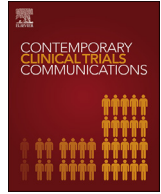




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The ENRICH study to evaluate the effectiveness of a combination intervention package to improve isoniazid preventive therapy initiation, adherence and completion among people living with HIV in Ethiopia: Rationale and design of a mixed methods cluster randomized trial



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ABSTRACT

Background: Isoniazid preventive therapy (IPT) prevents tuberculosis among HIV-positive individuals, however implementation is suboptimal. Implementation science studies are needed to identify interventions to address this evidence-to-program gap.

Objective: The ENRICH Study is a mixed methods cluster randomized trial aimed at evaluating the effectiveness and acceptability of a combination intervention package (CIP) to improve IPT implementation in Ethiopia.

Design: Ten health centers were randomized to receive the CIP or standard of care. The CIP includes: nurse training and mentorship using a clinical algorithm, tool to identify IPT-eligible family members, and data review at multidisciplinary team meetings; patient transport reimbursement; and adherence support using peer educators and interactive voice response messages. Routine data were abstracted for all newly-enrolled IPT-eligible HIV-positive patients; anticipated sample size was 1400 individuals. A measurement cohort of patients initiating IPT was recruited; target enrollment was 500 individuals, to be followed for the duration of IPT (6–9 months). Inclusion criteria were: HIV-positive; initiated IPT; age ≥ 18 ; Amharic-, Oromiffa-, Harari-, or Somali-speaking; and capable of informed consent. Three groups were recruited from CIP health centers for in-depth interviews: IPT initiators; IPT non-initiators; and health care providers. Primary outcomes are: IPT initiation; and IPT completion. Secondary outcomes include: retention; adherence; change in CD4⁺ count; adverse events; and acceptability. Follow-up is complete.

Discussion: The ENRICH Study evaluates a CIP targeting barriers to IPT implementation. If the CIP is found effective and acceptable, this study has the potential to inform TB prevention strategies for HIV patients in resource-limited countries in sub-Saharan Africa.

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1. Background

Despite global scale-up of antiretroviral therapy (ART), tuberculosis (TB) remains a leading cause of morbidity and mortality among people living with HIV (PLHIV). In 2014, an estimated 1.2 million new TB cases worldwide were among PLHIV; 74% were in

Africa [1]. TB is responsible for a quarter of deaths among PLHIV [1]. HIV infection greatly increases the risk of developing TB, which may result from reactivation of latent TB infection, or rapid progression to disease after recent infection [2]. Provision of isoniazid preventive therapy (IPT) reduces TB incidence among PLHIV by 35% [3], and when provided in combination with ART results in a greater reduction in TB risk [4,5] and severe illness [6] than does ART alone. World Health Organization (WHO) guidelines recommend PLHIV receive at least six months of IPT as part of a comprehensive package of HIV care, regardless of ART status [7].

Despite this compelling scientific evidence and strong endorsement by the WHO, countries have been slow to adopt recommendations and global implementation has been limited [8]. Furthermore where IPT has been provided in programmatic settings, uptake and completion have been suboptimal [1,9–11].

While studies have described various interventions to address this evidence-to-program gap [12], few have rigorously evaluated a multi-prong approach that targets known programmatic, structural and psychosocial barriers across the care continuum [10,11,13–18]. Implementation science research is needed to not only evaluate the effectiveness of combination approaches, but also to provide information on the acceptability of the interventions from the perspectives of both patients and health care providers, as well as pragmatic information on the implementation process [19].

Ethiopia ranks tenth among high-burden TB countries, with an estimated incidence of 207 per 100,000; approximately 10% of TB patients are HIV-positive [1]. The Federal Ministry of Health has recommended the use of IPT to prevent TB among PLHIV in its national guidelines since 2005. At the time of study start in 2012, 18% of PLHIV in Ethiopia were receiving IPT [20].

We describe the design of the **ENhance Initiation and Retention in IPT Care for HIV (ENRICH)** Study, a mixed methods cluster randomized implementation science study that aims to evaluate the effectiveness and acceptability of a combination intervention package designed to improve IPT initiation, adherence and completion among PLHIV in Ethiopia.

2. Methods/design

The ENRICH Study is a two-arm mixed methods cluster randomized trial. Ten health centers (the clusters) were randomized to deliver a combination intervention package (CIP) or standard of care (SOC), with stratification by size of the HIV patient population (i.e., ≤ 80 or > 80 patients enrolled in care).

2.1. Study setting

The study was conducted in Dire Dawa and Harari regions of Ethiopia, a low-income sub-Saharan African country of 97.0 million people [21]. These regions are the smallest in the country, both in terms of population and land mass, and their inhabitants reside mainly in urban areas [22]. The majority of PLHIV in Ethiopia receive HIV care and treatment in health centers staffed by one or two nurses, one or two pharmacy personnel, and a peer educator (PE); most health centers have a data clerk and at some, a health officer is also present. TB services including intensified TB case finding and provision of IPT are well-integrated with HIV services. Isoniazid and ART are dispensed in the on-site pharmacy.

2.2. Policy context and collaboration with the government of Ethiopia

The Regional Health Bureaus of Dire Dawa Administration and Harari, as well as executive authorities at each health center were initially engaged during the study conception and design stage,

when applying for funding. This participatory approach [23] was employed to ensure that the study aims were aligned with regional priorities for controlling the TB/HIV epidemic. By engaging these key stakeholders in the planning and implementation of the study, we aimed to foster local ownership and maximize the impact of the study's findings on policy and programming.

2.3. Health center selection

Ten of 11 public health centers supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in Dire Dawa and Harari regions were selected for participation. The remaining health center was excluded from the sampling frame because patient volume was very low (on average, < 10 patients newly-enrolled in HIV care annually). Hospitals were excluded to enhance generalizability, as increasingly, HIV care has been decentralized to health centers, both in Ethiopia and in sub-Saharan Africa more broadly. Two proximate regions were chosen to improve internal validity by ensuring comparability of health centers randomized to either study arm, and to maximize cost efficiency. Table 1 summarizes characteristics of participating health centers.

2.4. Assignment to study arm

Assignment to study arm was done at the health center level as opposed to the individual participant level. Health centers were stratified by HIV patient population size (current enrolled in HIV care), and then numbered sequentially within each stratum. Intervention status was randomly assigned within each stratum by an investigator using SAS v. 9.3 (SAS Institute, Cary, NC). All HIV-positive patients at health centers assigned to the SOC arm received standard of care according to national guidelines, while all those enrolled in health centers assigned to the CIP arm received the standard of care plus the intervention package. Given the nature of the interventions, patients, health care providers and study staff were not blinded to the assigned study arm.

2.5. Standard of care

At health centers randomly assigned to SOC, usual procedures for IPT provision were followed. As per national guidelines, patients are screened for TB at enrollment in HIV care and at each routine clinic visit using a simple symptom questionnaire [24]. Patients with a negative screen are assessed for IPT eligibility; and in the absence of contraindications (active hepatitis, regular and heavy alcohol consumption, or symptoms of peripheral neuropathy), are counseled by a nurse on IPT benefits, potential side effects, and adherence. After IPT initiation, patients are asked to return to the clinic monthly for monitoring of side effects, TB symptoms, and self-reported 30-day adherence, and to receive a 30-day supply of isoniazid. If adherence problems are noted, the nurse counsels the patient, and the patient is advised to regularly take the medication.

There is no standardized treatment literacy curriculum for IPT. Although PE are present at many health centers, their role is limited to supporting adherence to ART. On a biweekly basis, PEs attempt to contact patients who missed their appointment, however many patients do not provide phone numbers and outreach activities are often limited to those residing proximate to the health center due to limited human and financial resources.

2.6. Combination intervention package

At health centers randomly assigned to CIP, the intervention was to be delivered during regular clinic visits as part of routine care to all patients who enrolled in HIV care on or after January 1, 2013 and

Table 1
Baseline characteristics of health centers participating in the ENRICH study, July 2013.

Characteristic ^a	Total (N = 10)	Combination Intervention Package (N = 5)	Standard of Care (N = 5)
Urban setting, N (%)	10 (100)	5 (100)	5 (100)
Mean HIV program duration (SD), y	4.6 (1.6)	5.0 (2.7)	4.1 (2.3)
Median number of patients currently enrolled in HIV care (IQR)	230 (71–525)	120 (102–525)	340 (67–378)
On-site CD4 ⁺ count testing, N (%)	1 (10)	1 (20)	0 (0)
ART prescribed by, N (%)			
Nurse	10 (100)	5 (100)	5 (100)
Health officer	2 (20)	1 (20)	1 (20)
Peer educator program, N (%)	9 (90)	4 (80)	5 (100)
Patient support group, N (%)	1 (10)	1 (20)	0 (0)
Outreach program tracking patients who miss appointments, N (%)	10 (100)	5 (100)	5 (100)

^a SD = standard deviation; IQR = interquartile range.

were eligible for IPT. All nurses working at the HIV clinic were trained to implement the CIP. The CIP contained programmatic, structural and psychosocial components, including: 1) nurse training and mentorship on IPT using a clinical algorithm; 2) use of a Family Care Enrollment Form to identify family members eligible for IPT; 3) support for health care providers to review monitoring data on IPT initiation and adherence during monthly multidisciplinary meetings; 4) reimbursement of patients' transportation costs to monthly clinic visits; and 5) real-time adherence support using trained PE and interactive voice response (IVR) messages. Table 2 shows a comparison of study arms.

Programmatic components of CIP. All nurses working in the HIV clinic at CIP health centers participated in a two-day training on the scientific evidence and guidelines regarding IPT, the importance of integrating IPT into HIV care and treatment programs, and use of an IPT clinical algorithm and Family Care Enrollment Form during regular clinic visits. Refresher training was provided six months later. Job aids, including laminated desk charts and posters depicting the algorithm, were provided for each consultation room to support intervention delivery. Nurses used the algorithm to assess HIV-positive patients for IPT initiation as well as to monitor for and manage problems with adherence, TB symptoms and side effects. Nurses explained to HIV-positive patients that IPT can prevent TB in PLHIV, encouraged IPT initiation, and referred patients to the PE for further education. Nurses also delivered specific adherence messages and assessed IPT adherence at follow-up visits, referring patients to the PE for additional adherence counseling.

A Family Care Enrollment Form, consisting of a family tree, was placed in each patient chart for nurses to complete at enrollment, so that they could ensure that all family members were tested for HIV, and if HIV-positive, were linked to care, screened for TB, and initiated on IPT if eligible.

A doctor was hired as a part-time program monitor to visit each CIP health center on a weekly basis to provide ongoing mentorship to the nurses on IPT provision. A tool was developed so that the program monitor could compile monthly data on IPT initiation,

follow-up and completion for each CIP site, so that at multidisciplinary team meetings, HIV clinic staff could review the data, identify programmatic challenges, and develop solutions to improve quality of care.

Structural component of CIP. Patients were reimbursed for transportation costs in the amount of 35 Birr (approximately 1.8 USD) after each clinic visit while they were receiving IPT.

Psychosocial components of CIP. Psychosocial components of CIP were delivered by PE, HIV-positive individuals who completed IPT and were receiving HIV care at a CIP health center. The PE role encompassed social support, system navigation, referrals and advocacy. PE responsibilities included providing health information; communicating with patients; encouraging IPT initiation and adherence; offering support and empathy; providing referrals; and advocating for patients. Each health center had two PE. PE received a monthly stipend of 800 Birr (approximately 41.1 USD). All PE completed a seven-day training that included both didactic learning and interactive techniques including case studies and role-playing to develop skills; refresher training was provided six months later.

PE were assigned to patients when they initiated IPT, so that they could provide adherence support and answer questions about medications, side effects, and other issues that might arise during the patients' course of IPT. PE used an IPT treatment literacy curriculum to provide health education to patients in the HIV clinic. They also met individually with patients to provide IPT preparation and adherence counseling for the duration of IPT. A scripted, illustrated treatment literacy flipchart was developed for PE. It provides information on the natural history of TB, importance of preventing TB among PLHIV, use of IPT, common side effects and the importance of adherence.

To enable weekly communication with patients, PE were provided with airtime vouchers (100 Birr, approximately 5.1 USD) each month. PE discussed adherence and side effects and provided psychosocial support. In addition, PE were responsible for reviewing the appointment register on a daily basis, and contacting any

Table 2
Comparison of study arms.

	Standard of Care (SOC)	Combination Intervention Package (CIP)
TB symptom screening at enrollment in HIV care and at each routine clinic visit	X	X
For patients with negative screen, nurse assessment for IPT eligibility and, if eligible, counseling on IPT benefits, potential side effects, and adherence	X	X
Monthly clinic visits for IPT refills and monitoring of side effects, TB symptoms and self-reported adherence	X	X
Nurse training and mentorship in IPT using a clinical algorithm		X
Family enrollment form to identify family members eligible for IPT		X
Support to review monitoring data on IPT initiation and adherence during monthly multidisciplinary team meetings		X
Reimbursement of patient transportation costs to monthly clinic visits		X
Real-time adherence support using peer educators and automated interactive voice response messages		X

patients on IPT who missed a clinic appointment. They escorted patients to other services at the health center when needed. PE also participated in monthly multidisciplinary meetings at the HIV clinic to discuss patient challenges.

IVR system. The IVR system was developed and managed by Grameen Foundation (<http://www.grameenfoundation.org>) using an open-source MOTECH Suite application. Calls were recorded by local radio personnel in four languages (Amharic, Oromiffa, Harari, Somali) and sent via the Ethio Telecom mobile phone network (www.ethiotelecom.et). Research assistants (RA) utilized a tablet application developed by Dimagi using Commcare (<http://www.comcarehq.org>) to register patients initiating IPT to receive calls; this information was transmitted to MOTECH via the 2G cellular network.

The IVR system sent four types of automated messages, including: 1) medication reminders; 2) appointment reminders; 3) three-day adherence assessments; and 4) side effects assessments. Medication reminders were sent daily during the first month of IPT, then on a patient-specified schedule (daily or weekly) for the remainder of the IPT course. Appointment reminders were sent two and one days prior to each clinic visit. Adherence and side effect assessments were conducted once a month on separate days. The time of day for medication reminders was chosen by the patient.

To protect their confidentiality, patients entered a self-selected four-digit personal identification number (PIN) in order to access all IVR messages, until which time a popular melody was heard. Patients were asked to key a response to all IVR messages. All IVR calls ended by asking patients if they had questions or concerns and wanted to be contacted by clinic staff. Unanswered IVR calls were automatically re-sent 30 min later and if they were unanswered again, they were recorded as incomplete. The IVR system generated lists of patients who did not respond to the automated messages, experienced PIN failures, reported non-adherence or side effects, or requested to be contacted. Patients reporting non-adherence or side effects and those requesting to speak with clinic staff were to be contacted by the nurse or PE within 24 h.

As many patients receiving HIV care at study sites did not have a mobile phone, RA provided all adult HIV patients initiating IPT with a mobile phone and SIM card. RA described mobile phone use, PIN selection, and IVR call algorithms to patients in detail and practiced receiving and responding to IVR messages with patients until they felt comfortable with the technology. This training was enhanced after the first year of implementation based on patient feedback on barriers to IVR use [25]. Training was repeated a week after IPT initiation, and RA and PE provided additional troubleshooting for patients who consistently did not respond to the automated messages or repeatedly experienced PIN failures. Patients were able to use the phone for personal use and to call the clinic directly. RA dispensed airtime vouchers (35 Birr, approximately 1.8 USD) to patients at their monthly clinic visits, so that they were able to communicate with their PE or nurse in case of difficulties.

2.7. Study participants

The different groups of study participants are shown in Fig. 1.

All newly-enrolled HIV patients eligible for IPT. Routinely collected data were abstracted for all patients aged 18 or older newly enrolled in HIV care at the 10 health centers participating in the study between January 1, 2013 and November 30, 2015 who were eligible for IPT.

Measurement cohort. In addition, a measurement cohort of HIV patients initiating IPT was recruited. Inclusion criteria were: 1) enrolled in HIV care at a study site on or after January 1, 2013; 2) eligible for IPT per Ethiopia Federal Ministry of Health guidelines; 3) initiated IPT at study site on or after date of study initiation (July

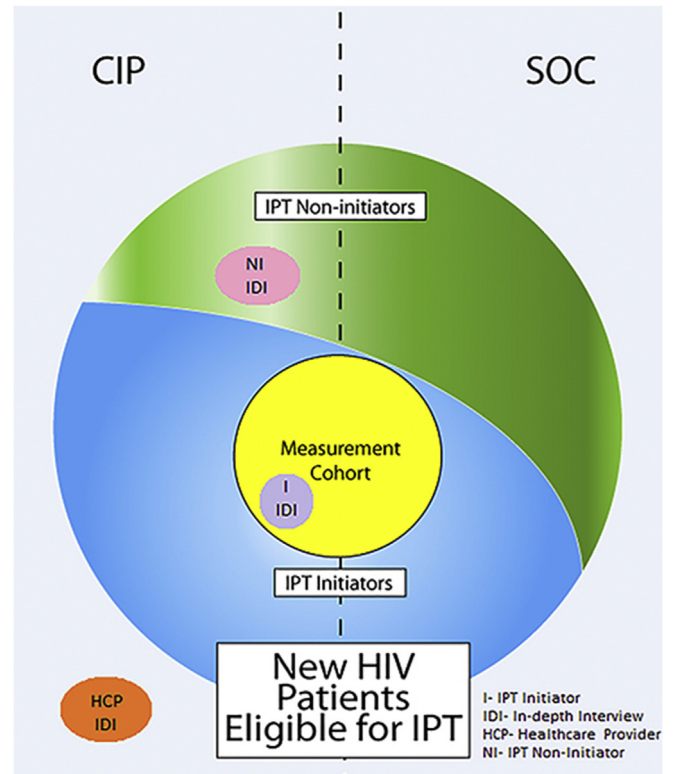


Fig. 1. Study Participants. All newly-enrolled HIV patients eligible for IPT at study sites in both conditions are represented by the large circle; those who initiated IPT (IPT initiators) are depicted in blue, while those who did not initiate IPT (IPT non-initiators) are depicted in green. A sample of IPT initiators from study sites in both conditions who enrolled in the measurement cohort are represented by the yellow circle. In-depth interview participants at CIP study sites included: 1) IPT initiators (I IDI), depicted by the white circle; 2) IPT non-initiators (NI IDI), depicted by the pink circle; and 3) health care providers (HCP IDI), depicted by the orange circle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1, 2013); 4) aged 18 or older; 5) Amharic-, Oromiffa-, Harari- or Somali-speaking; and 6) capable of and willing to provide informed consent within 3 working days of IPT initiation.

In-depth interview participants. Three groups of participants for in-depth interviews were recruited from CIP health centers: 1) IPT initiators; 2) IPT non-initiators; and 3) health care providers.

The inclusion criteria for IPT initiators were: 1) current measurement cohort participation at a CIP health center, or completed measurement cohort follow-up within the past 3 months; 2) received CIP for a minimum of 3 months prior to completion of in-depth interview; 3) Amharic speaking; and 4) capable of and willing to provide informed consent.

Inclusion criteria for IPT non-initiators were: 1) enrolled in HIV care at CIP site between January 1, 2013 and August 31, 2015; 2) eligible for IPT but had not initiated IPT by November 30, 2015; 3) aged 18 or older; 4) Amharic speaking; and 5) capable of and willing to provide informed consent.

Inclusion criteria for health care providers were: 1) nurse or PE working in a CIP health center during the study period; 2) Amharic-speaking; and 3) capable of and willing to provide informed consent.

2.8. Recruitment

Measurement cohort. Nurses were asked to inform HIV patients initiating IPT about the study and to refer them to the RA if they were interested in obtaining more information. Consecutively

eligible consenting patients were enrolled following a routine clinic visit.

In-depth interview participants. IPT initiators were recruited from the measurement cohort, so that study questionnaire data could be used to characterize them. IPT non-initiators were referred to the RA by HIV clinic nurses. Heterogeneous purposive sampling [26,27] was utilized for both groups, according to the following recruitment targets: 1) equal numbers of men and women; 2) equal numbers of participants aged 18–25 years and >25 years; and 3) proportional number of participants at each CIP health center, based on HIV patient intake. Health care providers were referred to the RA by the study coordinator. Convenience sampling was utilized [26], with the following recruitment targets: 1) at least one nurse per health center; and 2) all PEs.

For all participant groups, RA met with potential participants in a private area to provide further information about the study using a standardized script, assess eligibility and obtain written informed consent. RA conducting in-depth interviews did not administer quantitative questionnaires, to minimize social desirability bias.

2.9. Data collection

All newly-enrolled HIV patients eligible for IPT. RA abstracted demographic, clinical and laboratory data from the pre-ART, ART and IPT registers, patient intake form, HIV care/ART follow-up form, and TB screening form using a standardized tool. Standardized data quality assurance procedures were employed at all study sites to minimize the amount of missing data. Study staff regularly reviewed patient files, clinic registers, laboratory reports, and other source documents to ensure high completeness of key study variables.

Measurement cohort. Consenting participants in both conditions completed the same standardized assessments, including interviewer-administered questionnaires at baseline and at monthly follow-up visits coinciding with their clinic visits and monthly phone-based unannounced pill counts, for the duration of IPT (6–9 months). All questionnaires were conducted in Amharic, Oromiffa, Harari or Somali based on participant preference. In addition RA abstracted detailed information from clinic records on participants' clinic visits and medication refills.

Interviewer-administered questionnaires. The baseline questionnaire included measures of sociodemographic characteristics [28]; disclosure of HIV status; HIV- and TB-related knowledge and attitudes; depression (PHQ-9) [29]; alcohol (AUDIT) [30] and substance use; barriers to medical care; social support; health literacy; and social desirability [31]. The follow-up questionnaire included measures of self-reported 30-day adherence [32] and side effects. The end-of-treatment questionnaire included the same measures included in the baseline and follow-up questionnaires, as well as measures of utilization and acceptability of services.

Unannounced pill counts. Participants were called on their mobile phone at an undisclosed time between their monthly study visits and asked to count the pills remaining in their pill bottles or plastic envelopes [33]. A maximum of three attempts to contact the participant were made by the RA each month; after the first year of data collection, the number of attempts was increased to five.

In-depth interviews. In-depth qualitative interviews were conducted with consenting patients and health care providers using semi-structured interview guides [34] that were tailored for each participant group. Interviews were audio recorded, transcribed verbatim, and translated to English. Acceptability, preferences, and utilization of intervention components were explored among IPT initiators and non-initiators. Experiences delivering the intervention, perceived barriers and facilitators, and perceptions about acceptability and ease of uptake and delivery of the intervention

components were explored among health care providers.

Process documentation. Several instruments were also completed by study staff to document the implementation process. A brief semi-structured *Program Characteristics Survey* was administered by RA to the ART nurse at each health center in both study arms, prior to study implementation and on a monthly basis thereafter. The survey tracked implementation of intervention components to assess fidelity and potential contamination as well as system-level factors that may impact CIP implementation. At each CIP site, PE completed a patient encounter log and RA completed an intervention receipt log for mobile phone, airtime, IVR and transportation reimbursement to document the dosage of intervention components received by each patient, and the program monitor was requested to complete a supervision report during each mentorship visit to assess intervention quality [35].

2.10. Data management

Data for participant questionnaires and chart abstractions were collected on paper-based forms. Completed forms were stored in a locked filing cabinet at each health center and entered in the study database. The database was encrypted, password-protected and contained established quality control measures, including skip patterns, range limitations and consistency checks to enhance the accuracy and completeness of the data collected. In-depth interviews were audio-recorded using a digital recorder, immediately transferred to the study database, and deleted from the recorder. The database was backed up nightly to an encrypted external hard drive maintained in a locked filing cabinet.

Throughout the study, four levels of review were conducted to ensure completeness and accuracy of the study data. First, the study coordinator reviewed all completed study forms for errors and completeness. Second, the data manager verified all records entered into the study database against paper data collection forms. Third, during external monitoring visits the US-based project coordinator reviewed 10% of data collection forms entered into the study database for completeness and accuracy, comparing data collection forms with source documentation and hardcopy forms with the study database. In addition, the data analyst ran code to check for missing data and inconsistencies and flagged problematic observations for the study team to verify against paper-based study forms or with source documentation at the study site.

2.11. Primary and secondary endpoints

Primary outcomes are: 1) IPT initiation; and 2) IPT completion. Secondary outcomes include: 1) retention in HIV care; 2) IPT adherence; 3) ART adherence; 4) change in CD4⁺ count; 5) adverse events; and 6) acceptability. All outcomes pertain to the individual participant level. *IPT initiation* is defined as the percentage of HIV-positive, IPT-eligible patients newly enrolled in care during the period of observation who initiated IPT, based on review of clinic records. *IPT completion* is defined as the percentage of HIV-positive patients who were administered at least 180 doses of isoniazid within nine months of IPT initiation [36], based on review of clinic records. *Retention* is defined as the percentage of patients who attended their HIV clinic visit six months following IPT initiation (within a one-month window). Deaths and transfers will be considered not retained. *Adherence* will be determined separately for IPT and ART and is defined by the percentage of total prescribed doses ingested in the past 30 days, averaged across the number of months on treatment, using data from the unannounced pill counts and monthly interviews. *Change in CD4⁺ count* is defined as the difference in CD4⁺ count six months after IPT initiation among patients on ART. *Adverse events* were assessed through monthly

questionnaires about perceived side effects; and chart review to determine toxicity requiring discontinuation of isoniazid as well as cases of TB diagnosed while on IPT. *Acceptability* of intervention components will be characterized via in-depth qualitative analysis and interpretation [37]. Table 3 lists the study outcomes for each group of participants.

2.12. Sample size and power calculations

Our target sample size for all newly-enrolled HIV patients eligible for IPT was 1400 patients. Power calculations for all newly-enrolled HIV patients eligible for IPT were based on our primary outcomes IPT initiation and IPT completion. Based on previous programmatic data we anticipated there would be on average 140 IPT-eligible patients newly enrolled in HIV care at each of the 10 study sites over a 24-month observation period, for a sample size of 1400 patients. When the study was designed, available data demonstrated that only 39% of eligible patients at the study sites had initiated IPT. Assuming a two-sided Farrington & Manning Likelihood Score Test with $\alpha = 0.05$ and an intra-cluster correlation coefficient (ICC) of 0.05, we will have 98% power to detect a difference in IPT initiation from 40% (SOC) to 70% (CIP) (PASS 2008, NCSS Statistic Software). In the WHO PROTEST initiative, median IPT completion across six pilot sites was 38% [11]. Assuming 500 patients ($n = 50$ per site) will initiate IPT during the study period, a 10% increase in IPT completion in the SOC arm because of study participation, a two-sided Farrington & Manning Likelihood Score Test with $\alpha = 0.05$ and an ICC of 0.05, we will have 88% power to detect a difference in IPT completion from 50% (SOC) to 75% (CIP). As per standard practice, patients who die or are lost to follow-up during the course of IPT are considered to have not completed IPT, and thus power calculations for this outcome do not include an allowance for attrition.

Our target sample size for the measurement cohort was 500 participants. Power calculations for measurement cohort participants were based on the outcome change in CD4⁺ count adjusting for ART status. We conservatively estimated that 50% of HIV patients initiating IPT are on ART ($n = 25$ per site). Assuming an ICC of 0.05, with a two-sided T-test we will have 80% power to detect 0.60 standard deviation difference in mean CD4⁺ count between the two study arms.

2.13. Data analysis

An intent-to-treat analysis will be used. In addition, when measuring adherence in the measurement cohort, an as-treated analysis will be used to exclude participants who died or discontinued medications due to adverse events. Generalized linear mixed models (Proc Glimmix procedures in SAS v9.3 with a random intercept for study site) will be applied to test for a difference between study arms for dichotomous (IPT initiation, IPT completion,

retention) and continuous (IPT adherence, ART adherence, change in CD4⁺ count) outcomes to account for clustering of characteristics that may occur among patients attending the same study site. These approaches will provide appropriate adjustments to the standard errors accounting for potential non-independence of observations [38]. Models will include fixed effects for study condition, patient characteristics, time-varying adherence measures and CD4⁺ count (for change in CD4⁺ count) and random effects for site.

For analysis of acceptability of the CIP, two investigators will independently review the first five interviews from each group of participants to develop a preliminary checklist of codes using a grounded theory framework [37,39]. The individual checklists will be compared and reconciled to create a coding dictionary, which will be used to independently code each interview. Additional codes will be added if they emerge during the analysis of subsequent interviews. These codes will serve as building blocks for qualitative concepts and themes. Themes will be crosschecked to enhance inter-rater reliability, and negative case analysis and critical reflexivity will be used to strengthen analytic credibility [37,40]. Data from patients and providers will be analyzed separately and comparatively. Data analysis will explore contextual factors related to the acceptability of CIP components among patients; detect differences, if any, between men and women; and will shed light on common and divergent characteristics of patients' and health care providers' barriers and facilitators.

2.14. Monitoring

As this is an implementation science study with minimal risks, a data monitoring committee was not needed. Study staff were trained to assess for adverse events and to notify the principal investigator immediately if they learned of an adverse event. If there was an adverse event, an incident report was to be completed describing the incident, what caused it, and steps that would be taken to prevent recurrence, and the Columbia University Medical Center Institutional Review Board and the Ethiopia National Research Ethics Review Committee were to be informed as per their respective reporting guidelines.

Internal monitoring of each study site was performed by the study coordinator on a monthly basis, to ensure that each site was adhering to the study protocol and standard operating procedures. External monitoring visits were performed semi-annually by a US-based project coordinator and included review of each site's performance, completion and storage of data collection forms, data entry, and adherence to confidentiality guidelines.

2.15. Ethics and consent process

The protocol and any modifications were reviewed and approved by the Columbia University Medical Center Institutional Review Board and the Ethiopia National Research and Ethics

Table 3
Study outcomes.

Study Outcome	All newly-enrolled, IPT-eligible HIV Patients	Measurement Cohort	In-depth Interviews: IPT initiators	In-depth Interviews: IPT non-initiators	In-depth Interviews: Health care providers
IPT initiation ^a	X				
IPT completion ^a	X				
Retention in HIV care	X				
IPT adherence		X			
ART adherence		X			
Change in CD4 ⁺ count		X			
Adverse events		X			
Acceptability of intervention components			X	X	X

^a Primary outcomes.

Review Committee, and is registered with ClinicalTrials.gov (protocol # NCT01926379). RA obtained written informed consent from all measurement cohort participants and patients and health care providers completing in-depth interviews.

Consent forms and all identifying information obtained at study enrollment to track participants were stored in separate locked filing cabinets at study sites in a locked room. Upon enrollment, participants were assigned a unique identification number. The study questionnaires, data abstraction forms, interview recordings, transcripts and translations, and databases included participant unique identification numbers only; no participant names or identifiers were recorded. A master list with each participant's name and unique identification number is stored in a locked cabinet at each site, and will be maintained only long enough to permit the investigators to review and audit the data, following which this document will be destroyed. Investigators have and will maintain access to the full trial dataset.

2.16. Dissemination

A dissemination strategy was developed to ensure that study findings are shared with key stakeholders, regardless of the magnitude or direction of effect. This strategy includes a dissemination meeting in Ethiopia with the Regional Health Bureaus of Dire Dawa Administration and Harari, and health care providers and patients from participating health centers; a dissemination report for the Regional Health Bureaus; presentations at scientific conferences; and publications in peer-reviewed journals. Investigators will adhere to recommendations from the International Committee of Medical Journal Editors regarding authorship. De-identified data will be made publicly available following publication of primary and secondary outcome papers in accordance with National Institutes of Health Data Sharing Policy [41].

3. Trial status

Enrollment of measurement cohort participants began in July 2013 and ended in May 2015. Recruitment for in-depth interviews began in January 2016 and ended in April 2016. Follow-up procedures including clinical and laboratory record abstraction was completed in May 2016.

4. Discussion

The ENRICH Study aims to evaluate a CIP designed to improve IPT initiation, adherence and completion among HIV-positive patients in Ethiopia. The study utilizes an implementation science framework to not only assess the effectiveness of the intervention package, but also to evaluate the acceptability of the interventions from the perspectives of both patients and health care providers, and provide pragmatic information on the implementation process. The study interventions target programmatic, structural and psychosocial barriers to IPT implementation that have been identified in resource-limited settings, and were selected for their promise and feasibility of implementation and scale-up in HIV programs in diverse contexts. The goal of this study is to improve TB prevention among PLHIV in Ethiopia, and generate generalizable knowledge that can be applied to similar settings.

We chose a cluster randomized design for several reasons. First, intervention delivery at the health center level contributes to the study's implementation science approach as it mimics the way in which the CIP would be delivered outside of a study setting. In addition, given the small size of the health centers and their lack of prior experience with research studies, it was deemed more feasible for health center staff to provide all patients at the site with

the same intervention package, rather than deliver the CIP to some patients and not others, as is done in an individual randomized design. Furthermore, although there was no evidence to endorse that the CIP would be superior to the SOC, individual randomization may have resulted in some patients randomized to SOC feeling that they were receiving substandard care, which might have influenced their engagement in care and thus key study outcomes, namely IPT initiation and completion.

Our study has several strengths. First, randomization allows causal attribution of observed outcomes to the CIP by comparing them to the counterfactual scenario, while reducing selection bias [42]. Second, use of mixed methods [43,44], whereby utilization of qualitative research tools in a sequential explanatory phase follows collection and analysis of quantitative data, will allow us to evaluate acceptability and utilization of intervention components, and assess reasons for IPT non-initiation. Third, the participatory approach, with stakeholder engagement in both the design and implementation phases, has fostered Regional Health Bureau ownership, and will help to ensure successful integration of study findings in policy and programmatic contexts. In addition we are testing an innovative combination intervention that builds on the evidence base of prior scientific work, while addressing the diverse barriers to IPT initiation and completion among PLHIV.

Limitations of the study design include the potential for unanticipated health system inefficiencies to impact CIP implementation, including interruptions in drug supply and laboratory commodities as well as health care worker shortages. However changes in any of these factors are likely to be comparable across study arms and reflect system dynamics captured in implementation science. In addition, the dependence on routinely collected programmatic data for some study outcomes means that data may be incomplete for some participants. Standardized data quality assurance procedures were implemented at all study sites to minimize the amount of missing data. Furthermore as the study is limited to two regions, there is the potential for contamination and migration, which would diminish our power to detect a difference between study arms. However given the goal of assessing CIP effectiveness in a programmatic context, it is essential to evaluate impact in realistic scenarios, while aiming to understand the findings by monitoring spillover and crossover through process documentation. Lastly, the study design precludes assessment of the effectiveness of individual components of the CIP, which would necessitate a substantially larger sample size. However, qualitative data will highlight patient and health care provider perspectives on the utility of individual intervention components, and process data will demonstrate utilization of each study intervention.

5. Conclusions

The ENRICH Study aims to improve IPT initiation, adherence and completion among patients enrolled in HIV care. Achieving this goal will result in improved health outcomes among PLHIV. With one of the world's most severe epidemics of TB, Ethiopia would greatly benefit from the identification of an effective strategy to integrate this evidence-based preventative therapy into HIV service delivery programs. If this study demonstrates that the CIP is effective and acceptable, these findings can be used to advocate for its adoption as standard of care to prevent TB among HIV-positive patients in other resource-limited countries in sub-Saharan Africa.

Author's contributions

AAH conceived the study design, developed the protocol, led study implementation and drafted the manuscript. YHM, SS, TG, AD and ZM conceived the study design, developed the protocol, led

study implementation, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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