Simplified Isoniazid Preventive Therapy (SPIRIT) Strategy to Reduce TB Burden

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GLOSSARY OF KEY TERMS

ART	Antiretroviral therapy
DHO	District Health Officer
DTLS	District TB/Leprosy Supervisor
FGD	Focus Group Discussion
HIV	Human Immunodeficiency Virus
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
KII	Key Informant Interview
LFTs	Liver Function Tests
MoH	Ministry of Health
PLWHIV	Persons living with HIV
RCT	Randomized, controlled trial
RRF	Reduced Refill Frequency
SMS	Short Message Service (i.e. “texting”)
SPC	Single Pill Combination
SPIRIT	Simplified Isoniazid Preventive Therapy
SSA	Sub-Saharan Africa
TMP-SMX	Trimethoprim-Sulfamethoxazole

1. Introduction

The failure to use isoniazid (INH) preventative therapy (IPT) in HIV-infected individuals in Sub-Saharan Africa represents one of the single biggest implementation gaps between evidence and practice in today's response to the HIV epidemic. IPT reduces TB incidence by 40%.[1,2] Yet today, in Africa, less than 2% of eligible individuals receive IPT[3] and TB remains the largest killer of HIV-infected persons.[4] Given the existence of both clear guidelines recommending IPT from international organizations and national health ministries in Africa, as well as simple symptom-based clinical algorithms for identifying persons eligible for IPT that can be applied by front line health care workers,[5] a remaining critical requirement for IPT scale-up is strengthening the link – mediated by middle management in most health systems – between health ministry policy and clinics.

In the Republic of Uganda, the 112 local District Health Officers (DHOs) are the highest-ranking health officials based in the field and outside of the capital city, and serve as key middle managers working at the nexus between policy and implementation. In Uganda, <1% of eligible HIV-infected patients have initiated IPT.[3] Our preliminary work has identified three barriers among DHOs to IPT uptake. First, knowledge of scientific evidence of the efficacy of IPT has not diffused among DHOs (and downstream to providers). Second, the system is already perceived as operating at capacity, and adding yet another two pills (INH and Vitamin B6) to prevent a long-term outcome is not prioritized. Third, geographic remoteness and poor infrastructure (e.g. roads and internet) dilute managerial efficacy and accountability between DHOs and the front line workforce.

To catalyze IPT implementation across Uganda, we propose to test a multi-component "SPIRIT" (Simplified INH Preventive Therapy) intervention targeting DHOs – whom we view as critical dissemination agents – in two geographical regions in Uganda. Our intervention is based on the empirically-validated PRECEDE model,[6] which suggests that health promotion strategies are most effective when they combine: (1) "predisposing factors" comprised of knowledge, attitudes or beliefs that affect behavior; (2) "enabling factors" that facilitate change by making the behavior "easier"; and (3) "reinforcing factors" which include anticipated consequences following a behavior.[7]

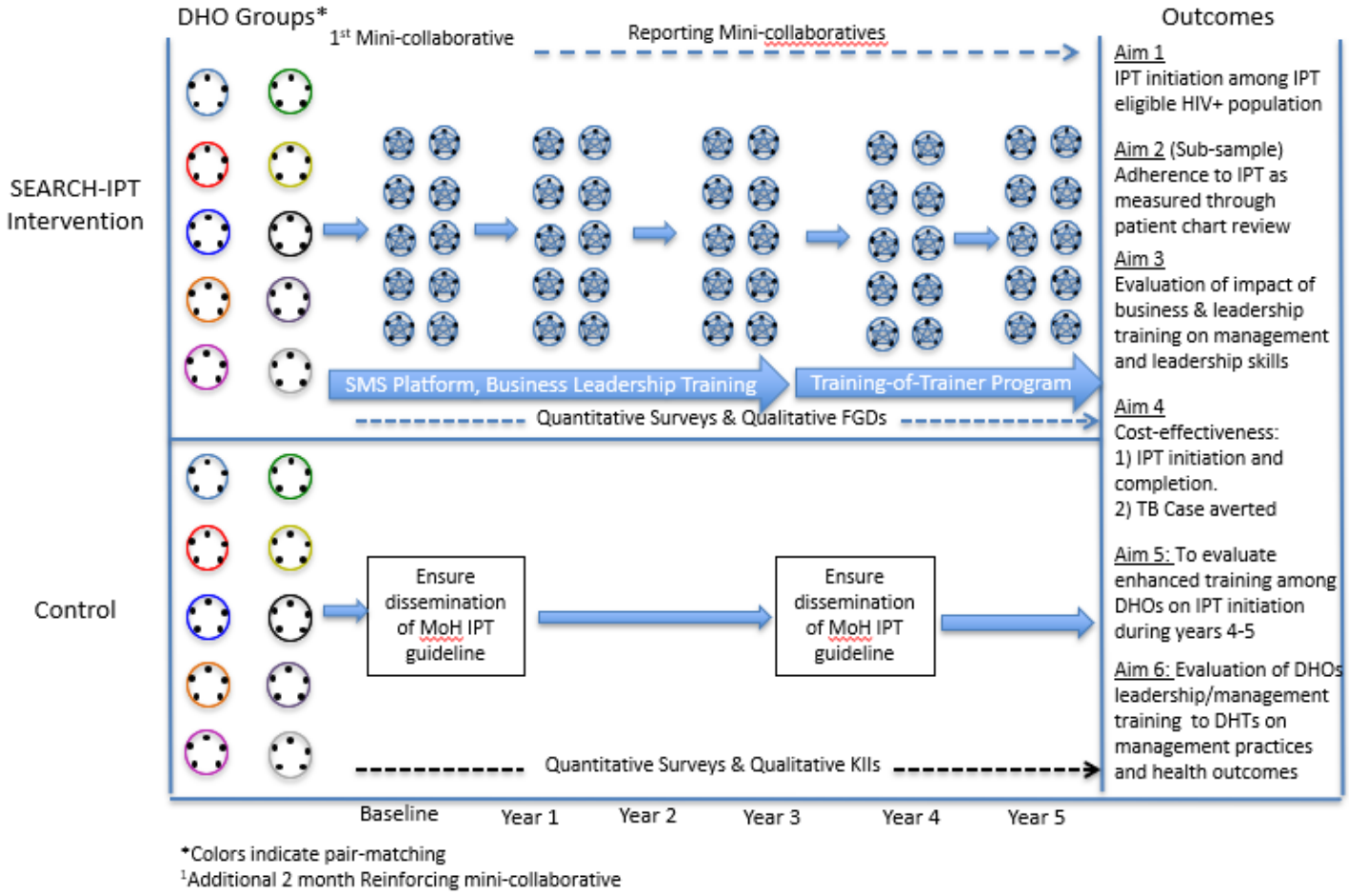
The SPIRIT intervention therefore, first, convenes intervention groups of DHOs into mini-collaboratives to disseminate knowledge about efficacy of IPT and to *predispose* them towards deployment of IPT. Small-world network theory suggests that random links between mini-collaborative members will speed diffusion of this predisposing information and accelerate attitude change towards IPT within the group.[8] Theories of social influence and persuasion suggest that, because of their authority and influence, attitude change among DHOs will result in changes in practice among the front line providers they oversee.[9] Second, we will also deploy a two-way SMS system for DHOs and health care workers, based on local input and a behavioral construct, to facilitate communication between "hub" and "spoke." Third, we will provide DHOs data on their district IPT uptake and share these data with their peers in the collaborative, thereby using a reputational approach to *reinforce* implementation of IPT.

1.1 Study Synopsis

We will evaluate the effect of the SPIRIT intervention on provider prescription and patient use of a 6-month course of IPT among all adults in HIV care in Uganda. SPIRIT is a multicomponent intervention based on the PRECEDE model of behavioral change targeted primarily at the level of the DHO. The SPIRIT intervention deploys predisposing (teaching collaborative); enabling (SMS); and reinforcing (reporting collaborative) components. The study design is a cluster randomized trial where the unit of randomization is a group of 4-6 DHOs: seven groups randomized to the intervention and seven to the current country standard of care. The primary endpoint of the study is the rate at which eligible HIV-positive adults (defined by the Ugandan Ministry of Health) receive a prescription for INH in health facilities overseen by DHOs participating in the SPIRIT trial. Secondary endpoints include: a) IPT completion measured through analyzing successful INH refill patient-visits; b) DHO and health worker attitudes towards IPT; c) TB incidence; d) DHO leadership and management skills and e) costing and cost-effectiveness. The overall goal of the proposal is to test the effectiveness of a scalable approach to increasing IPT uptake through a behavioral change model targeting DHOs (middle managers) within the Uganda health infrastructure. In a second phase of the trial (Phase 2: Years 4-5), we will: a) evaluate the impact of enhanced business management training, focused on SPIRIT intervention DHOs in

the Southwestern Uganda region, on IPT initiation in the region during Phase 2; and b) implement a training of trainers (ToT) curriculum among DHOs enrolled in the SPIRIT trial from the southwestern region of Uganda to determine if DHO-provided business management training of their District Health Team (DHT) members can improve the management skills of the DHT members. **Figure 1** provides a schematic overview of the SPIRIT study:

Figure 1. SPIRIT study schema. For illustration we show 10 DHO groups per arm with 5 DHOs per group. The trial will enroll 14 DHO Groups: 7 intervention and 7 control. In Years 4 and 5 (Phase 2), the trial will be limited to the 14 districts in the Southwestern region of Uganda.



1.2 Background & Rationale

Tuberculosis (TB) remains a major cause of death among persons living with HIV; yet, proven prevention strategies such as isoniazid preventive therapy (IPT) that can reduce TB by 40% are not being fully deployed.[3] The data to support efficacy of IPT for TB prevention in HIV-infected adults are extremely robust.[10-14] Randomized trials and cohort studies conducted in both high and low TB prevalence settings show that IPT reduces the incidence of active TB by approximately 40 percent,[1,2] is safe to administer,[13,15] and is not associated with an increase in isoniazid resistance among TB breakthrough cases.[16] IPT provides independent protection against TB among persons receiving antiretroviral therapy (ART), even at high CD4 cell counts.[17] In a recent post-trial extension study of a large randomized trial of IPT among HIV-infected adults with high CD4 cell counts in Africa, IPT recipients had significant reductions in mortality compared to IPT non-recipients, independent of ART.[18] WHO guidelines recommend IPT for all persons living

with HIV (PLWHIV), regardless of the results of reactive tuberculin skin testing, a marker for highest TB risk.[5] Yet despite these compelling data, the 2014 Global TB report showed that globally, fewer than 2% of PLWHIV in Africa are receiving IPT.[3]

Some of the reasons for poor uptake of IPT in Africa in the past - no country policy and lack of protocols for providers to rule out active TB disease - are no longer barriers. Based on data cited above, IPT is recommended for TB prevention by the WHO and at the country level. From a provider perspective**,** the inability to exclude active TB in IPT candidates (posing a risk for single drug treatment of undiagnosed active TB) has been a legitimate concern for the widespread uptake of IPT. However, there are now evidence-based country protocols for ruling out active TB supported by existing and new data,[19] and from trials in HIV-infected patients with both high CD4 cell counts (TEMPRANO study)[17] and low CD4 counts (REMEMBER study),[20] showing that simple clinical algorithms with or without the addition of new diagnostics, such as the Xpert MTB/RIF assay, can identify a high proportion of PLWHIV who are candidates for IPT.

A study of IPT implementation targeting the "middle managers" of the health system - the 112 District Health Officers (DHOs) responsible for public health in Uganda - is likely to have the highest impact at scale. Although the behavior of health care workers has often been the focus of implementation interventions, for public health interventions in which adoption at scale is a crucial goal, targeting the "middle managers" of the health system – the DHOs – may achieve a greater overall impact, because each DHO oversees budgetary, education and operational aspects of public health over a catchment area of >300,000 residents. In light of the heterogeneity in disease burden between districts, an intervention targeting DHOs vs a single intervention for all health providers in Uganda creates potential efficiency by influencing the highest level of regional authority and permitting flexibility for DHOs to facilitate implementation within their region.

Birken reports four major "points of influence" of a middle manager in a theoretical framework where health policy moves (or not) to implementation and effectiveness.[21] These points of influence include 1) information diffusion; 2) synthesis of data; 3) day-to-day activity; and 4) "selling" of implementation. In designing SPIRIT, we used formative data to conceive of an intervention to overcome current barriers (real or perceived) to IPT implementation at the DHO level. The SPIRIT intervention is based on the PRECEDE model of behavioral change[6] and exploits specific "points of influence" within the DHO's role as middle manager. Some components of the intervention, such as making a single pill combination of INH/B6/septrin available, also serve as "enablers" for front line providers and patients for IPT uptake, thus mitigating the risk of reliance on one level of the health system in our intervention strategy.

Social network analysis assumes interpersonal connections rather than individual "rational agent" characteristics drive the spread of behaviors,[22-26] including practice patterns of health care professionals. Sociologists have long observed that new ideas and practices – from adoption of contraceptives to new farming practices – spread through interpersonal contact.[27] The importance of interpersonal contact in dissemination extends, perhaps exquisitely so, to health care provider behavior. A seminal study in diffusion science from the 1950's and still cited today found that opinion leaders in a community of physicians drove uptake of a new antibiotic through interpersonal contact.[28] Since then, numerous studies have documented the effect of social networks on issues ranging from reducing unnecessary caesarian sections to uptake of novel diagnostic and treatment strategies.[29-32] Although pharmaceutical companies commonly use network principles to influence drug sales,[33] public health research has not fully exploited these principles to promote dissemination of evidence-based interventions. The SPIRIT intervention will utilize the social networks of DHOs as an agent of behavioral change to catalyze IPT uptake.

The SPIRIT intervention incorporates contemporary understandings of relational influences on attitude change, namely that attitude change is motivated not only by absorption of new knowledge, but by normative concerns for ensuring coherent and favorable evaluations of the self (resolving cognitive dissonance, or a conflict between one's knowledge and behaviors), and satisfactory relations with others given the rewards/punishments they can provide.[9] We posit that DHOs will catalyze IPT uptake via their roles both as credible sources of clinical expertise for front line providers, and as key actors in health systems empowered with oversight (dispensing rewards and punishments e.g. hiring, firing, retrenchment) of providers. The SMS messaging component will facilitate the influence of DHOs via enhancing their communication with providers.

Examining cost-effectiveness and resource utilization of any intervention is critical to evaluate value and sustainability in an era where resources are being stretched to treat PLWHIV patients new to and already in care. Modeling studies support the investment in IPT as cost-effective.[34-36] Preventing a TB case is not only cost saving in terms of potential mortality and downstream effects, but also in the morbidity associated with the disease. SPIRIT is designed to test an intervention that is intentionally "simple" by targeting DHOs, mobilizing existing systems, inserting IPT into ongoing ART care structures, and facilitating patient adherence via an SPC. However, there are costs associated with DHO training, introducing a new medication (the SPC INH/B6/septrin) on the formulary, as well as maintaining stocks of the SPC. Our proposal includes a specific costing domain that will measure these processes and provide useful information for countries considering using the SPIRIT strategy to achieve countrywide scale-up of IPT.

Scale up of IPT is long overdue, and research such as that proposed here is needed to assess how to effectively achieve roll out at the country level. Uganda is an ideal location for this study given: a) a high TB burden and large population of PLWHIV; b) government policies supporting IPT use in PLWHIV; c) DHO authority and residence within the community; d) high uptake of TB screening already achieved in ART clinics; and e) high level stakeholder "buy-in" for a sustainable IPT program. The benefit is clear: **Testing an intervention that could improve worldwide delivery of IPT for PLWHIV in high TB burden countries could dramatically reduce global morbidity and mortality from TB.**

2. Study Objectives

Aim 1: Determine if the SPIRIT intervention increases IPT initiation. We will form 14 groups of 4-7 District Health Officers and randomize half to the SPIRIT intervention and half to control (country standard) in a cluster randomized trial. The primary outcome will be the rate at which eligible HIV-infected adults receive a prescription for INH in health facilities overseen by DHOs participating in the SPIRIT trial. In all DHO groups the primary outcome will be measured over the 12-36-month period following the intervention initiation to account for INH stockouts and intervention start up time. We will use health information systems already in place to collect data about visits, IPT eligibility and IPT initiation. For secondary outcomes, we will conduct pre-/post-intervention surveys, focus group discussions, and key informant interviews to assess changes in knowledge, attitudes and practices regarding IPT among the DHOs and front line health workers in intervention and control groups, to assess mechanisms through which the intervention achieves outcomes.

Aim 2: Evaluate the effect of the SPIRIT intervention on IPT completion and TB incidence. Even if the intervention increases IPT initiation, quantifying actual use of IPT by patients and downstream effects on population health status (e.g. reduction in TB incidence) are important to assess impact and thereby enable policy makers to prioritize this intervention more widely. A subset of adult patients who received a prescription for IPT will be randomly sampled to measure IPT completion through patient chart review. TB incidence will also be measured on the overall population of HIV-positive adults in care at health facilities overseen by the DHOs.

Aim 3: Evaluate the impact of business training on leadership and management skills among SPIRIT intervention vs. control DHOs. At the completion of the 36-month period following SPIRIT intervention initiation, we will evaluate leadership and management skills, assessed by cross-sectional leadership and management survey measures, among SPIRIT intervention DHO groups who participated in business training within the SPIRIT intervention and control DHO group members.

Aim 4: Evaluate the cost and cost-effectiveness of SPIRIT. Using effectiveness measures obtained in Aims 1 and 2, and standard time and motion and costing methods, we will estimate the cost and cost-effectiveness of SPIRIT vs. standard of care in our sampled population from Aim 2. Outcomes of interest will include program costs per: a) IPT initiation b) IPT completion and c) TB case averted.

Aim 5: To evaluate the effect of enhanced business training among DHOs in the southwestern Uganda region on IPT initiation during years 4-5 of trial follow-up (Phase 2). Building on business training introduced within the SPIRIT intervention, we will provide additional management training ("Gap Analysis") to a subset of SPIRIT intervention DHO groups, in the southwestern Uganda region, in order to evaluate the impact of enhanced business training on ongoing IPT initiation, at quarterly business training meetings.

Aim 6: **To determine if having DHOs provide business leadership and management training to their District Health Teams (DHTs) can improve district-level management practices and health outcomes**. We will implement a "training of trainers" (ToT) curriculum during Phase 2 of the trial, in which we will provide intervention group DHOs from Southwestern Uganda with training on how to provide business leadership and management training (modeled after the business training the SPIRIT intervention DHOs received in the first phase of the trial) to their DHT members. DHOs oversee and lead District Health Team members (i.e., assistant health officers and disease-specific focal persons) in addressing public health priorities for each district in Uganda. At the completion of Phase 2, we will determine whether DHO-provided training of DHTs impacted management practices and health outcomes at the district level, in districts in SPRIT intervention vs. control DHO groups in the Southwestern Uganda region.

Our overall objective is to determine if a multi-component implementation intervention (SPIRIT) that targets DHOs can increase IPT initiation and completion among HIV-infected persons, and decrease TB incidence, as compared to country standard practices, in a cluster randomized trial in Uganda.

3. Study Site & Population

3.1 Study Setting

This study is evaluating the impact of the SPIRIT intervention on the implementation of IPT in two major geographic regions of Uganda: the Southwest, East and Eastern-Central regions (with the exception of Kampala and Wakiso (Kampala's surrounding suburb)). There are an estimated 1.5 million PLWHIV in Uganda.[37] Following ART scale-up over the last decade, Uganda's ART program, supported by a combination of PEPFAR funding (CDC and USAID), the Global Fund, the Ugandan government and other NGOs, now offers HIV care to 800,000 persons (~570,000 persons on ART) at 1,500 facilities. The MoH is the governing body of the Uganda Health System. The MoH is responsible for coordination and provision of technical guidance for the public health system; within the MoH, the AIDS Control Program coordinates service delivery in public and private facilities and public health programs. Within the MoH are District Health Officers (DHOs) who oversee health facilities and health budgets in their assigned districts (112 total in Uganda as of 2017) and bear overall responsibility for the training and oversight of providers and implementation of MOH policy. DHOs are responsible for coordination of various HIV Implementing Partners (IPs), including the Private not for Profits, and ensure that linkages and referral mechanisms between IPs and other district entities are functional in offering comprehensive services for HIV treatment and prevention.

3.2 Study Population

Aim 1: IPT Initiation: The target population for the SPIRIT trial intervention is DHOs, the DHOs' TB support staff, and the health facilities they oversee in the geographic regions participating in SPIRIT (the Southwest, East and East-central regions). The target population for the trial's primary outcome is all HIV+ adult (≥15 years) patients who are eligible for IPT by Uganda Ministry of Health Guidelines (in each pair-matched DHO group), and in care at a facility overseen by DHOs participating in the SPIRIT trial.
Aim 2: IPT Completion & TB Incidence: Adherence and TB incidence will be measured in a sub-sample of HIV+ adults prescribed IPT at a facility overseen by the DHOs (N=800), using patient chart review. TB incidence will also be measured among all HIV+ adults in care at health facilities overseen by the DHOs participating in the SPIRIT trial based MoH TB Registry entries.
Aim 3: The Aim 1 study population.
Aim 4: Cost and Cost-effectiveness: The study population for Aim 4 will be the sub-sample from Aim 2.
Aims 5 & 6: The target populations for the Phase 2 intervention period are DHOs and their respective District Health Team (DHT) members included in the training-of-trainers (ToT) curriculum and evaluation from the Southwestern Uganda region of SPIRIT. DHOs oversee all health aspects of a district and manage DHTs, comprised of a group of 6-8 health care professionals including the TB, HIV, Malaria and Laboratory focal persons, clinic in-charges, district biostatistician, and maternal and child health officer. The target population for Phase 2 leadership and management outcomes are the DHT members. The target population for Phase 2 health outcomes are district residents in the Southwestern region districts participating in the SPIRIT trial.

4. Study Design

The overall study design is a pair-matched cluster randomized trial. In Phase 1, the clusters correspond to groups of DHOs and are pair-matched within region on predictors of the primary outcome (IPT uptake). The primary outcome of IPT initiation as well as key secondary outcomes of IPT completion and TB incidence, and will be measured among providers and patients in facilities overseen by the DHOs. A sub-sample of adults prescribed INH will be followed longitudinally and assessed for adherence, TB incidence, and costing outcomes (Aims 2 and 4). In Phase 2, we will evaluate the impacts of enhanced business training among Phase 1 SPIRIT intervention DHOs from Southwestern Uganda on IPT initiation (Aim 5) and determine the effect of DHO-provided business training (following DHO participation in a training of trainers' curriculum) on the leadership and management skills of the District Health Team (DHT) members they supervise and health outcomes that DHTs oversee in Southwestern Uganda (Aim 6).

5. The SPIRIT Intervention Trial

5.1 Recruitment & Enrollment of Study Participants

5.1.1 Recruitment

Prior to the start of the study, Dr. Kwarisiima (Uganda PI), the SPIRIT Project Coordinator and study research assistants, will work with the Uganda Ministry of Health to obtain contact information for all Uganda DHOs and, whenever possible, for their respective District TB Supervisors. SPIRIT study staff will initiate contact with the DHOs' offices and/or the District TB Supervisors' Offices by email, phone or in-person, to recruit for participation in the trial.

5.1.2 Consent Process

Upon contacting the DHOs' offices, the SPIRIT Uganda PI or Project Coordinator will describe the SPIRIT trial, and screen for enrollment. All eligible DHOs and/or District TB Supervisors (or other DHO-appointed TB focal person) that agree to participate will provide written consent prior to randomization. If a DHO or TB supervisor departs for a new position, we will consent the incumbent DHO or TB supervisor for study participation.

5.1.3 Screening for Enrollment

Study staff will screen all DHOs and/or District TB Supervisors reached during recruitment (5.1.1 above) for the exclusion criteria noted below.

5.1.3.1 Inclusion Criteria

(a) District Health Officer or District TB Supervisor (or other DHO-appointed TB focal person) in Uganda.
(b) By definition, the DHO or District TB Supervisors in Uganda are all ≥18 years of age

5.1.3.2 Exclusion Criteria

(a) Planned departure from position as DHO or TB District Supervisor prior to randomization.

5.2 Randomization

The SPIRIT trial investigators will form up to 14 groups of 4-7 DHOs (Figure 1). When possible, groups will be formed based on geographic, socio-demographic, and health systems characteristics. The groups will be pair-matched on geographical, socio-demographic and health systems characteristics to improve statistical efficiency. For both the creation of the groups and construction of matched pairs, geographic proximity will be optimized to facilitate DHO mini-collaboratives in the SPIRIT intervention and minimize contamination between arms. Randomization will be performed using a random number generator in standard statistical software, and overseen by the study statistician. One group in each of the 7 matched pairs will be randomized to the intervention, and one to the control condition.

5.3 The SPIRIT Intervention

The SPIRIT Intervention package will be offered to DHOs in intervention groups. The SPIRIT package is based on the empirically validated PRECEDE framework and informed by theories of social networks, social influence and behavior change. We segment the intervention into three components: SPIRIT-1, SPIRIT-2, and SPIRIT-3.

5.3.1. SPIRIT-1: The Teaching Collaborative

Study staff will form up to 7 mini-collaboratives directly from the intervention groups of 4-7 DHOs each (Figure 1), along with any support staff the DHOs may bring, including the District TB Supervisor. Each mini-collaborative of DHOs will be led by an opinion leader ("coach" - selected by the SPIRIT investigators) with HIV and TB expertise, to spread new scientific knowledge about IPT and the clinical ability to rule out TB, and to facilitate discussion between DHOs. Additional training at the Teaching Collaboratives (and the Reporting Collaboratives – see below) may include skills, such as business and management training provided by business leaders, that aim to assist the DHOs and the District TB Supervisors, in overseeing any new or ongoing initiatives to improve IPT implementation. This additional training may also act to incentivize DHOs and District TB Supervisors to continue engaging in SPIRIT intervention mini-collaborative meetings (both Teaching and Reporting) for their personal and professional development.

The rationale for this approach is that research on the link between implementation and program outcomes show that outcomes may not be achieved by didactic training alone and that "coaching" is critical for success.[38] Coaching can facilitate: a) "buy in" from participants; b) sharing of best practices; and c) a productive environment for accountability. By creating a collaborative, the SPIRIT intervention seeks to enable a group to form bonds so that perspectives in favor of IPT can spread within the group.[39]

Implementation: We will hold these meetings twice a year for three years during the SPIRIT intervention, with 1-2 additional meetings in the first year of the intervention period. At each meeting, the group may generate ideas about how best to implement the SPIRIT intervention (see 5.3.2. SPIRIT-2 below), and to discuss lessons learned from the use of novel components of the intervention. We will also be communicating with the DHOs and District TB Supervisors with phone calls using a pre-specified script up to two times between each of these meetings to discuss progress toward IPT implementation.

5.3.2. SPIRIT-2: The Toolkit

The rationale for this approach is that by investigating a "toolkit" of options to ease IPT implementation, we will support DHOs to scale up IPT through the study of the comparative effectiveness of material contributions to their day-to-day function of managing front line providers and clinics. These contributions to improve IPT implementation may include:

1) SMS interventions: Following initiation of DHO mini-collaboratives, a text messaging strategy using local input into behavior constructs will be developed and implemented, to allow text messaging between DHOs, clinic directors, front-line health care workers, and/or clinic patients. Based on pilot work, message domains may include: Informational, motivational, social monitoring and problem solving components. SMS interventions will enhance DHO influence on provider behavior and provider communication with DHO offices, by crossing boundaries of time and space that normally limit communication between DHOs and facilities. For example, messages might read: "Remember that TB can be latent for years!" (informational); "TB is the leading killer of HIV patients" (motivational); "Are you making progress with IPT dispensing to HIV+ patients? Please let me know how it's going" (social monitoring); or "Hope all is well at the facility" (social support). SPIRIT study staff may provide technical guidance and support for SMS implementation in SPIRIT intervention communities, in contrast to SPIRIT control communities. DHO SMS message costs related to the study will be covered by the study. DHOs will receive instruction that no personal health information should be transmitted through SMS.

2) Comparative delivery/refill strategies of INH/B6 (or INH/B6/TMP-SMX SPC), including Community Adherence Groups (CAGs), pharmacy only visits (POVs), 90-day supply (vs. 30-day supply) of INH/B6 to reduce refill frequency, or other strategies developed or discussed in the teaching collaboratives.

3) Adherence and side effect monitoring strategies, including mobile phone monitoring of clinic patients, point-of-care liver function testing, or other strategies developed in the collaboratives;

4) Clinic-based patient education strategies.

5.3.3. SPIRIT-3: The Reporting Collaborative

By creating 7 mini-collaboratives of 4-7 DHOs each, defining targets as a group, and reconvening every 6 months for 3 years (with the additional option of 36 months for a final report back), each collaborative has an opportunity to share progress and results. Incentives in this schema will work through a reputational mechanism. The coach will prepare summaries of data about progress and uptake at each site with the DHOs before the meeting and then present a comparative report showing results across all districts. The coach will provide a trusting and non-critical environment where comparisons can be used to gently reinforce behavior. In

addition, the gaps or differences between sites will allow and prompt discussion of problem solving. This intervention is based conceptually on the IHI Breakthrough Collaboratives Series,[40] but differs in notable ways such as the use of much smaller groups and the focus on a predetermined outcome.

5.4 The Control Condition

The only intervention for DHOs in the control groups will be the guaranteed provision of both printed and electronic versions of Uganda Guidelines for IPT. These 7 "groups" created for the purpose of the randomization will have no required group meetings and will follow usual country standards for IPT.

5.5 INH Provision

INH and B6 will be provided by the Uganda Ministry of Health (MoH), at the request of the Districts, susceptible to drug availability. INH/B6 supply may also be supplemented and distributed by Implementing Partners, with support from the study.

5.6 Measures

For collection of the primary outcome of IPT uptake in eligible patients, we will leverage existing health information systems. All patients (≥15 years of age) with HIV in Uganda receive clinical documentation through MOH form 257 (the "Blue Card"). This card documents basic demographics, clinical and laboratory characteristics, TB screening, and prescription of all medications including INH. Although this routine data collection may be sub-optimal in completeness and accuracy, we have extensive experience in strengthening accurate data collection within routine health systems in Uganda, including investments in data entry, quality control mechanisms such as sampling charts, and asking clinicians for reconciliation when data are missing. These data are the basis of clinic-level measures of IPT initiation and TB cases, documented in the registries, which will be used to evaluate the primary outcome and key secondary endpoints. In the primary outcome, we will rely on registry data, and in IPT completion sub-study (Aim 2), we will take a census-based approach, using all de-identified individual level data available from sampled participants (N=800). We will also measure Aim 1 implementation processes as guided by Proctor's approach to implementation outcomes.[41] *We will measure fidelity to Aim 1 procedures through quantitative assessments of each of the SPIRIT components (Table 1).*

Table 1. Process Measures of fidelity to the SPIRIT intervention

Intervention component	Process measures
SPIRIT 1: Teaching Collaborative	1. Proportion of scheduled trainings for DHOs completed and DHO attendance 2. DHO knowledge about efficacy and delivery of IPT pre- and post-training 3. Number of DHO-led trainings for front line providers conducted (as fraction of planned) and attendance
SPIRIT 2: Toolkit: (e.g. SPC, SMS)	1. SMS delivery (technical); frequency and content (e.g. motivational, informational, problem solving) 2. Provider action derived from SMS interaction 3. Occurrence/frequency of drug stock outs at health facilities
SPIRIT 3: Reporting Collaborative	1. Attendance of DHOs at the reporting collaboratives 2. Number of IPT uptake reports generated 3. Number of reports discussed and actions derived and enacted from collaborative discussions

5.6.1 Outcomes measurements:

The primary outcome of IPT uptake is the rate at which eligible HIV-infected adults who receive a prescription for INH at a health facility overseen by DHOs participating in the SPIRIT trial. IPT initiation will be measured among the two largest clinics in each district and over the 24-month period, beginning 12 months after the intervention start in each pair-matched DHO group. The 12-month lead-in is to account for ramp-up of the SPIRIT intervention and for INH stock-outs. The denominator of this rate is the person-time-at-risk of starting IPT, accounting for prior starts and other changes in the active care population. The numerator is the number of HIV-infected adults prescribed INH. In other words, the primary outcome is the incidence rate of IPT prescriptions among eligible HIV-positive patients. The primary outcome will be compared between SPIRIT intervention and control groups.

Secondary outcomes will include:
1) Changes in DHO and providers' knowledge and attitudes related to IPT in both intervention and control arms over time, as measured by quantitative surveys and data from focus group discussions (FGDs) within intervention districts and Key Informant Interviews (KIIs) within control districts. We will compare these changes across study arms.

2) In addition, for frontline providers, we will compare measures of social influence of DHOs on their own attitudes and practices in the intervention vs. control arms. These measures include perceptions of DHO credibility, salience of information from DHOs, and level of exposure to DHO influence (via assessment of quality and quantity of communications from DHOs).
3) Additional clinical secondary outcomes will include: a) IPT completion - as measured by sufficient INH refill visits to complete 180 doses of INH in a nine-month period, recorded on IPT registry or "blue card" clinical data from clinics overseen by DHOs participating in the SPIRIT cluster randomized trial; and b) TB incidence, as measured from government TB registry data from each district. We will compare these outcomes (IPT completion and TB incidence) by study arm, within the sub-sample described for Aim 2 (below).

The schedule of evaluation for outcome measures is shown in Table 2.

Table 2. SPIRIT Trial - Schedule of Evaluations

		Baseline	2-4 Months	6 Months	12 Months	18 Months	24 Months	30 Months	36 Months
Intervention	DHOs & TB support staff	- Pre-test - Teaching Mini-collaborative - Quantitative survey	- Reporting Mini-collaborative	- Reporting Mini-collaborative	- Reporting Mini-collaborative - FGDs (sample)	- Reporting Mini-collaborative	- Reporting Mini-collaborative - FGDs (sample)	Reporting Mini-collaborative	- Post-test - FGDs (sample)
	Frontline provider sample	Quantitative survey			Quantitative Survey		Quantitative Survey		Quantitative Survey
Control	DHOs & TB support staff	- Pre-test - Distribute MoH IPT Guidelines - Quantitative survey			- Distribute MoH IPT Guidelines - KIIs		- Distribute MoH IPT Guidelines - KIIs		- Post-test - KIIs
	Frontline provider sample	Quantitative survey			Quantitative survey		Quantitative survey		Quantitative survey

5.6.2 Mixed methods assessment of intervention mechanisms and implementation processes

1) We will conduct quantitative surveys of intervention and control DHOs and a sub-sample of providers at baseline and three times following the intervention to measure knowledge, attitudes and practices related to IPT. Among providers, surveys will ask additional questions regarding perceptions of DHOs' credibility, salience of information from DHOs, and level of exposure to DHO influence (including quantity and quality of interpersonal communications).
2) We will collect qualitative data through 2-3 Focus Group Discussions (FGDs) in sub-samples of DHOs (e.g., combining 2 to 3 DHO groups per FGD) annually during the intervention and following the intervention. The FGD guide will be designed to elicit, in the intervention arm, DHOs' perceptions of intervention content and impact on attitudes and practices. In the control arm, IPT-related secular trends, including perceptions of change in policy, policy communications, attitudes, and practices in the absence of intervention will be measured through KIIs in a sample of DHOs/DTLSs.

DHOs/DTLSs and frontline providers selected to participate in quantitative surveys, FGDs, and KIIs will provide written informed consent prior to participation. All data collection will be conducted in local languages and/or English, depending on interviewee preference.

5.7 Statistical Analysis

Overview of statistical analyses for IPT uptake: The target population for the primary outcome is all HIV+ adult (≥15 years) patients who are eligible for IPT within 36 months of intervention start (in each pair-matched DHO group), and in care at a facility overseen by DHOs participating in the SPIRIT trial. The analytic population for the primary outcome is all adults in active HIV care in the largest two clinics in each district of the trial. The primary outcome (Section 5.6.1 above) for each randomized group is the rate at which these patients receive a prescription for INH over the 12-36 month period following the intervention start. In the primary analysis, we will account for prior INH starts and changes in the analytic population. All DHO groups are followed for three years total.

Estimation of the impact of the SPIRIT intervention on this outcome will be based on a two-stage analysis. In the first stage we will estimate IPT uptake for each DHO group. IPT uptake will then be compared between SPIRIT intervention and control arms with targeted maximum likelihood estimation (TMLE), adjusting using a pre-specified algorithm, and accounting for the pair-matched design and limited numbers of independent units.[42] As a secondary analysis, we will implement the unadjusted effect estimator. Hypothesis testing will be based on a two-sided test at the α=0.05 significance level. We also propose to examine possible effect modifiers and mediators (e.g. HIV prevalence, TB screening, loss to follow-up rates, study time, drug shortages and drug availability).

Analyses of secondary quantitative outcomes (IPT completion, TB incidence: see Aim 2) will be implemented analogously.

Analyses of qualitative data: Focus group facilitators and key informant interviewers and recorders will be engaged to participate in coding and interpretation of data in collaboration with Camlin and other investigators. Team members will prepare and load translated FGD and KII transcripts into Atlas.ti software[43] for coding and interpretation. An initial analytical code list will be defined by Camlin on the basis of theory and initial empirical data, with iterative refinement as new data are loaded. At defined stages of the analysis process, codes and definitions will be refined or expanded as needed. In team meetings, members will discuss coding of rich or difficult segments of text to achieve consensus, and Camlin will lead training exercises to ensure consistency in the application of codes to the data. Code query reports will be generated to explain patterns and identify emergent themes in the FGD and KII data.

5.7.1 Data Collection & Management

SPIRIT-1 and -3 Collaboratives Data: 1) *Audio transcripts* of participant (DHO/TB supervisor) discussions during mini-collaboratives (SPIRIT-1 and SPIRIT-3) may be obtained following enrollment and randomization, for analysis of both fidelity of training by coaches, as well as for evaluation of intra-collaborative communication and content. 2) DHO/TB Supervisor knowledge as measured by *pre- and post-training testing*. 3) DHO/TB Supervisor attendance and participation in training.

Health Center (Clinic-level) Data: All data, including data on INH prescribing and refills, will be obtained either from encounter forms (“blue cards”) at local health centers and recorded onto standardized case record forms by study staff, or from centralized Uganda MoH health registries. Data will also be obtained from MoH TB Registries at the clinical level. Afterwards, the forms will be entered directly into an electronic database. Data integrity checks will be written into the database to limit the entry of incorrect data and ensure entry of data into required fields. Data may be double entered to verify accuracy of entry. The database will be transferred regularly via a secure electronic transfer to the data center facility in Kampala and stored on a secure server.

Qualitative Data: Staff will record interviews on audio devices using study IDs (not participant names), and transcribed interviews and translations will be data entered into appropriate software on password-protected study computers. Data from interviews will be transferred via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

5.7.2 Sample Size & Accrual

Sample size considerations for the primary outcome of IPT uptake: In the control condition (standard of care), we anticipate 10% of eligible individuals will receive IPT. We anticipate that 50% of eligible individuals will receive IPT in the intervention condition. Assuming 12 DHO groups per arm and an extremely conservative matched pair coefficient of variation k_m of 0.4, this study will be powered at >95% (Figure 2).[44] If we more than double the anticipated rate of IPT use in the control condition to 25% (vs. 50% in the treatment condition), the power remains at >90%. Of note, unlike a traditional sample size calculation where the investigators must "enroll" to reach a desired sample size, we use routine health systems data and therefore calculate anticipated power from a fixed sample size based on the number of DHO groups. As shown in Figure 2, these power calculations are not sensitive to the number of patients enrolled in each DHO group. We expect 1,000-25,000 patients in each DHO group.

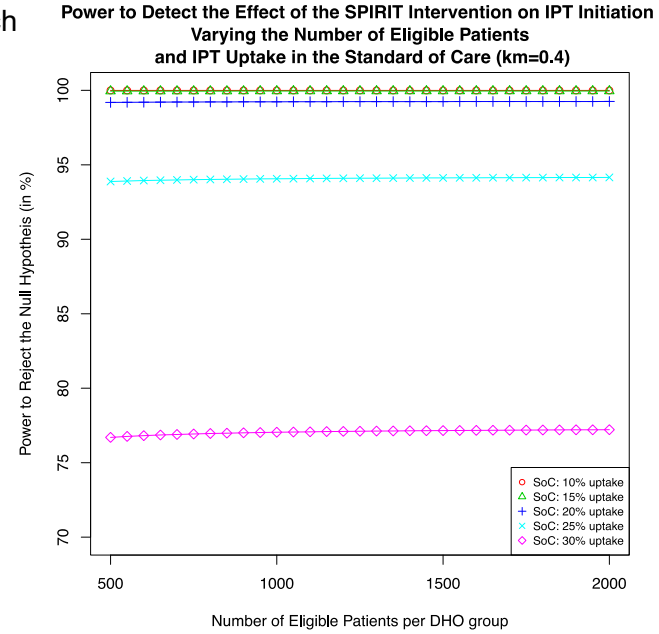


Figure 2 (right): Power calculations for the primary outcome of IPT uptake, assuming 12 DHO groups per arm and varying the outcome among the standard of care (SoC) and the number of patients

6. IPT Adherence & TB Incidence in the SPIRIT Trial

Rationale: The population health impact of our DHO intervention aimed at reducing TB depends not only on IPT prescribing, but also on adherence and completion of IPT by patients. Thus, to understand the implementation pathway, it is important to measure an adherence outcome, which we propose to assess through the analyses of INH refill visits, as metrics of long-term pill consumption. Because ART use can both affect risk for TB in HIV+ persons, and be indirectly affected by our DHO intervention, we will also measure ART refills in our sampled subset of Aim 2. As another secondary outcome, TB incidence contributes to quantifying the magnitude of the public health effect of SPIRIT.

6.1 IPT Registry Sampling Approach

Aim 2 will employ a sampled approach for adherence measurement through INH refill visit measurements, as measured by review of MoH IPT refill registries. In the sampling approach (see details below in 6.6.3. Sampling Approach & Sample Size Considerations), de-identified INH refill data will be collected from approximately 800 HIV+ adults prescribed INH in Uganda (400 from SPIRIT Intervention groups, and 400 from control groups).

Additional measures of TB incidence (through MoH TB registry data) will be measured on the broader population of HIV-positive adults in care at health facilities overseen by the DHOs via MoH TB case registry counts.

6.2 IPT Completion

There is no gold standard for IPT completion in the field and prior studies have utilized patient self-report, pill counts, INH refill visits, and or blood/urine measures of INH metabolism.

INH refill visits will be measured from “blue card” clinic data or MoH IPT registries in the Aim 2 sub-sample (see Section 5.6.1. above). INH refill visit measurements will include both the number of refill visits (i.e. 5, if prescribed monthly), and the number of pills dispensed. INH completion by INH refill visit measurement will be defined as dispensation of 180 pills of INH within 9 months of INH initiation.

6.2 Active TB Incidence

HIV-associated TB case detection will be obtained from the standard reporting system where local case entry is catalogued in MoH TB clinic registries and submitted through the DHO to central TB control. We will collect TB incidence data from MoH TB registries in all districts participating in the SPIRIT trial. We will compare HIV-associated TB incidence in SPIRIT intervention vs. control groups, as described above (see Section 5.7 above).

6.3 Antiretroviral therapy (ART) Adherence

We will record ART regimen, viral load, and ART adherence status during IPT registry and “blue card” review during IPT Registry sampling for Aim 2. We will compare ART adherence and viral suppression (<400 copies/mL) by SPIRIT intervention vs. control district status to test the hypothesis that the SPIRIT intervention increases ART adherence and viral suppression, as a result of promoting daily pill taking by intervening to improve INH adherence.

6.4 Data Management & Statistical Considerations

6.4.1 Data Collection & Management

Staff will record all Aim 2 study de-identified data, obtained from IPT registry and “blue card” data (re: INH refills), and TB disease evaluation data (e.g. sputum microscopy results or x-ray results) using either paper lab logs, or password-protected study computers. Data from these logs or devices will be entered and transferred via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

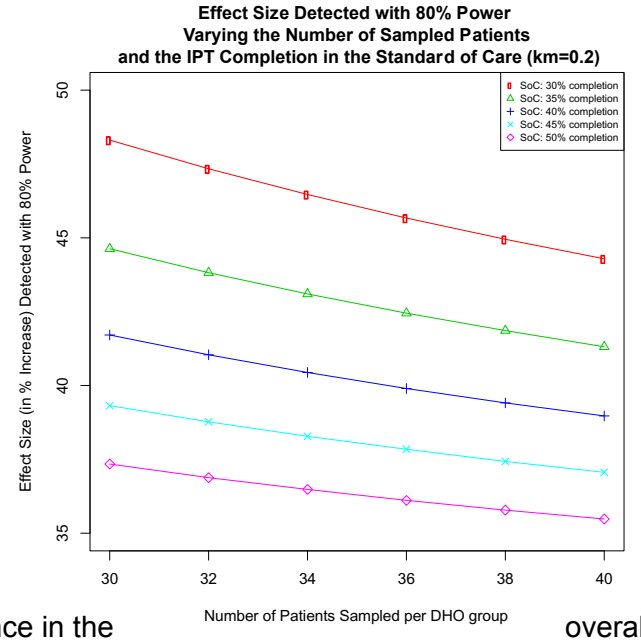
6.5.2 Analysis

6.5.2.1 IPT completion:

Primary outcome: We will examine INH completion, defined as an indicator of dispensation of 180 pills of INH within 9 months of INH initiation, as the primary outcome of Aim 2 among sampled patient charts in intervention and control groups (see Section 6.5.3. below). The effect of SPIRIT on INH completion will be

estimated with TMLE, analogously to the primary endpoint of IPT uptake (see Section 5.7 above). We will account for clustering by randomization group and by DHO within randomization group. In all analyses, we will adjust for the sampling probability to make inferences about the target population of IPT-prescribed, HIV-infected persons in Uganda.

Figure 3 shows the effect size that we are powered to detect when IPT completion (as measured by hair levels) is 30-50% in the control arm. These calculations assume 30-40 patients sampled per DHO group, 12 DHO groups per arm, and a matched pair coefficient of variation k_m=0.2. Assuming IPT completion is 44% under the standard of care, we anticipate at least 80% power to detect a 40% increase in IPT completion due to the SPIRIT intervention (Figure 3).[44]



Additional secondary analyses: We will examine the effect of SPIRIT on ART adherence and viral suppression in the sub-sample of patients for Aim 2.
Qualitative analysis: Data collection and analyses will be similar to those described for Aim 1.

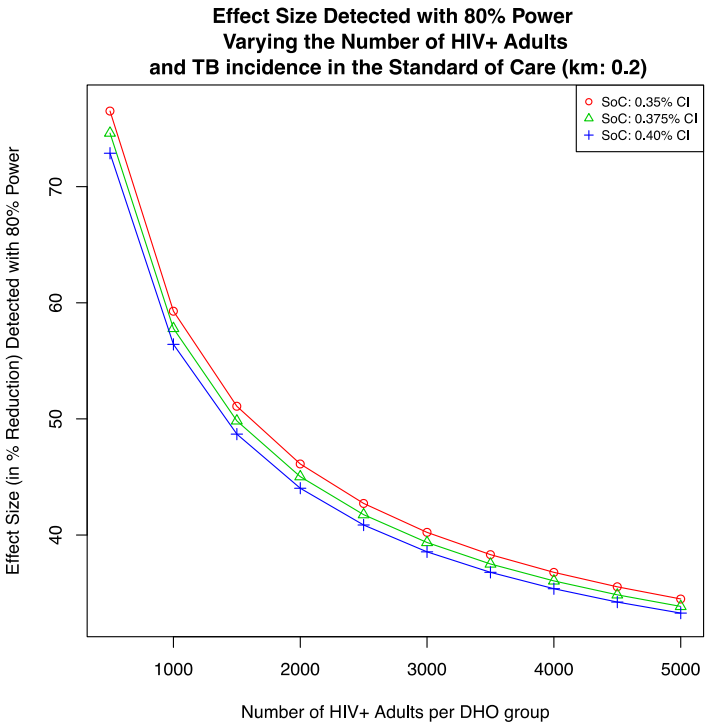
Figure 3 (right): Effect size (in percent increase in IPT completion) detected with at least 80% varying the completion under the standard of care (SoC) and number of patients sampled per DHO group. We assume 12 DHO groups per arm and a matched pair coefficient of variation km=0.2.

6.5.2.2 TB incidence:

Primary outcome: We will examine the impact of the SPIRIT intervention on the incidence rate of TB among all HIV-positive adults at a health facility overseen by DHOs participating in the SPIRIT trial. The analysis of TB incidence in the overall population will mirror the primary analysis of Aim 1. Assuming an incidence rate 200 cases per 100,000 person-years in the standard of care,[45] and 10% completion of IPT (which conservatively reduces TB incidence by 40%,[1,2] the incidence density method suggests a two-year cumulative incidence of approximately 0.38% in the control arm. Figure 4 shows the effect size that we are powered to detect when the control cumulative incidence is 0.35-0.40%.[44] Since the outcome is rare, these calculations are more sensitive to the number of patients per DHO group. However, we are relying on existing data collection systems ("blue card" forms and MoH TB clinic registries). Therefore, we anticipate capturing TB case reports on at least 3000 patients per DHO group. Assuming a control incidence of 0.38%, at least 2800 eligible patients in each DHO group, 12 DHO groups per arm, and a matched pair coefficient of variation k_m=0.2, we will be powered to detect 40% reduction in TB incidence in the overall population.

The analysis of TB incidence in the sub-sample of Aim 2 will mirror the analysis of IPT completion (Section 6.5.2.1). We will adjust for clustering and the sampling probability to make inferences about the target population of IPT-prescribed, HIV-infected persons in Uganda.

Figure 4: Effect size (in percent decrease in TB incidence) detected with at least 80% varying the incidence under the standard of care (SoC) and number of HIV-positive adults per DHO group. We assume 12 DHO groups per arm and a matched pair coefficient of variation k_m=0.2.



6.5.3 Sampling Approach & Sample Size Considerations

In our sampling approach for adherence measures and intensified TB case finding, we first stratify on the DHO randomization group. Then within DHO groups we will sample a minimum of thirty patients who are prescribed INH. To preserve generalizability, the sampling of patients may be further stratified by facility characteristics (e.g. size, DHO, SPC availability) and may be staggered across study time. We aim to perform chart review among 800 patients total, 400 per SPIRIT trial arm.

7. Evaluate the impact of business and leadership training on management and leadership skills among SPIRIT intervention vs. control DHOs.

Rationale: The SPIRIT intervention seeks to increase routine, appropriate use of isoniazid at the clinic systems level, in part by providing leadership and management training during teaching mini-collaboratives. As a result we hypothesize that self-reported confidence in DHO leadership and management skills will be greater in intervention than control DHOs.

7.1. Teaching Mini-Collaborative Business Leadership and Management training

As noted in the SPIRIT-1 intervention (see Section 5.3.1.), additional training at the Teaching Collaboratives (and the Reporting Collaboratives) includes business and management training provided by business leaders, that aim to assist the DHOs and the District TB Supervisors in overseeing any new or ongoing initiatives to improve IPT implementation. DHOs are trained as clinicians and public health officers, but their qualifications and training do not include formal leadership and management training. Through additional business training, the SPIRIT intervention seeks to increase DHO leadership and management competency, thus improving implementation of IPT.

7.2. Measures

Measures obtained will include:

1. The Leadership Business Description Questionnaire (LBDQ),[46] adapted for the DHOs to provide self-reported quantitative assessment of their leadership and management skills, and measured at the completion of the SPIRIT trial, Phase 1.
2. Qualitative Key Informant Interviews (KIIs): Management and Leadership assessments, using interview guides based on the World Management Survey[47], implemented among DHOs participating in qualitative interviews at the completion of the SPIRIT trial, Phase 1.

7.3. Outcomes

The primary outcome for the analysis of business training is the quantitative assessment of leadership and management skills as measured by the Leadership Business Description Questionnaire in intervention vs. control DHO groups at the completion of the SPIRIT trial, Phase 1. Qualitative outcomes will include DHOs' perceptions of business training content and impact of the business training on attitudes and practices.

7.4. Data Management & Statistical Considerations

7.4.1. Data Collection & Management

Staff will conduct the adapted LBDQ survey and KIIs at the completion of the SPIRIT Trial, Phase 1. Data from these surveys will be entered and transferred via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

7.4.2. Analysis

Analyses will evaluate the impact of the SPIRIT Phase 1 intervention on LBDQ scores between randomization arms using TMLE, implemented analogously to the primary endpoint of IPT uptake (see Section 5.7 above).

8. Costs & Cost-Effectiveness of SPIRIT

In order to generate evidence that can address key questions concerning optimal resource allocation and provide guidance to policymakers, we will use rigorous methods to determine the costs of the SPIRIT intervention and assess its cost-effectiveness – particularly the cost per person initiating and completing IPT as well as the costs per TB case averted and disability-adjusted life years (DALYs) averted.

8.1 Costs

We will use standard micro-costing techniques to measure the cost of each component of the SPIRIT intervention. This will include costing of training activities and efforts made to transfer knowledge to DHOs in meetings; costs associated with utilizing opinion leaders to teach DHOs; costs of the SPC for administering INH, SMS system development and implementation, and other communication efforts; and costs of biannual meetings held with DHOs. This costing process will quantify the resource and associated unit costs required to deliver each intervention step, organized in standard expenditure categories—personnel, supplies, equipment, services (e.g. electricity), space, and overhead. Costs will be allocated to each intervention step to the extent possible and review of the division of shared resources and staff time, noting and reporting uncertainties in these divisions. Information required to determine costs will be obtained through examination of expenditure records, discussion with program managers and staff including pharmacy, care delivery labs and observation of service delivery for a sample of patients. Focused "time and motion" studies to allocate staff time across tasks within and outside the intervention will also be carried out to properly account for health care workers' time devoted to the intervention. Donated and subsidized resources will be appraised at market value. We will assess costs from the societal perspective, i.e. including costs to patients and their family members in the form of out-of-pocket expenditures and also lost productivity. To assess costs incurred by patients, we will administer short questionnaires to patients selected for participation in the Aim 2 sub-sample at intervention and control facilities that elicit their expenditures for transportation to receive treatment and the value of the time lost in accessing care by clients and accompanying family members and time lost due to illness.

8.2 Costs Analysis

Costs will be estimated as the sum of the product of resources (e.g. staff minutes) times unit costs (e.g. compensation levels). We will assess costs twice in each of the two Aim 1 trial arms: once before and once after adoption of SPIRIT, in order to compare costs of standard of care to SPIRIT. "Economic" costs (the true value of resources consumed or "opportunity cost") will be assessed by identifying the value of subsidized or donated resources with information from data bases (e.g. wage rates) and donors, and, as needed, three price quotes from appropriate market sources. Costs for capital items (equipment) will be amortized on a straight-line basis over expected useful life, and assuming no salvage value. We will further allocate expenditures across three areas: i) medications ii) service delivery iii) indirect costs consisting of intervention overhead and administration. If possible, we will document changes in unit cost over time as programs potentially achieve greater scale, experience, and efficiency. We will also estimate the changes in HIV medical care costs due to use of changes in TB case rates. We will accomplish these calculations using projected costs for TB care.

After computing the intervention cost per participant initiating and completing IPT, we will quantify ***net costs*** – i.e. program costs adjusted for added or averted health care costs. We will base changes in short-term health care costs on household surveys (household expenditures for illness episode and hospitalizations). Longer-term health care costs will be projected using clinical simulation modeling, based on observed changes in health status (e.g. TB- or HIV-related morbidity), combined with estimates from the trial and published studies of the costs of managing these conditions. We will explore uncertainty in this measure with sensitivity analyses.

8.3 Health Effects

Health effects will be quantified in two ways. First, we will use directly measured study outcomes pertaining to health-related events (TB cases, deaths, hospitalizations). Second, we will integrate the health impact of averted TB cases using **disability-adjusted life years (DALYs)**, including lost years of life and the collective disability effects of adverse events. DALY estimates will be for the short term (during the trial) and the long term (5, 10, and 20 years) using clinical modeling. We will estimate future changes in DALYs among infected individuals by projection duration of survival and morbidity given best estimates of projected IPT initiation rates and use of ART. We will conduct extensive sensitivity analysis on our assumptions, to describe the range of probable DALYs averted. We will also calculate the DALYs averted due to each TB infection averted due to IPT, using data from our own ongoing studies and published estimates of TB transmission rates.

8.4 Cost-effectiveness Analysis
We will calculate efficiency (CE) indicators, such as program cost per person starting IPT, per person completing IPT and per TB case averted. We will calculate the standard CE ratio, net cost per DALY averted, with net costs equal to program costs adjusted for changes in health care costs due to the intervention. We will calculate this ratio with and without the projected long- term effects. All future costs and health effects will be discounted at 3% per year, per standard practice. We will conduct extensive univariate and multivariate sensitivity analysis. Importantly, if the intervention yields net savings (i.e., negative net costs) as well as health benefits, the intervention is classified as "dominant" and no CE ratio is calculated.

9. SPIRIT Enhanced Business Training & "Training-of-trainers" curriculum

9.1. Objective
Objective: To evaluate the effect of enhanced business training among intervention group DHOs from Phase 1 (Years 1-3 of trial follow-up) in the southwestern Uganda region on IPT initiation during years 4-5 of trial follow-up (Phase 2). We propose to extend the SEARCH-IPT study for two additional years which will occur during Years 4 and 5 post trial baseline enrollment (Phase 2).

9.2. Eligibility criteria

9.2.1. Inclusion criteria
(a) District Health Officer or District TB Supervisor (or other DHO-appointed TB focal person) from the Phase 1 Southwestern Uganda region which includes 2 intervention and 2 control DHO groups (of 5-10 DHOs/group)
(b) By definition, the DHO and District TB Supervisors in Uganda are all ≥18 years of age

9.2.2. Exclusion criteria
(a) Planned departure from position as DHO or TB District Supervisor prior to enrollment.

9.3. Enhanced Business Training
Building on business training introduced within the SPIRIT intervention, we will provide additional management training (using a technique referred to as "Gap Analysis"[48]) to a subset of SPIRIT intervention DHO groups, in the southwestern Uganda region, in order to evaluate the impact of enhanced business training on ongoing IPT initiation at quarterly meetings.

9.4. "Training-of-trainers" curriculum intervention
The "Training-of-trainers" (ToT) curriculum will include materials to support business training including slides and information materials that cover leadership and management skills taught to SPIRIT intervention-group DHOs over the first 3 years (Phase 1) of teaching mini-collaboratives. The ToT program will be designed such that intervention DHOs will provide business management and leadership training quarterly to their respective District Health Teams (DHT).

9.4 Measures
9.4.1. Measures to evaluate the effect of enhanced business training will include changes in IPT initiation (as measured in Phase 1: see section 5.6.1), change in self-assessed leadership and management skills as measured by the modified LDBQ (see section: 7.2) and qualitative interviews (see section 7.2), as well as measures of attendance during enhanced business training sessions among intervention group DHOs.
9.4.2. Measures of implementation of the ToT intervention will include DHO fidelity to the training curriculum materials when DHOs provide quarterly business training to their respective DHTs, as measured by participation observation during meetings by our study staff and time spent on training at quarterly meetings.

9.5. Outcomes
The outcomes for this study aim will include changes in IPT initiation rates in Phase 2 intervention vs. control districts (see section 5.6.), and fidelity to implementation of the ToT program as defined by completion of trainings covering the full ToT curriculum.

9.6. Data Management & Statistical Considerations

9.6.1. Data Collection & Management
Staff will record all attendance at meetings on paper lab logs, or password-protected study computers. Data from these logs or devices will be entered and transferred via a secure electronic transfer to our data center facility in Kampala and stored on a secure server.

9.6.2. Analysis
The statistical analyses of IPT uptake will use the same methods as described for Phase 1 (see Section 5.7), limited to the SPIRIT trial intervention and control districts from the Southwestern region of Uganda. However, the outcome will be evaluated by district, rather than the pair-matched DHO groups evaluated in Phase 1.

10. "Training-of-trainers" curriculum impact on district-level management and health outcomes

10.1 Objective
Objective: To determine if having DHOs provide business leadership and management training to their District Health Teams (DHTs) can improve district-level management practices and health outcomes.

10.2 Recruitment & Enrollment of District Health Team (DHT) members

10.2.1 Recruitment
The SPIRIT Project Coordinator and study research assistants will work with the DHOs participating in the SPIRIT trial from the Southwestern Uganda region to obtain contact information for their DHT members. SPIRIT study staff will initiate contact with the DHT members by email, phone or in-person, to recruit for participation Phase 2 of the SPIRIT study.

10.2.2 Consent Process
Upon contacting the DHT members, the SPIRIT Project Coordinator or study research assistants will describe the business training planned for Phase 2 and the objectives of the study, and screen for enrollment. All eligible DHT members that agree to participate will provide written consent. If a DHT members departs from his/her position, we will consent the incumbent DHT member for study participation.

10.2.3 Screening for Enrollment
Study staff will screen all DHOs and/or District TB Supervisors reached during recruitment (10.2.1 above) for the eligibility criteria noted below.

10.2.3.1 Inclusion Criteria
(a) District Health Team (DHT) member in Uganda from the Phase 1 Southwestern Uganda region districts
(b) By definition, the DHT members in Uganda are all ≥18 years of age

10.2.3.2. Exclusion criteria
(a) Planned departure from position as DHT Member prior to enrollment.

10.3 Outcome Measures

10.3.1 Leadership and Management Measures
We will use a mixed methods approach to evaluate self-perceived business leadership and management skills among DHT members in intervention and control districts that includes longitudinal self-assessment surveys with the modified LDBQ survey and focus group discussions (among intervention DHT members), key informant interviews (among control DHT members) guided by components of the World Management Survey, as described above (see Section 7.2). We will also conduct evaluation of implementation processes such as DHT attendance at DHO-led business training meetings and the number and content of health care quality improvement initiatives/actions taken by DHT members during Phase 2.

10.3.2 District Level Health Measures

We will obtain publicly available health outcomes as measured by the Uganda Ministry of Health at the district level from all Phase 2 districts in Southwestern Uganda. Health outcomes will include the metrics shown in **Table 3**, supplemented by other District-level health outcomes measured by the Ministry of Health and selected by DHOs or study investigators.

Table 3: District-level health measures

District Health Team Member	District-Level Health Metrics
Assistant District Health Officer: Maternal and Child Health	1st antenatal care (ANC) visit attendance during 1st trimester
Cold chain technician	DPT3 Immunizations
District TB/Leprosy supervisor	TB treatment completion or TB cure
Malaria Focal Person	Pregnant patients receiving intermittent preventive therapy for malaria (IPTp)
HIV focal person	ART Quarterly report: Missed visits (proportion of scheduled visits missed among patients living with HIV active in care)
Health Facility In-Charges	Out-patient Department (OPD) new patient attendance

10.4. Data Collection

Annual leadership and management surveys will be conducted at Phase 2 baseline (trial year 3) and years 4 and 5 of follow-up. Focus group discussions and key informant interviews will be audio recorded and translations will be data entered into appropriate software on password-protected study computers. Data from interviews will be transferred via a secure electronic transfer to our data center facility in Kampala and stored on a secure server. District level health metrics (**Table 3**), all of which is de-identified (aggregate data at the District level) will be obtained by study staff in collaboration with the Ministry of Health via electronic data queries from the Ugandan District Health Information System (DHIS2).

10.5 Analysis

For analysis of our primary outcome of interest among DHT members in Phase 2, we will compare changes in self-reported proficiency in business and leadership skills from Phase 2 baseline to Year 5 of follow-up, as measured by LDBQ survey responses, among DHT members in intervention vs. control districts using the same methods as for Phase 1 (see Section 5.7). We will also compare secondary outcome measures, including district-level health metrics and the number of quality improvement initiatives, from Phase 2 baseline to Year 5, in intervention vs. control districts. Qualitative data analyses will employ qualitative assessment methods as described for Phase 1 above (Section 5.6.2).

11. Human Subjects

11.1 Risks to Human Subjects

Potential Risks to Human Subjects

There are relatively few risks to study participants, as the proposed research intervention aims to improve implementation of recommended Uganda Ministry of Health IPT guidelines. There are no "experimental" drugs in this study. We will be measuring the uptake of standard and approved drugs-- isoniazid and B6 that will be provided through the Uganda health system. The primary risks involved in study participation are inadvertent disclosure of HIV or suspected TB status by study staff with associated stigma (Aim 2).

11.2 Adequacy of Protection against risks

11.2.1 Informed Consent

Trained research staff will obtain informed consent, as follows:

1. Aim 1 – Cluster randomized trial: Written informed consent will be obtained from DHOs and their TB District Supervisors or other DHO-appointed TB focal person, for participation in the SPIRIT Aim 1 cluster randomized trial, including behavioral surveys.
2. Aim 1 – Behavioral surveys: Written informed consent will be obtained from frontline clinic providers participating in behavioral surveys.
3. Aim 4&5 – 'Training-of-trainers' curriculum: Written informed consent will be obtained from District Health Team members.

All consent forms will be translated into the local language and back translated into English to ensure correct use of language. Consent forms will be read aloud to participants by trained staff. The informed consent will describe the purpose of the study, all the procedures involved, and the risks and benefits of participation. Interviewers will ask participants to summarize the study and explain the reasons why they want to participate. Either a signature or a thumbprint (for those who cannot read) will be acceptable to confirm informed consent for participation in the study, in the case of written consent forms.

11.2.2 Risk of HIV/Suspected TB disclosure

Given the sensitive and private nature of HIV care and suspected TB evaluation data of participants collected during implementation of research Aim 2, extra cautions will be put in place to ensure maintenance of privacy, confidentiality, and security of the data obtained during chart review. Only deidentified data will be collected and recorded, minimizing any likelihood of inadvertent disclosure during chart review. Data collection and storage procedures will include the use of encrypted, password-protected devices and servers.

11.2.3 Data Security

All information will be recorded using study identification numbers, rather than participant names, and stored securely in locked offices at a study data center. All study computers will be password encrypted and kept in locked offices.

11.2.4 Institutional Review Board Approval

The proposed research study will be reviewed and approved by the IRBs of all the participating institutions in the U.S. and Uganda. This includes the UCSF Committee on Human Research (CHR), the Makerere University School of Medicine - Research and Ethics Committee (SOM-REC), the Uganda National Council of Science and Technology (UNCST), and the Uganda National Drug Authority (NDA). All study staff are required to undergo training in human subjects' research, and good clinical practice (GCP).

11.3 Potential benefits of the proposed research to the participants and others

The primary benefits of the proposed research are: a) the proven benefits of wide-scale adoption of isoniazid preventive therapy to patients accessing HIV care in Ugandan Ministry of Health associated clinics, with associated reductions in active TB and TB-associated mortality risk; b) improved access to health education for District Health Officers (DHOs) in the intervention arm of the study; c) the potential for improved communication between DHOs and their clinic staff via study SMS communications; and d) improved management and leadership skills among DHOs and their DHT members (in the southwestern region only)

among intervention participants. The public health benefits may include decreased TB incidence with subsequent decreased TB transmission.

11.4 Importance of the knowledge to be gained

The minimal risk in this study is far outweighed by the importance of knowledge to be gained. Given the public health importance of achieving higher uptake of IPT among HIV-infected persons in sub-Saharan Africa, it is vital to have a proven intervention that can be used to overcome IPT implementation barriers at a country level scale. Our study will provide information on the effectiveness of a multi-component intervention at the middle management, health systems level that can be adapted and deployed across countries and regions, and be utilized as new advances in TB prevention emerge.

12. Publication of Research Findings

The findings from this study may be published in a medical journal. No individual identities will be used in any reports or publications resulting from the study. The researchers will publish results of the study in accordance with NIAID, UCSF, UNCST, and Makerere University guidelines.

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