/adults as a booster strategy in TB endemic countries. According to the WHO preferred product characteristics, a TB vaccine for adolescents/adults should show ≥50% efficacy in preventing confirmed pulmonary TB, protect participants with or without past Mtb infection, and be protective in many geographical regions (38). For infants/children, the efficacy of a pre-exposure TB vaccine should be 80% or higher compared to 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 over BCG. As described earlier, Figure 1 highlights the current TB vaccine pipeline and shows which vaccine candidates are being evaluated in PWHIV.

Consensus statement: Trials of TB vaccine candidates should include PWHIV with careful assessment of safety, immunogenicity and efficacy specific to this group.

3. Which vaccine candidates should be prioritized for study in PWHIV on ART?—Context: As only a fraction of Mtb infected persons goes on to develop clinical disease, there are two critical time points for prevention using vaccines: pre-infection or post-infection. Pre-infection (POI) vaccine strategies are appropriate for use in newborns in endemic settings or slightly older adolescents in lower burden regions. Post-infection vaccine strategies include POD in Mtb infected persons, therapeutic vaccination in those with TB disease to reduce the proportion of TB patients with unfavourable treatment outcomes, and POR in TB patients who have been successfully treated (39). TB vaccine

candidates evaluated in PWHIV are summarized in Table 1 and Supplementary Appendix pg 1–2. Viral vectored, subunit protein adjuvanted and whole cell (killed) TB vaccines induce variable humoral and cellular immunity in PWHIV, although responses in ART naïve persons tend to be poorer.

Consensus statement: For adolescents/adults with HIV balancing potential safety, immunogenicity and efficacy, subunit protein/adjuvanted TB vaccines and inactivated mycobacterial vaccines should be prioritised for development in people with HIV, followed by non-replicating viral vectored vaccines. Similarly, for infants/children 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 prioritized for evaluation among PWHIV, including infants/children.

4. What are the trial design considerations of TB vaccine trials that include PWHIV?—

Including PWHIV in TB vaccine trials raises many important design issues that should be considered. These trial design considerations can be divided into 8 sub-considerations: 1) participant characteristics; 2) standard of care (SOC); 3) eligibility criteria; 4) efficacy endpoints; 5) statistics; 6) ethics; 7) regulatory policies; and 8) community involvement. We have provided context and consensus statements for each sub-consideration below.

4.1: When should PWHIV be included in TB vaccine trials?: Context: PWHIV are at high risk of TB disease and would benefit from participating in TB vaccine trials as soon as safely possible to minimize the time to accessing effective TB vaccines that come to market.

Consensus statement: Among adolescents/adults and infants/children with HIV:

Subunit, viral vectored, inactivated, and novel mRNA or DNA TB vaccines, once developed, may 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 may be evaluated in Phase 2, Phase 3, and post-licensure trials, depending on CD4 count and viral load and if there is prospect for more benefit than harm. That is, the safety and efficacy signal in PWHIV supports further development.

Pregnant women with HIV on ART:

- May be included in Phase 2, Phase 3, and post-licensure trials of subunit, viral vectored, and inactivated vaccines.
- Should not be considered for planned trials of BCG and new live attenuated vaccines, as WHO does not recommend BCG for pregnant women.

4.2: What should the SOC be for PWHIV in TB vaccine trials?: Context: An effective TB vaccine for PWHIV would complement existing tools for TB prevention in PWHIV, which includes early disease detection, prompt diagnosis and treatment, infection prevention and control, and TPT.

TPT is the WHO standard of prevention for PWHIV (1). Isoniazid preventive treatment in conjunction with ART is more effective in reducing the risk of TB 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 TB risk in PWHIV (41). As the combined effect of TPT with immune modulation is greater than either intervention alone, it is reasonable to assume that TPT with TB vaccines may have a synergistic effect on reducing the risk of developing TB disease. However, offering TPT to eligible participants with HIV in TB vaccine trials may reduce the apparent effectiveness of TB 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 preventative trials are being designed to allow for a lower incidence due to PrEP uptake (42).

Consensus statement: All PWHIV participating in TB vaccine trials must be on ART. As WHO recommends TPT as SOC for people with HIV regardless of Mtb infection status, TB vaccine trial participants with HIV (on ART), regardless of age, Mtb infection status, phase of trial (1–3) or mechanism of action (POI, POD, POR), should either previously have completed a course of TPT prior to enrolment or be offered TPT during the study if they previously have not completed a course of TPT and have no evidence of active TB disease. TPT should not be provided in trials of live attenuated TB vaccines, as it may reduce the activity of live attenuated TB vaccines. Persons eligible for TPT who have not previously taken TPT should be advised to complete a course of TPT prior to enrolling in the trial.

4.3: What are the HIV-specific eligibility criteria?: Context: 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 TB vaccine trials that include participants with HIV. PWHIV receiving ART should therefore only be considered for inclusion in TB vaccine trials if viremia and CD4+ T-cell counts meet pre-specified thresholds.

Consensus statement: Eligibility criteria for people with HIV on ART differ depending on CD4+ T-cell count. Participants with HIV with CD4+ T-cell counts <100 cells/mm3 or HIV RNA >200 copies/mL:

- Should be excluded from trials of BCG and live attenuated vaccines
- May be included in Phase 1b/2 trials of subunit, viral vectored and inactivated TB vaccines
- May 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 ≥100 cells/mm3 or HIV RNA <200 copies/mL may be included in:

- Phase 1b/2 trials of subunit, viral vectored, and inactivated TB vaccines
- Phase 2 trials of live attenuated TB vaccines
- Phase 3 trials of subunit, viral vectored, inactivated, and live attenuated TB vaccines, if shown to be safe and immunogenic in Phase 2 trials.

4.4: What are the HIV-specific efficacy endpoints for PWHIV?: Context: TB among PWHIV is often paucibacillary, extrapulmonary or subclinical, particularly among those with marked immunosuppression (43, 44). POI vaccine trials in infants, uninfected adolescents or adults evaluate Mtb infection as the endpoint. The gold standard diagnostic for Mtb infection is the interferon gamma release assay (IGRA), which measures cytokine production from Mtb antigen stimulated blood cells. Also, it has been shown that higher IGRA levels or sustained conversion predicts a greater risk of TB disease progression. Whether this holds true for PWHIV is currently unknown, as is how accurate IGRA is in this population. POD vaccine trials typically evaluate clinical bacteriologically confirmed pulmonary TB disease as a highly specific endpoint using solid and liquid culture methods and nucleic acid amplification assays.

Subclinical TB occurs frequently in PWHIV and may have a role in Mtb transmission. A benefit of including subclinical TB as an endpoint in POD/POR/therapeutic vaccine studies is that it may decrease the sample size and reduce the duration of follow-up, as subclinical TB would contribute to the number of endpoints and occurs earlier than clinical TB disease. The decrease in sample size, however, assumes that the vaccine will be equally efficacious at preventing clinical and subclinical TB. It's unclear whether prevention of subclinical TB should be a priority for POD, POR and therapeutic TB vaccines for the following reasons: preventing subclinical TB would be a higher bar for the vaccine to achieve; the evidence that subclinical TB substantially contributes to TB transmission is still circumstantial; identifying and treating subclinical TB disease may compromise the ability to show efficacy against clinical TB.

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

Consensus statement: Efficacy endpoints for participants with HIV overall should be the same as for people without HIV in POI, POD, POR and therapeutic TB vaccine trials. As paucibacillary, extrapulmonary or subclinical TB occurs more commonly in PWHIV, consideration should be given to also include these as endpoints in TB vaccine trials among PWHIV. So as not to compromise evaluation of efficacy in preventing clinical (symptomatic) TB disease, subclinical TB should ideally only be assessed at the end of follow-up. As sustained Mtb infection is used as an endpoint in POI trials, the risk of TB among PWHIV with sustained TB infection should be established.

4.5: What are the trial design and statistical considerations?: Context: Statistical considerations for TB vaccine trials involving PWHIV include comparator arms, immune-bridging, and sample size. TPT history, participant preferences and values, and local policy should also be considered when designing POD TB vaccine efficacy trials.

Consensus statements: As a comparator arm, placebo gives the best chance of minimizing 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-naïve infants who are well controlled on ART; rather, BCG should serve as the SOC comparator. Similarly, the comparator arms for testing safety and efficacy of live attenuated vaccines in older children, adolescents and adults who are well controlled 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 this age group.

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

4.6: What are the ethical considerations?: Context: PWHIV have a more urgent need for TB vaccines than the general population given their significantly higher risks of developing TB disease, drug-drug interactions, and poorer TB treatment outcomes (1–3). Consequently, delays in developing an effective TB vaccine for PWHIV would have greater individual-level consequences than for the general population. Excluding PWHIV from TB vaccine trials would also worsen existing health disparities. The differentially higher burden of TB among PWHIV justifies their inclusion in TB vaccine trials with some degree of greater in-trial risk compared to participants from the general population.

Consensus statement: 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 PWHIV.

4.7: What are the regulatory considerations?: Context: In order to increase enrolment of underrepresented populations including PWHIV in later phase clinical trials, sponsors can follow the U.S. FDA Guidance for Industry (45). Sponsors developing a TB vaccine are encouraged to submit an Investigational New Drug Application even if the U.S. market for that vaccine is limited and the primary target population is outside of the U.S. (46, 47). Expedited program designations are available to facilitate development of qualifying TB vaccines for PWHIV (48). TB is on the list of qualifying tropical diseases eligible for a Tropical Disease Priority Review Voucher, which includes TB vaccines developed for PWHIV (49). Furthermore, sponsors can use the European Union-Medicines for all (EU-M4all) procedure, which aims to facilitate prequalification by the WHO and registration by national regulatory authorities by providing a scientific opinion of the benefit-risk balance of the product, as well as the African Vaccine Regulatory Forum.

Consensus statement: Communication with regulatory authorities should occur early and throughout the development process.

4.8: How should community be involved?: Context: In the past few years, HIV vaccine efficacy trial design has been modified to account for volunteer willingness to take PrEP (42, 50). This newer trial design was implemented after extensive community engagement and deliberations with community advisory boards (CABs) and other local leaders (51). This type of creative next-generation trial design can be applied to the TB vaccine field to ensure PWHIV are included safely. Additionally, CABs and other community stakeholders significantly enhance enrolment and retention of participants in clinical trials, especially in underserved populations (52, 53).

Consensus statement: 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.

5. What is the role of immunological correlates of protection in PWHIV?— Context: Currently, there are no CoPs accepted by regulatory authorities for TB vaccines. Concerted efforts are being made to analyse immune responses from TB vaccine clinical trials that have shown some measure of efficacy (54, 55). CoPs identified in these trials will require validation in larger Phase 3 or implementation studies. Ultimately, establishing CoPs for specific classes of vaccines could enable immune-bridging of vaccines to more inclusive populations; this could help accelerate licensure and broaden indication for these populations, even if they are not adequately represented in the efficacy trials. One other avenue for TB vaccine trials is the human infection challenge platform, where volunteers are vaccinated and challenged with either BCG or another attenuated mycobacterial strain. Done with strict regulatory and safety oversight, these studies could help down select potential immune correlates and help inform future studies in PWHIV.

A more detailed immunological characterization of PWHIV at baseline may be required, as the quality and quantity of innate and adaptive immune responses of virally suppressed individuals may vary (56–58).

Consensus statement: CoPs and other immunogenicity endpoints identified in PWHIV should be applied to and evaluated in people with HIV using immune-bridging studies. Collection of standardized sets of samples across trials is essential to enable such immune-bridging studies. Immunogenicity trials (Phase 1b/2) should include PWHIV to maximize the chance of identifying a CoP that could enable immune-bridging.

6. What are the gaps in preclinical models for studying TB vaccines in PWHIV?—Context: The nonhuman primate (NHP) model of simian and simian/HIV immunodeficiency virus (SIV/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 TB vaccines to model what happens in PWHIV (59).

These SIV/SHIV NHP models can help tailor preclinical studies to be relevant to PWHIV. Importantly, SIV/SHIV NHP models provide an opportunity to look at possible effects of ART and TPT co-administration; study correlates in an unbiased fashion; and further understand the impact 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 NHP models have not yet been shown to be predictive of protection from TB in humans. The NHP model can also help identify tissue-specific correlates that can then be measured in human trials and subsequently modify the tissue-specific assays to those that can use plasma or sputum samples. The NIH recently funded several centres to focus on preclinical models for identifying vaccine CoP (60).

Consensus statement: It is necessary to invest in NHP SIV/SHIV models (with and without ART) for TB vaccine studies. Novel vaccine platforms, such as mRNA and DNA TB vaccines, should be evaluated in NHP SIV/SHIV models, keeping in mind that NHP models have not yet been validated as predictive of protection from TB in humans.

CONCLUSIONS

We developed consensus statements to accelerate the development of TB vaccines for PWHIV. The consensus statements address a number of strategic questions that make the case for including PWHIV as early as possible in clinical development of TB vaccines and also addresses gaps in preclinical models that may portend challenges in future development of a variety of vaccine candidates. The safety and efficacy of TB vaccines in PWHIV needs to be optimized to maximize individual benefit and population level impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1.

Framing Questions.

- What is the use case or rationale for developing TB vaccines for people with HIV?
- What is the landscape of TB vaccine candidates for people with HIV?
- Which vaccine candidates should be prioritized for study in people with HIV (infants, children, adolescents, and adults)?
- What are the trial design considerations of TB vaccine trials that include people with HIV?
- What is the role of immunological correlates of protection in people with HIV?
- What are the gaps in preclinical models for studying TB vaccines in people with HIV?

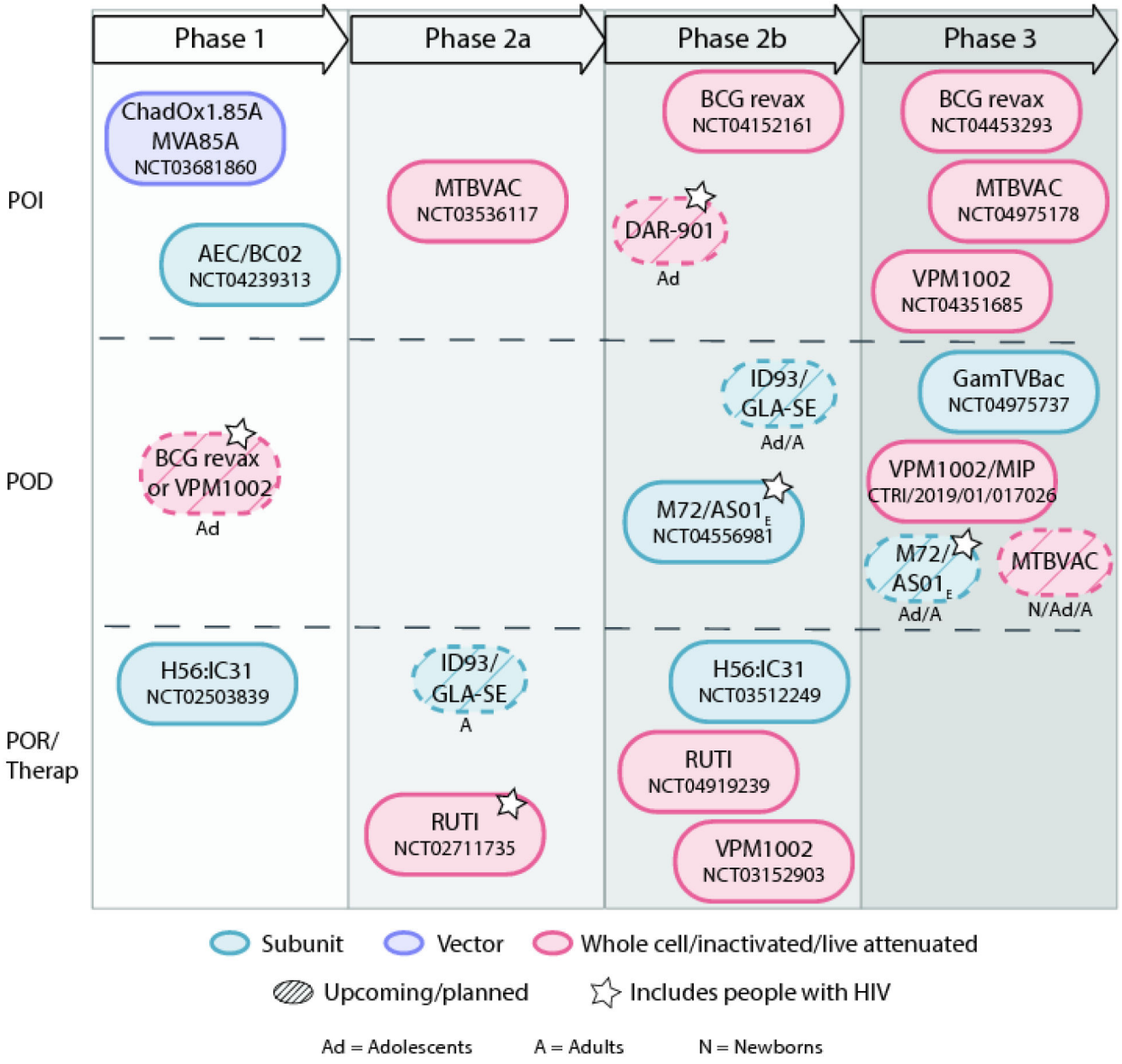

Figure 1. TB vaccine pipeline in 2021.

Ongoing trials were identified through clinicaltrials.gov, WHO International Clinical Trials Registry, and Clinical Trials Registry of India. Upcoming or planned trials were identified by references 14–16. Figure adapted from reference 17.

Table 1.

TB vaccine trials conducted in people with HIV.

	MVA85A (TB011)	MVA85A (AERAS-485)	Ad35/85A85BT B10.4 (Aeras-402)	M72/AS01E	M72/AS01E	H1:IC31	RUTI	*M. obuense* (DARDAR)[1]	*M. obuense* (DAR901)
Product type	Viral vector	Viral vector	Viral vector	Subunit/adj	Subunit/adj	Subunit/adj	FCMtb[2]	WC inact.	WC inact.
Phase	2a	2	2	2	1/2	2	2	3	1
Participants (n)									
HIV+	12	136	26	80		48	47	2000	
HIV+ ART	12	513		80	37				6
TB+	12								
HIV/TB+	12								
HIV−				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 & abscesses	Safe in all	Safe in all
T-cell responses	HIV+ ART similar to uninfected with 85A-specific CD4 durable to 3 years; HIV+ no CD4 durable responses	Mostly monofunctional 85A-specific CD4 and low CD8; No difference between HIV+ ART and HIV+	Mixed CD4 & CD8 to 85A and 85B, which decreased by 6 months; mostly bi and polyfunctional	HIV+ ART higher M72-specific CD4 than uninfected or HIV+ out to 3 years; mostly polyfunctional; no CD8 detected	M72-specific CD4 peaked one month post 2nd dose but durable to 7 months; mostly polyfunctional; no CD8 detected	H1-specific CD4 peaked one month post 2nd dose but durable to 6 months; mostly bi and polyfunctional; no CD8 detected	Polyantigenic IFN-γ highest with 25 μg; uninfected higher than HIV+	Polyantigenic IFN-γ and proliferation increased at 2 months post last dose	No difference between uninfected and HIV+ ART
Humoral responses	Not measured	Not measured	Binding Ab to 85A and 85B	Binding Ab to M72 peaked one month post 2nd dose but durable to 3 years; uninfected ≈ HIV+ART>HIV+	Binding Ab to M72 peaked one month post 2nd dose but durable to 7 months	Not measured	Not measured	Binding Ab to lipoarabinomannan increased at 2 months post last dose	No difference between uninfected and HIV+ ART
Reference and trial ID	[19,23] NCT00480558	[21] NCT01151189	[26] NCT01017536/ DOH-27-0809-2497	[27,28] NCT01262976	[32] NCT00707967	[31] PACTR201105000289276	[22] NCT01136161	[25,29] NCT00052195	[24] NCT02063555

[1] 39% efficacy for secondary endpoint of definite TB.

[2] FCMtb = fragmented, detoxified, heat inactivated (FCMtb) and liposomed Mtb