Drinkers' Intervention to Prevent Tuberculosis (DIPT Study)

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Glossary of Terms

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUDIT-C	alcohol use disorders identification test (alcohol screening tool to identify hazardous drinking)
ART	antiretroviral therapy
CITI	Collaborative Institutional Training Initiative
CM	contingency management (behavioral change model based on the theory of operant conditioning, specifically positive reinforcement of the desired action)
DBS	dried blood spot
EtG	ethyl glucuronide (a metabolite of ethanol that can be measured in the urine as a marker of recent heavy drinking)
HBsAg	hepatits B surface antigen
HIV	human immunodeficiency virus
INH	isoniazid
IPT	isoniazid preventative therapy
IsoScreen	validated point of care method to detect isoniazid metabolites in urine
LC/MS-MS	liquid chromatography/tandem mass spectrometry
MEMS	medication event monitoring system
NIAAA	National Institute of Alcohol Abuse and Alcoholism
PEth	phosphatidylethanol (phospholipid that can be measured in blood as a marker of prior 3 weeks' drinking)
POC	point of care
PPD	purified protein derivative
SAE	serious adverse event
SEARCH	Sustainable East Africa Research on Community Health
TB	tuberculosis
TST	tuberculin skin test
Xpert MTB/RIF	molecular assay by Cepheid for the rapid detection of tuberculosis and rifampin resistance
URBAN-ARCH	Uganda Russia Boston Alcohol Network for Alcohol Research on HIV/AIDS
WHO	World Health Organization

1. Study Synopsis

TB is the leading cause of death among persons with HIV worldwide. Globally, approximately 25% of persons with HIV are heavy drinkers, and heavy alcohol use is associated with a 3-fold higher risk of TB disease compared to no alcohol use, thus HIV-infected persons who drink alcohol are at high risk for TB. Six months of isoniazid (INH) preventive therapy (IPT) reduces TB incidence and mortality by 30-50% above the positive impact of antiretroviral therapy (ART). However, INH can be toxic to the liver, and thus many heavy alcohol users in resource-limited settings such as east Africa are not offered IPT. In addition, heavy alcohol users have poorer ART adherence and data suggest decreased IPT adherence as well. Thus interventions are needed to both decrease alcohol use and increase IPT adherence, and thereby reduce INH toxicity, TB morbidity and mortality in this high-risk population. The use of incentives to promote healthy behavior has been shown to be a highly effective approach for reducing substance use and for improving adherence to HIV and TB regimens in high-income countries. Reducing alcohol use may create a window for safe and effective IPT use by decreasing hepatotoxicity and increasing IPT adherence; however, additional interventions for IPT adherence may be needed. The use of incentives conditional on reduced alcohol use or increased INH adherence in resource-limited settings has been previously limited by the lack of reliable, rapid tests for these behaviors. Recent technological advances allow for point of care (POC) urine testing for recent alcohol use with an ethyl glucuronide (EtG) dipstick that is positive for 3 days after heavy drinking, and INH pill-taking using the IsoScreen urine test to test for 24-hour INH ingestion, thereby creating an opportunity to test incentive-based interventions during IPT among heavy drinkers. We propose leveraging two established cohorts of persons with HIV in Uganda for a randomized 2x2 factorial trial among HIV/TB co-infected adults with heavy alcohol use (n=680 persons. 340 each U01 cohort). **Aim 1** is to determine whether economic incentives contingent on reduced alcohol use assessed by POC EtG tests conducted at INH refill visits reduces heavy alcohol use over six months of IPT compared to the control. **Aim 2** is to determine whether economic incentives contingent on INH positive POC urine tests at these visits compared to the control increases IPT adherence over six months. **Aim 3** is to examine the longer-term impact of the intervention on HIV virologic suppression, and examine mediators of an effect. Primary outcomes will be self-reported heavy alcohol use augmented by phosphatidylethanol (PEth) concentrations, and INH adherence, measured using medication event monitoring system (MEMS), with additional measurements of pill ingestion by INH levels in hair samples. Using incentive-based interventions to reduce alcohol use and increase medication safety in low-income settings is novel. This study to optimize IPT in HIV/TB co-infected drinkers will provide new information on low-cost strategies to reduce alcohol use and increase IPT adherence in low-income countries.

2. Introduction

TB is the leading cause of death among persons with HIV worldwide, and HIV-infected drinkers are at very high risk for TB disease and mortality. Globally, an estimated 25% of persons with HIV are heavy drinkers, and the risk of TB disease is 3-fold higher among heavy drinkers compared to non-drinkers.[1,2] Six months of isoniazid (INH) preventive therapy (IPT) reduces TB morbidity and mortality by 30-50% above the benefit of antiretroviral therapy (ART).[3] However, INH can be toxic to the liver, and as a result in many high TB/HIV prevalence settings, such as east Africa, heavy drinkers are not offered IPT. Thus interventions to reduce alcohol use are needed to decrease INH toxicity during IPT among HIV/TB infected drinkers. It is also well established that heavy drinkers have poorer ART adherence[4], and there is growing evidence of reduced IPT adherence in drinkers.[5] However, interventions to reduce drinking have had limited impact on ART adherence, and further interventions to increase IPT adherence among HIV/TB infected drinkers are likely needed.

The use of incentives to promote healthy behavior is a highly effective approach for reducing substance use and for improving adherence to HIV and TB regimens in resource-rich settings.[6] Economic incentives to reduce alcohol use may create a window for safe and effective IPT use over six months by decreasing hepatotoxicity. Decreases in alcohol use may also improve IPT adherence, or additional incentives for IPT adherence may be needed. Such strategies to reduce alcohol use have not been studied in low-income countries and the effectiveness of incentives to optimize IPT in HIV/TB co-infected drinkers is unknown.

Thus, we designed the **DIPT** (**D**rinkers' **I**ntervention to **P**revent **T**B) study to leverage two established cohorts of persons with HIV in Uganda for a randomized, 2x2 factorial trial among HIV/TB co-infected adults with heavy alcohol use

(n=680 persons. 340 each U01 cohort). Participants will be randomized to one of four arms: Arm 1: no incentives (control); Arm 2: economic incentives for decreasing alcohol use only; Arm 3: economic incentives for IPT adherence only; Arm 4: economic incentives for decreasing alcohol use and for IPT adherence (rewarded independently). All arms will receive alcohol and adherence counseling. The two cohorts allow for sufficient sample size and provide heterogeneity in clinical setting and drinking patterns.

2.1. Specific Aims

Aim 1: Determine the effectiveness of economic incentives contingent on point-of-care (POC) urine ethyl glucuronide (EtG) <300 ng/mL (Arms 2 & 4) versus no alcohol incentives (Arms 1 & 3) to reduce heavy drinking over 6 months, among HIV/TB co-infected adult drinkers receiving IPT. We will randomize participants to low-cost escalating prize incentives for EtG negative urine tests at IPT refill visits (Arms 2+4), versus no incentives (Arms 1+3).

- Hypothesis: Incentives will be more effective in promoting decreased alcohol use during IPT versus the control, resulting in less hepatotoxicity and greater IPT adherence in the intervention versus the control group.
- Outcomes: Primary: Non-heavy drinking determined by self-report (Alcohol Use Disorders Identification Test – Consumption [AUDIT-C], prior 3 months, negative) *and* phosphatidylethanol (PEth) <35 ng/mL at three *and* six months. Secondary: IPT adherence and hepatotoxicity.

Aim 2: Determine the effectiveness of economic incentives contingent on POC (IsoScreen) INH urine positive tests (Arms 3 & 4) versus no INH incentives (Arms 1 & 2) on INH adherence among HIV/TB co-infected adult drinkers. We will randomize participants to low-cost escalating prize incentives for INH positive urine tests at IPT refill visits (Arms 3+4), versus no incentives (Arms 1+2).

- Hypothesis: The incentive strategy will result in greater INH adherence versus the control.
- Outcomes: Primary: INH adherence measured as >90% pill-taking days by medication event monitoring system (MEMS) cap opening over six months. Secondary: INH concentration in hair at 3 and 6 months.

Aim 3: Assess the impact of economic incentives on HIV virologic suppression and explore their mechanisms of action, six months after trial completion. We will follow all study participants for six months after trial completion.

a) Assess the impact of the 3 separate incentive interventions (Arms 2,3,4) vs. no incentives (Arm 1) on HIV virologic suppression.

- Hypothesis: The intervention arms will be associated with greater viral suppression versus control.
- Outcomes: Primary: The proportion with undetectable HIV viral load six months post-IPT completion. Secondary: Active TB rates six months after IPT completion.

b) Explore the mechanisms that may drive the economic incentives to increase virologic suppression. Potential mediators will be reductions in alcohol use and level of IPT adherence.

This study will leverage new low-cost POC tests for alcohol use and INH pill-taking for the first study of incentive-based alcohol and adherence interventions in low-resource settings; these interventions may improve the safety and effectiveness of life-saving medications for heavy alcohol users in many settings.

3. Background and rationale

There is an urgent global need to decrease the high mortality of tuberculosis (TB) in persons with HIV. TB is the leading cause of death in persons infected with HIV, accounting for 390,000 deaths in 2014 (20-33% of HIV-associated deaths).[7,8] At least one-third of the 37 million people living with HIV worldwide are latently infected with TB; these individuals are 26 times more likely to develop active TB than those without HIV. Although aggressive strategies to find and treat all active TB cases are needed to reduce HIV/TB mortality, the best-known strategies to prevent new active TB cases in HIV/TB infected persons are via both ART and TB preventive treatment. Recent studies, including the TEMPRANO trial, have shown the additive benefit of IPT and ART in reducing mortality for patients at all CD4 counts,[3,9-11] with IPT-associated decreases in active TB and mortality ranging from 30% to 50%. Thus the World Health Organization

(WHO) recommends IPT, intensified TB case finding, infection control, and ART for persons with HIV in resource-limited settings.[12]

Heavy drinking is common among HIV-infected persons and heavy drinkers are at increased risk for active TB and poorer TB treatment outcomes. In several studies of persons in HIV care in sub-Saharan Africa (SSA), a median of 25% of persons self-reported heavy drinking,[13-18] with heavy drinking defined as exceeding recommended limits, e.g. via the NIAAA drinking limits (women: >7 drinks/week or >3 drinks/occasion; men:>14 drinks/week or >4 drinks/occasion) or via the AUDIT-C.[19,20] Heavy alcohol consumption is an established risk factor for HIV,[21,22] and for TB infection via increased immunosuppression and increased time spent in settings where TB is prevalent.[1] The risk of active TB is increased 3-fold among heavy drinkers compared to non-drinkers,[1,23-25] and heavy drinkers with TB are more likely to have sputum smear positive disease, slower presentation to care, worse TB treatment response, and higher mortality while on TB treatment.[1,26] Thus, HIV-infected drinkers are at high risk of morbidity and mortality due to active TB disease and should be a priority for TB preventive treatment.

Interventions are needed to reduce the risk of INH-related toxicity among HIV/TB co-infected drinkers. INH is metabolized by the liver, and the rate of Grade 3/4 (serious) hepatotoxicity due to INH ranges from 0.1-4.0% of all patients.[27] Most INH-associated hepatotoxicity is reversible by stopping therapy, but liver injury can, rarely, lead to liver transplantation or death, with mortality rates of 0.05-0.10%.[28] Alcohol users are considered at increased risk for INH-related hepatotoxicity. In the U.S., alcohol users with latent TB infection may be given IPT, with liver enzyme monitoring recommended to improve safety.[29] However, the WHO lists "regular and heavy alcohol consumption" as a contraindication to IPT in resource-limited settings, given the challenges of clinical oversight and liver enzyme monitoring.[12] It is therefore important to attempt to reduce the risk of toxicity by intervening to reduce drinking. In a research setting, comprehensive monitoring is feasible, thus INH can safely be given to drinkers (see Safety Considerations) while studying interventions to optimize IPT. Thus, Aim 1 of this study is to conduct a trial to determine whether an incentive-based intervention can reduce drinking in HIV/TB co-infected heavy drinkers receiving 6 months of INH to reduce the risk of hepatotoxicity.

Interventions are needed to improve adherence to TB preventive therapy among HIV/TB co-infected drinkers. Alcohol use has been consistently associated with reduced HIV ART adherence overall[4,30,31] and in event-level studies with missed doses tied to drinking episodes.[32] In a longitudinal study in Uganda, heavy alcohol use was the strongest independent predictor of poor ART adherence.[33] While the literature on INH adherence is less extensive, alcohol use has been associated with lack of completion of IPT [5,34-36] as well as discontinuation of active TB treatment.[37-39] Thus, for HIV/TB co-infected drinkers at high risk of active TB, interventions are needed to increase IPT adherence. In theory, reducing drinking alone should have a positive impact on adherence, but prior interventions to reduce drinking have shown limited impact on ART adherence.[40] Interventions to improve adherence, beyond reducing alcohol use, may be needed; therefore, we will also examine whether an incentive intervention can further increase IPT adherence in Aim 2.

Incentive-based interventions have been effectively used to promote several types of health behavior change. The behaviors targeted include reductions in substance use (via contingency management [CM][41]) and HIV prevention behaviors such as HIV testing[42] and medical male circumcision.[43] In these approaches, derived from both economic and psychology-based theories of decision making, incentives are provided conditional on a behavior, such as demonstrating drug abstinence using a urine test or getting an HIV test. CM is based on the theory of operant conditioning, specifically positive reinforcement. In CM, re-enforcers (e.g., prizes or vouchers) are provided when an individual engages in a behavior (i.e., submitting an alcohol-negative urine sample) that is incompatible with the target problematic behavior (i.e., alcohol use).[44,45] From a behavioral economics perspective, incentives are provided to leverage two complementary decision-making tendencies: (1) "present-bias" – the tendency to over-value immediate benefits and costs;[46] and (2) "delayed reward discounting", in which individuals discount long-term benefits and costs.[47] Incentives capitalize on these tendencies by creating an immediate and salient benefit (e.g. immediate prizes to leverage present bias) for a behavior (e.g. reduced substance use or increased INH pill-taking) that has benefits in the future, in an effort to offset delayed reward discounting.

Previous approaches to reducing drinking in persons with HIV have had limited success.[40,48] Multi-session interventions, considered most likely to have an effect,[49] have shown inconsistent effects for reducing alcohol use.[50-53] On the other hand, interventions using incentives to reinforce reduced substance use, including alcohol use,[54-56] have consistently been highly successful. CM studies have shown moderate to large effect sizes of >0.42 for reducing substance use in meta-analyses.[2,41,57] However, these strategies have not been tested in low-income countries. There is also strong evidence from high-income settings that incentive-based interventions can improve medication adherence. In a meta-analysis of 15 trials of incentives to reinforce adherence to a variety of medications, the effect size of intervention versus control on adherence was 0.77 (95% confidence interval (CI): 0.70-84).[58] However, the evidence on incentives specifically for adherence to TB preventive therapy is sparse.[59] Of three trials described in a recent systematic review, one found a large, significant effect of incentives compared to receiving outreach on adherence,[60] whereas two found no effect of incentives,[61,62] leading the authors of the review to call for more research in this area.[59] Therefore it is crucial to determine if incentive-based approaches can reduce alcohol use and improve medication adherence to provide a strategy for safe and effective IPT in HIV/TB co-infected drinkers in low-resource settings.

A new test makes interventions reinforcing reduced alcohol use feasible in low-resource settings. While CM has been highly successful in reducing use of a variety of substances, only a handful of studies have applied this intervention to alcohol use, because previously there was no reliable marker that could rapidly detect alcohol use in bodily fluids, other than ethanol, which is metabolized at the rate of approximately one drink per hour. However, there have been recent advances in alcohol biomarkers; ethyl glucuronide (EtG) is a metabolite of alcohol use that can be detected in urine for several days, depending on the amount of alcohol consumed and the cutoff used.[63-65] We recently found that using urine EtG testing to reward abstinence resulted in reduced drinking among mentally ill patients (McDonell, see Preliminary Studies).

A major limitation to implementation of an EtG-based incentive intervention is that it requires either access to a commercial laboratory or a $40,000 urine analyzer. However, a recently developed POC urine EtG dipstick test provides a low cost ($3) testing option with immediate results. This EtG dipstick uses a cutoff level of 300 ng/mL, a threshold that balances sensitivity and specificity and is 98% concordant with the benchtop-based immunoassay (see Preliminary Studies). These dipsticks may be an effective method for reinforcing reductions in heavy drinking as part of an incentive intervention in low-resource settings.

A new test makes reinforcing INH pill-taking feasible in low-resource settings as well. A new screening test, the IsoScreen, is a validated POC method of detecting INH metabolites in urine.[66-68] It uses the Arkansas method which involves mixing urine with reagents and determining color change,[69] but encloses the toxic reagents in a pre-packaged cartridge so the operator is not exposed to them. The IsoScreen showed 90-95% sensitivity and 98% specificity for detecting INH consumption in the prior 24 hours in two studies.[67,68] Thus, this test (~ $8 each) is safe and feasible for use in incentive-based interventions in many settings.

Technologies also allow for objective measures of long-term alcohol use and IPT adherence. While the urine EtG and IsoScreen tests provide immediate results and are useful tools for reinforcing short-term behavior change, longer-term measures are needed to measure alcohol use and IPT adherence over the entire trial period. Self-reported measures of alcohol use and adherence have limitations,[70-73] especially in settings where socially desirable responses are likely to be high,[74] such as behavioral intervention trials.

For alcohol, the abnormal phospholipid phosphatidylethanol (PEth) is formed only in the presence of alcohol, and is therefore highly specific. PEth has an estimated half-life of 4-12 days, indicating that it will be positive several weeks after heavy drinking.[75] PEth has shown >95% sensitivity and 100% specificity in comparisons of patients entering alcohol treatment compared to abstainers and light drinkers,[76-79] and several studies have shown correlations of PEth with cumulative measures of alcohol consumption of >0.70.[75] PEth is now an endpoint in alcohol treatment trials.[80,81] PEth can be measured from dried blood spots (DBS) that are easy to store, non-infectious, and easy to transport.

For IPT adherence, INH in small hair samples captures INH adherence over a period of weeks to months, and is an innovative biometric to assess long-term adherence/pill-taking.[82] We (Gandhi) have validated a method to analyze INH in small scalp hair samples using liquid chromatography/tandem mass spectrometry (LC/MS-MS).[82] We have examined INH levels in the hair of adults on directly observed daily IPT; all had detectable INH levels with a median of 7.6 ng/mg

(inter-quartile range (IQR) 4.7-11.8).[82] Like DBS, hair is non-infectious, and easy to store and transport. As of the date of this submission, studies of clinically meaningful cut-points for INH hair levels are in progress but not completed. Thus we will use MEMS-measured bottle openings, the current reference standard for adherence,[83] as our primary outcome measure for Aim 2, and include INH hair concentration, an emerging biologic marker of IPT adherence, as a secondary outcome.

Understanding whether short-term interventions to reduce heavy alcohol use and promote medication adherence impacts long-term HIV virologic suppression is needed. In a recent analysis of individual-level predictors of having a detectable viral load among 8,828 HIV-infected adults in the SEARCH study (see Preliminary Studies), binge drinking (>5 drinks per occasion) was associated with increased odds (adjusted Odds Ratio (aOR): 1.62, 95% CI: 1.28-2.05) of detectable viremia.[84] In another prospective cohort of persons prescribed ART in Uganda, problem alcohol use was the strongest predictor of increased odds of viral failure; the association was mediated through reduced ART adherence.[33] Therefore, interventions to increase ART adherence and thereby increase viral suppression in heavy drinkers in SSA are urgently needed.

In Aim 3, we hypothesize that the proposed alcohol (Aim 1) and IPT adherence (Aim 2) interventions will improve ART adherence, leading to increased viral suppression that persists after incentives are withdrawn. Our Aim 3 hypothesis is supported by two observations. First, Petry et al. have demonstrated that reductions in alcohol or drug use targeted by incentive interventions can lead to improvements in other health behaviors, including reductions in HIV-risk behavior, cigarette smoking, other drug use, psychiatric symptoms and hospitalizations.[55,85-87] Second, there is evidence that short-term incentives can result in behavior changes that persist after incentives are removed, due to the formation of healthy habits.[41,88-90] However, some studies report diminishing impact after withdrawal of incentives,[2,57] and it has been suggested that incentives displace intrinsic motivation, with no long-term positive impact on behavior.[91] Given this mixed evidence, we will examine whether incentives to reduce alcohol use and improve IPT adherence result in improvements in ART adherence that persist after incentives are withdrawn, as measured by HIV virologic suppression six months post-intervention. As there is no measure of IPT efficacy other than lack of progression to active TB, we will also monitor for active TB by trial arm during and after IPT in this high-risk, HIV/TB co-infected population.

3.1. Preliminary Studies

We will leverage two well-characterized cohorts of persons with HIV in Uganda:

(1) Uganda Russia Boston Alcohol Network for Alcohol Research on HIV/AIDS (URBAN ARCH). We (Hahn and Muyindike) have been conducting alcohol/HIV research in Mbarara, Uganda since 2006. Our several prospective cohort studies described drinking patterns among persons with HIV in Uganda,[48,92-95] the harmful impact of alcohol use on HIV outcomes,[96-98] and the use of alcohol biomarkers in this population.[99-105] In the Uganda URBAN ARCH studies, we recruited 465 current drinkers, 48% were male, and retention was 90% at both 6- and 12-months. Based on suggested PEth cutoffs of 35 ng/mL and 210 ng/mL,[106] we found that 33% of current drinkers could be categorized as moderate risk drinkers and 30% as excessive drinkers, respectively, with the median PEth level among current drinkers of 76 ng/mL (IQR 16-274).

We were recently funded via a renewal to our Uganda URBAN ARCH study (U01 AA020776-06) to conduct a single arm study to determine the level of INH-related toxicity among HIV/TB co-infected drinkers receiving 6 months of INH. Beginning April 2017, we will enroll 200 current drinkers (100 heavy, 100 not heavy) and 100 non-drinkers and determine the rate of hepatotoxicity and adherence to INH overall and by drinking level. This cohort, as well as the URBAN ARCH consortium (U24 AA020778; PI Jeffrey Samet), will be leveraged for this study; however, the proposed DIPT study will recruit and enroll new participants.

(2) Sustainable East Africa Research on Community Health (SEARCH) is a large NIH and PEPFAR supported community cluster-randomized controlled trial (NCT 01864603) in Uganda and Kenya led by Drs. Diane Havlir and Moses Kamya. Drs. Chamie, Kwarisiima and Thirumurthy have been co-investigators since the start of SEARCH. SEARCH tests the hypothesis that an HIV "test and treat" approach for all people living with HIV can lead to reductions in HIV incidence and improvements in overall community health. Over 340,000 persons have been enrolled in 32 communities, in partnership with the Ministries of Health and HIV implementing partners in Uganda and Kenya. SEARCH has demonstrated high levels of community engagement in multi-disease health campaigns and home-based testing,[107] high

levels of engagement in HIV care and ART in Ministry of Health clinics,[108] and recent achievement of the 90-90-90 UNAIDS targets with 81% virologic suppression after three years of intervention.[109] In the ten SEARCH trial communities in southwestern Uganda, 27% of HIV-infected adults are current drinkers. Among a sample of 485 HIV-infected adults in SEARCH in Uganda, we found a significantly higher prevalence of latent TB infection (TST ≥5 mm) among drinkers (28%) compared to non-drinkers (19%; p=0.047; unpublished data). Furthermore, we achieved high rates (75%) of IPT completion among non-drinkers without incentives in a pilot IPT implementation study in SEARCH communities in Uganda (unpublished data), and funding for a large IPT implementation trial among non-drinking, HIV-infected adults in Uganda was recently awarded (R01 AI125000).

We (Thirumurthy, Chamie) have experience implementing low cost incentive-based HIV prevention interventions in east Africa. We (Thirumurthy) completed a RCT of an incentive intervention in Kenya that compensates men for transport and opportunity costs associated with male circumcision. The results show that incentives of $8.75-$15 increased odds of circumcision uptake within 2 months by factors of 4.3 and 6.0, respectively.[43] Furthermore, in pilot studies in rural Uganda, we have studied incentives to increase HIV testing uptake among men by implementing both standard ("fixed") and lottery-based incentives. After our first HIV testing campaign in a community of >6,000 residents in southwestern Uganda in 2011, we obtained input from local leaders and offered a small, fixed incentive to men who participated in HIV testing at a 2012 repeat campaign. Male participation rose from 34% in 2011 to 46% in 2012.[110] This work has led to two RCTs of novel incentive strategies, including lotteries, for promoting HIV testing and treatment (Chamie/Thirumurthy): one for HIV testing among men (N=2,532), and another of escalating incentives rewarding HIV virologic suppression in rural southwestern Uganda (NCT 02890459).

We (McDonell and Petry) have found contingency management to be highly effective to reduce alcohol use. We have demonstrated the efficacy of CM for alcohol abstinence in treatment settings,[54,56,65] and have implemented EtG-based CM intervention in two disadvantaged populations: (1) adults who suffer from co-occurring serious mental illness treated in the public mental health system; and (2) American Indians and Alaska Natives,[111] gaining experience in the cultural and logistical adaptation of incentive-based approaches in low-resource and rural settings.[111] In a recently completed RCT of 79 adults with alcohol dependence and serious mental illness that used EtG biomarkers to verify alcohol abstinence, those randomized to CM were 3 times more likely to submit an alcohol-negative EtG sample during treatment, and reported lower levels of alcohol use and heavy drinking during follow-up, relative to controls.[55] While standard CM is based on frequent monitoring (≥2 visits per week) to reinforce sustained periods of abstinence, we (McDonell) found high attrition (50%) using the standard schedule, due to difficulties obtaining transportation in a pilot study of rural Natives. These results suggest that less frequent visits, such as those implemented in an efficacious smoking cessation trial (2, 4, and 24 weeks),[112] are needed to for feasible implementation in low-resource settings.

We (McDonell) have found that EtG validly measures recent alcohol use by benchtop immunoassay and dipstick. We analyzed EtG in urine samples from 121 adults with alcohol use disorders in a CM trial using a spectrophotometry-based immunoassay (Thermo Fischer Scientific) conducted on a benchtop analyzer.[65] Of visits with reported heavy alcohol use (>3/>4 drinks/occasion for women/men; n=810 visits), using a cutoff of 300 ng/mL, EtG was detected in 84% one day after last drink, in 75% two days after last drink, in 69% 3 days after last drink, in 64% four days after last drink, and in 63% 5 days after the last drink. Specificity was 91%. These data suggest that an EtG cutoff of 300 ng/mL is highly sensitive (69-75%) and specific for detecting heavy alcohol use for 1-3 days, with lower detection rates beyond that window. In another study, we studied 49 urine samples of five heavy drinkers (manuscript under review). The samples were tested for EtG by benchtop analyzer and a commercially available POC dipstick with a 300 ng/mL cutoff. The agreement at the 300 ng/mL cutoff level was 98% (kappa=0.95), suggesting that the low-cost dipsticks accurately assessed EtG levels.

We (Hahn) have characterized PEth in this study population and used it to augment self-report. In a study to validate PEth among persons with HIV in Uganda (n=77), PEth was 88% sensitive and 89% specific for detecting any alcohol use at a cutoff of 10 ng/mL, and the Spearman correlation with the number of drinking days was 0.75.[101] Implementing PEth testing, we found that PEth detects high levels of under-reporting,[105] and self-reported alcohol use doubled in a study in which participants were told that specimens were being collected to determine how much they

were drinking.[103] We also found that patterns of alcohol use among 208 persons entering HIV care differed dramatically when examining self-report alone versus a composite measure of PEth and self-report.[102] Thus we have shown that PEth is a valid objective biomarker of alcohol use, which can be used both to increase and augment self-report to improve the detection of heavy drinking.

Our recent data suggest a PEth cutoff of 35 ng/mL for heavy drinking. We (Hahn) have recently analyzed data from 25 participants in a study of atrial fibrillation (R01 AA022222, PI Marcus) who wore an ankle Secure Continuous Remote Alcohol Monitor (SCRAM) to continuously monitor alcohol excreted in sweat when drinking at least 2 drinks. PEth was highly correlated (Spearman r=0.72) with the number of drinking episodes detected by the SCRAM over four weeks. The area under the receiver operator curve for PEth versus frequent (≥3x per week) drinking (of ≥2 drinks) was 0.93 (95% CI: 0.83-1.00). PEth was 83% sensitive (95% CI: 44%-97%) and 90% specific (95% CI: 68%-99%) at a cutoff of 34 ng/mL. While there is no agreed upon PEth cutoff for heavy drinking, this cutoff is nearly identical to that proposed by European laboratories (35 ng/mL) for differentiating low and no intake from moderate and excessive intake,[106,113] and is similar to a cutoff of 45 ng/mL, which was 65% sensitive and 95% specific for risky drinking among reproductive-aged women.[114]

We (Gandhi) have developed methods to analyze ART and INH concentrations in small hair samples and proven the utility of hair samples as a key outcome. We (Gandhi) have helped pioneer the use of small hair samples to monitor ART adherence for patients on ART.[115-132] We have demonstrated that hair concentrations of ARVs are the strongest independent predictor of virologic suppression,[116,117,129-132] and have a linear relationship with ART dose taken.[133] We have also developed methods to detect levels of INH in hair;[82,134] however, appropriate cutoffs for INH hair concentration representing optimal adherence have not yet been established. We have demonstrated high rates of acceptability and feasibility (>95%) of collecting hair samples for ART monitoring in African settings, including samples of short (previously shaved) or braided hair.[124,131,135] Thus, INH concentration in hair is an emerging biomarker for INH measurement, and is our secondary outcome in Aim 2.

4. Study design overview

This study is a randomized controlled trial (RCT) of economic incentives to promote (1) reduced alcohol consumption via incentivizing EtG negative urine tests, and (2) INH adherence via incentivizing INH positive IsoScreen urine tests. The trial will be conducted during the 6 months of IPT and we will use a 2x2 factorial design (Figure 1) so that we can efficiently evaluate the effects of the two interventions separately and in combination. Aim 1 and 2 outcomes will be measured 3 and 6 months post-randomization. The primary outcome for the Aim 1 alcohol intervention will be non-heavy drinking at 3 *and* 6 months. The primary outcome for the Aim 2 adherence intervention will be proportion of participants with >90% INH pill-taking. To assess longer-term impacts of the alcohol reduction and INH adherence interventions on HIV viral suppression (Aim 3) we will follow all study participants for six months after trial completion to determine HIV viral suppression (primary outcome), as well as active TB rates.

4.1. Study setting

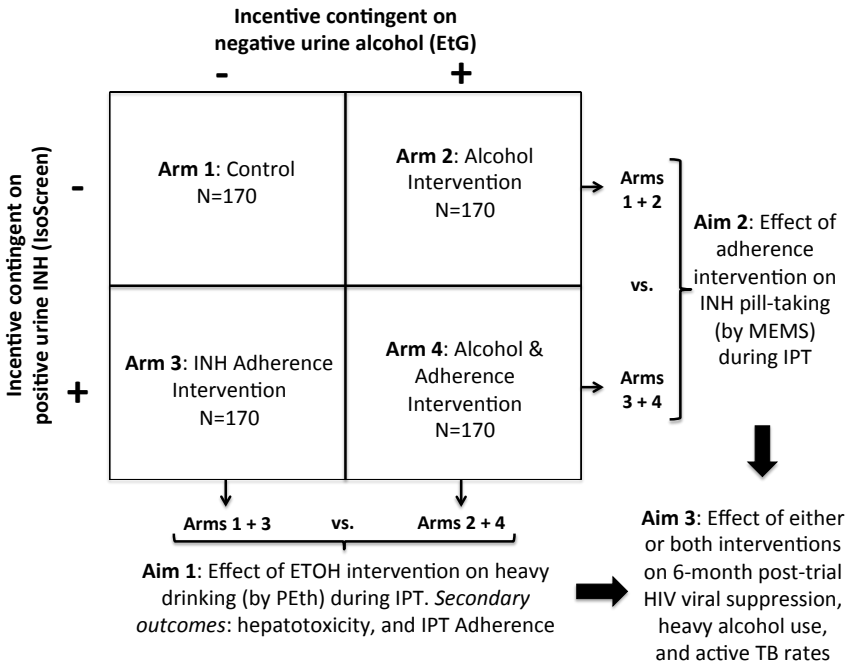
The DIPT study will take place in southwestern Uganda, where the adult HIV prevalence is 8%[136] and TB infection prevalence is estimated at 28-50%.[137,138] Heavy alcohol use is common while other substance use is rare.[139] This is an appropriate setting for this intervention, because trials conducted in settings across Africa with similar HIV and TB prevalence have demonstrated that 6 months of IPT is effective in decreasing active TB incidence and mortality,[3,140] in contrast to settings in southern Africa which have very high TB transmission and where longer durations of IPT may be needed.[141,142] We will leverage the existing Uganda URBAN ARCH and SEARCH HIV clinical cohorts; each cohort will enroll 340 patients and up to 5 pilot participants.

The DIPT 1/2 cohort will be based at the Immune Suppression Syndrome (ISS) HIV Clinic of the Mbarara Regional Referral Hospital (MRRH), the site of the Uganda URBAN ARCH cohort, and its affiliate clinic, the Mbarara Municipality Clinic. There are over 12,000 active patients at the ISS Clinic; 25% are current drinkers.[143] The ISS Clinic and pharmacy use electronic medical records (EMR) that will be leveraged for patient recruitment, tracking, and active TB outcomes.

The DIPT 2/2 cohort will be enrolled from the 10 HIV clinics in southwestern Uganda taking part in the SEARCH study. Each SEARCH community is within the catchment area of a government and PEPFAR-supported ART clinic. In southwestern Uganda, >10,000 HIV+ adults are on ART at these 10 clinics, providing an ample population base for DIPT 2/2 enrollment. Among HIV+ SEARCH participants in southwestern Uganda, 27% are current drinkers. SEARCH has digitized medical records at these 10 clinics, including data on alcohol use and TB disease surveillance; this infrastructure will be leveraged for patient recruitment, tracking and HIV and TB outcomes in DIPT 2/2. Recruitment may also occur at additional HIV clinics in Southwestern Uganda as needed to meet study target enrollment.

Rationale for the two cohorts: The two cohorts in these paired U01s allow for sufficient sample size, and provide heterogeneity in clinical setting (a peri-urban Regional Referral Hospital versus rural Ugandan clinics), and in drinking patterns (primarily commercial beer versus home-brews). These two U01s also create synergy by joining together investigators focused on HIV and co-morbidities from the alcohol measurement and intervention fields (Hahn) with the HIV behavioral economics and TB/HIV implementation science fields (Chamie), and create a collaboration "between currently NIAAA-funded PI(s)/PD(s) with established alcohol research programs and other PI(s)/PD(s) with expertise in HIV/AIDS, and related comorbidities research, … forming new substantial collaborations." (RFA-AA-17-014).

Figure 1. Study schematic for 2x2 factorial trial design (Aims 1 & 2).



5. Study Procedures

5.1. Recruitment

Participants will be recruited from persons reporting alcohol use at their clinic visits.

a) DIPT1/2 participants will be recruited from HIV-infected persons at the Mbarara Municipal Clinic (MMC) in Mbarara, Uganda. Participants will also be recruited from the electronic medical records of persons attending the Mbarara ISS clinic. The AUDIT-C is conducted routinely at the initial clinic visit. Our prior studies showed that 64% of those reporting any alcohol use at initial clinic visit were heavy drinkers,[102] thus ISS clinic patients reporting any alcohol use will be invited for further screening.

b) DIPT 2/2 participants will be recruited from HIV-infected persons at SEARCH clinics in southwestern Uganda, including newly diagnosed HIV-infected persons entering the cohort. We will invite adults in the SEARCH study who have reported any alcohol use (asked annually), as well as adults not participating in the SEARCH study but attending a SEARCH-associated HIV clinic, for further screening. Recruitment may also occur at additional HIV clinics in Southwestern Uganda as needed to meet study target enrollment.

For all sites of enrollment, a clinic staff member who is also a member of the research team, e.g. the screener, record room staff or clinic counselor, will initially approach those meeting these criteria. Persons meeting the initial eligibility criteria will be asked by the study screener or clinic staff member if they are interested in taking part in a research study. Those who agree will be screened to determine further eligibility criteria. The screener will review clinic medical records for potential participants, to determine preliminary study eligibility (i.e. age, no history of prior active TB, current drinker). Those who are eligible will be referred to the RA to undergo informed consent.

5.2. Screening

Eligibility screening will be a two-stage process. If preliminary eligibility is established during recruitment, a research assistant (RA) will seek informed consent for further screening to determine current heavy alcohol use confirmed by urine EtG and AUDIT-C positive for prior 3-month drinking, determine current pregnancy status (for women), rule out active TB and existing liver enzyme (ALT/AST) elevations (our prior data show mild elevations in <8% of patients), and to assess tuberculin skin test (TST) status (Figure 3). Active TB assessment will be based on the WHO 4-symptom screen,[12] with further testing (chest X-ray and/or sputum Xpert MTB/RIF assay) for those with positive symptom screens. Those diagnosed with active TB will be offered TB treatment at their local TB clinic. Patients will be asked to return in two days for TST reading.

During the second phase of screening (i.e. baseline line visit), a RA will seek informed consent from individuals who meet the inclusion criteria below for further study participation. The baseline visit will include collection of tracking information, a baseline survey, and blood draw. Liver enzyme testing will be repeated at the baseline visit if it has been longer than one month from the screening tests.

Individuals who are not eligible for the study may return to be screened again after three months.

5.2.1. Inclusion criteria

Trial inclusion criteria for all sites will be:

a) HIV-infected adult (≥18 years) prescribed ART for at least 6 months;
b) Current heavy alcohol use confirmed by urine EtG and AUDIT-C positive for prior 3-month drinking;
c) Positive TST (≥5 mm induration);
d) AST and ALT <2x the upper limit of normal (ULN);
e) Fluent in Runyankole or English
f) No history of active TB, TB treatment, or TB preventive therapy;
g) Lives within 2-hour driving distance or 60 km of the study site.

5.2.2.Exclusion criteria

Exclusion criteria for all sites will include:

a) Prescribed nevirapine (NVP, an ART drug that is declining in usage due to high risk for hepatotoxicity);
b) Initiating Dolutegravir (DTG), or has initiated DTG within the past 3 months;
c) Plans to move out of the catchment area within 6 months;
d) Prescribed anti-convulsion medications or history of recurring seizures;
e) ALT or AST elevations (≥2X ULN);
f) Suspected or confirmed active TB as determined by symptom screening and followed by chest X-ray and sputum testing;
g) History of prior active TB treatment or prior IPT.
   - As fewer than 3% of HIV-infected persons have received IPT in Africa, prior IPT will be rare.[144]
h) Pregnant at the time of screening
i) Gross inebriation or inability to provide informed consent.

5.2.3. Informed consent process

The informed consent process for both the screening and trial will take place in a private room at the ISS Clinic or research offices for the DIPT 1/2 cohort / in a private room in the clinics participating in the SEARCH study for the DIPT 2/2 cohort. The RAs will meet with eligible participants selected for recruitment to introduce the study and gauge potential subjects' interest. Potential participants will be told the purpose of the study and the reasons that they have been approached for participation.

The informed consent process will be guided by a written consent document, but will mainly consist of an interactive conversation between the RA and the potential study participant. We have separate consent forms for the screening procedures and study procedures. The RA will use the informed consent document (available in Runyakole, subjected to translation, back-translation, and revision for accuracy, clarity, and ease of comprehension) as a guide to discuss all content in the document with the potential participant. After each major section and any key points, the RA

will pause and check for understanding—for example, by asking the participant to repeat back, in their own words, what "the right to refuse" means.

Other key points to check with participants during the screening consent include: (1) they understand that the screening consent process is to assess their eligibility for the study only, and that they are not consenting to the main study; (2) they will be asked to give a urine specimen sample; (3) they will be asked to undergo blood specimen collection via venipuncture; (4) they will be asked to consent to a TST, where the RA will place a purified protein derivative (PPD) in the participant's skin to be read 48-72 hours later; (5) they will be asked to return two-three days after the screening procedures for additional assessment including the TST reading and review of their laboratory results to determine eligibility.

Key points to check with the participants enrolling in the trial include: (1) they will be asked to undergo blood collection via venipuncture, provision of a small hair sample at 3 and 6 months after enrollment, and research assessment procedures; (2) they will be asked to repeat blood specimen collection, and urine collection (if in Arms 2, 3 or 4) and research assessment procedures at follow-up visits (week 2 and months 1, 2, 3, 4, 5, and 6 and 12) following enrollment; (3) some participants will be randomized to be eligible to receive incentives based on point-of-care urine tests that meet pre-specified criteria; (4) they will be asked to provide their name and locator information to allow the investigators to locate them for future visits; (5) they will receive a reminder call prior to their study visits; (6) they may be removed from INH if they become pregnant or develop toxicities (Grade 3 or 4); and (7) they may be asked to participate in further studies in the future.

5.3. Enrollment and randomization

After eligibility is determined, we will enroll and randomize participants, using a 2x2 factorial design, to either, both, or neither of the incentive interventions, as follows:

Arm 1: No intervention control;

Arm 2: Escalating incentives for EtG negative urine tests;

Arm 3: Escalating incentives for IsoScreen positive urine tests;

Arm 4: Escalating incentives for EtG negative urine tests and for positive IsoScreens (rewarded separately) (Figure 1). All participants will receive brief alcohol and adherence counseling according to Uganda Ministry of Health guidelines.[145]

Randomization will be 1:1:1:1, stratified by gender, and by study site. To ensure balance with respect to the number of participants in each arm, we will use the permuted blocks strategy (using random block sizes of 4 and 8 because the study is not double-blinded).[146] To allow for simultaneous enrollment at multiple sites, we will use pre-printed scratch cards revealing randomization arm as in our previous studies.

This will be an open label study as we will not be able to blind participants or research assistants to the study arm. However, we will not reveal study arm to clinic counselors and clinicians so all study arms will receive the same standard clinical and counseling procedures.

5.4. Intervention

5.4.1. Aim 1: Alcohol reduction intervention

We will compare an economic incentive-based intervention, to no incentives, in order to promote reductions in heavy alcohol use over six months of IPT in HIV/TB co-infected adults. In the Aim 1 intervention arms, participants will be told at baseline and at each study visit that each time they come to a monthly IPT refill visit and have a negative urine EtG test (detects alcohol consumption), they will instantly win a prize by drawing a lottery scratch card. Prize types and probabilities of winning a low, medium, or high-valued prize are described in section 5.4.3. The number of lottery scratch cards awarded per participant will increase by one card at each subsequent visit with a negative urine EtG results, thereby providing an escalating prize incentive (best practice for incentive-based interventions[2,147,148]) for sustained reductions in alcohol use (see Figure 2).

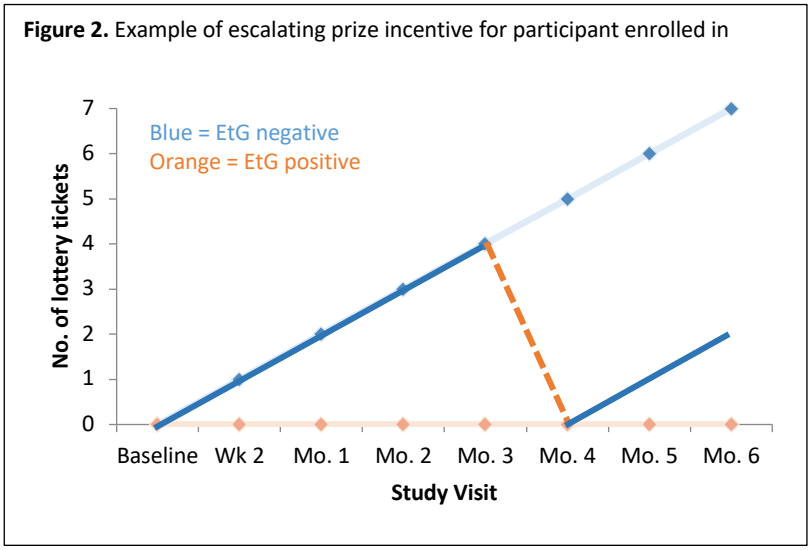


Figure 2. Example of escalating prize incentive for participant enrolled in

If a participant has a positive urine EtG test, no lottery scratch cards will be given for alcohol use reduction, and the participant will "reset" to drawing one lottery card if the urine is EtG negative at the subsequent visit. Escalating incentives with a "reset" were chosen to offer greater reward for continuous, rather than intermittent, reductions in alcohol use over the full six months of IPT, so as to minimize risk of hepatotoxicity on INH.[27] INH refill visits will be scheduled at the beginning of the week whenever possible, as our previous data show that the majority of heavy drinkers use alcohol during weekend days.

5.4.2. Aim 2: INH adherence intervention

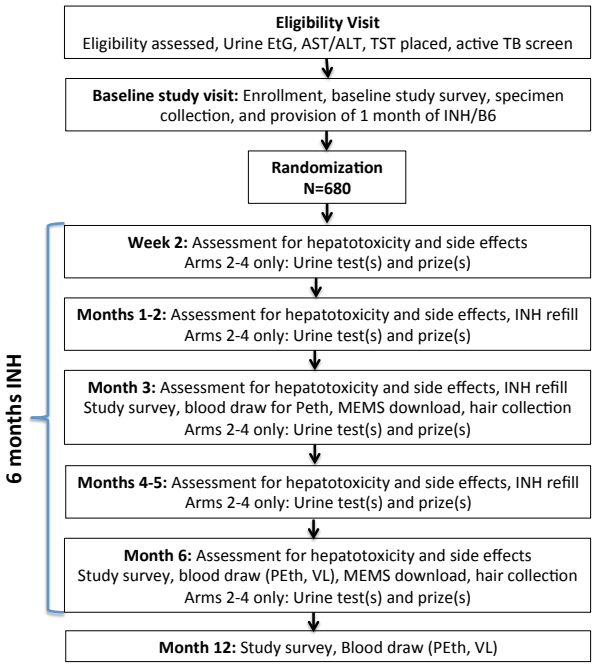
We will compare an economic incentive-based intervention to promote adherence to INH during six-months of IPT, to no incentives. Similar to Aim 1, in the Aim 2 incentive-based intervention, participants will be told at baseline and at each study visit, that each time they come to a scheduled clinic visit and have a positive urine IsoScreen (INH) test, they will have a chance to instantly win prizes by drawing a lottery scratch card that will reveal a low, medium or high value prize. The Aim 2 escalating prize incentive design will be identical to the Aim 1 incentive design, to avoid confusion among participants and research assistants, and simplify trial implementation.

Briefly, the number of scratch card draws allowed per participant will increase by one at each subsequent visit with positive urine IsoScreen results, and a negative urine IsoScreen will result in no lottery scratch cards at that visit, with a "reset" (i.e. one scratch card drawn) at the subsequent visit. Prizes and probabilities of winning medium and high-value prizes will be as in Aim 1, and are described below. Those randomized to both Aim 1 and 2 incentive interventions (persons in Arm 4) will be eligible to receive lottery card draws separately for each test (i.e. prizes awarded independently).

5.4.3. Prizes

Prizes will be chosen during a preparatory phase in consultation with community members and clinic staff at each site. The value of the prizes will reflect a balance between cultural acceptability, cost (i.e. scalability), and efficacy. Prizes that are too low in value may be dismissed as insufficient to reinforce reductions in heavy drinking or INH adherence,[149] and several studies have demonstrated that increasing the magnitude of a reward can result in greater uptake of a desired behavior.[43,150,151] However, using prizes that are too high in value could limit scalability of the proposed interventions to real-world clinical settings, and be perceived as coercive. On this basis, we will limit low-value prizes to no more than US$5, representative of one week's worth of wages in rural Uganda.[152] We will limit high-value prizes to no more than ten times the low-value amount (US$50).[151] The value of medium value prizes will range between the low and high-value amount, and the probabilities of winning will range from 1-5% for high-value prizes and 5-10% for medium-value prizes. All lottery scratch cards will have at least a low-value prize (guarantee of winning). Past prizes used in our studies have included cell phone airtime (low value), T-shirts (medium value) and cell phones (high value). We will reinforce the incentive system at each INH refill visit verbally and using visual aids, similar to those we (Chamie, Thirumurthy) are using in an ongoing study of escalating incentives for HIV virologic suppression in southwestern Uganda (R01 MH105254; NCT:02890459).

Figure 3. Study visit flow chart: Aims 1, 2 & 3.



5.4.4. Aim 3: Impact assessment of intervention

At month 12 (6 months after the Aims 1 and 2 trial completion), we will perform a study interview with participants regarding their health and alcohol use, measure PEth levels and plasma HIV viral load, and conduct TB case-finding through symptom screening, with follow-up chest x-ray and/or sputum MTB/RIF Xpert assay for symptomatic persons (Table 2).

5.5. Study visits

As previously described, eligibility will be a two-stage process in order to determine drinking status, TST status, and rule out active TB and liver enzyme elevations. Baseline visits will include collection of tracking information, a baseline survey (Table 2), blood draw, and repeat liver enzyme testing if it has been longer than one month from the screening tests.

Visits for INH refills and assessments for toxicity (assessment of side effects and liver enzyme testing) will occur at week 2 and months 1 through 6 for all study participants. Urine will be collected and prizes administered as described above for Arms 2, 3, and 4. Hair collection will occur at 3 and 6 months or at the time of the INH discontinuation if outside of the 3- and 6-month time point for all study participants (see below). Follow-up interviews and blood collection will occur at months 3, 6, and 12 (Table 2). Screening for symptoms of active TB, and sputum testing and chest X-ray if symptoms are reported, will occur at every follow-up visit.

Retention: High retention (90% at six months, 85% at one year) will be maintained as in our prior studies using follow-up phone calls, alerts when patients come to their home clinic, and home visits when needed. To encourage high retention, participants in all study arms, including control, will receive travel reimbursements (low-value unconditional cash transfers) of up to US$5 for attending study visits (see Figure 3).

Missed or late visits: If a participant misses a scheduled visit, the visit will be rescheduled within the coming 4 weeks after the missed visit, and missed visits (i.e. no-show for a clinic appointment >3 days after the scheduled clinic appointment date) will automatically prompt an incentive "reset" to baseline (i.e. drawing one card only if the incentive condition is met). Late or early visits, defined as coming to an appointment more than 3 days of an assigned appointment date, will result in an incentive "reset" to baseline. On rare occasion, exceptions to the protocol for early, late, and missed visits may be considered at the discretion of the study coordinator and study PIs. All participants will be allowed up to 9 months from INH initiation to complete a 6-month course (180 tablets) of INH, taking missed visits/refills into account. Participants that miss ≥3 months of visit time will be considered as having failed to complete IPT.

5.6. Specimen collection and laboratory procedures

Specimen processing, storage, and shipment: Initial specimen processing will be conducted at the MUST Clinical Laboratory (DIPT 1/2), and SEARCH laboratories (DIPT 2/2), or other affiliate laboratories in Southwestern Uganda, with quality assurance checks instituted for correct labeling of the specimens and temperature maintenance of the freezers. We will build upon the specimen tracking and inventory application used for Uganda ARCH study. Specimens will be transferred to the US for PEth testing at the United States Drug Testing Laboratories (USDTL), and for hair testing at UCSF. The laboratory testing (ALT/AST, CD4 count, sputum testing, hepatitis B surface antigen [HBsAg], and HIV viral load) will be conducted onsite in Uganda.

Blood testing: Blood will be collected at baseline, 3, 6, and 12 months for testing as noted above.

a) **PEth:** DBS will be spotted from venous blood samples onto Whatman 903 filter paper, stored at -80°C to promote stability, and shipped in batches to the United States Drug Testing Laboratories, where the PEth level will be determined using LC/MS-MS for the 16:0/18:1 homologue as described.[153] We will obtain a Materials Transfer Agreement to ship the DBS to the U.S.; no laboratories in Africa conduct this test.
b) **HIV viral load:** Plasma HIV viral load will be measured using the Cepheid Xpert HIV-1 RNA assay, run on an existing GeneXpert platform in Mbarara, Uganda, that has been in use for our (Chamie, Thirumurthy) ongoing incentive trials. This assay has been validated relative to the Abbott RealTime HIV-1 assay.[154,155]
c) **Liver enzymes (ALT and AST):** Same day testing will be performed for safety of providing INH refills.

Urine EtG and IsoScreen testing methods: At each INH refill visit, participants in Arms 2, 3, and 4 will be asked to provide a urine sample in a sterile cup. The urine will be received by a RA, who will check that the urine is between 32°C and 40°C (to confirm lack of tampering), and conduct the EtG dipstick test (Arms 2 and 4) and/or the IsoScreen test (Arms 3 and 4). Urine EtG screening at the study eligibility visit will be collected and temperature checked in the same fashion.

Urine pregnancy testing: For women of childbearing age, their screening visit urine sample will be used to test for pregnancy. Women who are pregnant at the screening visit will be excluded from the trial. Women who enroll into the trial will be asked at each follow-up visit whether they may have become pregnant. Those who answer yes will be provided a urine pregnancy test following the same procedures as the screening test.

Hair testing: INH concentrations will be measured in hair samples in all participants at 3 and 6 months. Hair collection methods have been outlined in previous papers.[117,135,156] We will request that participants do not shave or cut their hair for one month prior to their 3- and 6-month visits; in the case that a participant does not have enough scalp hair to collect, we will schedule the participant for a hair collection visit 3-4 weeks later. Hair samples will be kept at room temperature and in a dark place prior to batch shipment (without biohazardous restrictions) to the Hair Analytical Laboratory at UCSF for INH measurement as described above.

Table 2. Schedule of study specimen and data collection.

	Eligibility	Baseline	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 12
ALT and AST testing	◆		◆	◆	◆	◆	◆	◆	◆	
CD4 count, hepatitis B surface antigen, platelet count, creatinine		◆								
HIV viral load		◆							◆	◆
Urine EtG (All Arms at Eligibility; Intervention Arms 2+4 thereafter)	◆		◆	◆	◆	◆	◆	◆	◆	

Urine IsoScreen (Intervention Arms 3+4)			◆	◆	◆	◆	◆	◆	◆	
Urine Pregnancy test (women)*	◆		◆	◆	◆	◆	◆	◆	◆	
INH MEMS cap data download			◆	◆	◆	◆	◆	◆	◆	
Hair collection for INH level						◆			◆	
DBS for PEth testing		◆				◆			◆	◆
Study interview		◆				◆			◆	◆
Assessment for active TB (symptoms, chest X-ray, Xpert if symptomatic)	◆			◆	◆	◆	◆	◆	◆	◆

*Pregnancy test given to all women at Screening, and as-needed at follow-up visits (based on self-reported potential pregnancy)

5.7. Measurements

5.7.1. Outcome variables

Reducing heavy alcohol consumption: The main goal of the Aim 1 intervention is to reduce the level of drinking to a level most likely to decrease the risk of INH toxicity. Thus we have chosen no/non-heavy alcohol consumption as the Aim 1 primary outcome. While we are incentivizing negative urine EtG tests at INH refill visits as our *intervention*, our *trial outcome variable* captures reducing drinking over the six-month duration. We will consider PEth <35 ng/mL *and* AUDIT-C negative (modified to refer to the prior 3 months) at 3 *and* 6 months as refraining from heavy drinking during the entire period of risk. The AUDIT-C will be used because it is comprised of ranges for typical numbers of drinks and frequency of heavy drinking, rather than precise number of drinks consumed (as in the Timeline Follow Back), which can be difficult to quantify for the traditional and home-brewed beverages frequently consumed in rural African settings.[99,157] We have adapted the AUDIT-C to cover the prior 3 months (as opposed to the past year) as a measure of current drinking, and use standard cutoffs (≥3 for women and ≥4 for men) to represent heavy drinking. We will use 35 ng/mL as the PEth cutoff as described above (see Preliminary Studies). We will examine other measures of heavy drinking in sensitivity analyses, including number of drinking days in the prior 30, number of heavy drinking days (defined as ≥4 or ≥5 drinks/occasion by women and men), and PEth as a continuous variable.

IPT adherence. As above, we are incentivizing positive IsoScreen tests at INH refill visits, but our second trial *outcome variable* is IPT adherence over the entire six months. While there is no gold standard for determining medication adherence, MEMS adherence has been highly predictive of undetectable HIV viral load,[83,158,159] is considered the reference standard,[72,83,160,161] and therefore will be our primary measure of adherence. MEMS adherence will be defined as the number of pill bottle openings (no more than 1 per day counted) divided by the number of prescribed doses (180, unless taken off the medication early). The primary outcome for Aim 2 will be the proportion of participants that achieve >90% MEMS adherence to INH during prescribed IPT. We will examine other measures of INH adherence in secondary analyses, including drug concentration (ng/mg) in hair samples at 3 and 6 months, and continuous MEMS adherence.

Hepatotoxicity. A secondary outcome will be treatment discontinuation due to a Grade 3/4 hepatotoxicity at any time during the treatment period. Grade 3/4 hepatotoxicity is defined as in previous trials[3] as ALT or ALT >3-5x ULN and symptoms (nausea, vomiting, jaundice, or fatigue) *or* ALT or AST >5x ULN, regardless of symptoms. Study clinicians, blinded to intervention arm, will determine treatment discontinuation.

HIV viral suppression. The primary outcome for Aim 3 will be HIV viral suppression 12 months post-enrollment. We will also examine viral load six months post-enrollment as a secondary outcome for Aim 3.

Active TB. A secondary outcome for Aim 3 will be active TB at any time during the 12 months post-enrollment. Active TB will be defined as confirmed (if Xpert MTB/RIF assay positive) or suspected (based on chest x-ray findings or response to anti-TB treatment in symptomatic, Xpert assay negative persons).

5.7.2. Other measures

Covariates: Several covariates (Table 3) will be used to describe the study population (demographics, mental and physical health variables, alcohol use and HIV viral suppression at baseline) that may act as potential confounders if not equally randomized.

Moderators: We will examine gender as a potential moderator of intervention effects because drinking patterns between men and women differ widely in SSA,[162,163] and there is some evidence that alcohol interventions may not be equally effective among men versus women.[164-167] We will also examine alcohol use severity at baseline (AUDIT score >16) as a moderator because dependent drinkers may have differing responses to alcohol interventions.[168,169] To examine whether baseline measures of sensitivity to economic incentives and psychological measures of treatment readiness impact intervention efficacy, we will examine level of delay discounting (measured using scales of time preferences we have used in Kenya[170]) and a treatment readiness scale.[171]

Table 3. Covariates

Domain	Baseline	3-, 6- and 12-month	Individual variables
Demographics	◆		Age, sex, religion, household assets (as a measure of SES),[172] and literacy
Health	◆		Medical Outcomes Study-HIV scale for quality of life and overall physical and mental health functioning,[173-177] body mass index, CD4 cell count, active hepatitis B viral infection, smoking, and duration on ART
Alcohol use	◆	◆	AUDIT, AUDIT-C, drinking patterns (days of the week), bar attendance, heavy drinking measured by level of intoxication
ART adherence	◆	◆	ART adherence Single Item Rating Scale.[178,179] Visual analog scale, viral suppression (the direct result of adequate adherence)
Psychosocial scales	◆		Center for Epidemiologic Studies Depression Scale (16 items),[180] Stages of Change Treatment Eagerness Scale (19 items)[171]
Discount rate (high vs. low)	◆		Time preferences (a measure of present bias and temporal discounting: i.e. tendencies towards instant versus delayed gratification), highly predictive of HIV mortality[170]

5.8. Data management

Data management and quality assurance will be conducted separately for the DIPT 1/2 and DIPT 2/2 cohorts, leveraging the data management systems already in place within each site. As in the Uganda URBAN ARCH and SEARCH cohorts, tracking information will be entered into a database that will generate reminders for follow-up visits. The questionnaire data, assessments of side effects at refill visits, and laboratory results will be entered into a laptop computer in Uganda while offline, and later uploaded to a secure server at UCSF. The MEMS adherence data will be uploaded to UCSF monthly, or more frequently as needed. All study assessments will be identical at both sites for data harmonization. At each site, all data will undergo weekly checks for completeness and range criteria. We will pool the data from the two sites for analysis.

5.9. Statistical analysis plan

This study will use an intent-to-treat analysis including all participants according to their randomized assignment (excluding pilot particpants). Descriptive statistics will be calculated for all variables at baseline to characterize the study population and assess whether there appear to be differences across randomized groups; any baseline covariate that differs by study arm despite randomization will be included in adjusted analyses.

Up to two patients at each site will be recruited as pilot participants prior to the official start of the trial. Enrollment of pilot participants will enable staff to trouble-shoot any unanticipated issues in the SOPs during implementation. Data from these individuals will not be included in the analyses outlined below.

5.9.1. Aim 1 analyses

The primary analysis will use multiple logistic regression models where the main independent variable is a binary variable representing assignment to economic incentives for non-heavy alcohol use (yes vs. no). The model will additionally control for assignment to incentives for IPT adherence (yes vs. no) and randomization stratification factors (i.e., gender and study cohort), to improve efficiency, and potential confounders not balanced on randomization.

The secondary outcome of treatment discontinuation due to hepatotoxicity will be analyzed using the same approach. However, if the number of hepatotoxicity events is sparse, the penalized likelihood method will be used.[181] We will conduct similar analyses using INH adherence >90% as the outcome to evaluate whether there is an impact of economic incentives for decreasing alcohol use on IPT adherence. We will use linear regression models to examine continuous secondary outcome variables such as PEth levels, and will explore transformations for variables that are not normally distributed. If an appropriate transformation is not identified, a median regression model will be used.[182,183]

Statistical power: With 680 participants enrolled, we anticipate 612 participants will complete both 3- and 6-month follow-up (i.e. 10% loss to follow-up). Assuming 2-sided tests, with an overall significance level of 0.05, and that 15% of controls will have no heavy drinking based on our prior data, the proposed study has 80% power to detect an absolute difference of 10% (i.e. 25% vs. 15% in the intervention and control arms, respectively) in the proportions with no heavy drinking using a chi-square test with continuity correction.

5.9.2. Aim 2 analyses

Similar to the analyses for Aim 1, multiple logistic regression models will be used to analyze the primary analysis of IPT adherence >90%, where the main independent variable is assignment to incentives for IPT adherence (yes vs. no). The model will also include a variable for assignment to economic incentives for decreasing alcohol use (yes vs. no) and randomization stratification factors, as above, and potential confounders not balanced on randomization. Continuous secondary outcomes (i.e. hair levels of INH and % doses taken across 6 months based on MEMS) will be analyzed using multiple regression models as described above.

Statistical power: Based on studies showing poor completion of IPT among drinkers,[35,184] we conservatively assume 50% in the control group will achieve this outcome. With 612 evaluable subjects, the proposed study has 80% power to detect an absolute difference of 12% (i.e. 62% vs. 50% in the intervention and control arms, respectively) in the proportions completing >90% of IPT using a chi-square test with continuity correction.

5.9.3. Aim 3a analyses

We will use multiple logistic regression models including variables to represent the study arms and will also adjust for gender and study site (randomization stratification factors) to improve efficiency, as in Aims 1 & 2. The 3 pairwise comparisons of primary interest are between each intervention (Arms 2, 3, and 4) vs. control (Arm 1) and we will adjust for the multiple comparisons using the Hochberg sequential test procedure.[185] A secondary outcome of interest is virologic suppression at trial completion, analyzed using the same approach as above.

Statistical power: We expect 15% loss to follow-up at 6 months post-trial. We assume a conservative analysis based on a Bonferroni adjustment for multiple comparisons. For an overall type I error rate of 5%, we assume each of the 3 pairwise comparisons will be conducted at an alpha level of 0.0167. We expect that 67% of participants in the control group will have viral suppression at 6 months post-trial (SEARCH data). Given this assumption, the proposed study has 80% power to detect an absolute difference of 17% in the proportions with undetectable viral load for any of the 3 comparisons of interest (e.g., 84% vs. 67% in Arms 2,3, and 4 versus Arm 1, respectively) using a chi-square test with continuity correction.

5.9.4. Aim 3b analyses

We will explore reductions in alcohol use and level of IPT adherence as potential mediators that may drive the interventions to improve HIV virologic suppression. Thus we will evaluate whether a) reduction in alcohol use is related to virologic suppression; b) the interventions are related to reduction in alcohol use; c) the interventions are related to virologic suppression; and d) the effect of the interventions on virologic suppression reduces appreciably when reduction in alcohol use is added to the model.[186] However, because interpretation of the degree of mediation in logistic models (e.g. for the binary outcome refraining from heavy drinking) is complicated by their inherent nonlinearity, we will conduct additional analyses using a causal inference approach to mediation that derives direct and indirect effects for

binary outcomes.[187-190] We will use the Stata mediation package to conduct these analyses.[191,192] In addition to alcohol, we will also assess whether IPT adherence level is in the causal pathway between the interventions and viral suppression.

5.9.5. Additional analyses

Intervention effects over time. For Aims 1 & 2, we will conduct secondary analyses to assess intervention effects separately at 3 and 6 months and to assess for possible intervention by time interactions. We will use generalized linear mixed effects models that include subject-specific random intercepts and slopes for continuous outcomes and generalized estimating equations (GEE), with an independence working correlation matrix and logit link for dichotomous outcomes. Additional analyses will also be performed using mixed effects logistic regression models for correlated binary outcomes.

Moderators. We will perform additional analyses to explore potential moderators of the incentive interventions. For Aims 1 and 2, the potential moderators of interest are: sex, baseline level of alcohol use, readiness to change, and discount rate. Although we do not expect interaction between the two interventions, we will assess and test this as well. For each aim, we will fit separate models including 2-way interactions between randomization group and each potential effect moderator, as well as a model testing the interaction between the two interventions. If an interaction is significant, subsequent stratified analyses will be conducted to explore the effect of the economic incentives intervention by categories of the moderator.

Missing data. Participants who meet eligibility criteria and enroll in the study will be compared with eligible participants who decline enrollment, using the 2 independent samples *t*-test and Fisher's exact test. We will similarly test for differences between participants lost to follow-up and those who complete the study. In addition, data collected to the point of lost to follow-up will be compared to the data of those who complete the study to examine missing data mechanisms. In situations where missing data occurs, we will document the reasons for the missing data whenever possible. If it is reasonable to assume that data are missing at random, multiple model based imputation methods[193,194] will be applied if needed.

6. Safety considerations

6.1. Potential Risks

Potential risks to participants, and their likelihood and seriousness to the human subjects: The potential risks associated with the study are risks due to study drugs, loss of confidentiality, stress from the study interviews, and risks associated with blood draws, including pain and, rarely, infection and/or bruising. The risks are described in detail below:

- ***Medication risks***
    - **INH:** Serious side effects are: an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; or hives); unusual weakness or fatigue; nausea, vomiting, or loss of appetite; abdominal pain; yellow skin or eyes; dark urine; numbness or tingling in hands or feet; seizures; blurred vision; confusion or abnormal behavior. (Source: http://www.rxlist.com/isoniazid-drug/patient-images-side-effects.htm). Very recent data from a randomized trial presented at the 2018 Conference for Retroviruses and Opportunistic Infections (CROI) found an increased risk of adverse pregnancy outcomes among HIV-positive women taking INH during pregnancy compared to HIV-positive women who initiated INH post-partum. (Source: http://www.croiconference.org/sessions/randomized-trial-safety-isoniazid-preventive-therapy-during-or-after-pregnancy). Recently, following a country-wide scale-up of INH in Uganda ("100-day push"), several clinics reported cases of death thought to be a result of liver failure, possibly attributable to INH-drug-induced liver injury. Anecdotally, the deaths appear to have occurred primarily in patients who started on INH and Dolutegravir at the same time. The deaths occurred in clinical settings with limited laboratory (LFT) monitoring. In response, the Uganda MoH and Uganda National Drug Authority (NDA) have set up a pharmacovigilance plan and had a visit from members

of the World Health Organization, to consider a response to these clinical observations. In July 2020, the Uganda MoH revised their Consolidated Guidelines for the Prevention and Treatment of HIV to advise delaying initiation of IPT for individuals who have newly initiated on DTG (within three months).

- **Vitamin B-6:** Most common side effects include: nervous system abnormalities (such as tingling feelings, shooting pains, numbness, and not being able to feel pain or temperature). (Source: http://patient.info/medicine/pyridoxine-tablets).

Study participants will be given information on the TB preventive therapy (INH) as well as Vitamin B-6. Participants will also be given instructions on how to use the MEMS device. The study staff will be trained to assess for all possible side effects of INH and Vitamin B-6 and will follow established protocols for identifying and monitoring any ongoing adverse events, including referrals to treatment. Study participants will be actively monitored for adverse events, particularly those related to INH, and Vitamin B-6 as in the most recent FDA's Drug Safety Announcement. Symptoms will be assessed at each follow-up study visit for the duration of treatment (at 2 weeks, 1, 2, 3, 4, 5, and 6 months), and additionally at 7 months, as needed for those who develop hepatotoxicity. RAs will document hepatotoxicities and side effects on CRFs, completed in real-time, as they receive the information from the participants, and submit completed forms to the study physicians for weekly review.

Other risks

- **Tuberculin Skin Testing (TST):** Risks of TST testing with subcutaneous placement of purified protein derivative (PPD) are rare, but include a very low risk of a severe allergic reaction to the skin test (https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm). Participants with a history of a severe reaction to a TST in the past will not be given a TST during this study.

- The loss of confidentiality may lead to disclosure of HIV infection, TB infection, or disclosure of drinking status. Stigma associated with such disclosure may include social harms such as disruption of family (e.g., breakup of couples following HIV detection in one spouse), discrimination (e.g., a loss of employment or status in community), physical harm such as domestic violence (e.g., acts of physical violence directed at people who have been diagnosed with HIV), and psychological harm such as embarrassment (e.g., being questioned by family members about alcohol use). There may be some discomfort with the nature of the interviews, since alcohol use will be discussed. There is also the very slight but present chance of a breach of confidentiality inherent in any study that handles confidential data.

- Psychological stress could be caused by the interview in which participants will be asked sensitive questions regarding substance use and HIV status and progression. Distress caused by the length of the interview is also possible. The RAs will be trained to address these issues with a calm, non-judgmental attitude. These minimal risks are not likely and will be minimized further by only selecting patients who understand the study and are willing to participate.

- Phlebotomy associated risks include bruising, bleeding, infection, phlebitis, and pain. Bruising is common, minor pain with needle stick is universal, the other risks are rare.

- Hair Collection: The risk of a cut to the skin from scissors during hair collection is extremely low. We have been collecting small hair samples from HIV-positive participants on antiretroviral therapy in the NIH-funded Women's Interagency HIV Study (WIHS), a large multicenter prospective study of HIV-infected and at-risk HIV- uninfected women, every six months since 2002. We have collected over 20,000 hair specimens in the WIHS via the collection procedure outlined in the research plan above and have never had an injury or any other adverse event reported from the collection process.

The risk of cosmetic effects from hair collection is also extremely low. The human scalp loses an average of 100 strands of hair per day, so the amount of hair we propose to collect for this project is less than what a participant's scalp would typically lose on an average day. Moreover, the size of the hair sample collected for the INH assays is extremely small and collection is usually easily accomplished from participants with short or limited amounts of hair. Over the past 12 years of collecting hair from participants in the WIHS cohort, we have never registered any complaints that the process has been disruptive to hair styles and we have high rates of acceptability of hair collection in the overall study (ranging from 88-97%, depending on the site). We have also been collecting hair from HIV-infected women and their infants in Uganda (Dr. Havlir's PROMOTE study), HIV infected pregnant women in South Africa, and participants in several pre-exposure prophylaxis (PrEP) trials. We have experienced high rates of acceptability of hair collection in each of these studies (~95%), have not registered any reports of adverse events, including accidental skin cuts or disruption of hair styles, in any of these studies.

- Biohazard exposure is an additional risk, as the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products. Personnel will be trained in and follow standard laboratory procedures to minimize the risk of contamination.

- Another risk stems from the use of economic incentives, which might be viewed as coercive. However, the expected value of the economic incentives at each visit (taking into account low probabilities of high value awards) is relatively low (US$5 per lottery draw). A recent publication by the Ethics Working Group of the HIV Prevention Trials Network (HPTN) has also made the case that the use of incentives for health promotion does not necessarily undermine individual autonomy.[195] Instead, incentives can help overcome economic obstacles or motivational deficiencies; they can promote engagement in health-related behaviors that participants regard as beneficial or worthwhile, but do not undertake due to behavioral biases such as present-biased preferences or delayed reward discounting. Our past experience implementing economic incentive interventions in Kenya and Uganda has also demonstrated that such interventions are acceptable to both communities and ethical review boards.

Alternative procedures: The alternative is to either not consent to the study or to withdraw from the study at any time after consented. We will be clear with participants that there is no obligation to enroll in or continue with the study. Any participant may decline any study procedure at any time—this will not affect the person's ability to receive care at any HIV clinic. Any potential study participant who does not wish to enroll in the study but wishes to learn more about their alcohol consumption will be referred to their doctor.

6.2. Protection against risks

All adverse events (AEs): The Field Coordinator will complete descriptions of AEs on an AE reporting form that will be sent promptly to the Principal Investigator (PI) and all study investigators. Additionally, AEs will be reported to the Data and Safety Monitoring Board (see below), which will conduct further review of data from the DIPT Study and re-evaluate the risks to the participants.

Planned procedure for protection from risks due to medications: Study participants will be given information on the medication and advice on how to take the prescribed medications. They will be advised on the dosage and told not to double up on pills if any are missed. The staff will be trained to assess for all possible side effects of the medications and will follow established protocols for identifying and monitoring any AEs. Study participants will be actively monitored for AEs, particularly those related to INH and Vitamin B-6. Symptoms will be assessed at each follow-up study visit (at 2 weeks, and 1, 2, 3, 4, 5, and 6 months; 7 months as needed for those who develop hepatotoxicity.) by a trained clinical officer, and participants will be trained to recognize symptoms of hepatotoxicity. ALT/AST testing will also occur at these visits. Results of the ALT/AST testing will be given to the RAs by each cohort's research laboratory within 24 hours of testing. All participants will be given the phone number of the clinical officer to call in case symptoms develop between visits. In the case of suspected toxicity, the clinical officer will notify one of the two study physicians, who will determine whether a Grade 3/4 toxicity has occurred, and will recommend stopping treatment if INH is considered the

cause. The physicians will be blinded of the participant's study arm. If hepatotoxicity is discovered by ALT/AST results after the patient has left the clinic, the RA will contact the participant immediately via phone to inform them, and will make a follow-up home visit to retrieve the dispensed medications from the participant. In addition, the clinical officer will notify the study clinic for continued patient follow-up. Study participants will remain in the study following treatment discontinuation for follow-up monitoring, but will no longer be eligible to receive incentives for positive IsoScreen urine tests.

Women of childbearing age will be asked about possible pregnancy at each follow-up study visit for the duration of INH treatment (at 2 weeks, 1, 2, 3, 4, 5, and 6 months), and additionally at months 7-9, for those who do not complete the regimen within the first 6 months. Women who report that they may have become pregnant will be offered a urine pregnancy test. Women who are confirmed to be pregnant will be discontinued from INH treatment. Study participants who become pregnant will remain in the study following treatment discontinuation for follow-up monitoring, but will no longer be eligible to receive incentives for positive IsoScreen urine tests.

Individuals who are prescribed Dolutegravir (DTG) will not be enrolled into the study until they have been on DTG for at least 3 months, to prevent starting DTG and INH at the same time.

Participants who are discontinued from INH treatment (due to toxicities or pregnancy) may still be eligible to receive incentives from EtG testing if they are in study arms 2 or 4.

Planned procedure for protection from risks due to phlebotomy: Trained RAs (trained clinical officers) or laboratory technicians will collect all specimens using standard sterile procedures. The phlebotomist will report any complications resulting from blood draws to the field study coordinator, who will make an immediate report to the Principal Investigator. The Principal Investigator will take responsibility for reporting such AEs to the relevant IRBs and NIH within ten days.

Planned procedure for protection from risks due to TST: The RAs (trained clinical officers) will conduct the TST in participants using standard sterile procedures. RAs will report any complications resulting from the TST to the field study coordinator, who will make an immediate report to the Principal Investigator. The Principal Investigator will take responsibility for reporting such AEs to the relevant IRBs and NIH within ten days.

Planned procedure for protection from risks due to alcohol use: During our study assessments, we may uncover probable alcohol dependence, using an AUDIT-C score of 8 or more. In this case, or at the participant's request over the course of the study, we will continue with study activities but also refer patients to their clinicians at the study clinics for DIPT 1/2 / to the treating clinicians at the SEARCH study clinics for DIPT 2/2. In addition to the referrals, we will offer brief alcohol counseling to participants enrolled in all study arms at the baseline study visit as part of standard of care.

Planned procedure for protection from risks due to lack of biohazard containment: As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the NIH.

Planned procedure for protection from risks due to use of economic incentives. It will be explained to participants that incentive payments will be conditional on the specified behavior (reduced alcohol use and/or INH adherence), and that the expected value of each lottery card is approximately US$5. Coercion is unlikely in this case because the incentives are not so large in value that they exceed the likely costs associated with retention in care and meeting the desired health behaviors.

Planned procedures for the protection of loss of confidentiality: The primary risk of participating in this study is the loss of confidentiality. While many participants in our current studies have disclosed their HIV status to their family, we consider loss of confidentiality an important risk of the study and have implemented the following procedure to reduce the risk to confidentiality.

- We will discuss the possibility of HIV, TB, or alcohol-related stigma with the potential participants during the informed consent process for the study. We will ask potential participants to think about persons in their family, group of friends, neighborhood, or workplace, who don't know their HIV or TB status, and how they might react to discovering that the participant is infected with HIV or TB, or drinks alcohol. Enrollment will be deferred for those who are unsure about ramifications of participating. Persons who decline or defer enrollment in the study will be assured that this will not affect their HIV care.

- We will ensure that all study visits and telephone calls for tracking or study visit reminders, may be deferred for any reason and that participation in the study may be ended at any time. Telephone calls may be ended at any time with a pre-agreed upon word or action.
    - Study staff will be trained to apply the same measures of confidentiality and sensitivity during phone calls as they do with all other data collection activities.

- We will provide referrals to all participants and persons considering enrollment to social support services provided by the MRRH Counseling Program or other equivalent counseling program available in the area, as desired. These services include the option of participating in support groups where issues of disclosure can be discussed, and the individual can learn from peers about high-risk disclosure situations and how to minimize risk.

- To ensure confidentiality of participation, all instruments, forms, and biologic specimens will be coded with a unique participant identifier that renders the data anonymous to persons outside the study. All data will be kept in locked cabinets and on secure servers. Research records will be kept confidential to the level allowed by law. Records with identifying information, such as contact information and consent forms, will be stored separately from survey information. No individual identities will be used in any reports or publications.

- All staff in contact with participants and/or data will be trained on procedures for maintaining privacy and will sign a pledge of confidentiality. They will also take CITI human subjects training courses.

- We will provide participants with information on how to contact the local field staff to report incidents such as HIV-related disruption of families, acts of discrimination, and physical harm. This information will also be written on the take-home consent form.

6.3. Potential Benefits

Participants may benefit from receiving TB preventive therapy, which has been shown to reduce the risk of active TB and decrease mortality rates in persons with HIV infection. Participants in the intervention study arms will be rewarded with prizes (US$5 average expected value) for decreased alcohol use and adherence to INH. Collateral benefits include receipt of refreshments (DIPT1), transportation reimbursements, and the receipt of results from laboratory tests (CD4 cell counts, HIV viral load, HBsAg, ALT/AST testing, active TB screening). PEth biomarker and INH hair concentration results will not be disclosed to participants due to the lag in testing and the non-routine nature of these tests in this population. Otherwise, participants are not promised any direct benefit. The risks to the participants are reasonable in relation to the anticipated benefits to the participants and other HIV-infected patients because results of this study will inform guidelines for providing TB preventive therapy to HIV-infected drinkers worldwide.

6.4. Data safety monitoring plan

Day to day data and safety monitoring will be the responsibility of the Principal Investigator of each DIPT cohort. We will follow guidelines set forth by the UCSF IRB regarding AEs. AEs will be reported to the IRBs within 10 days of awareness of the AE. Serious adverse events (SAEs) will also be reported to the NIH and will be reported to the IRBs and the NIH within 2 days. We will additionally submit an annual report of all AEs to NIAAA.

AEs will be monitored for each subject participating in the study and attributed to the study intervention by the Principal Investigator with review by the physicians/co-investigators according to the following categories:

1. Definite: Adverse event is clearly related to the intervention.
2. Probable: Adverse event is likely related to the intervention.
3. Possible: Adverse event may be related to the intervention.
4. Unlikely: Adverse event is likely not to be related to the intervention.
5. Unrelated: Adverse event is clearly not related to the intervention.

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe adverse event

In addition to grading the AE, the Principal Investigator will determine whether the AE meets the criteria for a SAE. An AE is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect
5. results in death
6. may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, based upon appropriate medical judgment, or
7. adversely affects the risk/benefit ratio of the study

An AE may be graded as severe but still not meet the criteria for a SAE. Similarly, an AE may be graded as moderate but meet the criteria for a SAE. The Principal Investigator and the study physicians/co-investigators will determine the grade of the event as well as its "seriousness."

Planned procedure for protection from risks due to medications: Study participants will be given information on the medication and advice on how to take the prescribed medications. They will be advised on the dosage and told not to double up on pills if any are missed. The staff will be trained to assess for all possible side effects of the medications and will follow established protocols for identifying and monitoring any AEs. Study participants will be actively monitored for AEs, particularly those related to INH and Vitamin B-6. Symptoms will be assessed at each follow-up study visit (at 2 weeks, and 1, 2, 3, 4, 5, and 6 months; 7 months as needed for those who develop hepatotoxicity) by a trained clinical officer, and participants will be trained to recognize symptoms of hepatotoxicity. ALT/AST testing will also occur at these visits. Results of the ALT/AST testing will be given to the RAs by each cohort's research laboratory within 24 hours of testing. All participants will be given the phone number of the clinical officer to call in case symptoms develop between visits. In the case of suspected INH related toxicity, the clinical officer will notify a study physician, who will determine whether a Grade 3/4 has occurred, and will recommend stopping treatment if INH is considered the cause. In such events, increased liver enzyme monitoring will occur until ALT and AST return to <2X the upper limit of normal. In the case of severe liver enzyme elevations (>10X the upper limit of normal), hospitalization will be advised. Study participants will remain in the study following treatment discontinuation for follow-up monitoring. The physicians will be blinded of the participant's study arm.

Planned procedure for protection from risks due to alcohol use: During our study assessments, we may uncover probable alcohol dependence, using an AUDIT-C score of 8 or more. In this case, or at the participant's request over the course of the study, we will continue with study activities but also refer patients to a clinician at each study site. In addition to the referrals, we will offer brief alcohol counseling to participants enrolled in all study arms at the baseline study visit as part of standard of care.

Risk assessment

Participation in the DIPT Study may present more than minimal risk, as intervention participants will be administered study medications, which could cause AEs. However, as the TB preventive therapy and vitamin B-6 will be administered at recommended dosing, and as AEs will be monitored closely, the overall risk of the study drugs is low. These risks are addressed in detail above. The risk of AEs of the study drugs are best addressed by appropriate study procedures. The Principal Investigators of DIPT 1/2 and 2/2 and co-investigators will be responsible for assuring that study procedures are adhered to regarding monitoring, managing, and reporting adverse effects of the study drugs by meeting regularly with study staff, reviewing procedures, and performing quality control reviews of study forms.

In addition, other risks to participants include social harm due to loss of confidentiality, disruption of family (e.g., breakup of couples following HIV detection), discrimination (e.g., loss of employment or status in community), physical harm (e.g., acts of physical violence directed at people who have been disclosed as HIV-infected) and embarrassment (e.g., being questioned about alcohol use). Should any of these or other incidents occur, the on-site Field Coordinators will immediately report them to the Principal Investigator, who will in turn report them to the appropriate IRB(s) and to the NIH within ten days of learning of the incident, and notify all study co-investigators. We will ask study participants to return to the research field site as well as provide participants with a palm card containing information on how to contact the local field staff to report such incidents.

The Field Coordinators will be trained to complete descriptions of AEs on an AE reporting form that will then be sent electronically to the US PI. The PI will also report any instances where a US or international IRB takes any action relating to the study. The PIs will make at least two site visits per year to inspect the quality assurance protocol and to review study procedures, including recruitment and data collection.

Interim analyses

No interim efficacy or futility analyses are planned because the primary risk, hepatotoxicity, will be examined by the investigators and the data and safety monitoring board on an ongoing basis. However, the study team, including the project directors, statistician, co-investigators, field coordinators, and RAs, led by the Principal Investigators, will monitor the progress of the study, participant recruitment, accrual and retention at twice monthly conference call meetings. All AEs will be discussed. They will also examine factors external to the study when interpreting the data, such as scientific developments or the new availability of information that could impact the safety of the participants, such as new pertinent FDA Drug and Safety Announcements, the performance of the study, or the ethics of the study.

Data and Safety Monitoring Board (DSMB)

To ensure the safety of the participants and the validity and integrity of the data, we will leverage the URBAN ARCH consortium DSMB. The URBAN ARCH DSMB will assume the same responsibilities for the DIPT Study. The DSMB will also be valuable for further ensuring the quality and scientific validity of the study. All safety data will be reviewed every 6 months by the URBAN ARCH DSMB. The DSMB is chaired by Theodore Colton, PhD (Boston University School of Public Health), and comprised of Josiah Rich, MD (Brown University School of Medicine) and Lynn Fiellin, MD (Yale School of Medicine). We will additionally include a consultant hepatologist to the DSMB specifically for reviewing trials of hepatotoxic drugs, including the DIPT Study.

The DSMB will meet by conference call at a minimum of every 6 months. They will be charged with evaluating the quality of trial administration, monitoring safety issues, and providing guidance on scientific, methodological and ethical issues. Specifically, the DSMB will review the plans and processes for identifying individual or patterns of adverse events and review accumulating safety data. Following each meeting, the DSMB will make recommendations on continuation, modification, or termination of the study.

Data Management and Security to Protect Privacy

UCSF, in collaboration with the MUST and IDRC data management teams, will ensure high quality forms, monitor data quality, and track and link the multiple data sources. The team will jointly develop data collection forms, design the database management system for data entered and for participant tracking, implement procedures for quality control, and provide statistical programming and collaborate in report writing and presentation of study results.

Electronic data will be collected using password-protected laptop computers. The data team will design, develop and maintain the electronic data collection forms, participant and data tracking, and underlying SQL database systems, and implement procedures for data quality control, including multiple checks for entered data. Electronic data collection

forms will be designed to read easily, have clear instructions, preprogrammed skip patterns, real-time range checks and internal logic to minimize missing data and resulting in "cleaner" data at capture. The databases will be located on secure, password-protected servers in Uganda and the US.

7. 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 NIH, UCSF, UNCST, MUST and Makerere University guidelines.

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List of study materials for DIPT

- Questionnaires
    - Screening
    - Baseline
    - 3, 6 month visits
    - 12 month visit (end of study)

- Consent forms
    - Screening
    - Main study