

Peer-led Implementation of TB-HIV Education and Adherence Counseling in Uganda (TEACH)

Study Protocol

Version 1.2

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PROTOCOL SUMMARY

Title	Peer-led Implementation of TB-HIV Education and Adherence Counseling in Uganda (TEACH)
Target Population	≥1920 persons newly diagnosed with TB, including 578 persons living with HIV
Sites	16 TB treatment units located in clinics and hospitals in Central Uganda
Study Design	Parallel, cluster-randomized trial, with staggered site initiation
Study Duration	12 months for enrollment; Up to 14 months for follow-up to allow 6 months of TB treatment, two months to ensure final outcome assessments are complete, and 6 months of post-TB treatment surveillance. In addition, the 14 months allows up to two months for ART initiation, and 12 months of follow-up afterwards.
Objectives	<p><u>Aim 1:</u> To evaluate the effectiveness and implementation of a peer-navigation strategy for TB education and counseling (TB-EC) to improve TB treatment success and ART retention compared to usual care. We will conduct a parallel, cluster-randomized trial with phased rollout of sites in site volume-matched pairs, enrolling ≥1920 adults (≥578 living with HIV) initiating TB treatment at 16 TB units in Uganda. The unit of randomization is the health facility; the unit of analysis is the individual participant, with clustering accounted for using mixed-effects models. The two arms of the trial will be</p> <ul style="list-style-type: none"> • <u>Usual Care TB-EC Strategy (Comparator Strategy):</u> <ol style="list-style-type: none"> 1) TB-EC routinely delivered by health facility staff 2) Use of Ministry of Health endorsed TB education flipchart 3) Involvement of a designated treatment supporter (community DOT) • <u>Peer-Navigation TB-EC Strategy (Experimental Strategy):</u> Usual Care TB-EC Strategy plus <ol style="list-style-type: none"> 1) Individual-level components <ol style="list-style-type: none"> a. Peer navigators b. Illustrated TB-EC booklet with a structured checklist of core topics c. Individualized adherence planning d. Behavior-change messaging from peer navigators 2) Clinic-level components <ol style="list-style-type: none"> a. Task-sharing of TB-EC with trained peer navigators b. Workflow restructuring to accommodate peer navigators c. Community of practice for peer navigators d. Implementation Champion at each site <p>Our co-primary outcomes will be the effectiveness measures of TB treatment success and ART retention. Our implementation outcomes will be secondary, with the two lead outcomes defined as adherence to TB treatment and adherence to ART, each measured at five months. We will also assess multiple secondary implementation outcomes, including timely initiation of TB medication and of ART; adherence to these medications at 2 months, and persistence in attending monthly refill visits for TB treatment and quarterly ART refill visits. Finally, as secondary effectiveness outcomes, we will assess TB recurrence-free survival 6 months after TB treatment completion, and HIV RNA suppression 6 months after ART initiation, and overall survival at 12 months.</p> <p><u>Aim 2:</u> To evaluate social-behavioral mechanisms for the effects of peer navigation on implementation outcomes. We will measure social and behavioral factors (<i>i.e.</i>, TB knowledge, perceived social support, stigma, and self-efficacy) using validated scales among peer navigators in both trial arms and conduct mediation analyses to identify causal mechanisms of impact on adherence.</p> <p><u>Aim 3:</u> To assess the implementation feasibility, acceptability, appropriateness, fidelity, and context of peer-navigation. We will conduct a nested, convergent mixed-methods study involving</p> <ol style="list-style-type: none"> 1) Surveys of peer navigators and healthcare workers on the feasibility, acceptability, and appropriateness of peer navigation, 2) Direct observation and interviews with peer-PWTB dyads and focus groups with HCW to characterize implementation fidelity/adaptation and contextual factors.

Protocol Background

TB is the leading cause of infectious death, both overall and among people living with HIV (PLH), despite the widespread availability of highly effective treatment. In 2024, there were 1.23 million TB deaths globally, including 150,000 deaths in PLH.¹ Standard TB treatment cures >95% of persons with drug-susceptible TB², which accounts for 98% of PWTB worldwide.³ For PLH with TB, timely initiation or continuation of ART within two weeks of initiating TB treatment, as per local and international guidelines^{4,5}, is proven to reduce mortality by 75% and help PLH achieve similar TB treatment outcomes as PWTB without HIV.⁶⁻⁸ Sex also strongly affects diagnosis and outcomes of HIV⁹ and TB.³

Failing to initiate and adhere to TB treatment and ART leads to poor TB/TB-HIV outcomes (Figure 1). Not linking PWTB to treatment at TB diagnosis is common and contributes to excess mortality.¹⁰ Medication nonadherence after initiation is also common^{11,12} and has major implications: missing as few as 1-2 doses/week of TB medications is associated with a 2-to-29-fold higher risk of treatment failure.¹³ Examining the ability to reach all persons with HIV-TB with ART, a recent meta-analysis of 27 studies of PWTB newly diagnosed with HIV found a pooled ART uptake of only 53% (95%CI 42-63%).¹⁴ Clinic understaffing, stigma, and a lack of TB-HIV service integration were the most common barriers to ART uptake. Better staff education, multidisciplinary care, and peer support were the most potent enablers of timely ART initiation.¹⁴

Preliminary data from Uganda show that stepwise and cumulative losses in adherence and completion remain high across the TB/TB-HIV treatment cascade. Using TB register data¹⁵, Co-I Katamba *et al.* found

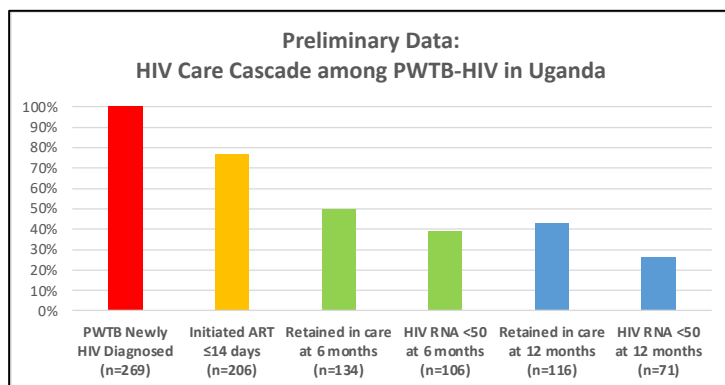


Figure 1. HIV care cascade among PWTB newly diagnosed with HIV at 7 TB units in Central Uganda in 2022. ~35% of PWTB-HIV were ART-naïve.

that 20% of new TB patients did not start TB treatment within 2 weeks of diagnosis. Using the Behaviour Change Wheel¹⁶, they found low TB knowledge and TB stigma to be major barriers, with education and restructuring of TB service delivery acting as possible facilitators.¹⁷ Routine data from 31 TB units in Central Uganda found only 8 sites with treatment success ratios >80%.¹⁸ Although most data¹⁴ on the ART care cascade for PWTB-HIV precedes the major global push to meet the UNAIDS 95-95-95 goals, our group found that major gaps persist in 2022: just 77% started ART ≤14 days; ≤50% were retained in care at 6-12 months, and ≤40% were virally suppressed at 6-12 months (**Figure 1**).

An extensive quantitative and qualitative literature has identified low TB literacy and demotivation as two principal barriers to TB treatment adherence.^{11,12,19-21} Education, defined as interventions to enhance knowledge, attitudes, and practices; and counseling, defined as interventions to provide tailored advice and skills for problem-solving, are two feasible and low-cost approaches to promoting adherence.²² Unfortunately, operational guidance on implementation of TB/TB-HIV EC is limited and incompletely specified in the international TB and HIV guidelines^{23,24} as well as in the Uganda National TB Programme guidelines.⁴

WHO guidelines recommend TB education and counseling (TB-EC) with integrated HIV content as the preferred implementation strategy to promote adherence to TB treatment and ART. However, there is limited evidence on the effectiveness or implementation of TB-EC in high TB-HIV burden settings. A Cochrane systematic review identified only 3 small studies on TB education and counseling to promote adherence, all of which focused on TB preventive therapy in high-income countries; no trials of education and counseling adherence interventions for TB disease treatment were identified.²⁵ Two more recent studies demonstrated the benefits of multidimensional counseling and social support interventions, but in one, from Senegal²⁶, the content and training of counseling were not specified, and in the other, from Ethiopia²⁷, the benefits for person-important outcomes were minimal. In our prior work in Uganda and South Africa, health workers reported little time for counseling, describing TB-EC as often short, non-standardized, or non-existent, regardless of the recipient's HIV status.^{28,29} Integration of HIV-TB services has been associated with decreased TB mortality³⁰, but analyses of ART outcomes among PWTB living with HIV are underpowered.³¹ There is a particular need to fill this gap since existing global health financing models have collapsed in 2025, and high TB-HIV burden countries like Uganda are now rapidly adopting integrated service-delivery models for TB-HIV services.

Evidence from the HIV literature supports peer navigation as an effective strategy to promote ART adherence, but this has not been applied to TB-EC. Peer navigation, defined as “trained personnel who help

patients overcome modifiable barriers to care and achieve their care goals by providing a tailored approach to addressing individual needs,” has proven effective in many chronic medical conditions.³² Although its core components and mechanisms of action still need to be defined, studies suggest that peers draw on shared identities, circumstances, and life experiences to more effectively serve target populations.³³ Peer-navigation programs empower patients by enhancing knowledge transfer, engagement in care, and adherence to therapy to optimize health outcomes.³⁴ Studies of PLH show that peer navigation reduces missed clinic appointments³⁵, improves retention in care³⁶, accelerates ART initiation³⁷, and increases viral suppression.³⁸ Moderate-quality evidence from systematic reviews finds that 86-90% of studies of peer support as a single intervention showed significant positive effects³⁹, and 86% of studies of 1:1 peer support found significant improvements in adherence, emphasizing the effectiveness of peer navigation for HIV engagement.⁴⁰ However, the benefits can be inconsistent if peer navigation is not adapted to the local context and target populations.⁴¹ Factors influencing peer navigation outcomes include trust in the peer-client relationship, peer accessibility, and the presence of peer supervisors.⁴² Finally, HIV peer-navigation studies documenting high fidelity to protocols and adaptation to target populations and context were more effective than ones that did not tailor their approaches.⁴³ Larger, well-controlled studies with long-term data on effectiveness, implementation, and impact mechanisms are needed.⁴⁴ Unstructured support via family DOT does not improve TB outcomes.⁴⁵ Only one small positive study has examined peer navigation for TB⁴⁶, despite calls for more peer interventions by PWTB.⁴⁷

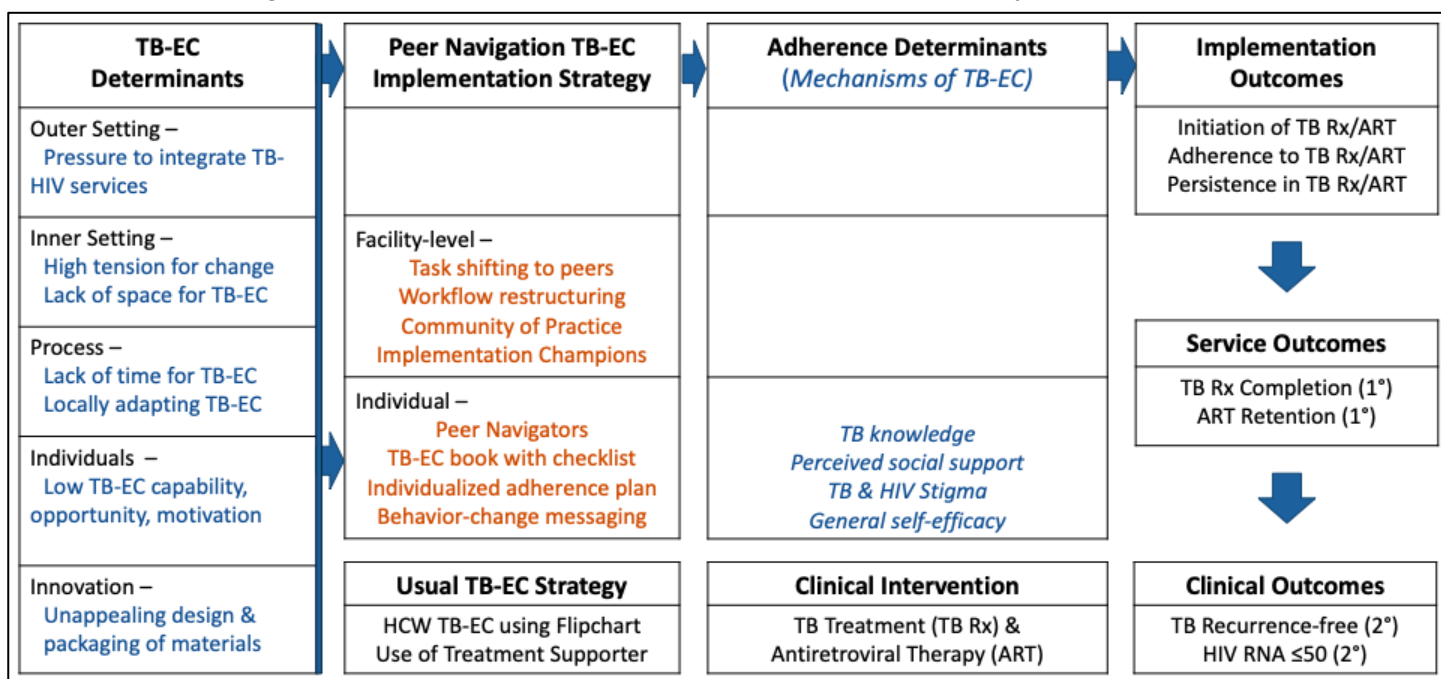


Figure 2. Implementation Research Logic Model (IRLM) for the Peer-Navigation Strategy. We used the IRLM to specify Proctor’s implementation, service, and clinical outcomes (Column 4) for our clinical interventions: TB treatment (TB Rx) & antiretroviral therapy (ART) (Column 2, Row 5). We applied the Capability-Opportunity-Motivation Behavioral (COM-B) model to identify adherence determinants (Column 3) using focus groups with healthcare workers (HCWs) and PWTB/TB-HIV. We applied the Consolidated Framework for Implementation Research (CFIR, Column 1), to identify determinants of standard TB Education and Counseling (TB-EC) delivery (Column 2, Row 4), focusing on the Innovation (*i.e.*, adaptability, relative advantage, complexity, design), Individual (*i.e.*, innovation deliverers), Inner Setting (*i.e.*, physical & work infrastructure, communications, culture, mission alignment) domains. Finally, we used the Behavior Change Wheel framework and Behavior Change Techniques Taxonomy to adapt TB-EC and tailor our multi-component, peer-navigation strategy (Column 2, Rows 1-3) to specify mechanisms for TB-EC to improve client outcomes.

We have developed a community-engaged, theory-informed strategy to promote TB-EC delivery and adherence to TB treatment and ART (Figure 2). In 11 FGDs exploring the experiences of healthcare workers (HCW) and PWTB⁴⁸ with TB-EC, we found that PWTB wanted TB-EC to improve TB knowledge and adherence, and reduce individual and household stigma. However, HCWs felt they lacked the training to deliver effective TB-EC. Both HCW and PWTB agreed that unappealing TB-EC materials, as well as limited time and private clinic space for TB-EC, further curbed their motivation to engage in TB-EC. Yet, both HCW and PWTB strongly advocated for change and suggested bringing in trained peer navigators to deliver TB-EC, following counseling models used in HIV clinics. Based on these suggestions, we used CFIR and the Behaviour Change Wheel framework to develop a targeted “peer-navigation” strategy with 3 components: (1) task-sharing of TB-EC between HCWs and current or former PWTB; (2) restructuring of TB clinic workflows to incorporate dedicated

time for TB-EC earlier in the diagnostic journey; (3) printed education materials, including a *checklist* of essential TB-EC topics; (4) *individualized adherence planning*; and (5) *behavior-change messaging* tailored to adherence barriers. We developed the checklist using existing TB-EC materials⁴⁹ and drawing on adherence principles identified in a systematic review of TB-EC materials.⁵⁰ We designed the first 2 components to enable TB units to initiate TB education while clients wait for TB evaluation results, freeing time and space for individualized HCW counseling after TB diagnosis. We designed the last 3 components to make peer-client interactions more comprehensive, individualized, and motivating. In a pre-post study of 161 PWTB, our peer navigation strategy was found to be feasible and acceptable, and it significantly improved TB literacy and treatment outcomes.⁵¹ Mean within-subject TB disease knowledge increased by 16% (95%CI 12-19%, $p<0.0001$) and TB treatment knowledge by 40% (95%CI 36-44%, $p<0.0001$). Successful TB treatment completion increased from 70% to 87.5% (+17.5%, 95%CI 4-31%, $p=0.011$).⁵² Study limitations included possible unmeasured confounding due to secular trends, a lack of data on ART outcomes, and the contextual disruption of the COVID pandemic during the final months of the peer navigation period. These initial results strongly support a large, well-controlled trial of peer navigation to improve HIV/TB outcomes. In the preparation phase for this trial, we conducted an adaptation exercise using ADAPT-ITT⁵³, to refine this strategy, and add additional components at two levels, to address both facility-level and individual-level implementation determinants, as described further below.

A multi-modal approach to TB/ART adherence monitoring, including novel point-of-care (POC) urine assays, is a strength. Digital adherence technologies pairing electronic pillboxes and medication sleeves with SMS⁵⁴ are widely promoted for HIV and/or TB, yet systematic reviews show high costs⁵⁵, inconsistent effectiveness^{56,57}, selection biases in per-protocol analyses from clinical trials⁵⁸, and inequitable access to mobile technologies.⁵⁹ Monitoring of adherence using biological specimens offers alternatives, but implementation is limited by high assay costs, the low acceptability of blood draws, and the frequent inaccessibility of hair in African populations. In contrast, POC urine assays for isoniazid (INH) metabolites offer a feasible, acceptable, low-cost biomarker^{60,61} for TB medication adherence, and are highly sensitive and specific for semi-quantitatively detecting doses of isoniazid-containing regimens taken within the prior 48-72h.^{62,63} Novel, low-cost POC urine tenofovir assays are highly sensitive and specific for dichotomously assessing adherence to standard ART regimens taken within the prior 4 days.^{64,65} When combined with refill attendance, self-report measures, and clinical outcomes, these biomarkers provide a pragmatic indicator of adherence behavior in implementation trials. Furthermore, if these tests prove feasible, sharing results with PLH/PWTB before assessing adherence by self-report⁶⁶ could provide a future, testable strategy to enhance real-time adherence monitoring and facilitate tailoring of TB-EC using behavior change messaging.

We propose a hybrid type 2 study, guided by a novel tool from Curran *et al* for choosing hybrid study type.⁶⁷ A hybrid type 2 trial is appropriate for four reasons. First, existing data on TB-EC effectiveness is of only low-to-moderate quality.⁴⁵ Second, although TB treatment and ART delivery are highly standardized under WHO^{5,68} and Uganda NTP guidelines⁶⁹, data is needed on whether locally adapted TB-EC strategies can improve programmatic TB/TB-HIV outcomes.⁷⁰ Third, the determinants of medication adherence in Uganda⁴⁸ and beyond¹² are well-known, as are the possible implementation strategies.^{21,71} Thus, a Type 2 study will help us evaluate if the peer-navigation TB-EC implementation strategy can overcome these barriers to adherence.⁴⁸ Fourth, a Type 2 study will allow us to adapt a novel TB-EC strategy to the local context and evaluate its real-world effectiveness and implementation.⁵¹ If the strategy proves effective, concurrently generating new knowledge about implementation will add rigor and promote reproducibility and scalability.⁷²

This proposal advances NIH HIV Research Strategic Goal 3 for 2021-2025, “to promote implementation of research discoveries for public health impact globally.” It also addresses NIH OAR HIV research priorities, including “addressing HIV-associated coinfections”; “improving health outcomes of people with HIV”; developing “implementation strategies to improve systematic uptake of evidence-based treatments in diverse settings and populations”; and using “novel design approaches, such as mixed methods, and alternative clinical trial designs to estimate and improve outcomes and public health impact.”

This study features an innovative design of the implementation strategy. A growing evidence base suggests that implementation strategies co-designed with community partners and tailored to address factors that impede delivery are more impactful than those developed without community consultation or a theoretical basis.^{73,74} We and others have repeatedly shown that tailored strategies can overcome a variety of implementation problems with TB and HIV-related interventions.⁷⁵⁻⁷⁷ The proposed peer-navigation strategy has been developed using such an approach⁴⁸, and its implementation and evaluation will apply up-to-date theoretical approaches in implementation science.⁷⁸⁻⁸⁰

This study features an innovative multi-component implementation strategy. Implementation strategies that include multiple components can address multiple barriers to uptake and are therefore associated with greater impact than single-component strategies.⁷³ However, multi-component strategies are also more costly to implement, so we have decided to target multiple related endpoints in this study (*i.e.*, adherence to both TB treatment and ART). We consider this an innovative, yet rarely used approach to potentially enhance impact and cost-effectiveness.

This study features innovative measurements of intervention fidelity. We will assess adherence to TB medications and ART through a multi-phase process evaluation that frames adherence as a dynamic process with multiple distinct phases from initiation to implementation to persistence. We will measure TB and ART adherence using established scales and validated point-of-care urine biomarker assays for isoniazid metabolites and tenofovir. Many of these aspects are novel and informed by an NIH Notice of Special Interest (**NOSI**) in adherence research (NOT-OD-21-100), including its call for multi-level, multi-component, and peer-led interventions.

This study features innovative measurements of implementation fidelity. Recent editorials and research agendas emphasize the need for studies exploring mechanisms of change as a key element of fidelity.^{73,81} Our plans to apply rigorous, causal methods to assess the social and behavioral mechanisms by which peer-led TB-EC improves TB/TB-HIV adherence is thus highly responsive. Such measures are almost never employed, as a recent systematic review found that only 3% of NIH-funded trials with adherence as an outcome assessed behavior change mechanisms.⁸²

Aim 1: Evaluating the effectiveness and implementation of Peer-Navigation for TB-EC

Introduction

We will conduct a parallel, cluster-randomized trial in Uganda to evaluate the effectiveness and implementation of a novel, peer-led TB education and counseling (**TB-EC**) strategy to improve TB and HIV treatment outcomes among persons with TB (**PWTB**), including persons with and without HIV. Here, we outline the study procedures for this aim.

Study Objective

To evaluate the effectiveness and implementation of a peer-navigation strategy for TB education and counseling (TB-EC) to improve TB treatment success and ART retention compared to usual care.

Hypotheses

Effectiveness

1. The peer-navigation strategy will increase TB treatment success compared with usual TB-HIV education and counseling.
2. The peer-navigation strategy will increase retention in ART care after TB treatment initiation.

Implementation

3. The peer-navigation strategy will improve TB medication adherence compared with usual care.
4. The peer-navigation strategy will improve ART adherence compared with usual care.

Study Design

We will conduct a parallel, cluster-randomized, hybrid Type 2, effectiveness-implementation trial with phased rollout at 16 health facilities in Central and Eastern Uganda. Following a three-month run-in period (October, 2025 through January, 2026) to refine and establish the feasibility of data collection procedures at participating sites, we will publicly randomize the sites. Once the trial begins in March 2026, two new sites will launch every four weeks in pairs matched based on the monthly average of TB disease notifications in the run-in period, with one site assigned to the experimental implementation strategy (*i.e.*, peer navigation) and one to the comparator strategy (*i.e.*, usual care). Clusters remain in their assigned arm (*i.e.*, experimental or usual care) for the entire

trial. For statistical efficiency, effectiveness outcomes are designated as primary outcomes while implementation outcomes are prespecified secondary outcomes.

Trial Design Characteristics

The TEACH study is a pair-matched, cluster-randomized trial. Health facilities are randomized 1:1 to the peer-navigation strategy or usual TB-HIV education and counseling. Allocation occurs at the facility level. The intervention model is a cluster-randomized parallel assignment. Due to the nature of the intervention, participants and providers are not blinded (open-label design).

Study Setting and Sites

The study will be conducted at 16 sites.

Site-level Inclusion Criteria

- Hosts a national TB programme (NTP)-recognized TB treatment unit
- Notified at least ~100 PWTB annually during the period 2022-2024
- Located within 180 km of Kampala

Site-level Exclusion Criteria

- ≤40 km from another included site
- Existing TB treatment adherence program in addition to usual NTP adherence-support package of healthcare worker TB education and counseling and use of treatment supporters
- Don't agree to participate in a study

In total, we considered 34 sites for trial participation. Study staff visited all sites in early 2025 to collect data on standard TB and HIV-TB treatment practices and to verify numbers of notified PWTB, treatment outcomes, and persons with HIV-TB averaged over three years from 2022-2024 (Table 1).

Table 1. Study Sites, by number of eligible persons with TB (2022-2024)

Facility Name	Level	Type	Location	Eligible PWTB	TB Rx Complete	% Complete	Eligible HIV-TB	% HIV
Kiboga	General Hospital	Public	Rural	327	251	77%	28	9%
Mityana	General Hospital	Public	Urban	277	227	82%	112	40%
Kasanda	H/C IV	Public	Rural	220	163	74%	89	40%
Iganga Islamic	H/C III	Private-Not-for-Profit	Urban	203	178	86%	76	37%
Kawolo	General Hospital	Public	Urban	188	119	63%	0	0%
Bugiri	District Hospital	Public	Urban	169	127	76%	170	101%
Bukuya	H/C IV	Public	Rural	148	109	74%	9	6%
Nakaseke	District Hospital	Public	Rural	142	109	75%	58	41%
Nkozi	General Hospital	Private-Not-for-Profit	Rural	134	25	19%	33	25%
Kigandalo	H/C IV	Public	Rural	130	80	61%	19	15%
Kyanamukama	H/C IV	Public	Rural	128	105	83%	100	78%
Butenga	H/C IV	Public	Rural	121	87	72%	63	52%
Nawaikoke	H/C IV	Public	Rural	112	65	58%	9	8%
Nakifuma	H/C III	Public	Rural	105	57	54%	19	18%
Buwenge	H/C IV	Public	Rural	99	65	66%	40	40%
Kiganda	H/C IV	Public	Rural	96	78	81%	60	63%
Total				2599	1844	71%	885	34%

Alternate Sites:

Facility Name	Level	Type	Location	Eligible PWTB	TB Rx Complete	% Complete	Eligible HIV-TB	% HIV
Kamuli	General Hospital	Public	Rural	188	168	89%	36	19%
Mpigi	H/C IV	Public	Urban	132	117	89%	76	58%
St. Benedict	General Hospital	Public	Rural	212	190	90%	31	15%

Ultimately, the three sites shaded in grey were excluded, either because a large proportion of their TB diagnoses and treatment initiations occurred in the community rather than at the health facility (Buwenge) or because they had non-standard peer or nurse-led adherence support interventions at the sites (Kigandalo and Kiganda).

Study Population

Consecutive adults (aged ≥ 18 years) starting treatment for TB/TB-HIV in public and private, not-for-profit primary care clinics in Uganda will be the target study population. Below are the inclusion and exclusion criteria:

Individual Inclusion Criteria

- Age ≥ 18 years
- Registered as a new, relapse, failure, lost-to-follow-up person with TB in the on-site NTP TB Treatment Register
- Screened and invited to participate within 30 days of TB treatment initiation

Individual Exclusion Criteria

- Diagnosed with possible or confirmed drug-resistant TB
- Transferring their TB care into the clinic from off-site
- Residing >~40 km from the enrolling clinic
- Lacking mental capacity to provide informed consent

Study Duration

We will conduct our cluster randomized trial over 26 months, with individual participants followed for at least 6 months after the end of TB treatment. Under both the usual care and the peer-led TB-EC strategies, participants usually have up to 10 clinical visits, including 1-2 visits for diagnosis and TB treatment initiation, and 8 visits for follow-up and medication refills (4 bi-weekly visits in weeks 2-8, then 4 monthly visits in months 3-6). Health workers have discretion to drop some of these visits to give longer follow-up intervals, especially for persons doing well with treatment. Alternatively, persons may have additional visits in the event of adverse drug events or if treatment is extended because of extensive disease or a slower than usual response to treatment. Each visit requires ~30-60 minutes plus waiting time. Most of these visits will be devoted to clinical activities that directly support the person with TB in their treatment, such as the ~15-30-minute peer-led TB-EC sessions at each visit. In addition, there will be research activities at the baseline TB treatment initiation visit, at the two- and five-month visits, and at the end-of-treatment visit. According to WHO guidelines on ascertaining treatment outcomes, participants should complete 6 months of treatment as detailed below, for a total of 180 daily doses of TB medication within 8 months of treatment initiation. The additional two months are provided in case there are minor treatment interruptions (e.g., either prescribed to address adverse treatment effects, or unprescribed due to missed or delayed follow-up visits).

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Figure 3. Enrollment Schema. 12 months of enrollment, with 14 months of follow-up (i.e., 8 months for assessment of TB outcomes, plus 6 months for post-treatment surveillance). *Note:* The planned 8-month run-in period was reduced to 3–4 months because of interruptions in funding.

Last Updated: March 16, 2026

Standard TB Treatment and Usual Care Strategy

Standard TB/TB-HIV Treatment Protocols. All TB units follow Uganda NTP guidelines⁶⁹ recommending WHO-standard 4-drug, 6-month treatment regimens for drug-susceptible TB disease, starting with an 8-week “intensive phase” (*i.e.*, daily isoniazid, rifampicin, pyrazinamide, and ethambutol plus pyridoxine, also known as vitamin B6, all typically dispensed as a 14-day medication supply at every other week refill visits). HIV testing is recommended before or at the time of TB diagnosis, and subsequently every 3 months for those testing HIV-negative.⁴ As per WHO/NTP, PLH should start (or resume ART, if treatment was interrupted) within 14 days of TB diagnosis. If doing well at the 8-week (“2-month”) visit, clients transition to the 2-drug “continuation phase” (*i.e.*, daily isoniazid, rifampicin, and vitamin B6), with monthly refill visits. Monitoring for adverse effects is based on symptoms and signs. Monitoring for response to TB treatment includes sputum smear microscopy at two months, and if positive, again at 5 months. It is also recommended to collect sputum for smear microscopy at the end of treatment visit, to document cure; otherwise, the outcome is designated as treatment completed. HIV treatment monitoring includes CD4 count measures every three months, and viral load assessment six months after ART initiation and then annually.

Usual TB-EC Implementation Strategy. National TB Program guidelines recommend that TB unit staff provide TB education and counseling, but do not specify the topics, frequency, or duration. Most sites have a TB education and counseling flipchart in the TB unit that staff may use to counsel PWTB, with or without their treatment supporters. Guidelines recommend that all PWTB designate a treatment supporter to oversee community directly observed therapy (DOT) by observing PWTB take their pills daily. Treatment supporters or other designees may be allowed to attend follow-up visits to collect medications instead of the PWTB attending.

Peer-Navigation TB-EC Strategy

Experimental Implementation Strategy (Peer-Navigation TB-EC). The proposed experimental implementation strategy includes multiple components at multiple levels, and will be introduced concurrently at each intervention site during a 1-month training and run-in period:

Individual-level implementation components.

- (1) ***Peer Navigators.*** Peer navigators are lay persons with lived experience of TB or TB/HIV (sometimes referred to as expert clients) who will be recruited to assist with delivering adapted TB education and counseling (TB-EC) at participating sites. Drawing on their personal experience as persons living with TB (or rarely as treatment supporters), peer navigators will all complete a specific training program to deliver TB-EC that we will develop and deliver during the 4-week run-in period before we launch the trial at each site. Peer navigators will provide TB-EC during TB evaluation, at the time of treatment initiation, and throughout follow-up visits, offering daily support within the clinic to address gaps arising from limited health-care worker time and training in TB-EC. By integrating peer navigators into routine service delivery, this component is designed to enhance the adoption of TB-EC by expanding the workforce capable of providing individualized, person-centered education and counseling. Their involvement aims to strengthen engagement, improve continuity of support, and ensure that core TB-EC content is delivered consistently across clinical encounters.
- (2) ***Illustrated TB-EC Book with embedded checklist.*** To ensure each enrolled participant receives the relevant education and counseling, the TB-EC Checklist lists the twenty essential topics (**Table 2**) that every person with TB (PWTB) should understand. It also provides a structured tool for peer navigators to guide client education across multiple clinical encounters. We adapted the checklist for Uganda using TB-EC materials from Médecins Sans Frontières South Africa. The 20 core TB-EC topics are covered in 4 short modules:
 - a. ***TB Disease Knowledge*** (before TB testing),
 - b. ***TB Treatment Knowledge*** (after TB testing),
 - c. ***Adherence Planning*** (after diagnosis); and
 - d. ***TB & HIV Monitoring*** (at return visits for medication refills).

Peer navigators will review each topic with clients during TB evaluation, at treatment initiation, and throughout follow-up visits, ensuring that individuals progressively master all core content. By reinforcing key information at baseline, again at two weeks, and as needed thereafter, the checklist is designed to strengthen TB knowledge and build the adherence skills necessary for successful treatment initiation, sustained adherence, and eventual completion. This component addresses critical gaps in patient understanding by standardizing educational content and supporting consistent, iterative learning tailored to each client's needs in a way that is more engaging and person-centered than standard TB-EC materials.

- (3) Individualized adherence planning. During the Adherence Planning module, peer navigators will help PWTB complete a brief individualized adherence plan on key treatment and follow-up topics (items 13-17). They may take the plan home for reference. The goal of the individual adherence plan is to elicit individual needs to facilitate adherence and persistence in treatment through targeted counseling.
- (4) Behavior-change messaging. Each TB-EC module includes person-centered messaging prompts from the Behavior Change Techniques Taxonomy⁸³ (Table 1, Column 2).

Clinic-level implementation strategy components.

- (1) Task-sharing of TB-EC with peer navigators. In collaboration with clinic leaders, the research team will recruit, interview, and employ persons with lived experience of TB, including current and former PWTB (including some PLH), as part-time peer navigators. We will select 6-8 individuals/site, typically from those doing well on the continuation phase of TB treatment or who have completed TB treatment within the past two years. We will provide a daily living wage, transportation costs, personal protective equipment (*i.e.*, N95 respirators), and on-site supervision by an experienced TB-HIV community health worker (**CHW**). After an initial ~5-day training conducted at or near the site, including didactics and role-plays, peer navigators will complete a ~3-week probationary period under the oversight of the CHW supervisor, clinic TB focal person, and implementation champion, as peer navigators provide TB-EC to clients and demonstrate that they have attained competency. Peer navigators will also attend weekly group problem-solving sessions (*i.e.*, Community of Practice meetings) convened by these supervisors to share challenges they face as peer navigators delivering TB-EC- as in prior studies.^{84,85} We will contract with peer navigators to work ~2 clinic days/week (~8-10 days/month) with 4 weeks of annual leave and 4 days of sick leave, and require 8 weeks' notice for termination of employment. This plan provides an adequate workforce of 2-3 peer navigators per clinic day, with 1-2 peer navigators providing group education in the clinic waiting area and 1 providing individual adherence and follow-up counseling in the TB unit. Peer navigators will record all PWTB counseled in a logbook for daily review with their supervisor. Logbooks will be stored in the TB unit in locked cabinets. Peer navigators not reaching or maintaining competency or leaving their positions will be replaced with newly recruited peers to serve in this role. The goal of task-sharing of TB-EC with peer navigators is to increase physical and social opportunities for those in the inner setting of the clinic to inform and support PWTB with individually tailored, high-quality TB-EC.
- (2) Workflow restructuring. As in prior studies⁸⁶⁻⁸⁸, we will work with TB unit staff at intervention clinics during site launch to restructure the flow of TB-EC services as needed to facilitate TB-EC through peer navigation. An experienced research team member will co-lead a workflow mapping exercise with the site-level TB focal person during pre-service training. In three 60-90 minute sessions with intake, lab, ART clinic, and TB unit staff, we will map workflows and identify structures (*e.g.*, waiting areas) and processes (*e.g.*, timing of TB-EC, screening, testing, reporting) for change, describing plans using the Model for Adaptation Design and Impact (**MADI**).⁷⁹ As noted above, we will engage lead clinic administrators and each district-level TB supervisor in this process during group problem-solving sessions attended by peer navigators and their supervisors.⁸⁶⁻⁸⁸ As in prior studies^{76,84}, we will provide a modest budget to aid workflow changes (*e.g.*, updated signage and seating). Staff will implement changes in workflow through training. The goal of workflow restructuring is to overcome health-system barriers related to the CFIR constructs of physical and work infrastructure, using collaborative processes that address the CFIR constructs of communications, culture, and mission alignment related to TB-HIV/TB-EC services.
- (3) Community of practice meetings for peer navigators. With support from the implementation champion and TB focal person, the peer navigator supervisor will convene community of practice meetings. A community of practice is a group of individuals with a shared domain (work as peer health counselors) who form a community around a shared practice (TB-EC). Weekly meetings provide a structured forum for social support, shared learning, and accountability through performance review. In the meetings, peer navigators will collectively go over their logbooks, discuss challenges in delivering TB-EC, and engage in collaborative problem-solving to refine skills and strengthen the consistency of peer-navigation activities. The meetings will be held weekly, with timing determined jointly by peer navigators and the Implementation Champion to accommodate workflow and clinic demands. By addressing gaps in peer knowledge, skills, and social support, these sessions are designed to enhance both fidelity to TB-EC delivery and fidelity to the broader peer-navigation model. This component facilitates the ongoing adoption and adaptation of the peer-navigation program by creating an enabling environment for continuous improvement and reinforcing the capability, confidence, and cohesion of the peer workforce.

(4) **Implementation Champions.** An influential healthcare worker with expertise in TB-HIV care (e.g., TB focal person or clinic in-charge) will be selected in collaboration with facility leadership as an implementation champion to advocate for, support, and sustain the peer-navigation strategy. Champions will coordinate with facility leadership to recruit, train, and supervise peer navigators, while also monitoring the peer navigation program's performance to ensure consistent delivery and quality. By targeting key determinants of implementation (e.g., tension for change among clinic staff; staff capability, opportunity, and motivation) implementation champions will play a central role during the initial training period and throughout ongoing implementation. Their engagement with peer navigators will occur on a daily to weekly basis, and their role will be to promote high implementation fidelity, feasibility, acceptability, and appropriateness of the peer navigation strategy for TB-EC. This component is justified by its potential to mitigate social and motivational barriers that commonly impede adoption of new service-delivery approaches in high-burden TB-HIV settings.

Table 2. Individual-level Components of the Peer-Navigation TB-EC Strategy. The components include (1) Peer navigators, persons with lived experience of TB, equipped with printed educational materials designed to facilitate the other three individual components of the experimental strategy, including (2) a 20-point knowledge & adherence checklist (Column 1), (3) individual adherence planning (#13-17), and (5) behavior change messaging (Column 2), with the relevant behavior change mechanisms indexed by number to the Behavior Change Techniques Taxonomy.⁸³

GROUP TB/TB-HIV EDUCATION TOPICS CHECKLIST	BEHAVIOR CHANGE MESSAGING & MECHANISMS
<u>Front Cover:</u> Tuli Wamu Naawe	"We are together with you" (3.1-3.3, Social support-general, practical, emotional)
<i>Peer Navigator Introduction</i>	"I have lived through TB & been trained to guide you." (9.1, Credible source)
Part 1: What you need to know about TB (Before testing)	<i>TB/HIV Disease Knowledge Module</i>
1. What is tuberculosis (TB)? How is TB spread?	
2. What is HIV/AIDS? How is HIV spread?	
3. What is the relationship between HIV & TB?	
4. What are signs & symptoms of TB disease?	
5. What are signs & symptoms of HIV/AIDS?	
6. How is TB diagnosed? HIV? How do I produce sputum for TB dx?	"Let me show you" (6.1, Demonstrate & 4.1, Instruct to perform behavior)
<u>Summary:</u> What you need to know about TB & HIV	"TB is treatable & curable, just like malaria. (13.2, Framing via comparison) Take your drugs & you will be cured. (5.1, Information on health consequences) The drugs are free." (1.2 Problem solving / barrier reduction)
Part 2: Understanding how TB is treated & prevented (After testing)	<i>TB/HIV Treatment Knowledge Module</i>
7. How do health workers test for TB and give the right treatment?	
8. Why is HIV medicine important for people with TB/HIV?	
9. What do I eat or drink, & what do I avoid, while on TB/HIV medicine?	
10. Why is it important to not to miss your doses of TB/HIV medicine?	"The pills only work if you take them. I took my medicine every day for six months, and now I am TB free." (5.1, Information on health consequences)
11. What are the possible side effects of TB/HIV medicine?	"If you have any symptoms, stop your medicine & call/visit your health worker" (5.2, Make consequences salient)
<u>Summary:</u> How TB is treated and prevented	
INDIVIDUAL TB/TB-HIV COUNSELING TOPICS CHECKLIST	EXAMPLES OF BEHAVIOR CHANGE MESSAGING & MECHANISMS
Part 3: How to keep taking your TB/HIV medicine (After diagnosis)	<i>Individual Adherence Planning Module</i>
12. What is your personal goal in taking TB/HIV medicine?	"Keep your eyes on the prize." (1.1, Set goals for adherence & 1.3, outcome)
13. Where will you store TB/HIV medicine while at home/away?	"Do it the same way each time." (8.3, Form habits)
14. When will you take TB/HIV medicine & how will you remember?	"Take the pills at first light before eating." (7.1, Use prompts/cues)
15. When do you need to return for refills & how will you get here?	"Let us make a plan for your refill visit." (1.4, Engage in action planning)
16. Who can remind you about your medicine/refills & support you?	"Let us find a friend or family member to support you." (3.1, 3.2, 3.3, Social support - unspecified, practical, emotional)
Part 4: How you are doing on your TB/HIV medicine (Follow-up visits)	<i>TB & HIV Monitoring Module</i>
17. How are you feeling?	
18. What challenges are you facing in taking your TB/HIV medicine?	"Believe in yourself." (15.1, Reinforce capability, & 15.4 Self-talk)
19. Do you sometimes miss doses of your TB/HIV medicine?	
20. When are the TB/HIV monitoring visits?	
Peer Navigators Contact Information	
<u>Back Cover:</u> Tuli Wamu Naawe	"We are together with you" (3.1-3.3, Social support-general, practical, emotional)

Trainers from the Walimu study team will organize and deliver an on-site, in-person training on the peer navigation TB-EC at one new site per month, according to the waitlist scheme established during the randomization ceremony. This will include recruiting and training peer navigators, as well as training the health facility on how to work with and supervise them. After the in-person training, there will be a follow-up supervisory visit from the trainers 12 weeks after the peer navigators gain experience with the new components, but with the 4-week cross-over period.

Randomization & Blinding

After 3 months of baseline data collection, we will select 16 sites for randomization. In previous trials, <5% of sites have been excluded for data quality. The unit of randomization is the clinic. As explained above; sites will be matched in pairs based on TB client volume (which is the primary measurable site-level factor that could influence outcomes) then randomly allocated to intervention or control, and finally to a start time.

This sequence of allocation restricted by sites will be determined through a two-stage random drawing. In the first, so-called “Cluster Stage”, health facilities will be ordered from smallest to largest in client volume, and each assigned to a neighboring pair. The order with which these clusters will draw will be randomly determined, and then a representative of each health center in the pair will come forward to witness the draw of the intervention assignment, either experimental or usual care, until all sites are assigned to their intervention in their paired clusters. In the second and final stage, the two representatives of each cluster will assign one representative to draw, without replacement, 1 of 8 balls (labelled 1, 2, 3, 4, 5, 6, 7, 8) from an opaque bag to choose the sequence of launching the trial, at equally spaced, 4-week intervals during the trial period.

Given the complex, behavioral nature of the intervention, it is not feasible to blind providers or participants to the intervention, although all data analyses will be blinded.

Final allocation (January 30, 2026)

Launch Date	Facility Name	Allocation
3/16/26	St Benedict	Usual Care
	Nkozi	Peer Navigation
4/13/26	Nawaikoke	Usual Care
	Nakifuma	Peer Navigation
5/11/26	Iganga Islamic	Usual Care
	Kyanamukaka	Peer Navigation
6/8/26	Butenga	Usual Care
	Bukuya	Peer Navigation
7/6/26	Kamuli	Usual Care
	Nakaseke	Peer Navigation
8/3/26	Mpigi	Usual Care
	Bugiri	Peer Navigation
8/31/26	Kiboga	Usual Care
	Kawolo	Peer Navigation
9/28/26	Mityana	Usual Care
	Kasanda	Peer Navigation

Study Procedures

Recruitment of Participants

A research assistant at each site will work with routine healthcare workers at the study clinics to ensure that all eligible patients are consecutively screened and invited to participate in the proposed activities. Research assistants will oversee recruitment, informed consent procedures, and collection of all clinical and research data, with oversight by a full-time data manager overseeing all sites.

The facility staff will be oriented to [inclusion criteria](#) and encouraged to enroll all eligible individuals to the study. To support these efforts, the research assistant at each site will review the TB treatment register daily to ensure that all eligible patients are being recruited and to coordinate with TB facility staff to approach and recruit any eligible individual not yet recruited whenever feasible.

Cohort Retention

At enrollment, site staff will be trained to ensure that all required demographic and personal contact information, including telephone numbers, place of residence, and the contact information for a treatment supporter are recorded in the TB and HIV registers according to national TB program and national HIV program guidelines.

The timing of follow-up visits will be scheduled at enrollment according to routine TB program guidelines; however no additional efforts at retaining the cohort will be made outside of routine efforts conducted by clinic staff because minimizing losses-to-follow-up is among the primary study outcomes that the intervention seeks to change and we do not wish to contaminate our intervention with additional interventions that are not usual care, such as reminders from research staff to return.

Data Collection

Most data that we are collecting for study purposes is already collected as part of standard clinical care. Procedures that are part of standard clinical care include:

- Baseline Clinical and Demographic Data. (client name, date of birth, sex, client category, disease classification, type of TB patient, risk group, referral, sputum smear result, GeneXpert result, HIV status, other comorbidities, client phone number, name of treatment supporter, treatment supporter type, treatment supporter's phone number)
- TB Treatment Initiation Data. (Unit TB number, ART number, date of initiation, DOT treatment model, TB regimen name, number of daily doses dispensed, date of next appointment)
- TB Persistence Data. (date of actual follow-up visit, date of next appointment, side effects documented, ART regimen, number of daily doses dispensed, date of next appointment, smear microscopy result)
- ART Initiation Data. (ART number, date of initiation, date of next appointment, ART regimen, number of daily doses dispensed, CD4 count, HIV RNA, DSD model)
- ART Persistence Data. (ART number, date of actual follow-up visit, date of next appointment, side effects documented, ART regimen, number of daily doses dispensed, CD4 count, HIV RNA, differentiated service delivery (DSD) model)
- 12-Month Follow-Up Data. (TB-recurrence free survival, vital status)

Procedures to be conducted solely for research purposes include:

- Adherence Measures.
 - 7-day recall
 - Urinary INH and INH metabolites, measured by trained on-site RAs using point-of-care, urine colorimetric testing for isoniazid metabolites (Endana Labs, India)⁸⁹,
 - Urinary tenofovir metabolites, measured by trained on-site Ras using point-of-care urine tenofovir ELISA testing (Monica Gandhi HAL Lab, UCSF). For logistical reasons, urinary assays are measured concurrently.
- Overall Survival and TB Recurrence-Free Survival
 - Data collectors will telephone participants and/or treatment supporters to document TB recurrence-free survival using previously developed methods.
- Peer Navigator Logbook (Peer navigator name, participant name, date, type of TB-EC: group vs. individual, module, duration)

Study Outcomes

Primary Outcomes

Co-Primary Effectiveness Outcomes

1. **TB Treatment Success**, defined according to WHO as the proportion of persons with TB initiated on TB treatment documented in the TB register as having achieved
 - a. TB treatment completion (*i.e.*, a person with TB completing TB treatment without evidence of failure), OR
 - b. TB cure (*i.e.*, a person with microbiologically confirmed TB who was smear-negative in the last month of treatment and on at least one previous occasion).
 - c. The *time frame of assessment* will be at the end of TB treatment.
2. **ART Retention**, defined as the proportion of participants living with HIV and initiated on ART who are
 - a. Alive, and
 - b. Receiving ART, as evidenced by a documented ART medication pickup or ART supply at a clinical visit recorded in the on-site ART register or on the ART treatment card.
 - c. The *time frame of assessment* will be 6 months after ART initiation (± 30 days).

Secondary Outcomes

Lead implementation outcomes

1. **TB Treatment Adherence**, as measured by detectable urine isoniazid metabolite testing 5 months after TB treatment initiation (± 30 days), as a proportion of all participants
2. **ART Adherence**, as measured by detectable urine tenofovir testing 5 months after TB treatment initiation* (± 30 days), as a proportion of all participants living with HIV initiated on ART. The time point

Secondary effectiveness outcomes

1. 6-month post-treatment TB recurrence-free survival, as a proportion of all participants
2. 6-month post-ART initiation viral suppression (HIV RNA ≤ 50 copies/mL), as a proportion of persons living with HIV initiated on ART
3. 12-month overall survival, as a proportion of all participants

Secondary implementation outcomes

TB implementation outcomes:

1. **TB Treatment Initiation** within 2 weeks of TB diagnosis, as a proportion of all participants
2. **TB Treatment Adherence**, as measured by
 - a) Urine isoniazid metabolite testing 2 months after TB treatment initiation, within ± 3 days of the scheduled refill date, as a proportion of all participants
 - b) Urine isoniazid metabolite testing at both 2 months and 5 months after TB treatment initiation, within ± 3 days of the scheduled refill date, as a proportion of all participants
 - c) 7-day medication adherence recall⁶⁶, assessed 2 months (± 7 days) and 5 months (± 30 days) after TB treatment initiation, as a proportion of all participants
3. **Persistence**, defined as attending scheduled TB medication refill visits within ± 3 days of the scheduled monthly refill date, as a proportion of all participants

HIV implementation outcomes:

1. **ART Initiation** within 2 weeks of TB treatment initiation, as a proportion of all participants living with HIV
2. **ART Adherence**, as measured by
 - a) Urine tenofovir testing 2 months after TB treatment initiation*, within ± 7 days of the scheduled refill date, as a proportion of all participants living with HIV initiated on ART
 - b) Urine tenofovir testing at both 2 months and 5 months after TB treatment initiation*, within ± 7 days of the scheduled refill date, as a proportion of all participants living with HIV initiated on ART
 - c) 7-day medication adherence recall⁶⁶, assessed 2 months (± 7 days) and 5 months (± 30 days) after TB treatment initiation, as a proportion of all participants living with HIV initiated on ART
3. **Persistence**, defined as attending ART refill visits within ± 7 days of scheduled quarterly refill dates, as a proportion of all participants living with HIV initiated on ART.

Specification and Timing of Measurements and Outcomes[†]

	Month 0	Month 2	Month 3	Month 5	Month 6	Month 8	Month 9	Month 12
<i>Confirm eligibility and enroll ≤30 days after TB treatment initiation</i>	X							
Measurements (Timed from TB Diagnosis date)								
Clinical & Demographic Data, including multiple telephone contacts	X	X			X			
TB Effectiveness Outcomes								
1°: TB Treatment Success (Treatment Completion + Cure)					X	X		X
2°: TB Recurrence-free Survival								X
2°: Overall Survival								X
TB Implementation Outcomes								
1°: Adherence Measures (Urine INH metabolites ⁸⁹ , 7-day Recall ⁶⁶)		X		X				
2°: Initiation Measure (TB Treatment Initiation ≤2 weeks)		X						
2°: Persistence Measures (Attendance of refill visits)		X	X	X	X			
Measurements (Timed from ART Initiation date, except as indicated)								
ART Effectiveness Outcomes								
1°: ART Retention			X		X	X		X
2°: Virally suppressed (HIV RNA ≤50 copies/mL)					X			
2°: Overall Survival (Timed from TB diagnosis date)								X
ART Implementation Outcomes								
1°: Adherence Measures (Urine TFV ^{90*} , 7-day Recall ⁶⁶)		X		X				
2°: Initiation Measure (ART Initiation ≤2 weeks)	X							
2°: Persistence Measures (Attendance of refill visits)			X		X		X	X

Legend: *Urine-based adherence biomarkers for both TB and ART will be collected at the same scheduled TB treatment visit (2 months after TB treatment initiation ± 7 days and 5 months after TB treatment initiation ± 30 days) to simplify field procedures and minimize missed measurements. Because urine tenofovir assays reflect recent ingestion (approximately 48–72 hours), the exact timing relative to ART initiation does not materially affect the interpretation of the adherence measure. [†]Where multiple outcomes are listed, bolded outcomes and X's indicate the primary measure and timepoint for that outcome.

Aim 1 Sample Size Estimates and Statistical Analysis Plan

Sample Size Estimates

We estimate that a trial with 16 sites (8 per arm) and ~140 eligible patients/site over the 12-month recruitment period will result in $\geq 2,246$ PWTB recruited. Accounting for 15% attrition due to voluntary study withdrawals, ≥ 1920 enrolled PWTB will give $\geq 80\%$ power at alpha 0.05 to detect a $\geq 15\%$ increase in TB completion from a baseline of 75% at usual care sites to 90% at peer-navigation sites, assuming an intraclass correlation coefficient (ICC) of 0.001.⁵⁹ For ART retention at 6 months, we project ≥ 36 PWTB-HIV per site (already accounting for voluntary withdrawals) will provide ≥ 578 enrolled PWTB-HIV and give $\geq 80\%$ power to detect a $\geq 12\%$ increase from 50% for standard TB-HIV/TB-EC to $\geq 62\%$ at peer-navigation sites. Power calculations are adjusted to support 2 co-primary outcomes using a Bonferroni correction for multiple hypothesis testing.^{91,92} For the secondary implementation outcome of ART initiation within 2 weeks, 302 PWTB-HIV who are newly HIV-diagnosed and ART-naïve (*i.e.*, 35% of PLH) will give $>90\%$ power to detect a $\geq 15\%$ increase from 75% with standard TB-EC to 90% with peer navigation.

Statistical Analysis Plan

The unit of randomization is the health facility. The unit of analysis is the individual participant with pulmonary TB (PWTB). Analyses will account for clustering at the facility level using mixed-effects models with facility-level random intercepts.

We will assess the **effectiveness** of the peer-navigation strategy vs. usual care using two separate log-binomial, mixed-effects regression models, with TB treatment success and ART retention as the two outcome variables and study arm (peer-navigation strategy vs. usual care) as the independent variable in each model; the ART retention and other subsequent ART models will only include participants with confirmed HIV. Our primary analysis will consider the intention-to-treat population; as a secondary analysis, we will consider the per-protocol population including any PWTB with ≥ 1 documented interaction with a peer navigator. We will also conduct per-protocol analyses excluding persons who transferred their TB care out to another TB unit (for the TB outcome model) or their HIV care out to another HIV clinic (for the ART outcome model).

We will construct similar log-binomial, mixed-effects regression models for the implementation outcomes of treatment initiation (for TB treatment and for ART) and adherence. Each model will include a random intercept to account for clustering within sites, inducing a working exchangeable matrix. We will use robust score tests⁹³ to estimate intervention effects and assess the significance of the difference between the peer-navigation strategy and usual care, adjusting for multiple testing using the Bonferroni correction. In secondary analyses, we will include interaction terms of the intervention arms with pre-specified participant-level (e.g., age, sex, HIV status), peer-level (e.g., age, sex), and clinic-level characteristics (e.g., clinic volume, facility type, rural vs. urban location, public vs. private/not-for-profit ownership) to determine sources of heterogeneity of effects, again assessing statistical significance using robust score tests. Because participants may interact with different peer navigators across visits, we will investigate the heterogeneity of the causal effect for the characteristics of the peer navigator assigned at the first visit or for the average characteristics of peer navigators across all visits for each participant. Although the study is cluster-randomized, in secondary analyses, we will adjust for confounding by other known or hypothesized determinants of the outcome variables for the intervention-outcome effect estimates, focusing on those where we observe baseline imbalances.

We will report study findings using the CONSORT guidelines for cluster-randomized trials, including the embedded recommendations for pragmatic trials.^{94,95} We will record and document reasons for losses to follow-up and missing covariates. As part of our examination of missing data, we will assess differences in baseline characteristics across treatment arms. We will use two-sample t-tests (or Wilcoxon rank-sum tests) for continuous variables and χ^2 tests for categorical variables. In secondary analysis, we will use inverse probability weighting (IPW)^{96,97} to adjust for possible selection bias due to loss to follow-up and missing covariate values in the secondary covariate-adjusted analyses, to examine the impact of these potential sources of bias on the estimates and tests. We will also use multiple imputation as an additional sensitivity analysis to explore the impact of this alternative method for handling loss to follow-up and missing covariate data on the results.⁹⁸

Trial Reporting

Trial reporting will follow the CONSORT guidelines for cluster-randomized trials. A participant flow diagram will document the number of clusters randomized, clusters initiating the intervention, participants screened, enrolled, allocated to each study arm, completing follow-up, and included in analyses.

Aim 2. Within the Aim 1 study, we will conduct a longitudinal observational study nested in both arms of the cluster-randomized trial to assess the feasibility, acceptability, and appropriateness of a peer-navigation strategy for TB-EC. We will concurrently assess biological adherence using urine biomarkers. We will also perform a mediation analysis of social and behavioral factors (i.e., TB knowledge, perceived social support, general self-efficacy, HIV/TB stigma) to identify causal mechanisms of impact.

Aim 3. The team will also conduct a qualitative and mixed-methods studies to assess the implementation fidelity and context of the peer-navigation strategy for TB-EC:

- a. Process evaluation of intervention fidelity to quantify the adoption, reach, implementation, and maintenance of the peer navigation strategy,
- b. In-depth interviews with PWTB with and without HIV,
- c. In-depth interviews with and direct observation of peer navigators, and
- d. Focus-group discussions (FGDs) with healthcare workers.

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Last Updated: March 16, 2026

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