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Brief title: Alcohol Drinkers' Exposure to Preventive Therapy for TB (ADEPTT)

Official title: **URBAN ARCH (3/5) Uganda Cohort TB preventive therapy for HIV-infected alcohol users in Uganda: an evaluation of safety tolerability and adherence**

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SPECIFIC AIMS

Tuberculosis (TB) is the leading cause of mortality in persons with HIV worldwide, accounting for 20-33% of HIV-related deaths,[1,2] and is a high-priority area of research in HIV/AIDS by the NIH.[3] TB preventive therapy decreases both all-cause mortality and active TB in persons with HIV by 30-50% above and beyond the benefits of antiretroviral therapy (ART) alone.[4-8] Based on these findings, the World Health Organization (WHO) recommends isoniazid (INH) preventive therapy (IPT) for all persons with HIV in resource constrained settings.[9-11] However, the WHO warns against the use of IPT in persons with "regular and heavy alcohol use."[9] This exclusion stems from concern for increased hepatotoxicity in heavy drinkers in settings where liver enzymes are not routinely monitored. Heavy drinking in persons with HIV is very common, approximately 25%, in sub-Saharan Africa (SSA).[12-17] Heavy drinking increases the risk for active TB at least threefold;[18-20] thus, HIV-infected alcohol users should be prioritized for TB prevention. However, no studies have systematically assessed the safety of TB preventive therapy in heavy drinkers with or without HIV infection. It is critical to **examine the safety and tolerability of TB preventive therapy for HIV-infected drinkers,** given the high rates of HIV, TB infection, and alcohol comorbidities worldwide. While the risk of toxicity exists, the risk of TB disease could outweigh the toxicity harms. Thus, it is also crucial to **determine whether the mortality benefits outweigh the toxicity risks** for this significant portion of the HIV-infected population.

TB preventive therapy is only effective if taken consistently for the full course.[21] Alcohol use is an established risk factor for decreased ART pill taking[22] and active TB treatment discontinuation.[23] Whether HIV-infected drinkers on ART can be adherent to TB preventive therapy is not known. Therefore it is essential to determine the level of adherence to TB preventive therapy by HIV-infected drinkers on ART.

We propose the **A**lcohol **D**rinkers' **E**xposure to **P**reventive **T**herapy for **TB** (**ADEPTT**) study to examine 6 months of daily INH (6H) among N=300 persons co-infected with HIV and TB. Our main aim is to evaluate the safety and tolerability of the TB preventive therapy regimens overall among drinkers and by level of drinking. We will also determine adherence to the regimen at 3 and 6 months overall among drinkers and by level of drinking. Alcohol use will be measured by self-report and augmented by phosphatidylethanol (PEth), an established biomarker for alcohol consumption.[30] We will use objective measures of adherence including electronic medication monitoring (EMM) that records pill bottle opening, and INH concentration in hair, a novel measure of INH exposure.[31,32] We will actively monitor for hepatotoxicity, using the U.S. standard of care for laboratory monitoring during TB preventive therapy for heavy drinkers, thus it would not be ethical to include a no-treatment control group. We will use the safety, tolerability, and adherence results, the known efficacy and mortality benefit of TB preventive therapy in HIV-infected persons in SSA, together with our established decision analytic model of TB preventive therapy[33] to determine whether the clinical benefits of TB preventive therapy outweigh toxicity risks for HIV-infected drinkers in resource limited settings. Our study aims are:

Aim 1: To examine the safety and tolerability of 6H in HIV/TB co-infected drinkers, measured by hepatotoxicity and treatment discontinuation rates. *Our main aim is to estimate safety and tolerability overall among drinkers (primary) and by level of drinking (secondary).*

Aim 2: To determine the level of TB preventive therapy adherence overall among drinkers and by level of drinking, and at 3 and 6 months. *The main goal of this aim is to estimate adherence overall among drinkers (primary). Secondarily we will estimate adherence by level of drinking (heavy, current but not heavy drinkers, and non-drinkers) and compare adherence across drinking levels. We hypothesize that adherence will be highest among the non-drinkers.*

Aim 3: To determine whether the benefits of providing TB preventive therapy to HIV-infected drinkers in resource-limited settings outweigh the risks compared to no treatment. *We hypothesize that providing TB preventive therapy will result in longer life expectancy and quality-adjusted life expectancy than not providing TB preventive therapy (current standard of care).*

In this renewal application, we will leverage the Uganda cohort of the Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS (URBAN ARCH), which includes over 400 HIV-infected drinkers, to accomplish the study aims. The ADEPTT study will generate unique data on the safety and tolerability of TB preventive therapy for HIV/TB co-infected drinkers, and HIV-infected drinkers' level of adherence at 3- and 6-months. Our results will provide critical new insights for guidelines on how to best deliver TB preventive therapy to alcohol using, HIV/TB co-infected persons at high risk for TB disease and reduce morbidity and mortality.

B. BACKGROUND and SIGNIFICANCE

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).[1,2] At least one-third of the 37 million people living with HIV worldwide are infected with latent TB; these individuals are 26 times more likely to develop active TB disease than those without HIV. Although aggressive strategies to find and treat all active TB cases are needed to reduce HIV/TB mortality, the only strategy to prevent new active TB cases in exposed individuals is via preventive treatment.

Heavy drinking is common among HIV-infected persons and heavy drinkers are at high risk for active TB. In several studies of persons in HIV care in SSA, a median of 25% of persons self-reported heavy drinking,[12-17] with heavy drinking defined as exceeding the NIAAA drinking limits (Table 1) or via the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C).[34,35] Heavy alcohol consumption is an established risk factor for HIV infection,[36,37] and is also a risk factor for becoming infected with TB via increased immune system suppression and time spent in settings where TB is prevalent.[20] The risk of active TB is increased 3-fold among heavy drinkers compared to non-drinkers,[18-20,38] and heavy drinkers are more likely to have smear positive disease, slower TB treatment response, and higher mortality while on TB treatment.[20,39] Thus, HIV-infected drinkers are at high risk of morbidity and mortality due to active TB disease.

Preventive treatment for TB is life-saving among persons with HIV. Randomized trials conducted prior to widespread ART use showed high efficacy of IPT to prevent TB in those with HIV.[4] Recent studies, including the TEMPRANO ANRS trial, showed the additive benefit of IPT and ART in reducing mortality for patients at all CD4 counts.[4-6,8] IPT-associated decreases in active TB and mortality ranged from 30% to 50%, supporting the concomitant use of IPT and ART. Thus the WHO recommends IPT, intensified TB case-finding, and infection control for persons with HIV. Major implementation of IPT in HIV-infected persons in South Africa is underway,[1] scale up is occurring in Tanzania[40] and Botswana,[41] and calls for further roll-out have been made.[10,11]

The WHO lists "regular and heavy alcohol use" as a contraindication to IPT, but data on the hepatotoxicity of IPT in HIV-infected drinkers are limited. 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.[42] Most INH-associated hepatotoxicity is reversible by stopping therapy, but liver injury can, rarely, lead to the need for liver transplantation or death, with mortality rates of 0.05-0.10%.[43] In the U.S., concern about toxicity is mitigated by the ability to perform liver enzyme monitoring in patients deemed at highest risk of INH-related hepatitis.[44]

Alcohol users are considered at high risk for INH-related hepatotoxicity, based on an early study of IPT in which any and daily alcohol use were associated with 2- and 4- fold increases in toxicity rates, respectively.[45] However, the high rates of toxicity in this study have since been questioned.[46] Only a handful of studies since this 1978 publication have reported INH-related toxicity stratified by alcohol consumption level, and the findings of these subsequent studies have been mixed.[26,47-51] Thus, data are urgently needed on the safety and tolerability of TB preventive therapy in HIV-infected drinkers to inform worldwide guidelines.[52]

Adherence to TB preventive therapy among drinkers on ART is unknown. Among those with HIV, alcohol use has been consistently associated with reduced ART adherence,[22,53,54] and we (Jacobson) and others have found that alcohol use is associated with discontinuation of active TB treatment.[23,48,55] Reports of adherence to IPT among all comers range widely, from 19-96%.[52,56] While completion of 9-months of IPT in a study of persons

Table 1. Frequently used acronyms and definitions	
6H	6 months daily INH
ALT/AST	Alanine and aspartate aminotransferases
ART	Antiretroviral therapy
AUDIT-C	Alcohol Use Disorders Identification Test – Consumption
CRF	Case report form
Grade 3/4 hepatotoxicity	ALT or ALT >3x ULN and symptoms (nausea, vomiting, jaundice, or fatigue) OR ALT or AST >5x ULN
NIAAA heavy drinking	Men: ≥4 drinks/day or ≥14 drinks/week; Women: ≥3 drinks/day or ≥7 drinks/week
INH	Isoniazid
IPT	Isoniazid preventive therapy
EMM	Electronic medication monitoring
PEth	Phosphatidylethanol
TST	Tuberculin skin test
ULN	Upper limit of normal

with HIV in Uganda was 34%,[56] several studies in HIV-infected persons have shown good completion rates (82%-87%), with the highest rates among those on ART.[41,57-59] The addition of IPT to an established pill taking routine may be feasible, but adherence to and completion of TB preventive therapy among HIV-infected drinkers on ART is not known.

Valid measurement of medication adherence is critical to evaluating IPT. A key component of the scale up of TB preventive therapy for persons with HIV will ultimately be medication adherence. Self-reported adherence measures have limitations,[60-63] especially in settings in which socially desirable responses are likely to be high. This problem was recently illustrated by the lack of efficacy of pre-exposure prophylaxis for HIV in a large trial, due to patients' misreporting taking the prescribed antiretrovirals.[64]

EMM and pharmacy pill counts are considered objective measures, although limitations, such as when patients remove multiple pills at once, have also been noted.[60] Other objective adherence measures include drug concentrations determined in plasma, saliva, or dried blood spots (DBS).[65-67] However, those measures reflect recent drug administration and are affected by increased pill taking just prior to a visit.[68] Drug concentrations in hair, which reflect exposure over weeks to months,[69] have been linearly related to ART dose frequency[70] and strongly predictive of HIV viral suppression.[65,66,71-74] We (Gandhi) have pioneered methods to extract and analyze ART levels from hair samples,[75,76] demonstrated high feasibility and acceptability of hair collection in East Africa,[77-80] and established the feasibility of measuring INH in hair as well.[31]

PEth provides an objective measure of alcohol use. Patients in our study will be advised to reduce their alcohol consumption or abstain to avoid INH-related liver toxicity, thus under-report of alcohol use is a concern. While it will be important to examine the levels of hepatotoxicity by self-report measures available to clinicians prior to prescribing TB preventive therapy, accurate measurement of actual heavy alcohol use is also needed. We (Hahn) have utilized PEth, a sensitive and specific biomarker of alcohol consumption over the prior 3 weeks,[30] to improve our measurement of heavy alcohol use.[81,82]

The benefits and risks of TB preventive therapy for HIV-infected drinkers need to be compared. The WHO recommendation against IPT for HIV-infected "regular and heavy drinkers" in resource constrained settings[9] makes the assumption that the risk of toxicity from therapy outweighs the risk of developing active TB disease. Given the high prevalence of latent TB infection (LTBI) in endemic settings, the high risk of active TB for drinkers, and the serious consequences of TB disease, it is possible that TB preventive therapy, even without monitoring liver enzymes, has better long-term outcomes than avoiding therapy in this population.

Decision analysis modeling provides a quantitative approach to integrating multi-dimensional risk and benefits to identify optimal treatment strategies.[87] Decision models have examined use of IPT among those with HIV in resource limited settings;[88-91] however, none have incorporated the hepatotoxicity and adherence rates relevant to heavy drinking. We will leverage our (Linas') validated decision-analytic Markov model of TB preventive therapy[33] to examine TB preventive therapy benefits and risks in this population.

INNOVATION

The ADEPT-T study is unique in its focus on HIV-infected drinkers and for examining the safety and tolerability of and adherence to TB preventive therapy among a population at very high risk for developing active TB but potentially excluded from receiving treatment under the current guidelines. Innovation includes: (1) generating unique data on the safety and tolerability of TB preventive therapy in HIV-infected alcohol users, (2) using trial-based estimates in a decision analytic model to determine whether the benefit of treatment exceeds the harm, (3) monitoring adherence to standard INH TB preventive therapy (6H) in drinkers, a group at risk for low adherence, using objective adherence measures, (4) using an alcohol biomarker to augment self-report and avoid misclassification, because patients are advised to reduce their alcohol use and are thus likely to under-report, (5) examining a biomarker of INH concentration to represent long-term exposure to INH as an objective measurement of adherence, and (6) embedding this study in the existing Uganda ARCH cohort, a unique cohort of HIV-infected drinkers in Uganda with regular assessment of alcohol use and specimen collection.

STUDY DESIGN OVERVIEW

We propose a single arm trial of TB preventive therapy to assess its toxicity, measure adherence, and determine whether its benefits outweigh its risks when given to TB/HIV-infected drinkers (n=200). We will provide 6 months of INH to HIV/TB infected drinkers (n=200) and non-drinkers (n=100) to describe safety, tolerability, and adherence among drinkers and by level of drinking. We will conduct frequent monitoring for toxicity, and assess toxicity as well as adherence. We will evaluate the safety, tolerability and adherence by level of drinking, measured by self-report and augmented by phosphatidylethanol (PEth), an established biomarker for alcohol consumption. We will employ objective measures of adherence, including electronic medication monitoring (EMM) of pill bottle opening, pharmacy pill counts, and a novel measure of INH exposure, that is, INH concentration in hair. We will actively monitor for toxicity, using the U.S. standard of care for laboratory monitoring during TB preventive therapy for heavy drinkers. We will use the safety, tolerability, and adherence results, together with the known efficacy and mortality benefit of TB preventive therapy in HIV-infected persons in SSA, and our established decision analytic model of TB preventive therapy, to determine whether the mortality and quality of life benefits of TB preventive therapy outweigh the toxicity risks for HIV-infected drinkers in resource limited settings.

The target population will be HIV/TB-infected men and women who are either current drinkers (past 3 months, n=200) or non-drinkers (no alcohol in the past year, n=100), who meet screening criteria (i.e. $\geq$18 years old, on ART, TST positive, no history of prior active TB, live within 2 hours travel time of the study site), and are patients of the Mbarara Regional Referral Hospital (MRRH) Immune Suppression Syndrome (ISS) Clinic. This study will build on the foundation of the Uganda ARCH cohort, including its predecessor cohort as well. We will contact Uganda ARCH study participants (which included drinkers and non-drinkers) to determine their current eligibility for the proposed study. Those who are eligible and interested will be enrolled in the study of TB preventive therapy and receive continued follow-up as part of the Uganda ARCH cohort within the URBAN ARCH consortium. We will enroll additional participants recruited from the ISS Clinic, as needed, to meet our enrollment targets. A screening phase will include blood testing to test liver enzymes (ALT and AST) to rule out patients with elevations (>2x the upper limit of normal [ULN]), and to rule out active TB (symptom screening, and if symptomatic: AFB and Xpert MTB/RIF testing and chest X-ray if not pregnant). Once considered eligible for the study, INH and pyridoxine (vitamin B6) will be dispensed and the study will include regular assessments of hepatotoxicity and other side effects, measures of medication adherence, assessment of drinking, and collection of dried blood spots (DBS) for PEth and small hair samples (approximately 100 hair fibers) for PEth and INH concentration, respectively. After the course of INH (6 months, daily) is completed, study participants will participate in twice yearly study visits as part of the continued cohort. The follow-up cohort study visits will include a survey, symptom assessment and follow-up testing as needed to detect active TB, and blood collection for DBS for PEth, and storage in the URBAN ARCH repository. Baseline blood testing will also include tests for hepatitis B surface antigen, confirmation of HIV status, CD4 cell count, and HIV viral load.

NIH-REQUIRED PROGRESS REPORT

This report describes the progress of Uganda ARCH from September 2011 - November 2015. The aims of the study were the following: (1) To determine the effect of heavy alcohol consumption on HIV disease progression prior to the start of ART; and (2) To explore biological and behavioral pathways by which heavy alcohol consumption may accelerate HIV disease progression prior to the initiation of ART. Together with the predecessor cohort of HIV-infected drinkers entering HIV care in Uganda (Changes in Alcohol Consumption in HIV Positives in Uganda, R01 AA018631, 2010-2015) we recruited a total of 751 persons, including 465 current drinkers reported here (Table 2). Retention in the cohorts was 90% at 6- and 12-months.

Table 2. Baseline characteristics of the Uganda ARCH cohorts (U01 AA020776 and R01 AA018631), n=751.	
Male	41%
Age, median (Interquartile range [IQR])	31 (26-39)
CD4 cell count, median (IQR) cells/mm3	462 (330-638)
Log HIV viral load	3.79 (3.00-4.39)
Self-reported alcohol use, prior 3 months	62%
Among current drinkers (prior 3 months, n=465)	
Self-reported heavy drinking: AUDIT-C+	52%
PEth >=50 ng/ml	59%
Heavy drinking (AUDIT-C+ or PEth ≥50 ng/ml)	73%
PEth level, ng/ml, median (IQR)	75.8 (16.0-274.0)

The Uganda ARCH team was highly productive, meeting and exceeding our study aims. In total, eleven manuscripts were published,[30,81,82,92-100] four are under review, and seven conference abstracts were published (see Progress Report Publications List). Recent published manuscripts are as follows:

- Carrico A. et al. Unhealthy alcohol use is associated with monocyte activation prior to starting antiretroviral therapy.[82]
- Woolf-King S.E. et al. Development and validation of the East Africa Alcohol Expectancy Scale (AFEXS).[99]
- Hahn J.A. et al. Declining and rebounding unhealthy alcohol consumption during the first year of HIV care in rural Uganda, using phosphatidylethanol to augment self-report..[81]
- Asiimwe S.B. et al. Comparison of traditional and novel self-report measures to an alcohol biomarker for quantifying alcohol consumption among HIV-infected adults in sub-Saharan Africa.[101]
- Bajunirwe F. et al. Comparison of self-reported alcohol consumption to phosphatidylethanol measurement among HIV infected patients initiating antiretroviral treatment in south western Uganda.[93]

Dr. Hahn and several trainees from the University of California San Francisco (UCSF) and the Mbarara, Uganda, University of Science and Technology (MUST) leveraged the Uganda ARCH cohort into newly funded alcohol/HIV research studies and fellowships. Dr. Hahn received a prestigious K24 Mid-career Investigator Award in Patient-Oriented Research (NIA K24AA022586) to build her research and mentoring program in HIV/alcohol comorbidity, a UCSF Center for AIDS Research (CFAR) Established Investigator pilot award, and an award from the US Department of Defense. Three junior investigators (Dr. Stephen Asiimwe, Dr. Julian Adong, and Dr. Sarah Woolf-King) received UCSF CFAR pilot awards, and Dr. Adong received 2 training awards, allowing her to spend 4 months learning research methods and writing in San Francisco.

C. APPROACH

C.1 The proposed study builds on existing collaborative relationships. This research will be conducted in the context of the URBAN ARCH Consortium, leveraging the infrastructure developed over the past five years of the Uganda ARCH cohort as a collaborative effort between UCSF, Boston University (BU), Boston Medical Center (BMC), and MUST. The team includes international experts in alcohol and HIV epidemiology and biomarkers of alcohol use (Dr. Judy Hahn), clinical research in persons with HIV in Uganda (Dr. Winnie Muyindike), TB outcomes in resource limited settings (Dr. Karen Jacobson), decision analytic modeling (Dr. Benjamin Linas), clinical trial design and analysis (Dr. Debbie Cheng), and hair drug concentration (Dr. Monica Gandhi). Consultants include world experts in clinical trials of TB medications (Dr. C. Robert Horsburgh) and HIV/substance use research (Dr. Jeffrey Samet).

C.2 Preliminary data for this application

Little evidence of liver damage due to alcohol use. We (Hahn) conducted liver enzyme testing in 169 HIV-infected participants in the Uganda ARCH cohort at the baseline visit. A small proportion, 7.6%, had Grade 1/2

(mild/moderate) ALT/AST elevations (2-5x the upper limit of normal [ULN]), and none had Grade 3 elevations (≥5 times the ULN); there was no difference by drinking status (p=0.90). ALT/AST elevations were also low in our study of alcohol biomarkers in Ugandan HIV-infected drinkers (n=77).[30] *These very low levels of underlying liver injury among HIV-infected drinkers in Uganda, suggest that they are at low risk for hepatotoxicity.*

Under-report of alcohol consumption. We (Hahn) have repeatedly found evidence of under-reporting of alcohol consumption in several studies conducted among persons with HIV in Uganda.[81,93,96] For example, we found a doubling of self-reported alcohol use when specimen collection for alcohol biomarkers was introduced into an ongoing cohort study.[96] In another study, we conducted PEth testing on stored specimens, and found of those with quantifiable PEth, over half had denied prior month alcohol use.[93] *Objective measurement of alcohol consumption is needed; we will use PEth levels as a biological marker of heavy alcohol consumption.*

Reductions and rebounds in alcohol use over one year. We (Hahn) studied heavy alcohol consumption, defined as AUDIT-C positive or PEth ≥50 ng/ml, during the first year of HIV care and found a significant interaction with ART use, such that there was a decline in heavy drinking prior to ART start (per-month adjusted odds ratio [AOR] 0.91; 95% confidence interval [CI]: 0.83-0.99), but increases after ART start (per-month AOR 1.11; 95% CI: 1.01-1.22).[81] *Thus, drinkers may reduce alcohol use when advised to, but heavy drinking often rebounds. Repeated objective measurement of alcohol use will be needed to determine whether drinkers can reduce their alcohol use for the duration of a 3- or 6- month course of TB preventive therapy.*

Alcohol use leads to poorer TB treatment adherence In a retrospective cohort of 225 patients who received treatment for multi-drug resistant (MDR) TB in South Africa, we (Jacobson) found that self-reported recent alcohol use led to increased risk of treatment discontinuation (adjusted HR=2.1, CI 1.1-4.0, p=0.02).[23] *This work supports that alcohol is a particularly important variable in predicting poor TB treatment completion.*

Feasibility of measuring INH in hair. We (Gandhi) developed extraction and laboratory methods to measure INH concentration in small hair samples (20-30 strands, 2 mg). The method can quantify a wide range of INH levels in hair (0.05-50 ng INH/mg hair), with low error and high precision.[31] In a study of INH concentration in the hair from adults receiving 300 mg of INH daily for treatment of active TB (n=10), via directly observed therapy, the median concentration was 1.60 ng/mg, (interquartile range [IQR]: 0.64-1.15), while the median concentration was 8.8 ng/mg (IQR: 4.98 - 15.20) in a study of 38 children undergoing treatment for active TB.[31] *These data illustrate that INH taken in varied settings is detectable in hair.*

Prior model of TB preventive therapy widely used. We (Linas) have conducted comparative- and cost-effectiveness analyses of various strategies for identifying latent TB infection.[33] This work is part of the basis for current TB control policy in the U.S.[102] and WHO guidance for TB management in low burden countries.[103] *We will adapt this highly cited decision analytic model to the Ugandan context, integrating data collected in Aims 1 and 2, to develop clinically relevant guidelines for TB preventive therapy in HIV-infected heavy drinkers.*

C.3 Study methods for Aims 1 and 2.

C.3.1 Overview The ADEPTT study will include a single-arm trial of TB preventive therapy to assess its toxicity, measure adherence, and determine whether its benefits outweigh its risks when given to TB/HIV-infected drinkers (n=200 current drinkers, 100 past or never drinkers). After the course of TB preventive therapy is completed, study participants will have twice yearly study visits as part of the Uganda ARCH cohort.

C.3.2 Study design considerations. We made several key decisions in designing this study:

   (1) The primary outcome of this study is safety only, rather than the standard drug trial outcomes of safety and efficacy. We made this decision because, while a study examining the efficacy of TB preventive therapy for HIV-infected drinkers would be valuable, such a study would require thousands of participants and would be premature if safety cannot be established. Because the WHO guidelines exclude heavy drinkers due to safety concerns, we felt that careful examination of safety and tolerability would be a key contribution to the development of an evidence-based global recommendation on how to give TB preventive therapy to HIV-infected alcohol users in resource constrained settings.

   (2) We decided *not* to include an untreated control group, because we will be meeting the U.S. standard of care of providing TB preventive therapy to drinkers with ALT/AST monitoring.[44] Given the known reductions in morbidity and mortality of TB preventive therapy for persons with HIV, and the safety of this treatment when monitoring is conducted, an untreated control group would represent a lower level of care provision with questionable ethics.[44] In addition, it will not be necessary to have an untreated control group to determine the level of ALT/AST elevations without therapy, because we will have an estimate of the background level of elevations in this cohort of drinkers via baseline testing.

(3) <u>We will include only participants with positive tuberculin skin test (TST) results</u>. TB preventive therapy is more effective for persons with HIV who are TST positive,[7] although the WHO recommends providing IPT to all persons with HIV in resource limited settings because skin testing is often not available[9] and may have lower sensitivity.[104] However, in the research setting, TST testing is possible and we will limit our study population to TST positive participants who represent those most at risk for developing TB in this population.

(5) <u>The eligibility criterion for the proposed study is current (prior 3 month) drinking OR non drinking in the prior year</u>, while the WHO recommendations refer to "regular and heavy alcohol consumption". We will use "current drinking" because we have found that while half of current drinkers report heavy drinking by the AUDIT-C criteria (52%), a large proportion of current drinkers (21%) have high PEth levels (≥50 ng/ml) but do not report heavy drinking (Table 2, above). Thus, an eligibility criterion of current drinking will allow us to examine toxicities among drinkers who do not fully report their level of drinking so that future guidelines can account for under-reporting of drinking.

C.3.3 Study setting and eligibility. This study will be conducted in the Immune Suppression Syndrome (ISS) HIV Clinic of the Mbarara Regional Referral Hospital (MRRH) at MUST, the site of the Uganda ARCH. There are over 12,000 active patients at the ISS Clinic. The ISS Clinic and pharmacy use electronic medical records (EMR) via the Open Medical Record System (OpenMRS). Eligibility criteria will be: ISS clinic patient age ≥18, living within 2 travel hours of the clinic, fluent in Runyankole or English, on ART, and self-reported alcohol consumption in the prior 3 months or abstainer. Exclusion criteria will be as follows: plans to move in the coming 6 months, on nevirapine (NVP, an ART drug that is declining in usage due to high risk for hepatotoxicity), history of active TB, current active TB, prior TB preventive therapy, and ALT or ALT elevation (>2x ULN).

C.3.4 Enrollment – Eligibility screening and baseline study activities. Participants will initially be recruited from the Uganda ARCH cohorts, in which participants have given permission for re-contact for further study. Of the 465 current drinkers recruited in these cohorts, we estimate that we will be able to contact 75% (N=349), and that 60% of those will meet eligibility criteria (n=209). The remaining participants will be recruited from persons reporting any alcohol use on the AUDIT, approximately 25% of clinic patients,[109] which is routinely administered at initial ISS Clinic visit. We will also recruit patients who report no prior year alcohol use for the abstainer group. We will review the EMR for potential participants and those that meet preliminary study eligibility (i.e. age, on ART for 6 months) will be invited to meet with a research assistant to determine further eligibility. If further eligibility is established, the research assistant, a licensed clinical officer, will seek informed consent for further screening to rule out active TB, existing liver disease, and to assess TST status (Figure 1). A blood draw for ALT/AST testing will be performed, a TST will be placed, and if the participant reports symptoms of possible active TB (cough >24 hours, fever, weight loss, night sweats), further tests (chest X-ray and sputum collection for acid fast bacilli [AFB] stain and Xpert MTB/RIF assay) will be conducted. Those with abnormal chest X-ray results or a positive AFB or Xpert test will be brought to the MRRH TB clinic per hospital protocol. Patients will be asked to return in 2 days for TST reading, informed consent will be requested if active TB has been ruled out and TST is positive. After informed consent is obtained, the baseline visit will include study questionnaire completion, blood draw, and medication dispensing.

<u>**Aim 1**</u>: **To examine the safety and tolerability of 6H for HIV-infected drinkers, measured by hepatotoxicity.** *Our main aim is to estimate safety overall among drinkers (primary) and by level of drinking (secondary). We will additionally compare safety and tolerability by level of drinking in secondary analyses.*
<u>**Aim 2**</u>: **To estimate the level of adherence to TB preventive therapy, overall among drinkers (primary), by month on therapy. Secondarily, we will estimate adherence by drinking level and compare adherence levels across drinking levels.** *We hypothesize that adherence will be highest among non-drinkers.*

C.3.5 Intervention. The study intervention will include a single arm given (1) 6H: 300 mg INH daily for 6 months. All participants will also receive 25 mg pyridoxine (vitamin B-6) daily for the treatment duration to reduce the risk of INH-induced peripheral neuropathy.[111] Patients will be encouraged to continue taking all other concurrently prescribed drugs (i.e., ART and cotrimoxazole). Patients will receive adherence advice, advice to avoid hepatotoxic substances (e.g. acetaminophen, alcohol, herbal medicines), instructions on monitoring side effects, phone numbers for contacting the medical staff in case of serious side effects, and instructions on using the EMM bottle like a regular medicine bottle. The pills will be dispensed at the pharmacy where the participants receive their ART.

C.3.6 Follow-up study visits. Assessments for toxicity will occur week 2 and months 1 through 7 (Table 3). A clinical officer will screen for symptoms of hepatotoxicity and other side effects using a Case Report Form (CRF) based on the TEMPRANO ANRS adverse event grading[6] and perform ALT/AST testing. Treatment will be stopped if a patient develops a Grade 3/4 toxicity, as determined by the study physician. In addition, the monthly study visits while on medication will include pharmacy pill counts, EMM data downloads, and brief surveys on alcohol use and adherence. Hair collection will occur at 3 and 6 months. Blood collection will occur at baseline (for PEth, CD4 cell count, HIV viral load, and repository storage), 3 and 6 months, and every 6 months thereafter. Participants will also be given a card with phone numbers to contact the clinical staff if side effects occur between study visits; if side effects occur, participants will be asked to come in for additional ALT/AST testing and follow-up. These calls and visits will also be recorded in a CRF. All CRFs will be reviewed weekly by the study physician. Screening for symptoms for active TB, and sputum testing and chest X-ray if symptoms are reported, will occur at every follow-up visit, including those after the completion of the trial. High retention will be maintained as in our prior studies using follow up phone calls, alerts when patients come to the ISS clinic, and home visits when needed.

C.3.7 Data management. Data management and quality assurance will be jointly led by the UCSF and the BU Data Coordinating Center (DCC). As in the previous studies, tracking information will be entered into a database which will generate reminders for follow-up visits. The tracking database will also be used to automatically randomize patients to study arms. The questionnaire data, brief assessments, laboratory results, and the CRF data will be entered directly into a laptop computer in Uganda while offline, and later uploaded to a secure server at UCSF. The EMM adherence data will be uploaded weekly to a secure website, cleaned, and merged with the other study data. All data will undergo weekly checks for completeness and range criteria.

C.3.8 Measurements.
    Safety and tolerability. Safety will be assessed by the occurrence of a Grade 3/4 hepatotoxicity at any time during the assigned treatment period. Lack of tolerability will be defined as any treatment discontinuation prior to completion of the prescribed course due to side effects or ALT/AST elevations.
    Adherence. We will measure medication adherence using EMM, pharmacy pill count, self-report, and INH concentration in hair. While there is no gold standard for determining medication adherence, EMM adherence has been highly predictive of undetectable HIV viral load[112-114] is considered the reference standard,[62,112,115,116] and therefore will be our primary measure of adherence. EMM adherence will be defined as the number of pill bottle openings (no more than 1 per day counted)[113] divided by the number of prescribed doses over the study period. Adherence to vitamin B-6, which will be provided in a separate bottle, will not be part of the adherence measurement.
    Self-reported adherence measures will include the visual analog scale (VAS) which asks the patient to identify their past month percent adherence on a visual scale that ranges from 0 to 100%, and the Self Rating Single Item (SRSI) adherence scale,[117,118] which asks participants to rate their ability to take their medications as prescribed over the past month.[119] Both of these measures are brief[118] and are strong predictors of viral suppression.[118] Lastly, we will collect hair samples at 3 months and 6 months, and will measure the INH concentration (ng/mg) in the hair.
    Alcohol consumption. Heavy drinking will be defined as either PEth ≥50 ng/mL or AUDIT-C positive (≥3 for women, ≥4 for men). The AUDIT-C will be modified to cover the prior 3 months. By combining two highly specific measures, we will increase the sensitivity for detecting heavy alcohol use over using each measure alone, as in our previous analyses of heavy alcohol use by persons with HIV in Uganda.[81,82]
    We will collect self-reported measures of alcohol use at baseline using the AUDIT-C and the CAGE,[120] which are readily available for use in clinical practice. For analyses that examine level of drinking, we will categorize

the scores as low risk drinking, (women: AUDIT-C 0-2; men: AUDIT-C 0-3), heavy drinking (women: AUDIT-C 3-5; men: AUDIT-C 4-5), and very high risk drinking (AUDIT-C ≥8).[121] The corresponding cutoffs for the CAGE will be scores of 0, 1, and 2-4.[122] We will additionally measure alcohol consumption using tools that are not dependent on standardized drink volume or concentration, e.g. money spent drinking, level of intoxication, and PEth level, as in our previous studies.[101]

Covariates. Covariates measured at baseline will include gender, age, body mass index (BMI), CD4 cell count, HIV viral load, ALT/AST, active hepatitis B viral infection (HBsAg), symptoms of depression,[123] smoking, nicotine dependence,[124] and duration on ART – also recently added on baseline platelet count, FIB-4 score, and eGFR. Covariates measured at baseline and follow-up will include current ART regimen, and the VAS and SRSI for self-reported ART adherence.

Table 3. Schedule of study visits and activities.	Eligibility	Baseline	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Follow-up
Initial eligibility determined, ALT/AST and TST testing. Chest X-ray and sputum collected if symptoms of active TB are reported.	X										
Enrollment/ baseline: Study interview, blood draw, medication dispensing		X									
Toxicity assessment (side effects and ALT/AST testing)			X	X	X	X	X	X	X	X	
Medication refill, pharmacy pill count, and EMM data download, and brief alcohol and adherence assessments			X	X	X	X	X	X	X		
Hair collection for INH concentration						X			X		
Follow-up: Study interview, blood draw, and screening for active TB						X			X		X

C.3.9 Statistical analyses for Aim 1.

Primary analysis: Safety. The focus of this aim is the evaluation of safety among drinkers overall (primary) and by drinking levels (secondary). Thus the primary analysis set will be all participants who receive at least one dose of TB preventive therapy who are current drinkers. We will report the incidence of Grade 3/4 hepatotoxicity at any time during prescribed treatment along with 95% exact binomial confidence intervals (CIs).

Secondary analyses: Safety and tolerability will be estimated by level of alcohol use at baseline and during treatment. To examine safety and tolerability by alcohol consumption prior to treatment, we will report hepatotoxicity and treatment discontinuation stratified by level of drinking (heavy alcohol consumption, current but not heavy drinking, no drinking) at baseline. Fisher's exact test and exact logistic regression models adjusting for gender, hepatitis B co-infection, Cd4 cell count and/or viral suppression will be used to compare safety outcomes across drinking levels. To inform clinical practice, we will also report the outcomes by self-reported alcohol consumption levels using the AUDIT-C and the CAGE. We will also examine toxicity by level of PEth, using recently suggested PEth cutoffs. We will use generalized estimating equation logistic regression models to examine whether drinking level during the treatment period impacts safety and tolerability outcomes.

Secondary analysis: Comparison of hepatotoxicity rates to previous studies. We will also compare estimates and 95% CIs to those reported in published studies of TB preventive therapy in those with HIV, which found hepatotoxicity rates of 0.3-5.5%.

Sample size justification. We anticipate a total of 200 drinkers will be enrolled into the current study. Based on the Uganda ARCH cohort retention, we expect 90% 6-month study visit retention resulting in N=180 evaluable participants. We expect that the proportion of participants with any Grade 3/4 hepatotoxicity within the treatment period will be approximately at the midpoint of the range of toxicity rates published previously, i.e. 2.6%. Given this, we would expect approximately 5 safety events, and the length of a 95% exact binomial CI around the estimate would be 5.5%, (i.e. 0.9% to 6.4%).

To illustrate power for secondary analyses, we also calculate the minimum detectable difference to compare safety between alcohol groups. I.e., to compare toxicity between any group of drinkers (either heavy drinkers or moderate drinkers, each expected to be approximately 1/3 of the sample) to non-drinkers (1/3 of the sample), we will have 80% power to detect a difference in toxicity rate of 0.095 or greater if the toxicity rate in the lighter drinkers/abstainers is 1% and alpha is set to 0.05 based on a Fisher's Exact test.

C.3.10 Statistical analyses for Aim 2.

Primary analysis: The goal of this aim is to estimate the level of adherence overall among drinkers and by drinking level (including abstainers). The analysis will consist of all participants enrolled. For those who are advised to discontinue therapy by the study physicians, adherence up until discontinuation will be used; however, additional sensitivity analyses will be conducted using alternative imputation strategies (e.g. using the midpoint between best and worst weeks, and assuming the worst case scenario of zero for the discontinued time period). We will report the percent adherence using EMM data over the treatment duration and 95% CIs overall among drinkers and by drinking level (heavy, non-heavy, abstainer), and fit multiple linear regression models, controlling for gender, to compare adherence across drinking categories. If the data are skewed, transformations will be performed (e.g., log transformation) or median regression if no appropriate transformation is identified.

Secondary analyses: Alternate measures of adherence and adherence over time and by level of alcohol use. Secondary measures of adherence will be analyzed using the same approach as described above. We will additionally conduct all adherence analyses excluding the first 40 days to remove a possible Hawthorne effect that may occur when patients are aware they are being monitored, but that often abates after one month. We will also conduct repeated measures analyses of monthly adherence data using linear mixed effects regression models, with month on treatment included as a predictor, to test the hypothesis that adherence changes over time. We will additionally use these analyses to assess whether drinking level at baseline and during treatment (using time-updated covariates) impact adherence.

Secondary analyses: INH concentration in hair by drinking level. We will examine the level of INH drug concentration at 3 months and at the end of treatment overall among drinkers and by drinking level (3 groups). The analysis of this continuous measure will be as described for adherence, i.e. mean INH drug concentration will be estimated along with 95% CIs and the groups will be compared using multiple regression models.

C.3.11 Exploratory Aim 1 and Aim 2 analyses: predictors of toxicity and adherence. We will also perform analyses to identify potential predictors of hepatotoxicity and/or treatment discontinuation (grouped together to increase statistical power) and adherence measures. Several potential predictors will be considered including demographics, body mass index, time updated heavy alcohol use, ART adherence, baseline HbSag, measures of cirrhosis (Fib-4 score and/or platelet count), and kidney function (eGFR). Given the limited number of events compared to predictors of interest, we will build a regression model using the lasso (least absolute shrinkage and selection operator) method, a variable selection approach that fits a regression model including all independent variables and covariates of interest but constrains some coefficient estimates by shrinking them to zero to reduce variance.[130,131]

C.3.13 Missing data. We will evaluate differences in baseline characteristics between those lost to follow-up versus those who are retained to examine missing data mechanisms, e.g., missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).[132] If it is reasonable to assume that data are MAR, multiple model based imputation methods will be applied to account for the missing data.[132,133]

C.3.12 Aims 1 and 2 potential pitfalls. It is possible that our hepatotoxicity and treatment discontinuation estimates will be lower than in settings where baseline ALT/AST screening is not performed because we will exclude those with baseline elevations (>2x ULN). Based on our prior work (see C.2), we expect only a small proportion will be screened out. However, using the number screened out, we will be able to calculate "worst case scenario" hepatotoxicity rates assuming that these HIV-infected drinkers would have developed Grade 3/4 toxicities while on treatment. It is also possible that adherence rates in the study will be artificially high, due to the frequent adherence and toxicity monitoring. In that case, our estimates of adherence will represent the upper bound, while the comparison of adherence between the two randomization arms will remain important. If

we establish safety without frequent monitoring, then future studies could measure adherence under more real-world conditions.

C.4 Study methods for Aim 3.

> <u>Aim 3</u>: **To determine whether the benefits of providing TB preventive therapy to HIV-infected drinkers in resource limited settings outweigh the risks compared to no treatment**. *We hypothesize that providing TB preventive therapy will result in longer life expectancy and quality-adjusted life expectancy than not providing TB preventive therapy (current standard of care).*

C.4.1 Overview. We will utilize our previously developed Markov model that simulates TB preventive therapy and the lifetime clinical progression of a cohort of hypothetical individuals.[33] We will modify this model to fit the Ugandan context by including a detailed simulation of TB preventive therapy safety monitoring. We will then leverage the unique toxicity, tolerability, and adherence data collected in Aims 1 and 2, as well as the medical literature, to project long-term outcomes, stratified by level of alcohol consumption, assuming a variety of monitoring approaches. If our hypothesis is correct, this study will provide evidence needed to change the paradigm of TB preventive therapy and extend life-saving treatment to a population at very high risk of death from HIV/TB co-infection. Below we describe the proposed approach.

C.4.2 Model components. The following model components are part of our previously developed model and will be modified for the context of HIV-infected drinkers in Uganda as described.

TB epidemiology. The simulation model generates a cohort using the distribution in the target population of age, sex, prevalence of positive TSTs (>5

Table 4: Select model parameters for decision model proposed in Aim 3.	Parameter estimates	Data source
TB epidemiology		
Age/sex demographics		ADEPTT
Prevalence reactive TST		ADEPTT
Prevalence subclinical TB at baseline	0.085-0.094	[135,136]
Level of alcohol use prior to therapy		ADEPTT
TB preventive therapy		
Transitions between AST/ALT categories		ADEPTT
Probability of symptoms by AST/ALT	0.35	[137]
Toxicity-related mortality by AST/ALT	0.0-0.05	[137-139]
Adherence		ADEPTT
Health state utility for those with hepatotoxicity	0.65-1.0	[140]
Health state utility for those w/o hepatotoxicity	0.82-1.0	[140]
Progression to TB and TB mortality		
Incidence TB (per 100 person-years)		[141-143]
TST positive	3.41	
TST negative	3.06	
Hazard ratio for active TB		[144-147]
100% adherence vs. no therapy	0.11-0.41	
Partial (50%) therapy vs. no therapy	0.25-0.91	
TB-related case-fatality proportion	0.23	[148]
Health state utility with active TB	0.66-0.85	[140]
HIV and other non-TB mortality		
Life expectancy (starting age 31) CD4 >500	66 years	[149-152]
Standardized mortality ratio by CD4 count		[151-154]
CD4 350-499 cells/mm^3	3.5	
CD4 200-349 cells/mm^3	5.6	
CD4 <200 cells/mm^3	30.3	
Health state utility for HIV-infected persons	0.62-1.0	[155-157]

mm induration), and prevalence of sub-clinical (asymptomatic, so not identified) active TB. We will stratify all demographic and epidemiologic parameters by level of self-reported alcohol use at baseline, as above (any current drinking, heavy drinking, and very heavy drinking – see C.3.9), using the AUDIT-C that is available to treating clinicians in the real-world.

TB preventive therapy. The simulation of TB preventive therapy includes treatment discontinuation due to hepatotoxicity, as well as poor adherence or default. The model is structured to simulate any TB preventive treatment regimen. All parameters related to TB preventive therapy are regimen-specific and we will stratify them by level of alcohol use. We will model the benefits of TB preventive therapy as a relative reduction in the

rate of progression to active TB. In the model, patients with sub-clinical TB do not benefit from the preventive therapy.

Hepatotoxicity. We will substantially enhance our previous model to include detailed simulation of preventive therapy as follows: First, in every treatment month, simulated individuals on therapy will have a probability of developing an ALT or AST elevation and a probability of developing symptoms of hepatotoxicity. Simulated patients will fall into one of 6 toxicity-related health states (3 levels of ALT/AST levels; normal, 3-5x the ULN, >5x ULN) and 2 levels of symptoms (yes/no). The rates of movement between each of the 6 hepatotoxicity states will be a function of the treatment regimen, and an individual's level of alcohol consumption. Each toxicity-related state will be associated with toxicity-related quality of life, and mortality.

Importantly, the model will distinguish between the underlying true ALT/AST value and the clinical awareness of that value. For example, in the simulation model of no monitoring, patients without symptoms whose true ALT/AST is >5x ULN will not be identified, nor their treatment stopped, and they will have an increased risk of developing symptoms and death.

Adherence and treatment default. In each month while taking TB preventive therapy, simulated individuals have a probability of non-adherence and/or treatment default, i.e. treatment discontinuation that is unrelated to hepatotoxicity. Simulated patients who stop medications do not accrue the full benefit of prevention, though incomplete courses of therapy confer partial preventive benefits.[21] One challenge to incorporating treatment adherence data in a decision analytic model is that the effectiveness of various levels of adherence to TB preventive therapy is not known. We will therefore model discontinuation/default and low adherence in two ways: First, we will use WHO definitions of treatment loss to follow-up for active tuberculosis treatment to model TB preventive therapy adherence as a binary outcome (yes/no).[9] We will define "not adherent" as any patient who misses two consecutive monthly refill visits, or who, for 2 consecutive months, self-reports taking <80% of his/her intended doses of therapy, or whose EMM cap data indicates <80% of doses taken. In the simulation model, individuals will not accrue any benefits (or risks) of therapy after the month that the patient is classified as "non-adherent." Second, we will use EMM adherence data to model non-adherence as a continuous outcome. We will assume that taking fewer than the total number of TB preventive therapy doses throughout the entire course of therapy has the same effect as taking 100% of doses for fewer months than recommended. For example, we will assume that taking 50% of doses for six months of therapy provides similar treatment efficacy as taking 100% of all doses for only 3 months. We will compare the results of these two strategies and thus gain information on the relative importance of how adherence is modeled.

Progression to active TB and death. Individuals in the simulation model will have a monthly probability of developing active TB that is stratified by drinking status.[141,158] Those who develop active TB experience increased mortality and decreased quality of life. In addition, a portion of simulated patients with active TB will develop drug resistant disease, characterized by longer treatment courses, higher mortality, and lower quality of life than drug sensitive disease. We will model the effectiveness of TB preventive therapy as a relative reduction in the rate of developing active TB. A complete course of 6H provides a 30-50% reduction in reactivation,[4-8] with a larger absolute reduction in TB incidence among those who have reactive TST than in those who do not. Studies among HIV-infected persons in settings of TB incidence, similar to Uganda, demonstrate that the benefits of TB preventive therapy are durable for five years.[145,159] We will therefore model a 5-year reduction in the incidence of active TB, followed by a rapid return to the baseline TB incidence.

Competing risks of death Individuals in the existing model have an age- and sex-stratified risk of death from causes other than TB. In this proposed analysis of TB preventive therapy in HIV-infected persons in Uganda, the competing risks of death will reflect mortality related to HIV infection and all other non-TB mortality.

C.4.3 Data sources for the model. Whenever possible, we will use the novel data from Aims 1 and 2 of this study (Table 4, denoted as ADEPTT) for model parameters. Other model parameters will be obtained from the medical literature.

TB epidemiology. The ADEPTT cohort will inform the age and sex distributions, and the prevalence of reactive TST (>5 mm) at baseline and level of self-reported alcohol use. We will use published reports of the prevalence of subclinical TB from established African cohorts.[135,136]

TB preventive therapy. The ADEPTT study includes frequent assessment of ALT/AST and symptoms. These data, stratified by level of self-reported alcohol consumption, will inform all of the parameters governing movement between toxicity-related health states. Because the study will stop treatment at the identification of any Grade 3/4 hepatotoxicity, we anticipate no medication-related deaths in ADEPTT. Therefore, we will use the medical literature to inform mortality from each toxicity-related health state in the model, as well as the health state utility of patients with toxicity-related symptoms.[137-140]

Progression to active TB and death. Because the number of observable cases of active TB in the cohort after therapy is expected to be low, we will use the medical literature to inform the incidence of active TB, stratified by TST status, without preventive therapy,[141-143] and will account for the reported efficacy of TB preventive therapy.[144-147] We will use reports of health state utility with active TB collected in SSA.[140]

Competing risks of death. We will estimate mortality from all causes other than TB using long-term follow-up of cohorts of HIV-infected persons in SSA. We will use the literature to estimate non-TB mortality among a cohort of HIV-infected persons on ART in SSA with baseline CD4>500[149-152] and published reports of the HR for mortality by lower CD4 counts.[151-154] We will also use the medical literature to estimate health state utilities for HIV-infected individuals with and without TB.

C.4.4 Aim 3 analyses. We will use the model to simulate the long-term outcomes of a cohort of HIV-infected drinkers in Uganda with demographic and clinical characteristic similar to those of the ADEPT-TB cohort assuming that TB preventive therapy is provided to all HIV-infected patients who drink alcohol using each of the following TB preventive therapy and monitoring strategies:
(1) No therapy (standard of care)
(2) TB preventive therapy without hepatotoxicity monitoring unless patient is symptomatic (no monitoring)
(3) TB preventive therapy with hepatotoxicity monitoring at week 2 of therapy only (week 2 monitoring)
(4) TB preventive therapy with hepatotoxicity monitoring monthly throughout (monthly monitoring)
The simulated model outcomes will include: hepatotoxicity events and deaths, counts of treatment completion and non-adherence, cases of active TB, TB deaths, life expectancy, and quality-adjusted life expectancy. We will first compare life expectancy and quality-adjusted life expectancy for "no monitoring" to "no therapy" to determine whether TB preventive therapy provides net benefit to HIV-infected drinkers even when monitoring is simply not possible. Next, we will compare outcomes from "no monitoring," "week 2 monitoring" and "monthly monitoring", to identify the optimal monitoring approach in settings that have some ability to monitor liver functions tests. We will define the "optimal" approach as that which maximizes quality-adjusted life expectancy. Once we have modeled outcomes for the simulated cohort, we will investigate whether the approach to TB preventive therapy should differ based on level of drinking alcohol. We may find, for example, that no monitoring is needed for non-heavy drinkers, while it is necessary for heavy and very heavy drinkers.

C.4.5 Sensitivity analyses. We will use one- and two-way deterministic sensitivity analyses to test the role of uncertainty in driving conclusions and to identify model parameters that have the largest impact on outcomes. We will display the results of such deterministic sensitivity analyses in standard format, such as tornado diagrams and two-way sensitivity graphs.[160-162] Next, we will use probabilistic sensitivity analysis (PSA) to quantify the impact of simultaneous uncertainty in all model parameters on the qualitative conclusions of the analysis.[160,163] PSA defines every model parameter as a probability density function centered around the best estimate of that parameter's true value. PSA then performs thousands (typically 10,000) of iterations of the simulation, each time drawing a value for each model parameter from its defined probability density function. The end result is N (10,000) realizations of the simulation, each with its own life expectancy and quality-adjusted life expectancy. By comparing the percentage of the simulations whose conclusions concurred with the base case scenario, it is possible to quantify the degree of certainty in the conclusions of the analysis. Model parameters that will be inherently uncertain and candidates for PSA include the efficacy of TB preventive therapy, the rate of reactivation of TB, and the impact of less than perfect adherence.

C.4.6 Aim 3 potential pitfalls. We will conduct decision analytic modeling of monitoring TB preventive therapy in HIV-infected heavy drinkers in Uganda, but will not include costs or cost-effectiveness. We chose not to include cost-effectiveness analysis at this stage, because the constraint on monitoring TB preventive therapy in Uganda is likely feasibility, (i.e. due to stock outs of the test reagents), rather than cost. Therefore, we propose to investigate and compare clinical outcomes in a classical decision modeling framework without cost, for the time being. We include a secondary analysis of the optimal monitoring strategy in ideal circumstances. Another potential challenge is the approach to modeling HIV-related mortality. Study inclusion criteria ensure that all patients will be on highly active ART at baseline, but if we observe non-adherence to ART in the cohort over the long term, we will modify the model to include two strata: "on ART" and "off ART," with appropriate mortality estimates for each. Finally, estimates of health state utilities are inherently uncertain. We will use reports collected using standard instruments in the African context, and plan broad sensitivity analyses. Further, we consider both life expectancy and quality-adjusted life expectancy as primary outcomes.

C.5 Elements unique to this site. This study is situated in Uganda, a low income country with high prevalence of HIV (7.3%)[164] and heavy alcohol use.[165] Uganda is considered a TB endemic country with incidence of 161/100,000 population.[166]

C.6 Integration and synergy with URBAN ARCH Consortium components The URBAN ARCH Consortium will bring together multidisciplinary researchers to examine the consequences of alcohol use on comorbidities among people living with HIV so as to increase availability of treatments and improve outcomes. The Uganda ARCH team will work with the Administrative (Admin) and Biostatistics and Data Management (BDM) Cores to implement their projects (e.g., data and repository management, Data and Safety Monitoring Board, statistical analyses). The structure of URBAN ARCH will enable administrative and scientific integration, making the whole greater than the sum of its parts. The URBAN ARCH Steering Committee, comprised of all Principal Investigators, will meet monthly via web conference and annually in Boston. It is responsible for decisions regarding Core resource allocation and scientific priorities and is a venue to discuss analyses, challenges, and funding opportunities. The Committee is also a conduit for introducing trainees to URBAN ARCH investigators, which has previously resulted in several cross-cohort analyses and broadening of mentoring teams.

The cohorts have similarities and differences that allow for comparisons and contrasts, for example, high prevalence of injection drug use and hepatitis C virus (Boston/Russia); young age, homogeneous race, sizable percentage of women (all). Cross-cohort analyses are possible with the planned harmonized data collection, integrated data management systems, and stored biological samples. A cross-cohort analysis our group is well-positioned to pursue is to characterize PEth response by self-reported drinking level among HIV-infected drinkers across all sites. In this analysis we will examine predictors of heterogeneity in PEth response, i.e. whether PEth response varies by patterns of drinking and additional variables, such as gender, age, body mass index, hematocrit and hemoglobin. The URBAN ARCH studies will add evidence to improve the health and quality of life for HIV-infected drinkers.

C.7 Timeline and deliverables. The study timeline is below (Table 5).

Table 5. Study timeline.	Year 1	Year 2	Year 3	Year 4	Year 5
Finalize operating procedures, data systems, hire and train staff	X				
Enrollment, 6 months of TB preventive therapy	X	X X	X X	X X	X
Long-term follow-up		X X	X X	X X	X
DBS, hair, and plasma shipping		X	X	X	X
Manuscript preparation (see below)			X X	X X	X X

We plan to write the following manuscripts in years 3-5:
(1) Liver injury among HIV-infected drinkers in Uganda (baseline data)
(2) Latent TB infection and newly diagnosed active TB among HIV-infected drinkers in Uganda (baseline data)
(3) Safety and tolerability of TB preventive therapy for drinkers with HIV/TB co-infection in Uganda (Aim 1)
(4) Predictors of hepatotoxicity of TB preventive therapy among drinkers with HIV/TB co-infection on ART in Uganda (Aim 1)
(5) Adherence to standard TB preventive therapy in HIV-infected drinkers (Aim 2)
(6) INH concentration in hair by TB preventive therapy compared to other measures of adherence (Aim 2)
(7) Benefits/risks of TB preventive therapy for Ugandan HIV-infected drinkers - decision analytic model (Aim 3)
(8) Patterns of alcohol use among HIV-infected drinkers on TB preventive therapy (longitudinal data)

C.8 Future directions. This study will lay important groundwork for revising guidelines on how to best deliver TB preventive therapy to alcohol using, HIV-infected persons at high risk for TB disease. Future investigations may include developing interventions to improve TB preventive therapy adherence, along with interventions to reduce drinking for a beneficial impact on both toxicity and adherence. If the decision analytic models show that ALT/AST monitoring is needed, investigations of implementation of monitoring strategies will be needed.

C.9 Summary. In summary, this study will leverage an established cohort of HIV-infected drinkers with TB co-infection, to collect unique data that will guide recommendations about providing potentially life-saving TB preventive therapy. It will be the first to assess safety and tolerability of, and adherence to, TB preventive therapy in HIV-infected drinkers, a population that is at high risk for active TB. We will use these novel data to

conduct decision analytic modeling to examine whether the benefits exceed the risks for providing therapy to this population, and determine optimal monitoring strategies as needed. The results of this study will provide critical new evidence on how to deliver TB preventive therapy to reduce morbidity and mortality in HIV-infected drinkers.

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