

HPTN 058

A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institutes of Health

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
BUP/NX	buprenorphine/naloxone
CARES	China Comprehensive AIDS Response
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CDTC	Chiang Mai Drug Dependence Treatment Center
CNS	central nervous system
CORE	HPTN Coordinating and Operations Center (Family Health International)
COWS	Clinical Opiate Withdrawal Scale
CRPMC	Clinical Research Products Management Center
DAIDS	Division of Acquired Immunodeficiency Syndrome
DSMB	NIAID Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EAE	Expedited Adverse Event
EC	Ethics Committee
EDTA	Ethylenediaminetetraacetic Acid
FDA	US Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
ICH	International Conference on Harmonization
IDU	injection drug user
IFA	immunofluorescence assay
IND	investigational new drug
IRB	Institutional Review Board
IUD	intrauterine device
LAAM	Levo-alpha-acetyl-methadol
LDMS	Laboratory Data Management System
LL	local laboratory
mL	milliliter
NDA	new drug application
NIAID	US National Institute of Allergy and Infectious Diseases
NIDA	US National Institute on Drug Abuse
NIH	US National Institutes of Health
NL	HPTN Network Laboratory (Johns Hopkins University)
OHRP	Office of Human Research Protection
PSRT	Protocol Safety Review Team
QA	quality assurance
RCC	Regulatory Compliance Center
RIBA	Recombinant Immunoblot Assay
RNA	ribonucleic acid
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center
SMC	Study Monitoring Committee
SOP	Standard Operating Procedures
SSP	study-specific procedures
VCT	voluntary counseling and testing
WB	Western Blot

PROTOCOL TEAM ROSTER

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I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the FDA Form 1572, which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by the Division of AIDS (DAIDS), Reckitt Benckiser Pharmaceuticals, Inc. or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee, DAIDS, and Reckitt Benckiser Pharmaceuticals, Inc. for review prior to submission.

I have read and understand the information in the Investigator's Brochure and package insert, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

PROTOCOL SCHEMA

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors

Purpose: To determine the efficacy of a drug treatment intervention involving administration of a buprenorphine/naloxone (BUP/NX) combination for 52 weeks plus drug and risk-reduction counseling (hereafter referred to as “substitution treatment”) compared with short-term detoxification with BUP/NX plus drug and risk-reduction counseling (hereafter referred to as “detoxification treatment”) for the prevention of HIV transmission and death among opiate dependent injectors by reducing drug use and associated risk behavior.

Design: Phase III, multi-site, two-arm, open-label, randomized, controlled trial. An initial safety and feasibility phase will include the first 50 study participants at each site.

Study Population: HIV-uninfected, opiate dependent injection drug users who meet the eligibility criteria will be recruited from the community.

Study Size: 1500 opiate dependent injection drug users.

Treatment Regimen: Eligible, HIV-uninfected opiate dependent study volunteers will be randomized to one of two study arms as outlined below in a ratio of 1:1.

Study Arm	Intervention
Substitution Treatment Arm n=750	<ul style="list-style-type: none">• Sublingual BUP/NX daily up to 21 days (until dose stabilization) and then three times per week for 52 weeks; plus• Weekly individual drug- and risk-reduction counseling for twelve weeks, followed thereafter by monthly counseling sessions every four weeks through week 52.
Detoxification Treatment Arm n=750	<ul style="list-style-type: none">• Short-term detoxification with sublingual BUP/NX for 18 days maximum with a second detoxification possible at week 26; plus• Weekly individual drug- and risk-reduction counseling for twelve weeks, followed thereafter by monthly counseling sessions every four weeks through week 52.

Counseling in both study arms will use drug and risk-reduction counseling adapted from evidence-based interventions. This counseling strategy will be delivered by trained addiction/prevention counselors and will focus on achieving and maintaining individualized goals of drug use reduction and HIV prevention.

Study Duration: The total duration of the study will be approximately four and a half years. The initial safety and feasibility phase will take approximately 30 weeks at each site, with 26 weeks to enroll the targeted 50 participants plus four weeks to complete the last safety phase visit. The accrual period in the full study will be approximately 104 weeks following the safety and feasibility phase. Participants will be followed for a minimum of 104 weeks and a maximum of 156 weeks, depending on when they are enrolled. Behavioral and serologic assessments will take place at baseline and at 26 week intervals throughout the follow-up period.

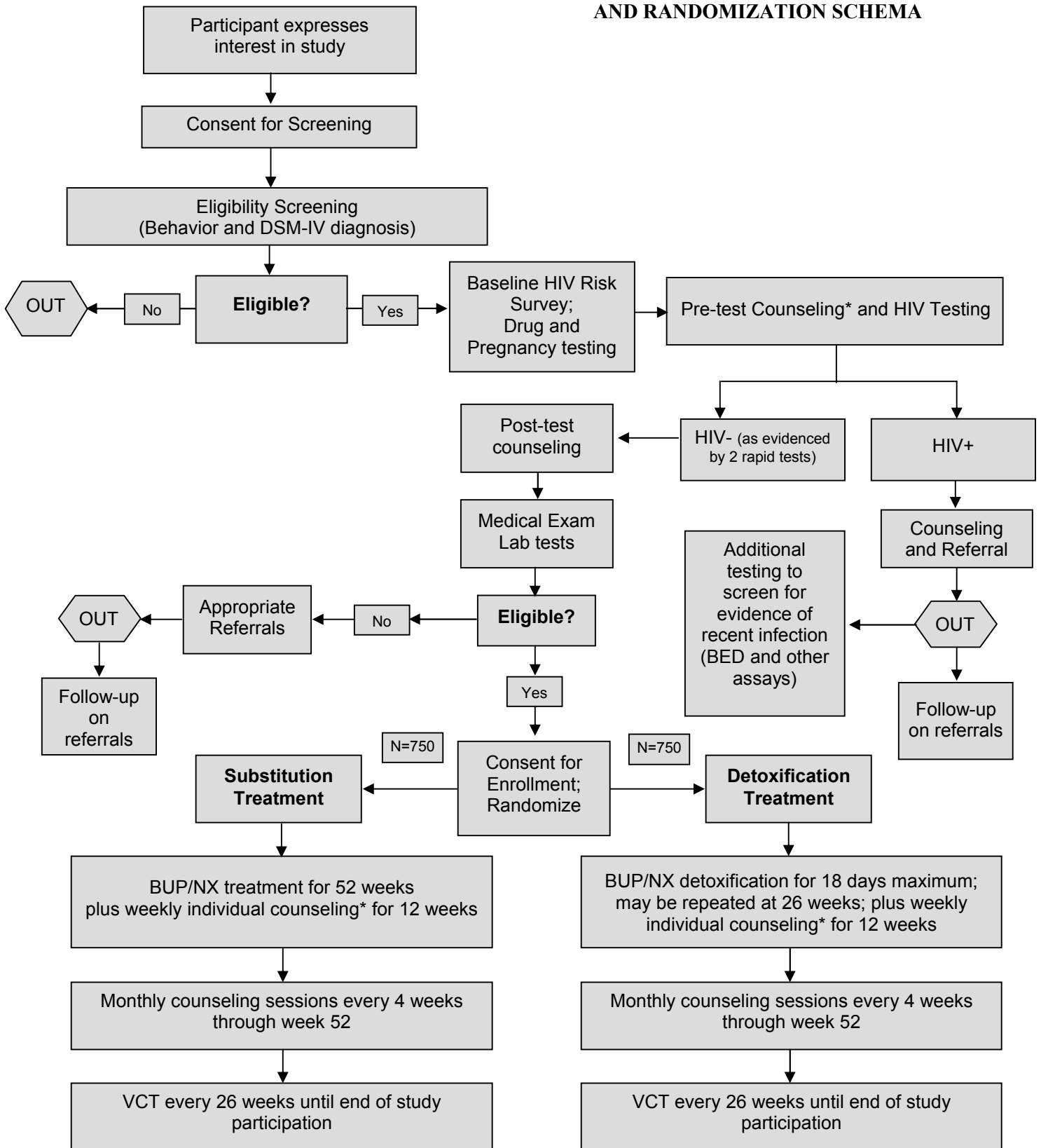
Primary Objective: To determine whether 52 weeks of substitution BUP/NX and counseling treatment in opiate addicted participants will achieve a long term (104 weeks) reduction in cumulative HIV incidence and death compared to short-term BUP/NX detoxification and counseling.

Secondary Objectives:

1. To determine if the substitution treatment reduces average HIV incidence and death compared to the detoxification arm; and reduces HIV incidence and death at 52 weeks and 156 weeks.
2. To determine if substitution treatment decreases average HIV incidence compared to detoxification treatment; and HIV incidence at 52, 104, and 156 weeks.
3. To compare the average rates of death in the two arms; and the rates of death at 52, 104, and 156 weeks.
4. To compare the self-reported frequency of injection, drug and sex-related HIV risk behaviors in the two study arms.
5. To compare the frequency of drug use measured by self-report and urinalysis in the two arms.

Study Sites: The study will be conducted at a minimum in HPTN sites in Guangxi and Xinjiang, China; Chiang Mai, Thailand; and other sites as needed.

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEMA



* includes risk reduction counseling

1.0 INTRODUCTION

Drug abuse and HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) are serious global health problems. Concurrent epidemics of injection drug use and HIV have been reported in 114 countries. Injection drug use currently is the major mode of transmission of HIV in Eastern Europe, Central Asia, East Asia, parts of South and Southeast Asia, North Africa, the Middle East, Southern Europe, and parts of North and South America. HIV epidemics among injection drug users (IDUs) often are characterized by rapid and even explosive spread. Reports indicate that in many countries HIV prevalence has increased from under 5% to more than 40 % in less than one year.¹ Diseases such as hepatitis C (HCV) and tuberculosis, as well as other societal costs, are strongly associated with injection drug use.

Effective HIV prevention among IDUs requires reaching the at-risk population and providing access to the means for behavior change to enable this population to reduce its injection and non-injection drug use as well as risky sexual practices. Drug treatment options vary from country to country, but most therapies rely on the principle of reducing the frequency of drug use, thus minimizing the risks associated with addiction and drug-seeking behavior, with the ultimate goal being rehabilitation and reintegration into society. HPTN 058 is designed to compare two such therapies in preventing HIV acquisition among injection drug users.

1.1 Background

The principal aim of this study is to determine the efficacy of a substitution drug treatment intervention using a buprenorphine/naloxone (BUP/NX) combination (brand name Suboxone®) combined with drug and risk-reduction counseling (referred to as “substitution treatment”) compared with short-term detoxification with BUP/NX combined with drug and risk-reduction counseling (referred to as “detoxification treatment”) for the prevention of HIV transmission among opiate dependent injectors by reducing drug use and associated risk behaviors. The interventions being tested in this study include both biomedical and behavioral components, and therefore draw on substance abuse treatment research involving pharmacological interventions (such as methadone) and counseling.

BUP/NX has been selected as the pharmacologic treatment agent for this trial given its known safety and efficacy in assisting patients to reduce or eliminate their opiate use. This sublingual BUP/NX combination was approved on October 8, 2002 by the US Food and Drug Administration (FDA) for use in the treatment of opiate dependence. Buprenorphine is the active ingredient that substitutes for the abused opiate(s); the addition of naloxone may mitigate misuse by precipitating withdrawal signs and symptoms if BUP/NX is injected by opiate-dependent individuals. (Refer to the Suboxone® package insert for more information.) The decision to use BUP/NX is rooted in its safety profile, its manageable administration schedule, and its limited risk of diversion. The use of BUP/NX for the treatment of opiate dependence therefore may be a more acceptable alternative than methadone in treating opiate dependence and potentially reducing HIV transmission among heroin injectors. The table on the following page compares various aspects of BUP/NX and methadone.

BUP/NX-Methadone Comparison

BUP/NX	Methadone
Fewer opiate effects than heroin or methadone	Continued opiate effects (e.g., sedation)
Limited risk of diversion, injection induces withdrawal	May be diverted and injected
Long acting requiring less frequent dosing	Requires daily dosing
May be administered in clinic setting	Specialized treatment centers preferred
Medical withdrawal may be easier than with Methadone	Medical withdrawal may not be as easy as with buprenorphine/naloxone
Less toxicity	Toxicity risk greater
Potential for drug-drug interactions with certain HIV medications	Potential for drug-drug interactions with certain HIV medications

1.1.1 Prior Research on Treatment Programs

Since the HIV/AIDS epidemic among injection drug users was first recognized in the early 1980s, a variety of prevention interventions have targeted this population.²⁻⁴ No intervention, however, has been as widely endorsed, nor as thoroughly examined as substance abuse treatment, specifically methadone treatment. Studies conducted in Australia, Europe, and the United States over the past 17 years have found, with few exceptions, associations between participation in substance abuse treatments and reductions in HIV risk behaviors and lower HIV prevalence and incidence rates.⁵⁻⁸ The majority of prior studies have examined the impact of methadone treatment among heroin injectors. The findings of these studies suggest that sustained treatment (one year or longer) with methadone is associated with protection from infection with HIV. Studies have shown that positive outcomes from substance abuse treatment are unequivocally contingent on adequate length of treatment. A research-based guide on the principles of substance abuse treatment, released by the National Institute on Drug Abuse (NIDA), notes that twelve months of treatment is the minimum duration required to achieve effectiveness.

The underlying mechanism of protection appears to be rather simple. Individuals who participate in effective treatment programs reduce the frequency of their drug use.⁹⁻¹⁶ Lower rates of use lead to 40% to 60% fewer instances of drug-related risk behavior.¹⁵⁻²⁰ In turn, lower rates of drug-related risk behaviors result in fewer exposures to HIV and fewer infections.^{18, 21-29} One observational study of injecting drug users found a six-fold difference in the rate of HIV seroconversion between participants in methadone maintenance treatment and those not receiving any treatment.²⁹

A number of studies have demonstrated that when active drug users are engaged in HIV counseling and testing coupled with behavioral risk reduction interventions, HIV risk behaviors are dramatically reduced. In a review of 36 publications on findings from NIDA sponsored community outreach studies,³⁰ several significant changes were identified between pre- and post-treatment (six months later) measures of drug use frequency and drug-related risk behaviors. When aggregated, these studies showed that 26% of participants reported that they were no longer injecting, and those who continued

to inject reported an average of 28 fewer injections per month. Nineteen percent fewer IDUs reported reusing syringes, and 27% reported ceasing the reuse of other injection equipment.

One of the more important results of efforts to implement and evaluate risk reduction interventions is the finding that active drug users can be engaged in meaningful education, counseling, HIV testing, and referral in the community, and that these activities are associated with at least short-term behavioral change. For the most part, enhanced behavioral interventions do not produce significantly greater reductions in drug use or drug-related risk behaviors than do the standard behavioral interventions.³¹

In one study, active injectors in Denver, Colorado were randomly assigned to either free methadone treatment or motivational and risk reduction counseling.³² Participants in the free treatment arm did enter methadone treatment at a higher rate and reported significantly fewer injections. However, participants in both arms reduced injection-related risk (syringe sharing) and no significant differences existed between the two arms on this measure. HIV incidence was too low to measure the impact of the intervention on new infections, and the follow-up was conducted for only six months.

1.1.2 Pharmacology of Buprenorphine and BUP/NX

Buprenorphine, a derivative of the morphine alkaloid thebaine,³³ has been available in numerous countries as an analgesic for parenteral and sublingual administration since the 1970s. As an analgesic, buprenorphine is approximately 25–50 times more potent than morphine.^{34–36} Typically, 0.3 mg of buprenorphine is considered to produce analgesia approximately equivalent to 10 mg of morphine when both medications are given parenterally.

Unlike methadone and LAAM (levo-alpha-acetyl-methadol), which can be characterized as full mu-opioid agonists, buprenorphine may be described as a partial agonist.³⁷ That is, buprenorphine produces sub-maximal effects relative to those produced by full mu-opioid agonists when a maximally effective dose of buprenorphine is given. Buprenorphine has a high affinity for the mu-opioid receptor and a low intrinsic activity.^{38,39} This high affinity makes buprenorphine extremely difficult to displace from the receptor by opioid antagonists. Further, buprenorphine dissociates very slowly from the receptor and, additionally, is very lipophilic.^{40,41} Both factors contribute to the relatively long duration of activity of buprenorphine. Buprenorphine binds with high affinity to the kappa-opioid receptor but functions there as an antagonist.^{42–44}

Buprenorphine has poor oral bioavailability,⁴⁵ less than 10% compared to that when given intravenously, secondary to extensive gastrointestinal and hepatic metabolism.⁴⁶ Given the low oral bioavailability of buprenorphine, and a concern that a parenteral dosage form should not be used for the treatment of opiate addicts, the sublingual route of administration has generally been considered to be the most appropriate for opiate dependence treatment. Initially, in many clinical studies assessing the safety and efficacy of buprenorphine, a sublingual solution was used. More recently, however, two sublingual buprenorphine tablet formulations have been developed: one containing only buprenorphine and one containing a combination of buprenorphine and naloxone in a 4:1 ratio (to reduce the potential for diversion and illicit use of buprenorphine). The bioavailability of the buprenorphine tablet has been reported to be about 50 to 65%⁴⁷ compared to the sublingual solution, though at steady-state this percentage may be

higher.⁴⁵ Naloxone itself has poor sublingual bioavailability.⁴⁸ Thus, when taken sublingually as directed, naloxone will not interfere with the therapeutic effects of buprenorphine. However, when opiate dependent individuals take the combined BUP/NX formulation parenterally, the naloxone component may be expected to produce signs and symptoms characteristic of opiate withdrawal.

1.1.3 Clinical Utility of Buprenorphine and BUP/NX

The results of a clinical study published in 1978 by Jasinski, et al,⁴⁹ fostered interest in and suggested the utility of buprenorphine for the treatment of opiate dependence. Over the next 25 years, numerous clinical laboratory and treatment-research studies, conducted in a variety of settings over different periods of time and using various schedules of buprenorphine administration, have provided evidence that buprenorphine can be used effectively and safely as an opioid-substitution pharmacotherapy.⁵⁰⁻⁵⁷ Recent clinical trials of buprenorphine and BUP/NX sublingual tablets in an office-based setting have shown buprenorphine to be effective and safe in the study paradigms.⁵⁸⁻⁶⁰

The efficacy of BUP/NX substitution therapy was recently demonstrated in a double-blind placebo controlled trial of BUP/NX and buprenorphine alone which found that both buprenorphine treatments resulted in a three fold increase in the percentage of urine tests that were opiate negative compared to placebo. Because of the greater efficacy of the treatment arms, the double-blind phase of the trial was terminated early. In the 48-52 week open label study that followed, the percentage of opiate-negative urine samples ranged from 35.2% to 67.4% (generally 50-60%) in multiple assessments.⁶⁰ Several other clinical trials have found similar efficacy rates for buprenorphine alone and in comparison to methadone. Few studies have adequately examined buprenorphine for opiate detoxification, and relapse rates and long-term outcomes have not been reported.⁶¹

It is likely that the agonist effects from higher therapeutic dosages of buprenorphine (approximately 12-16 mg/day of the sublingual tablet) will be comparable to methadone dosages in the 60 mg/day range.⁶²⁻⁶⁷ As a partial agonist, the effects of buprenorphine are dose-dependent within a limited range, above which increased doses do not produce corresponding increases in effect. However, there is much inter-subject variability in drug metabolism, absorption, distribution and elimination; therefore, each patient should be dosed to effect. Further, the same mu-opioid, partial-agonist profile that provides a ceiling to the therapeutic effects of buprenorphine also provides for a greater safety margin for buprenorphine.

In clinical practice, patients initiating treatment may be inducted onto therapy using either buprenorphine or the BUP/NX combination.⁶⁸ Consideration should be given to the type of opiate the patient has been abusing (e.g., heroin, morphine, methadone), the time since the patient last used opiates, and the current level of the patient's opiate dependence. Generally, the induction process will be easier in patients using shorter-acting (e.g., heroin) compared to longer-acting (e.g., methadone) opiates; patients experiencing mild to moderate withdrawal symptoms will be easier to induct than those who are not and who have recently (i.e., within the last 4 to 6 hours) used other opiates; and patients with lower levels of dependence will be easier to induct than those with higher levels. Initial doses of buprenorphine will typically range from 4 to 8 mg/day (i.e., 4/1 to 8/2 mg/day of the BUP/NX combination), although higher doses may be required. Administering the first day's dosage as two or three individual doses may also be useful. Dosages on subsequent days are then increased to the desired level.

While buprenorphine has been used effectively to substitute for other opiates and suppress the development of opiate withdrawal signs and symptoms, its partial agonist properties are also responsible for its potential to precipitate an opiate withdrawal syndrome under certain conditions. This precipitated withdrawal phenomenon has been observed or suggested by both preclinical^{34, 35, 69-71} and clinical studies^{72, 73}, respectively. It may not always be clear in clinical situations, however, whether withdrawal symptomatology is due to an insufficient or excessive dosage of buprenorphine being administered.

Of particular interest with respect to substitution therapy with buprenorphine has been the long duration of buprenorphine action, with a mean half-life of 37 hours. It was reported in some of the initial studies that at sufficient doses, buprenorphine could be effectively administered once daily.^{22, 74-76} Those findings were subsequently supported by results from numerous clinical trials. Later studies indicated that alternate-day, or even less frequent (e.g., three-times-weekly) dosing was suitable for nearly all patients.^{53, 77-91}

Abrupt discontinuation of buprenorphine appears to produce a mild to moderate opiate withdrawal syndrome.^{49, 72, 76, 92-94} Following abrupt discontinuation, subjective symptoms of opiate withdrawal begin within the first 3 days, peak between 3 and 5 days, and return to baseline in about 10 to 14 days.^{76, 93} There are limited empirical data regarding the optimal buprenorphine dose-reduction strategy. However, general recommendations derived from methadone treatment experience likely also apply to buprenorphine. That is, a gradual dose reduction is preferred over abrupt cessation or rapid reduction. Various dose tapering schedules have been utilized; for example, a 50% dose-reduction per time-interval, or schedules that involve reducing the buprenorphine dosage by an equal amount per period of time.^{68, 78}

1.1.4 Abuse Potential of Buprenorphine and BUP/NX

As is true for other opioids, buprenorphine should be considered to have a potential for abuse. As mentioned previously, however, the combining of naloxone with buprenorphine is expected to reduce the abuse liability of buprenorphine used clinically. Support for this assertion has been obtained from studies^{48, 60, 95-102} using various ratios of buprenorphine to naloxone (e.g., 2:1, 4:1 and 8:1), various subject populations (e.g., non-dependent, methadone-maintained, morphine-stabilized), and various routes of BUP/NX administration (e.g., sublingual, intramuscular). Further, a number of studies have also provided evidence that the naloxone component will not interfere with the therapeutic effectiveness of buprenorphine.⁵⁸⁻⁶⁰ Since 1983, reports of buprenorphine abuse have come from various countries,^{84, 103-116} although buprenorphine's relative availability and the availability of licit and illicit alternatives needs to be taken into account when interpreting these reports. Thus, buprenorphine abuse has often been associated with a lower cost and more ready availability than other opioid alternatives.

1.1.5 Buprenorphine Safety

The use of buprenorphine has not been associated with an adverse effect profile that would appear to limit its utility as an opiate dependence pharmacotherapy. Adverse effects reported following the administration of buprenorphine for opiate dependence treatment have included primarily sedation, drowsiness, headache, pain, sweating, nausea and constipation, and other effects typical of mu-opioid agonists in general.^{76, 117-119}

Tolerance to most of these effects can be expected to develop during continued buprenorphine therapy. The safety of buprenorphine is, like its pharmacodynamic profile, related to its partial agonist properties. In particular, the potential for severe drug-induced respiratory depression, a concern for medications such as methadone and LAAM, as well as drugs primarily used illicitly such as heroin, does not appear to be a relevant concern for buprenorphine. Even 32 mg of buprenorphine administered sublingually (approximately 70 times higher, corrected for differences in bioavailability, than a 0.3 mg analgesic dose given intramuscularly) produced only marginal effects on respiratory function in individuals not dependent on opiates,⁹⁰ and 12 mg given intravenously (also in individuals who were not opiate dependent) was shown to have a high margin of safety.¹²⁰

Deaths have been reported when buprenorphine has been combined with other drugs, particularly central nervous system depressants such as benzodiazepines.¹²¹⁻¹²⁴ These reports have come from France, where buprenorphine was approved for use in 1996 and where more patients have received buprenorphine therapy than in any other country. In these cases, buprenorphine tablets have typically been pulverized and then administered intravenously. Buprenorphine is widely available in France with minimal regulatory constraints on its use.¹²⁵⁻¹²⁷ However, even with fewer restrictions placed on buprenorphine compared to methadone treatment, buprenorphine appears to be a safe alternative to methadone. From 1994 to 1998, there were an estimated 1.4 times more buprenorphine-related deaths than methadone-related deaths in France.¹²¹ However, for each of those years (except for 1994 when no deaths were reported), the calculated death rate was always *higher* (ranging from 3.5 to 30 times higher) for methadone than for buprenorphine. Considering 1998 for example, the latest year for which data were available, buprenorphine was associated with slightly more than three times the number of deaths (13 compared to 4 for methadone), but there were over 10 times as many patients receiving buprenorphine (55,000) compared to methadone (5,360).

1.2 Rationale

In the prevention model to be tested, HIV infection among IDUs results from behaviors driven by an individual's use of substances. This use initiates and sustains a chain of events that culminates in infection. Effective interventions break this chain by reducing the frequency of drug use. When this treatment lasts for a sufficient period of time (estimated to be a minimum of one year), reduction in HIV incidence can be detected. The paradigm is straightforward yet thus far untested in a randomized trial. The strength of the data currently available derives its power from the consistency of findings among case-control, observational, and non-randomized HIV prevalence and incidence studies. Without randomized controlled trials, the lower rates of drug use, risk behavior, and infection cannot be attributed unequivocally to the treatment process. The most plausible alternate hypothesis is that drug users in treatment represent a self-selected group, who may also be more receptive to prevention messages. A direct test of this model is needed, and the HIV Prevention Trials Network (HPTN) is in a unique position to conduct such a trial and advance the scientific understanding of HIV prevention among drug using individuals.

In a number of regions in the world, HIV is spreading rapidly and is fueled primarily by injection drug use. Among HPTN sites, those in Thailand, Russia, and China appear to reflect these epidemiologic circumstances most directly. Incidence among IDUs is high in these sites, and prevalence is as high as 80% among IDUs in certain areas of Xinjiang,¹²⁸ lending urgency to the issue.

The Chinese Ministry of Health estimates that there were approximately 700,000 cases of HIV at the end of 2007 in China. About 32% of HIV/AIDS cases have been reported in China, with available HIV prevalence data indicating a focused, explosive spread of infection among IDUs, and less significant spread among non-injectors. Whereas seroprevalence rates among IDUs have been estimated between 20 and 70%, seroprevalence among pregnant women in antenatal clinics has been estimated between one and two percent in select sentinel surveillance sites. The prevalence of HIV among those screened for the HPTN 033 was 29% in Xinjiang and 25% in Guangxi, and the seroincidence was 8.8 and 3.1 per 100 person years respectively.

The NIDA HIV Prevalence Study enrolled 1,865 substance users from the Chiang Mai Drug Dependence Treatment Center. The prevalence of HIV infection among the 879 injection drug using participants enrolled in the study was 35.2%, with the use of injection drugs associated with HIV infection. As of December 2002, in the two-year follow-up incidence phase of the same NIDA-funded study retention was 97%. HIV incidence in the cohort was 7.89 per 100 person-years among the IDUs in follow-up.

HPTN 037 enrolled 182 HIV-negative injecting drug users and 245 of their sex and/or drug using network members, regardless of HIV status, from Chiang Mai city and surrounding rural areas. The prevalence of HIV among IDUs screened as index participants was approximately 10%. Average retention was about 92.3%. Available data from 037 indicates much lower incidence rates among this population than seen in the NIDA Prevalence Study.

Importantly, existing drug treatment strategies in much of Asia tend to take the form of short-term drug detoxification with little or no community based treatment or counseling available. While both China and Thailand do have methadone programs available, treatment slots are generally limited and short-term, and relapse is high.

Several Asian countries currently possess the momentum to introduce drug treatment as an HIV prevention intervention, and both China and Thailand are working toward expanding their methadone treatment systems. The timeline for and extent to which alternative treatment programs will be implemented and accepted by IDUs in these countries is unpredictable. Widespread implementation of such programs could pose challenges to the study in several ways. First, such expansion could reduce the overall rate of HIV transmission in the community. Second, and of greater concern, the availability of methadone may have a differential impact on the two arms of the study. Thus, extensive access to methadone maintenance treatment could compromise the ability of the study to maintain sufficient power to address the study objectives.

In the event of the widespread expansion of methadone treatment, the study will present an important opportunity to learn more about the impact of agonist treatment as HIV prevention. To this end, the study team will: 1) carefully monitor the number of available methadone treatment slots in the communities in which the study sites are located; 2) review the inclusion criteria for these programs throughout the course of the study; 3) work to develop mechanisms for sharing data with the parallel treatment systems in order to compare HIV prevalence and incidence, attendance, retention, and continued drug use. Investigators and protocol team members in both Thailand and China have close connections with the methadone treatment systems and are working to insure that the HPTN 058 project is viewed as complementary to the effort to expand methadone treatment in both countries. The study team plans to collaborate with methadone programs to help build infrastructure and provide training. Additionally, referrals to available treatment programs will be actively provided as a part of the counseling intervention. If a large proportion of participants ($\geq 20\%$) are concurrently enrolled and retained in these programs, an adjustment in the study size or modification in design sufficient to compensate for this may not be

feasible. This outcome would be a success for the greater public health, and the study would still be able to provide information about seroincidence and could be used to compare historical seroincidence trends at these sites to post methadone and BUP/NX treatment rates.

Although methadone has been shown to be safe and effective in the treatment of heroin dependence and is associated with reductions in HIV risk behaviors and infection, its public health impact has been severely limited both in the US and other countries. Because of the toxicity of methadone, diversion has been viewed as a significant public health risk given the potential of overdose. In many areas, there is public and political reluctance to use methadone. In Russia, for example, it is illegal to use mu-opiate agonists or partial agonists (methadone and buprenorphine) to treat heroin dependence. This reluctance is rooted in the perception that methadone treatment is merely the substitution of one addictive narcotic for another and thus does not deal with the central issues of dependence. There is also considerable concern that the difficulty of detoxification from methadone limits its utility for younger opiate dependent populations and those unwilling to remain in long-term treatment. Consequently, alternative treatment strategies that address concerns with methadone may have a greater likelihood of implementation.

Non-HIV related mortality among heroin injectors is also a major public health concern. In reviewing data from longitudinal studies of drug users published between 1987 and 1999 with observation periods ranging from 1969 through 1995, unadjusted mortality rates ranged between 0.9 and 3.2 per hundred person-years.¹²⁹⁻¹³² Standardized mortality ratios are substantially higher when cited in these reports and ranged from 3.5 to 63 per hundred person years. Thus, given the magnitude of mortality, prevention studies among IDUs must consider mortality in assessing incidence and evaluation of the impact of interventions.

1.2.1 Expanded Treatment Options

When available at all, access to treatment for illicit substance use is likely to depend on a number of economic and social factors. Methadone (and buprenorphine to a lesser extent) is available at the study sites on a very limited basis. However, as is the case in many parts of the world, methadone is not well accepted by many drug users nor is retention in treatment very high. As is true for many chronic conditions, a range of treatment options are needed to meet patients' needs. This study will expand treatment options currently available for IDUs in the proposed study settings. The counseling schedule and content in this study are more intense than current standards of care and will be provided for all participants regardless of study arm. The counselors will be specially trained to ensure the highest quality of counseling.

In addition, study participants will receive HIV testing every 6 months throughout the entire study and physical exams at screening and during the first year of study participation. Condoms will be provided to participants throughout the duration of their participation. For medical conditions identified through the study screening and/or follow-up procedures, participants will be provided or referred for appropriate care according to local standards. Care and treatment for HIV will not be provided by the study. Each site will develop a plan that documents, at a minimum, what services are available in the vicinity, the cost of these services (if any), length of time to receive services, and the name of a contact person at the referral site (Appendix IV). Local investigators will make reasonable efforts to determine whether these services are available to people in the study population and will note any significant barriers they observe or that are reported by study participants. When the participant wishes, the site

staff will facilitate access to the referral services (such as calling to make an appointment while the participant is at the study site) and may follow-up with the participant to see if the service was obtained. The list of available referral services will be monitored during site visits by sponsor representatives and will be updated by site staff at least bi-annually.

The appropriate use of the study intervention, BUP/NX treatment and drug and risk-reduction counseling, may be a cost effective way to reduce the morbidity, mortality, and incarceration associated with opiate addiction, as well as public health problems such as HIV, hepatitis B and C and other infectious diseases. The model of care being tested in this study has the potential to provide significant public health impact and economic benefit if successful since the cost of treating IDUs with BUP/NX will be more cost effective than treating the potentially large numbers of HIV/AIDS patients in the IDU population. If the trial finds that one year of substitution treatment with risk reduction counseling results in a sustained reduction in HIV incidence when compared to detoxification and counseling, it would suggest that the standard treatment in many countries, i.e., brief detoxification at best, is insufficient to prevent the HIV epidemic spreading among IDUs. If no difference in HIV incidence is detected at 24 months, the study results could suggest that HIV infection rates among opiate users could be reduced with the less intensive treatment approach (detoxification and counseling). A finding of no difference in incidence between the two arms could also suggest that longer-term substitution therapy may be advisable over one year of substitution treatment. In either case, the findings have important policy implications regarding HIV prevention among opiate dependent individuals.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objective of this study is to determine whether 52 weeks of substitution BUP/NX and counseling treatment in opiate addicted participants will achieve a long term (104 weeks) reduction in cumulative HIV incidence and death compared to short-term BUP/NX detoxification and counseling.

2.2 Secondary Objectives

The secondary objectives of this study are:

1. To determine if the substitution treatment reduces average HIV incidence and death compared to the detoxification arm, and reduces HIV incidence and death at 52 weeks and 156 weeks.
2. To determine if substitution treatment decreases average HIV incidence compared to the detoxification arm, and HIV incidence at 52, 104, and 156 weeks.
3. To compare the average rates of death in the two arms; and the rates of death at 52, 104, and 156 weeks.
4. To compare the self-reported frequency of injection, drug and sex-related HIV risk behaviors in the two study arms.
5. To compare the frequency of drug use measured by self-report and urinalysis in the two arms.

In addition, the study will provide an opportunity to assess the feasibility of community-based drug treatment in areas where such treatments are currently unavailable and to identify possible structural and attitudinal barriers to substance abuse and HIV care for IDUs. A review of local

and national laws and legal practices that pose risks of adverse social consequences for drug users and people with HIV will be conducted at baseline and annually at each site.

2.3 Study Design

This is a phase III, multi-site, two-arm, randomized, controlled trial to be conducted at a minimum in China and Thailand. An initial safety and feasibility phase will include the first 50 study participants at each site. Eligible HIV-uninfected opiate dependent injectors who agree to participate in the study and provide written informed consent will be randomized to one of two study arms in a ratio of 1:1. The two study arms are:

- “Substitution Treatment” Arm – sublingual BUP/NX administered daily up to three weeks (until dose stabilization) and then three times per week for 52 weeks in addition to weekly drug- and risk-reduction counseling for twelve weeks followed by monthly counseling sessions every four weeks through week 52;
- “Detoxification Treatment” Arm – short-term BUP/NX detoxification for 18 days maximum in addition to weekly drug- and risk-reduction counseling alone for twelve weeks followed by monthly counseling sessions every four weeks through week 52. The detoxification regimen may be repeated at the 26 week visit if the participant meets the same criteria for opiate dependence as at screening and has no contraindications for short-term study drug use. Women who receive a second detoxification will have another pregnancy test on the day of the first treatment dose and approximately four weeks later.

The total duration of the study will be approximately four and a half years. The initial safety and feasibility phase will take approximately 30 weeks. The accrual period in the full study will be approximately 104 weeks following the safety and feasibility phase. Participants will be followed for a minimum of 104 weeks and a maximum of 156 weeks, depending on when they are enrolled. Behavioral and serologic assessments will take place at baseline and at 26 week intervals throughout the follow-up period.

The treatment phase of the study will last for 52 weeks. A BUP/NX dose reduction period of approximately six weeks will occur between weeks 47 and 52 (inclusive) in those assigned to the substitution treatment arm. Those assigned to the detoxification arm will receive BUP/NX for a maximum of 18 days; detoxification may be repeated at 26 weeks if the participant in this arm is still injecting and meets criteria for opiate dependence (Section 4.4.1). Participants will be followed after enrollment for a minimum of 104 weeks and a maximum of 156 weeks, depending on when they are enrolled in the study. HIV testing and risk assessment will be conducted during the treatment and post treatment phases of the study. Additionally, participants in both arms will have routine urine testing for opiates and other commonly abused drugs. Safety will be assessed according to the procedures outlined in Section 6. Dosing ranges and adverse events will be reported to determine if the effects of the study drug (licensed in the US for the indication for which it is being used in the study, treatment of opiate dependence) are different in the study population than expected, based on experience in the US and Europe.

Because of the well-documented effects of buprenorphine in reducing craving and preventing withdrawal, the study will not be placebo-controlled as participants would quickly become unblinded following study drug administration. Additionally, the trial is designed to test the overall effectiveness of the HIV prevention strategy of providing BUP/NX coupled with drug- and risk-reduction counseling, as opposed to testing the efficacy of the medication as a treatment for opiate dependence. Thus, the use of placebo would be an inappropriate and costly design feature.

The study is designed to test the long-term effect of a 52-week treatment model on HIV acquisition. Past research among patients receiving methadone provides evidence that one year is the minimum amount of time required to achieve long-term sustainable changes in injection drug use risk behavior.⁵⁻⁸ The design will allow for the assessment of intervention effects for up to three years, both during and post-treatment. The sustainability of the intervention effects beyond the active treatment phase is a central tenet for the potential public health impact of this intervention.

In addition, the study will include an Informed Consent Evaluation Survey to evaluate the acceptability of a short Informed Consent Comprehension Quiz as a tool for judging participants' understanding of informed consent in internationally collaborative HIV prevention research and to measure participants' opinions about the quiz. As is standard in HPTN trials, participants will be asked to complete a standardized informed consent comprehension quiz following review of the enrollment consent. A short evaluation survey will be administered to study participants to explore their perceptions of this quiz after they have signed the enrollment consent form. Data on quiz perceptions will also be linked to participants' results on the informed consent comprehension quiz. This survey and the use of comprehension quiz data will be mentioned in the informed consent form for the clinical trial and participants will be informed that they can participate in the clinical trial even if they refuse to participate in this consent quiz evaluation process. Each site will participate until the DSMB is satisfied that an adequate sample size has been reached to determine trends.

2.3.1 Safety and Feasibility Phase

The study will begin with a safety phase during which each site will enroll 50 participants over a period of approximately six months. The primary purpose of this initial phase is to collect detailed safety data that will be made available to the sponsor and the appropriate oversight and regulatory authorities in Thailand, China, and the US, as needed. In addition, the feasibility and acceptability data on the first 50 participants in the study at each site will allow the sites to carefully plan for and establish appropriate full study operations, including procedures for study drug administration and monitoring.

The safety and feasibility phase will follow the same design as the full study, including 1:1 randomization, study drug administration, and counseling, but it will include a more intensive evaluation schedule for the first four weeks of an individual's participation in the study. For this initial phase, potential volunteers will be asked to sign a separate informed consent form that explains the additional evaluation requirements during the first four weeks of the study.

Evaluation of the initial safety and feasibility phase data will occur in two stages. The first stage will be site-specific (with available data from the two China sites likely combined) to be conducted after the 50th participant enrolled at each site completes four weeks of follow-up. The second stage will include data from all 150 safety and feasibility phase participants, in addition to other safety data accumulated up to that point, across all sites once the last participant enrolled completes four weeks of follow-up. The Statistical and Data Management Center (SDMC) will prepare comprehensive data summaries for each of the site-specific evaluations and the blinded interim evaluation for review by the Protocol Safety Review Team (PSRT) and at least one representative of the HPTN Study Monitoring Committee (SMC). The reviews will focus on both clinical and laboratory safety data and trial feasibility indicators such as screening, accrual, retention, and adherence to and acceptability of the study drug and

counseling regimens. Any safety concerns identified will be referred to the NIAID Data Safety Monitoring Board (DSMB) for unblinded review. The data summaries and minutes of the reviews by the PSRT/SMC will be provided to host country authorities as needed. The purpose of the aggregate review of the first 150 participants across all sites (and any other data accumulated by that time) is to ensure an early thorough review of all safety and feasibility data; however a separate review may not be necessary if the appropriate timing coincides with a routine SMC/DSMB review.

Barring any serious safety or feasibility concerns that necessitate significant changes in the study design or termination, participants who enroll during the safety and feasibility phase will continue study participation uninterrupted during the time that the data are being evaluated, including receipt of study counseling sessions and study drug. Full study accrual at each site will proceed during the interim data review for that site, unless otherwise directed by the sponsor, the PSRT and/or in-country authorities.

The remaining participants will be enrolled over a period of approximately 104 weeks. All participants will be followed for a minimum of 104 weeks and a maximum of 156 weeks, depending on when they are enrolled, with those enrolled earlier accumulating a longer duration of follow-up than those enrolled later in the study.

2.3.2 Assessments during the Safety and Feasibility Phase

Participants in the safety and feasibility phase will follow all procedures and undergo all assessments as specified for the full study in Section 5.0. In addition, after enrollment, the clinical and laboratory evaluations listed below will be conducted every week for the first four weeks for participants in both study arms. Evaluation of participants in the detoxification arm will allow for comparison with those in the substitution treatment arm and will minimize differences in contact and attention between the two groups.

The following assessments will be employed:

- Interim medical history
- Symptom-directed physical exam
- Hematology (Complete Blood Count [CBC] and platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Urine tests for drug use
- Assessment of social harms
- Acceptability assessment at week 4

Management, reporting and review of adverse events and social harms will follow the procedures specified for the full study in Section 6.0.

Each participant will complete an intervention acceptability assessment at the completion of the fourth week of the study. Study staff not involved in delivery of the counseling or drug intervention components will administer these assessments.

Adherence to the intervention components will be measured by participants' completion of the individual counseling sessions and drug dispensing visits as scheduled during the first four weeks of the study.

3.0 STUDY POPULATION

The target study population will be opiate dependent injection drug users recruited from the community using several methods including street outreach, publicity, and respondent-driven sampling in areas with high concentrations of drug use and HIV/AIDS. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be recruited, screened, and enrolled as described in Section 3.4. Issues related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively.

Participants will be enrolled at a minimum in HPTN sites in China and Thailand. Additional sites may be added in the future.

As described in Section 7, the protocol team, HPTN Study Monitoring Committee (SMC), and a NIAID Data and Safety Monitoring Board will monitor rates of accrual into the study as well as observed HIV seroincidence rates. Upon recommendation from one or more of these groups, if accrual problems are encountered at any site, the protocol team will consider whether to shift site-specific accrual targets across sites to ensure that the overall sample size is achieved in as timely a manner as possible.

3.1 Inclusion criteria

- At least 18 years old
- Able to provide written informed consent for study participation
- HIV-uninfected as evidenced by two different rapid tests on specimen obtained within 28 days of enrollment
- Meets Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opiate dependence, as determined by study clinician
- Positive urine test for opiates
- Injected opiates at least twelve times in the last 28 days, according to self-report
- If female, evidence of inability to become pregnant or self-reported willingness to use an effective method of contraception for the first twelve months of the study
- Able to provide contact information and stated willingness to be contacted by study staff as needed
- Stated plans to be available for study visits for at least two years

3.2 Exclusion criteria

- Current or recent (within the last 12 weeks) clinician-guided treatment for opioid dependence with methadone, LAAM, buprenorphine, naltrexone, or nalmefene, according to self-report
- Current enrollment in another HIV prevention or drug use intervention study
- Known clinically-diagnosed allergy to buprenorphine or naloxone, according to self-report
- Meets DSM-IV criteria for dependence on alcohol or benzodiazepines; requiring immediate medical attention for dependence on other substances (except tobacco) as judged by the study clinician
- Currently injecting substances other than opiates more than twice in the last 28 days, according to self report
- Psychological disturbance or cognitive impairment interfering with the participant's ability to comply with the study visit schedule and procedures, as judged by the local study clinician
- Pregnant or lactating
- Acute or chronic renal failure as judged by study clinician

- ALT greater than three times the upper limit of normal value
- Hemoglobin less than 8g/dL for men, less than 7g/dL for women
- Platelet count less than 50,000/mm³
- Total bilirubin greater than 2.5 times the upper limit of normal
- Any other medical or psychiatric condition that, in the opinion of the investigator, would make participation in the study unsafe, or otherwise interfere with the study objectives or interpretation

3.2.1 Women and Contraception

BUP/NX is a pregnancy Category C drug. The effects of it on fetal development have not been comprehensively studied; therefore a woman may enroll in the study only if she is unable to become pregnant or is using, or willing to use, an acceptable method of contraception for the first twelve months of the study. Available contraception in the study sites may vary, but acceptable options include, but are not limited to, hormonal methods, barrier methods (diaphragm or condom), and intrauterine devices, and complete abstinence from sexual intercourse. Women who report that they are abstinent will be counseled about contraceptive options and asked if they are willing to use an effective method of birth control in the event that they become sexually active. Male condoms will be offered at the study sites along with referrals to family planning providers. If a participant becomes pregnant during the trial and is on study drug, she will continue to be followed as a study participant but will be tapered gradually from BUP/NX and referred for appropriate care. Pregnant women will also be counseled about the risks and benefits of drug treatment during pregnancy and will be provided with referrals for alternative treatment options including methadone and buprenorphine (without naloxone) when available. Pregnancy outcomes will be ascertained from the participant by verbal report when possible.

3.3 Recruitment Process

Recruitment will be through street outreach, publicity, and respondent-driven sampling (snowball method), where IDUs who participate in screening are encouraged to bring their IDU friends to the study site. These recruitment strategies were particularly successful in HPTN 033 and 037. Each site will develop its own specific recruitment plan prior to initiating the study.

Outreach workers will primarily carry out recruitment activities. These staff will be trained not to pre-select individuals who fit their description of “drug users,” rather they will provide information to a range of individuals and encourage those individuals to pass information about the study to others in the community. Outreach workers will be research staff from the community and must be knowledgeable about the community’s health care and drug treatment resources as well as the local criminal justice response to drug users. They will be trained, as part of the study, in methods of approaching and communicating with potential participants, personal safety, and the importance of maintaining confidentiality. Outreach workers will identify and develop strategies for accessing settings and organizations frequented by drug users. In these geographic areas and settings, outreach workers will disseminate general information about the study verbally and via written materials as approved by the institutional review boards (IRB) or ethics committees (EC). They will provide information on available drug treatment resources in the community and encourage prospective participants to participate in screening activities at a local study site.

3.4 Screening and Enrollment Process

A total of 1500 participants will be enrolled in the study across all of the participating sites. Details of the screening activities will be outlined in the Study Specific Procedures (SSP) Manual. Screening will typically take place over one or more visits. Regardless of the number of visits required to complete all screening activities, participants must be enrolled within 28 days of the blood draw for HIV testing. Participants who do not enroll within 28 days or who are otherwise found to be ineligible may re-screen for the study once. Re-screening may be conducted after 30 days from the initial screening blood draw.

Screening Visit:

Prospective participants who present at the study site will receive a brief introduction to the study. Individuals who are interested in participating will be asked to provide written informed consent for screening before any study-specific screening procedures or testing are undertaken. The sample screening consent form is included in Appendix III. Screening may be discontinued if a participant is found to be ineligible after completing an individual screening assessment. However, HIV counseling and testing will be offered to all persons who consent for screening. Participants who meet initial study screening eligibility criteria, which includes diagnosis of opiate dependency, will be asked to provide demographic and locator information; risk assessment interviews will be done prior to HIV counseling and testing. A urine specimen for testing for pregnancy (for all women) and opiates and other drugs will be collected. Blood samples will be sent to local laboratories for assessment of CBC, platelet count, hepatitis, and liver and renal function tests.

Participants will be given their rapid HIV test result and post-test counseling the same day if possible. Individuals who test positive with one or both rapid tests will have their sample sent for confirmation. These individuals are not eligible for enrollment but will be offered confirmatory testing and referral to support services as described in Section 1.2.1; however, they may be rescreened according to protocol requirements if the Western blot result proves negative. All local health care and drug treatment services available to drug users will be actively discussed. Referrals to these services will be made by study staff when appropriate and desired by the participant. Potential participants with negative HIV test results will be offered further screening, including a physical exam and medical history. Pre-existing conditions, such as compromised respiratory function, may exclude some participants. Study clinicians may refer screening participants for further clinical evaluation if warranted prior to making final eligibility determination.

At selected sites, exploratory testing will be conducted on specimens from individuals who are confirmed to be HIV-infected at screening. The assays, which will be performed on batched specimens, will give a cross-sectional estimate of incidence within the IDU population. Since assays to screen individuals for evidence of recent infection are not approved for clinical use, results will not be provided to participants.

Randomization and Enrollment Visit

Participants will be asked to return in approximately one week to receive the results of laboratory tests. Those who meet all eligibility criteria will be asked to sign the enrollment consent after the study has been explained to them and they have completed a consent comprehension quiz. Participants will be asked to complete a short evaluation survey of the comprehension quiz after signing the consent form. Those who are hepatitis B (HBV) negative will be offered the first

dose of the HBV vaccine. Women will receive another pregnancy test prior to signing the consent form, and if negative, will be consented to enroll in the study. The sample enrollment consent form can be found in Appendix III. If the participant consents, he/she will be assigned to a treatment arm according to the randomization scheme developed by the SDMC. BUP/NX treatment will commence the same day as randomization in both arms. If it is not possible for a participant to begin dosing on the same day s/he signs the enrollment consent, study staff will wait to randomize the participant. The site will also schedule counseling visits to begin the same day, or within one week from randomization.

3.5 Participant Retention

Once a participant enrolls in the study, the study site will make every effort to retain him/her for the full study period (104 to 156 weeks, depending on when s/he is enrolled) to minimize possible bias associated with loss-to-follow-up. Retention rates of at least 90% at 104 weeks are targeted among participants who remain alive for the duration of the study. Study site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Thorough explanation of the randomization process and that neither staff nor participants may choose their treatment assignment.
- Thorough explanation of the importance of both study treatment groups to the overall success of the study.
- Collection of detailed locator information at the pre-test visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms to retain participants.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

3.5.1 Missed Treatment Visits

Participants in either study arm who miss study visits for more than two weeks may resume weekly counseling sessions (during the first twelve weeks of study participation) and monthly counseling sessions. Participants in the substitution treatment arm will be evaluated for resumption of BUP/NX treatment upon return to the study site and may resume study drug dosing based on clinical judgment and after consultation with the PSRT but may need to repeat BUP/NX induction. No participant will receive BUP/NX beyond 52 weeks from the time of enrollment.

If a participant in the substitution treatment arm misses study visits for more than two weeks a second time, the site staff will bring the case to the PSRT for review. The PSRT will consider the individual circumstances to determine whether the participant should be

discontinued or re-started on BUP/NX. These participants may continue counseling visits, monthly counseling sessions, and follow-up visits as regularly scheduled.

Participants who discontinue BUP/NX or counseling treatment prior to the scheduled end date, regardless of study arm or reason, will be asked to remain in the study and complete all monthly counseling and follow-up visits as originally scheduled unless otherwise specified. These participants will not be allowed to re-screen for the study.

3.6 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The site Investigator also may withdraw participants from the study *only* to protect the safety and well-being of the participant and/or the study staff and *only after* consultation with the Protocol Chair, the Medical Officer, the Protocol Statistician, and Coordinating and Operations Center (CORE) Protocol Specialist. Participation may also end if the sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study early.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.6) of participants who terminate from the study prior to the last scheduled follow-up visit. Study staff will record the reason(s) for all withdrawals from the study in participants' study records. Participants who withdraw voluntarily will not be allowed to re-screen for the study; however, with permission, HIV status will be ascertained.

Participants who discontinue BUP/NX or counseling treatment prior to the scheduled end date, regardless of study arm or reason, will be asked to complete all follow-up visits and assessments as originally scheduled unless otherwise specified.

4.0 STUDY TREATMENT/INTERVENTION

Detailed descriptions of each treatment arm and procedures for each will be included in manuals devoted to each arm.

4.1 Adherence

A high level of adherence to the intervention will be important for determining the effectiveness of each arm in preventing HIV acquisition. The aim is to optimize and monitor adherence without excessive or unsustainable resource utilization that would make the results of this trial less generalizable. Adherence will be monitored using attendance at counseling visits and dispensing of BUP/NX. In addition, study staff will provide counseling about the importance of each treatment arm and will ascertain reasons for non-attendance at scheduled visits.

Study clinicians will monitor adherence to the scheduled regimen by tracking completed dosing visits. Counselors will monitor attendance at weekly and monthly sessions. When a participant has missed a visit, either drug dispensing or counseling visits, staff will try to contact the participant within a day to re-schedule the visit.

4.2 Description of the Counseling Intervention

Opiate dependence is a chronic medical condition requiring intervention. Thus, all participants will receive drug- and risk-reduction counseling. The counseling will be conducted in individual sessions based on a model of relapse prevention. The counseling manual contents will draw from

various studies, such as EXPLORE, NIDA Collaborative Cocaine Treatment, and the HPTN 037 study, which has proven very acceptable in Thailand with IDUs. In the NIDA study,³¹ cocaine-abusing individuals were randomly assigned to individual drug counseling or one of two more intensive psychotherapy interventions, supportive-expressive therapy or cognitive therapy. The study concluded that the individual drug counseling produced equal or greater levels of abstinence than the more intensive psychotherapy.

Individual drug counseling focuses on the symptoms of drug dependence and related areas of impaired functioning and the content and structure of the patient's ongoing recovery program. This model of counseling is time-limited and emphasizes behavioral change. It gives the participant coping strategies and tools for recovery, and promotes self-help strategies. The primary goal of addiction counseling is to assist the addict to achieve and maintain abstinence from addictive chemicals and behaviors. The secondary goal is to help the addict recover from the damage the addiction has caused in his or her life.

As a part of the counseling intervention, counselors will actively provide participants in each arm with information about available drug treatment options in the community, such as drug free detoxification, methadone detoxification or maintenance programs. To standardize referrals, a script will be included in the counseling manual. ***Participants who choose to enroll in these programs will continue to complete all HPTN 058 study activities***, except BUP/NX will be discontinued with participants who receive methadone treatment in the community. To date, community-based methadone treatment is not readily available to IDUs at the China sites; however, pilot programs are developing and are expected to be operational during the conduct of HPTN 058.

Addiction counseling works by first helping the patient to recognize the existence of a problem and the associated addictive thinking. Within this counseling model, the patient is the effective agent of change. It is the patient who must take responsibility for working on and succeeding with a program of recovery. Although recovery is ultimately the patient's responsibility, the patient is encouraged to get a great deal of support from others. This includes counselors and other professionals and drug-free or recovering peers and family members.

These counseling services will be delivered weekly for 12 weeks followed by monthly counseling sessions approximately every four weeks through week 52. Weekly and monthly individual counseling visits will last about 45 minutes. Counseling sessions will be manualized with required skills-building sessions designed to improve the participant's ability to take active steps to reduce the risks associated with injecting behavior, to build problem-solving capabilities, and to improve adaptive behaviors in general. Site staff will conduct periodic reviews of counseling content and administration to assure quality of the counseling intervention.

4.2.1 Counselor Selection and Training

Counselors will be research staff who must have a good understanding of participants' worldview and health beliefs, and who have either the demonstrated ability or active interest in learning to counsel drug users. They must be able to fully understand the dimensions of family and interpersonal relationships, sex roles, drug use history and the openness with which sex and drug use are discussed in the selected study sites. Counselors will participate in intensive training, practice, and pilot testing prior to study initiation. They will be given a variety of teaching materials on HIV risk factors, drug use and practices, safer sex practices, and detoxification and will also provide

information on other available services in the community for study participants who may request or need additional professional help.

4.2.2 Monthly Counseling Sessions

The monthly counseling sessions, beginning during Week 16 and continuing through the end of Week 52, will also follow a standard manual. These sessions will re-emphasize key strategies conveyed and practiced during the first 12 weeks of counseling and focus on strategies for handling challenges faced by participants.

4.3 Description of the Drug Intervention

A detailed manual will guide BUP/NX administration for site clinicians, who will be medical doctors or staff of appropriate clinical training. The manual will provide instructions for drug induction, maintenance, and tapering phases, as well as how to monitor side effects and concomitant medications. The site clinician will be responsible for induction, dose adjustments, and tapering BUP/NX for participants in both arms. Site clinicians will not provide the study drug and HIV risk reduction counseling; they will instead focus on study drug adherence, instructions for use and management of side effects.

Selection of and training for the study clinicians is expected to be intensive and cover several months. As a starting point, clinicians must have either the demonstrated ability or active interest in learning to treat and manage opiate-addicted patients. The study team will develop a training program for site clinicians that will likely include classroom situations, seminars at professional society meetings, written and electronic documents, and other training venues.

4.3.1 BUP/NX Formulation and Administration

Additional instructions for BUP/NX administration, storage, and side effects are found in the current Suboxone® package insert.

Regimen

Participants who meet randomization criteria (see Section 3.4) will be randomized to one of two open-label treatment arms. BUP/NX treatment will commence the same day as randomization in either arm.

Study Product Formulation

The BUP/NX study product provided is a sublingual tablet each containing a combination of buprenorphine and naloxone.

BUP/NX study sublingual tablets are provided in two different strengths:

- 2 mg of buprenorphine with 0.5 mg naloxone
- 8 mg of buprenorphine with 2 mg of naloxone

The dose of BUP/NX is expressed as the amount of buprenorphine component of study product, Suboxone®.

Administration:

BUP/NX tablets are administered sublingually and placed under the tongue until they are dissolved. For doses requiring the use of more than two tablets, participants are advised to either place all the tablets at once or alternatively (if they can not fit in more than two tablets comfortably) place two tablets at a time under the tongue. Either way, the participant should continue to hold the tablet under the tongue until they dissolve; swallowing the tablet reduces the bioavailability of the drug. To ensure consistency in bioavailability, participants should follow the same manner of dosing with continued use of the product.

4.3.2 Treatment Supply Distribution and Accountability

Study Product Supply, Distribution and Pharmacy

BUP/NX (2 mg/0.5 mg) and BUP/NX (8 mg/2 mg) study tablets are manufactured and provided by Reckitt Benckiser Pharmaceuticals, Inc under the trade name Suboxone®.

Study Product Acquisition

BUP/NX tablets will be distributed to the study sites by the NIAID Clinical Research Products Management Center (CRPMC). The study site pharmacist can obtain BUP/NX through the CRPMC by following the instructions provided in the latest version of the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual.

Study Product Accountability

The site pharmacist is required to maintain records of all BUP/NX study products received and subsequently dispensed to the study participants. All unused study products drugs are to be held until the study is completed, terminated, or otherwise instructed by the sponsor. Specific instructions will be provided for the final disposition of the study product.

Study Product Storage

BUP/NX study product must be stored at controlled room temperature at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

4.3.3 Treatment Dose and Administration

To aid clinicians in determining the appropriate dose during the first two-to-three days, the study will use the Clinical Opiate Withdrawal Scale (COWS), an instrument measuring validated items of physical signs or symptoms of withdrawal, such as gooseflesh, vomiting, and sweating, to objectively assess withdrawal in both treatment arms.¹³⁴ The total score gives an index of the participant's withdrawal intensity and can be administered over time to track changes and adjust dosing. On day one, the clinician will wait until the participant shows at least mild opiate withdrawal by monitoring with the COWS. If the score indicates at least mild withdrawal (the higher the score the more severe the withdrawal), the clinician will give 4 mg for the first dose. COWS will be repeated in one hour; patients will receive further dosing as described below.

Detoxification Treatment Arm

Medical detoxification utilizing BUP/NX will be initiated in participants randomized to the detoxification arm on the same day that randomization occurs. Using the COWS as described above, dosing will begin with a titration over a period of 3 days under direct supervision in the study clinic. On the first day of treatment, patients will initially receive a 4 mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total first day's dosage of 8 mg. Up to 16 mg may be given on Day 2 and 32 mg on Day 3 depending on individual response.¹³⁵

Beginning on Day 4, participants will have their dosage of BUP/NX decreased by approximately 2 mg/day at the clinician's discretion until a dosage of 0 mg is reached. Thus the maximum number of days required for medical detoxification will be 18, i.e., for a patient who received 32 mg on Day 3 there will be 15 additional days over which the BUP/NX dose will be reduced to 2 mg with 0 mg being achieved on Day 19. Individuals who are inducted/stabilized on a lower maximum dosage will be medically detoxified over a shorter time period. Participants will come to the clinic daily (except on days when clinic is closed in which case a take-home dose will be given) for direct observation of dosing. Concomitant medications (such as acetaminophen for pain or loperamide for diarrhea) may be utilized in consideration of the cautions described in Section 4.5 of this protocol.

Detoxification may be repeated at the 26 week time point if the participant in this arm is injecting and meets the criteria for opiate dependence. The clinician will repeat the eligibility questionnaires and all laboratory tests. If determined to be eligible for second detoxification, i.e., meets DSM-IV definition of opiate addiction, positive urine test, currently injecting at least 12 times in last 28 days, and does not have any contraindications (e.g., elevated ALT), detoxification procedures will be repeated as described above.

Substitution Treatment Arm

Dosing will begin with a titration over a period of two to three days under supervision in the study clinic using the COWS as described above. On the first day of treatment, patients will initially receive a 4 mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total first day's dosage of 8 mg. On Day 2, up to 16 mg may be given. Up to 32 mg may be given on Day 3 and thereafter until three-times-weekly dosing begins. The induction strategy is primarily dependent on three factors: 1) time since last opiate use; 2) type of opiate (e.g., long or short-acting) used; and 3) degree of physical dependence. Therefore, each dosing schedule will be tailored to the individual participant.

Individuals randomized to the substitution treatment arm will come to the study site daily for direct observation of dosing until they have stabilized (for up to three weeks). Participants may be given a double dose or a take-home dose for days that the site is not staffed for dosing. After induction and stabilization, participants will be asked to come to the site for dosing three-times-weekly. The target dosage schedule for individuals whose daily dose was 16 to 24 mg/day is expected to be 32/32/48 mg administered on a three-times-weekly schedule (e.g., M/W/F); this is also the maximum three-times-weekly dosage. On rare occasions, for individuals who require more than 24 mg/day (i.e., 26, 28, 30, or 32 mg/day), it is unlikely that the 32/32/48 mg dosage schedule will be adequate. For those individuals, as well as for others who received 24 mg or less per day but for

whom the 32/32/48 mg three-times- weekly schedule is not adequate, dosing may be continued on a daily basis through Week 52 of the study, with take-home doses administered for those days on which in-clinic dosing is not possible (e.g., 32 mg on M/Tu/W/Th/F/Sat with a take-home 32 mg dose on Sun). Participants receiving daily doses may also be given alternative day take home doses, which would conform to the visit schedule of those participants on three-times weekly dosing, at the discretion of the local investigators.

When dosed on a daily basis, the maximum agonist effects of buprenorphine will likely occur in a dosage range between 16 to 24 mg/day for most individuals. While increased dosages may not produce corresponding increases in agonist effects, they may extend the duration of buprenorphine-induced blockade of concurrently administered opiates. In one study, individuals maintained on 8 mg/day of buprenorphine solution were shown to tolerate a 72-hour dose omission well.¹³⁶

Study participants in the substitution arm will undergo dose tapering for approximately six weeks at the end of the treatment phase (weeks 47-52). As with dose induction, the visit schedule and dosage during dose tapering will vary from participant to participant. Although data are lacking regarding the identification of an optimal dosage reduction regimen, it is generally believed that a gradual reduction of BUP/NX over a longer period of time (e.g., the six-week period of the present protocol) is likely more effective and better tolerated than more rapid dosage reduction over short (e.g., 3 days) to moderate (e.g., 10-14 days) periods of time. For example, an individual maintained on a three-times-weekly dosage of 24/24/36 mg given on M/W/F could have his/her dosage decreased over six weeks according to the schedule in the following table:

Week of Study	Day of Week	Dosage (mg) of BUP/NX (Expressed as Buprenorphine Component)
47	M	22
	W	20
	F	30
48	M	18
	W	16
	F	24
49	M	14
	W	12
	F	18
50	M	10
	W	8
	F	12
51	M	6
	W	4
	F	6
52	M	2
	W	2
	F	0

BUP/NX dosing is intended to be closely supervised, with the product dispensed to the participant at the study site with direct observation of dosing. However, if allowed by in-country authorities, study staff may on rare occasions give participants a supply of BUP/NX to take home when a participant is unable to come to the study site for dosing (e.g., on days when the clinic is not staffed for dosing services or because of travel). Under rare circumstances, such as serious participant illness or disability, study staff may visit the participant at home (with consent) to deliver the study medication. Sites may consider allowing participants to revert to daily dosing, though three times weekly supervised dosing is preferred.

4.4 Toxicity Management

All clinical and laboratory abnormalities will be followed closely until resolution. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of adverse events according to their best medical judgment and local practice. As described in Section 6.1, the PSRT will closely monitor participant safety data on an ongoing routine basis throughout the study. The PSRT will also participate in the decision-making regarding study drug discontinuation and resumption.

4.4.1 Criteria for Adjusting or Discontinuing Study Drug

BUP/NX dosage may be adjusted routinely during the induction and stabilization phase of the study for participants in the substitution treatment arm. Following stabilization, participants who meet any of the following criteria may have study drug dosage adjusted or discontinued with appropriate dose tapering:

- Intoxication with any drug at the time of the dispensing visit
- In need of temporary use of a medication that may interfere with BUP/NX (see Section 4.5)
- Serious adverse event (SAE) not related to withdrawal that is potentially related to the study drug
- Pregnancy
- Enrollment in another study that, in the judgment of the investigator, will interfere with full participation in or interpretation of HPTN 058
- Evidence of hypersensitivity to BUP/NX
- Participant's request
- Investigator's decision
- Continued dosing or dosing at the current level is contraindicated for any reason, as judged by the study clinician and/or PSRT (e.g. elevated ALT)

Decisions regarding resumption of study drug following discontinuation will be made in consultation with the PSRT. If drug interruption occurs for two weeks or longer, induction may need to be repeated. Further details regarding discontinuing or adjusting study drug will be specified in the treatment manual.

Participants who discontinue the study treatment (drug and/or counseling components) will remain in the study and continue all follow-up assessments as originally scheduled.

Those participants that were permanently discontinued from the study treatment under protocol version 1.0 will be eligible to re-start study medication prior to the dose tapering period after consultation with the PSRT.

NOTE: HIV seroconversion is not a reason for discontinuation of study drug, although those who receive protease inhibitors may have their BUP/NX dose adjusted.

4.4.2 Considerations for Women who Become Pregnant during the Study

BUP/NX is a pregnancy Category C drug. High doses of buprenorphine can pass through breast milk. Therefore, women who are pregnant or lactating are excluded from enrollment. During the informed consent process, local site staff will discuss the available data on BUP/NX and pregnancy with female study volunteers. Given the limited data on the safety of BUP/NX use throughout pregnancy, women who become pregnant will be discontinued from BUP/NX, with gradual tapering, for the duration of their pregnancy. Pregnant women will also be counseled about the risks and benefits of drug treatment during pregnancy and will be provided with referrals for alternative treatment options including methadone and buprenorphine alone when available.

Urine pregnancy tests will be performed approximately every four weeks during BUP/NX treatment. Pregnant women will be maintained in follow-up to ascertain study endpoint information. Clinical status of infants born to women who become pregnant while taking BUP/NX will be obtained by interview of the woman after delivery; if a woman withdraws from the study prior to completion of her pregnancy, every effort will be made to obtain this information. Reporting of fetal losses will follow DAIDS adverse event (AE) reporting requirements. Resumption of BUP/NX in women who have pregnancy losses, either spontaneous or elective, will follow the same procedures as those outlined in Section 3.5.1.

4.5 Concomitant Medications

Participants in the substitution treatment arm will be advised to consult with the study clinician before taking any other medications. Participants receiving the following medications should be monitored closely and *may* require dose adjustment:

Precautionary Medications

- CYP 3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, HIV protease inhibitors). Participants receiving CYP 3A4 inhibitors may need their dose of BUP/NX reduced.
- CYP3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin). The interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving BUP/NX should be closely monitored if inducers of CYP3A4 are co-administered.
- Narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other central nervous system (CNS) depressants

Use of the above mentioned medications by participants in the substitution arm should be avoided unless such medication is clinically indicated by his/her primary care provider and alternative medications are either not available or are suboptimal for the indication for which they would be prescribed. All concomitant medications taken by participants in both study arms from screening

through the first 52 weeks of study participation, including other medications used for drug treatment such as methadone, will be reported on applicable study case report forms. In addition to prescribed and over-the-counter medications, street drugs, vitamins, herbal remedies, and other traditional preparations will be recorded.

Participants in both arms of the study will be advised of the risk of death or severe respiratory depression if they intravenously misuse buprenorphine, or concomitantly self-administer benzodiazepines, other depressants, including alcohol, or other opiates. BUP/NX should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone. For more details about adverse reactions and warnings, please refer to the drug package insert.

5.0 STUDY PROCEDURES

An overview of the study procedures schedule is presented in Appendix I A and B. Participants randomized to the detoxification arm will be expected to complete approximately 45 to 60 visits (depending on whether or not a second detoxification is required) throughout the first year in the trial, while those in the substitution treatment arm will complete approximately 155-160 visits. The greater number of visits in the substitution treatment arm is due to three times weekly BUP/NX dispensing visits. Detailed instructions to guide and standardize all study procedures across sites will be provided in the SSP manual.

5.1 Screening Visit

Screening procedures will typically take place over two or more visits. All potential participants must provide independent written informed consent for screening before completing any other procedures. Thereafter, the order of the procedures specified below is suggested but not required, with the exception of the Risk Assessment, which must be completed prior to HIV pre-test counseling. The following procedures will initially occur as part of screening:

- Collection of demographic information
- Interviewer administered eligibility questionnaire, including DSM-IV diagnosis
- Urine collection (pregnancy and drug tests)
- Collection of locator information
- Risk Assessment (drug and sex behavior)

Screening may be discontinued after any one of the individual assessments listed above is completed if a participant is found to be ineligible; however, in order to protect the integrity of the entry criteria, staff will be careful to not reveal exact reason for ineligibility (e.g., injecting fewer than 12 times in past 28 days). HIV counseling and testing will be offered to everyone who consents for screening. Potentially eligible participants will then complete the following procedures:

- Pre-test HIV counseling
- Blood draw for the following laboratory tests:
 - HIV testing
 - Hematology (CBC and platelet count)
 - Hepatitis B surface antigen and hepatitis C antibody testing
 - Blood chemistry (creatinine)
 - Liver function tests (ALT, bilirubin)

Sites will follow the HIV testing algorithm for screening included in Appendix II-A. Sites will confirm all positive or discordant rapid tests. If a positive result is obtained for one or both of the rapid tests, a Western blot (WB) or Immunofluorescent Assay (IFA) will be performed using the same sample for confirmation.

When results of the HIV rapid tests are available (approximately 20-40 minutes later for most volunteers), participants will receive HIV post-test counseling. Individuals who require confirmatory testing are not eligible for the study but will be asked to return to the clinic in about a week to receive their results; however, they may be rescreened according to protocol requirements if the Western blot result proves negative. Individuals who are confirmed to be HIV-infected will be counseled in ways to prevent the spread of the virus and will be provided with appropriate referrals. Each site will keep an updated referral list of counseling services, support groups, and treatment providers in their areas (Appendix IV). The staff will assist potential participants with getting appointments if needed, and may follow-up to see if the service was obtained.

Potential participants who are determined to be HIV-uninfected will complete the following assessments:

- Physical exam
- Targeted medical history

When laboratory results are received by the site, approximately one week after the blood draw, staff will determine if individuals meet entry criteria. If a potential participant has abnormal test results, the site clinician may conduct further testing before determining eligibility and should provide participants with appropriate referrals if necessary. If laboratory tests indicate an individual is eligible, s/he will be asked to return to the site to provide informed consent for enrollment and randomization after the study is thoroughly explained to him/her. Those who are not eligible will be informed that they do not meet the requirements of the study and, if necessary, will be referred for appropriate medical care.

Participants who are randomized and who are not infected with hepatitis B will be offered the hepatitis B vaccine over the course of the following year though it is not a requirement for study participation.

5.2 Enrollment/Randomization

If all laboratory and interview screening indicates that the individual is eligible, then the study will be fully explained to the volunteer and written informed consent for enrollment will be obtained after the volunteer completes a consent comprehension quiz. Participants will also be asked to complete a short evaluation survey of the quiz after signing the consent form. Female participants will be asked to provide urine for another pregnancy test to confirm that the participant is not pregnant at the time of first dosing. Locator information will be reviewed. Regardless of the number of screening visits required, final eligibility determination and randomization must be completed within 28 days from the time of the first blood draw for the HIV test. Participants will provide consent for study enrollment on or before the visit at which they are randomized.

Eligible study volunteers who have consented for participation will be sequentially randomized to one of two study arms according to procedures outlined in Section 7.4 and detailed in the SSP Manual. The effective point of enrollment is randomization (assignment of study arm).

Participants must be present at the study site for enrollment/randomization. BUP/NX will be initiated on the same day that randomization occurs. If a participant states that s/he will not be available, or if staff are not available, to begin dosing on the day the enrollment consent is signed, study staff will wait to randomize the participant. All participants in both arms will be scheduled for weekly counseling, which may begin on the day of enrollment/randomization or within approximately one week of enrollment.

5.3 Intervention Visits

Detailed BUP/NX dosing and counseling treatment procedures will be specified in the SSP Manual, the counseling manual, and the BUP/NX administration manual. Refer to Section 4.0 for detailed descriptions of each treatment arm.

5.3.1 BUP/NX Dispensing Visits

Participants will come to the study site for BUP/NX administration routinely for the appropriate number of weeks, depending on randomization assignment, as described in Section 4.3.3. Study staff will determine with the participant the optimal routine schedule and will carefully explain the procedures for drug administration. Efforts will be made to make these visits as quick and convenient as possible to minimize participant burden and maximize adherence. Dispensing visits can be combined with counseling and follow-up visits.

5.3.2 Drug and Risk-Reduction Counseling Visits

At the enrollment visit, participants will be scheduled for the 12 weekly counseling sessions as described in Section 4.1. Approximately every four weeks, participants will be asked to provide urine for drug testing during the counseling visits for the first year of enrollment. Women will have pregnancy testing approximately every four weeks during counseling visits for those in the substitution arm, and only at the fourth week and again approximately four weeks after the second detoxification if conducted for women in the detoxification arm.

5.3.3 Monthly Counseling Sessions

Monthly counseling sessions will be scheduled approximately every four weeks beginning at week 16 through week 52. Refer to Section 4.2.2 for a description of sessions. At each of these sessions, participants will be asked to update their locator information and provide urine for drug and pregnancy testing (for women in the substitution treatment arm only). Monthly counseling sessions can be combined with dispensing and follow-up visits.

5.4 Assessments during Safety Phase

As described in Section 2.3.2 and shown in Appendix I-B, the first 50 participants enrolled at each site will undergo the following examinations and laboratory tests each week during the first four weeks of study participation in addition to the other activities listed in Section 5.5:

- Interim medical history
- Symptom-directed physical exam
- Hematology (CBC and platelet count)

- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Urine tests for drug use
- Assessment of social harms
- Acceptability assessment at week 4

5.5 Assessments During Full Study

In addition to intervention and laboratory visits, participants will be asked to come to the clinic every six months for clinical assessments including HIV testing and urine testing for opiates and other drugs. The week 24 counseling visit and the Week 26 follow-up visit may be combined into one visit to reduce participant visit burden. There should be no duplication of any laboratory test or the collection of any study information if the visits are combined. Visits will also include a behavioral assessment of HIV-related drug and sexual risk. More detailed assessments will be performed for all participants during the treatment phase of the study. The procedures for each visit are described below. Follow-up visits can be combined with monthly counseling sessions and BUP/NX dispensing visits.

ALT and bilirubin testing also will be performed at weeks 12 and 40 for all participants (in addition to tests completed at regularly scheduled follow-up visits); this blood draw will occur at the same visit as the urine test and counseling visit. Whenever clinically indicated, hepatitis B or C testing may be done by the study clinician.

Locator information will also be assessed at four-week intervals. To the extent possible, site staff will work with the participant to determine the best day of the week and time for this visit to be conducted each week (e.g., every Monday at 9 am). The counseling schedule will coincide with a BUP/NX dispensing visit, if possible, to minimize participant burden. Counseling visits may also be combined with follow-up visits.

5.5.1 26 and 52 Week Visits

These visits will include:

- Locator information update
- Symptom-directed physical exam, interim medical history
- Hematology (CBC, platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Hepatitis testing (Week 26)
- Administer HBV vaccine if appropriate
- Urine testing for opiates and other drugs
- Pregnancy urine test for women in substitution arm and women in the detoxification arm who are undergoing a second induction
- Risk assessment (sex and drug use)
- Rapid HIV testing with pre- and post-test counseling
- Social harms assessment
- Intervention acceptability assessment

Note: The week 24 counseling visit and the Week 26 follow-up visit may be combined into one visit to reduce participant visit burden. There should be no duplication of any laboratory test or the collection of any study information if the visits are combined.

5.5.1.1 Second Detoxification at 26 weeks for those in the detoxification arm:

If the participant indicates s/he is still injecting heroin and is interested in a second detoxification, the eligibility questionnaire (including the DSM-IV diagnosis) will be administered *in addition to* those assessments listed in Section 5.5.1.

5.5.2 78, 104, 130, and 156 Week Visits

These visits will include:

- Locator information update
- Risk assessment (sex and drug use)
- Urine testing for opiates and other drugs
- Rapid HIV testing with pre- and post-test counseling
- Social harms assessment

5.6 Interim Visits

All participant visits to the study clinic or other contacts will be recorded in the study records. Any adverse events reported at clinic visits, procedures or tests performed will be appropriately documented on applicable case report forms and in the source documentation, according to the procedures detailed in the SSP manual. Female participants will be encouraged to come to the clinic for testing if they think they may be pregnant at any point during the study.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

The drug being used in this study (BUP/NX) is approved by the US FDA for treatment of opiate dependence, the indication for which it is being used in the study, and has an established safety profile based on experience in the US, Europe, and Australia. There is no *a priori* expectation that the safety profile will differ in the HPTN 058 study population; nonetheless, close safety monitoring is planned. In addition to clinical and laboratory safety, social harms will also be monitored closely.

A multi-tiered safety review process will be followed. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the protocol team if unexpected concerns arise. Participant safety will also be monitored through a series of routine safety data reviews by the PSRT. The PSRT will convene routinely to review clinical and laboratory data and reports of social harms generated by the SDMC. The content, format and frequency of the safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will participate in the decision-making regarding discontinuation and resumption of study drug.

In addition, the study will be overseen by and periodically reviewed by the NIAID DSMB. The HPTN SMC will also periodically review the study with particular emphasis on performance indicators such as accrual, retention and adherence to/acceptability of the study interventions.

6.2 Adverse Event Reporting Requirements

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6). Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above may also be considered to be serious (October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a SAE.

The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated 6 May 2004. AEs that meet the criteria for expedited reporting to DAIDS must be reported on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and sent within 3 business days of site awareness to the DAIDS Safety Office. Both the DAIDS EAE Manual and the EAE Reporting Form are available on the RCC website: <http://rcc.tech-res-intl.com> and will be included in the Study Specific Procedures Manual. Contact and submission information for the DAIDS Safety Office is included in the EAE Manual, on the front page of the EAE Reporting Form (which is designed to serve as the cover page for submissions) and in the SSP Manual.

Specifically, the ‘standard’ level of reporting defined in the DAIDS EAE manual will be followed for the first 52 weeks of follow-up for participants in both study arms (from study enrollment until the participant completes 52 weeks of follow-up or is terminated from study participation for any reason). Conditions and illnesses identified in participants prior to randomization will be considered pre-existing conditions and will not be reported as adverse events, unless the condition worsens after randomization (increases in severity or frequency), in which case it would be reported as an AE.

The study drug in HPTN 058 is the BUP/NX combination (Suboxone), provided for 52 weeks to participants randomized to the substitution arm and, for participants randomized to the detoxification arm, up to 18 days beginning at randomization and/or within 30 days of the six month visit; therefore it is the relationship of all AEs to this product that is to be considered in determining the reporting requirements for each AE (e.g., whether the AE must be reported in an expedited manner to DAIDS).

All adverse events occurring in participants through week 52 will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004, which will be included in the SSP Manual and is available at the following website: <http://rcc.tech-res-intl.com>. All serious adverse events (SAEs), regardless of severity or relatedness, and all AEs that otherwise meet the criteria for expedited reporting to DAIDS (EAEs) occurring to participants in either study arm through week 52 will be reported on a standard AE DataFax case report form for entry into the study database. AEs that are not serious or do not otherwise meet the criteria for expedited reporting to DAIDS will be recorded in the study source documentation but will not be included in the study database. As noted above, for the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.

There will be no active reporting of adverse events after the period specified above (52 weeks of follow-up); however, unexpected, serious adverse drug reactions must be reported if the study site staff become aware of the events on a passive basis, i.e., from publicly available information.

Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities. The investigators will report information on AEs and SAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.

6.3 Social Harms Monitoring and Reporting Requirements

Adverse social events, “social harms” will be monitored closely throughout the study. At each follow-up visit, a series of structured questions will be used to probe for interpersonal, legal, housing and healthcare problems that have occurred as a result of study participation. All subjects will also be reminded of the importance of reporting problems to study staff between regularly scheduled visits and instructed on how to contact study staff should problems occur during intervals between visits. Additionally, social harms reported by anyone other than study participants, e.g., family or staff members, will also be monitored and documented in site source records. When these events are serious, including incarceration, physical abuse, suicidal behavior, or homicidal behavior, they will be reported on case report forms. Whenever problems are identified, additional data regarding the severity and resolution will be described and recorded on a case report form and will include a description of actions taken by the participant, the site staff, and others to resolve or respond to the problem. The nature and frequency of these social impact reports will be monitored by the PSRT as they occur. In addition, the DAIDS DSMB will routinely review these data.

Given the status of illegal drug use, the associated social stigma and perceptions of drug users held by many members of the communities in which the study will be conducted, social harms could occur purely as a result of participation in a study targeting drug users. These could include discriminatory treatment and violence associated with possible disclosure of participants’ drug or sex-related behaviors or of their HIV serostatus.

Prior to site activation, a review of local and national policies and practice affecting injection drug users will be conducted. The purpose of this review will be to verify that law, policies and enforcement strategies do not place participants in the research at significantly elevated risk of arrest, incarceration, physical harm, unwanted disclosure of drug use, or loss of access to health care relative to injection drug users not participating in the research.

The assessment will consist of two components. The first component will review and analyze the law relevant to injection drug use by examining laws concerning drug control, drug use, access to health care and privacy of medical information in each study country. This review will identify and collate constitutions and any treaties that have the force of law, statutes passed by the national, regional or local legislature, administrative regulations with the force of law and relevant court decisions interpreting these laws or regulations. This review will be conducted with the close involvement of independent legal experts in each study country.

The second component will assess how these laws are put into practice and what possible influence they have on the risks and benefits of IDU participation in the study. Qualitative data regarding the effects of law on IDUs will be gathered, along with data on stigma, social risk, and social attitudes as they apply to IDUs. These data will be collected via interviews with key informants in the legal and public health fields as well as current and former injection drug users. Data will be collected via standardized interview forms by independent researchers at each site.

The review will provide a narrative summary and analysis of the law and its likely effects on study participants. As these laws, policies and practice strategies can be expected to change over time, this review will be updated on an annual basis for the duration of HPTN 058.

To the extent possible, activities involving participants will be conducted in venues that mask the criteria for study participation. It is impossible and unwise to think that the primary purpose of the study can be kept secret (i.e., a prevention study for IDUs) from the community, including the police. An appropriate working relationship with the local law enforcement agency at each site, which recognizes the urgent need to prevent HIV in this population, has been established. Such relationships have assisted outreach staff whose presence in the community is understood and respected. Site staff do not disclose the names of participants to anyone other than members of the field research staff and have strict policies regarding the situations in which discussions of participants can take place, such as staff meetings on topics of recruitment and follow-up. All interview and laboratory data are securely stored in a confidential manner.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

The primary objective is to determine whether 52 weeks of substitution BUP/NX and counseling treatment in opiate addicted participants will achieve a long term (104 weeks) reduction in cumulative HIV incidence and death compared to short-term detoxification and counseling.

The study will be a phase III, multi-site, two-arm, randomized trial. In an initial safety phase, the first 50 study participants at each site will undergo randomization and in their first month receive more intensive monitoring, before reverting to the standard study monitoring schedule. These first 50 participants will therefore contribute to the full study analysis. A total of 1500 HIV-uninfected opiate dependent injectors who agree to participate in this Phase III study will be randomized to one of two study arms as outlined below in a ratio of 1:1.

Study Arm	Intervention
Substitution Arm n=750	<ul style="list-style-type: none"> • Sublingual BUP/NX daily up to three weeks (until dose stabilization) and then three times per week for 52 weeks; <u>plus</u> • Weekly individual drug- and risk-reduction counseling for 12 weeks, followed thereafter by monthly counseling sessions every 4 weeks through week 52.
Detoxification Arm n=750	<ul style="list-style-type: none"> • Short-term detoxification with sublingual BUP/NX for 18 days maximum with a second detoxification possible at six months; <u>plus</u> • Weekly individual drug- and risk-reduction counseling for 12 weeks, followed thereafter by monthly counseling sessions every 4 weeks through week 52.

Behavioral and serologic assessments will take place at baseline and at six-month intervals throughout the study period.

7.2 Endpoints

Ascertainment of HIV endpoints will follow a standard testing algorithm (Appendix II-B). Other endpoints are gathered via urine tests, structured interviews and questionnaires, and from external sources such as death certificates or other documentation of death, including certified letters from family members.

7.2.1 Primary Endpoint

- HIV-1 infection or death by the 104 week visit

7.2.2 Secondary Endpoints

Consistent with the secondary study objectives, the following endpoint(s) will be assessed:

1. HIV-1 infection every six months at scheduled study follow-up visits
2. Mortality
3. Continued opiate use as measured by self-report and urinalysis
4. Self reported frequency of injection
5. Self reported frequency of injection with previously used injection equipment (needles, syringes, cookers, cottons, and rinse water).
6. Self-reported frequency of unprotected sex or sex sold/traded for drugs

7.3 Evaluation of Safety Phase

In a cohort of size 50, the following table presents the probabilities that 1 or more, 3 or more, 5 or more, or 10 or more subjects will experience adverse events at different underlying (true) event rates. For example, if the underlying rate of an adverse event is 10%, then there is a 57% chance that an event rate of 10% or higher will be observed (5 or more events). Likewise, if the true adverse event rate is 30% and 20% is the maximum acceptable adverse event rate for the intervention, there is a 4% ($1 - 0.96$) chance that there would be an inadequate number of events to conclude that the intervention has an unacceptable level of harm.

True Event rate	P(1 or more events, n=50)	P(3 or more events, n=50)	P(5 or more events, n=50)	P(10 or more events, n=50)
1%	0.39	0.01	0.00	0.00
2%	0.64	0.08	0.00	0.00
5%	0.92	0.46	0.10	0.00
10%	0.99	0.89	0.57	0.03
20%	1.00	1.00	0.98	0.56
30%	1.00	1.00	1.00	0.96

7.4 Sample Size, Effect Size, and Accrual

The combined targeted event rate (HIV infections and Death) in the detoxification arm at 104 weeks is 12.5% HIV infected or dead, assuming 8.5% due to HIV infection and 4% from death. The hypothesized treatment effect is a 50% reduction in the proportion of HIV-1 infections and a 25% reduction in the proportion of deaths observed in the substitution arm relative to the detoxification arm at 104 weeks. The combined targeted event rate in the substitution arm at 104 weeks is therefore 7.25% HIV infected or dead.

In the proposed sites, projected annual seroincidence rates among injectors per 100 person years are 3.0 in Chiang Mai, 3.1 in Guangxi, and 8.8 in Xinjiang. Using enrollment ratios that favor the highest incidence site we project a baseline seroincidence rate of 5.4 per 100 person years.

Risk reduction counseling is expected to be 20% effective in reducing HIV infections but have no effect on deaths. The rate of infection at 2 years in the detoxification arm is thus calculated as $1 - (1 - 0.054 \times 0.8)^2 = 0.085$. This 20% overall reduction also accommodates the possible entry into methadone treatment in a small proportion of participants in the detoxification arm. The study team and oversight committees (SMC, DSMB) will closely monitor the number of participants in each arm of the study who enroll in methadone maintenance programs. Depending on the extent of methadone uptake in the study population, the sample size and power calculations could be adjusted, if necessary.

In Thailand, a mortality rate of 2.33 per 100 person years was observed in the OUR study. Among IDUs in Northern Thailand followed in HPTN037, the mortality rate was 4.0 (2.3-6.4) per 100 person-years. In HPTN 033, death rates of 1.68 and 0.44 were observed among IDUs in Xinjiang and Guangxi, respectively. Death rates are targeted at 4% at two years, based on a rate close to 2.0 per 100 person years.

Mortality has been reported to decrease as a result of effective treatment for opioid use among IDUs.^{137, 138} Analysis of the efficacy endpoint of HIV-free survival is free of the bias induced by the informative censoring that would result if HIV incidence were the primary endpoint and deaths were censored. Thus HIV free survival is chosen as the primary efficacy analysis for this intervention. Nonetheless, prevention of HIV infection remains a primary focus of the evaluation, and analysis of HIV infection rates will be an important secondary analysis.

7.4.1 Sample Size

To achieve 90% power for reduction in the probability of HIV infection or death at 104 weeks from 12.5% to 7.25% requires a total of 1345 participants, based on a normal approximation for testing the difference in binomial proportions, assuming variance under the alternative, and one-sided alpha of 0.025. Allowing for loss to follow-up at 104 weeks of 10%, a projected total enrollment of 1500 (750 participants per arm) is required.

A total enrollment of 1500 will yield an approximate sample of 1290 for the HIV-free survival endpoint, assuming an additional 4% loss to follow-up attributable to censoring due to death. The power for the HIV infection endpoint is given below for a range of potential rates for HIV infection, assuming 50% efficacy for the HIV infection endpoint.

Power for the HIV infection Endpoint.		
Substitution Arm	Detoxification arm	Power
3.5%	7.0%	92.8
4.25%	8.5%	88.0
5.0%	10.0%	80.7

7.4.2 Effect Size

Effectiveness estimates for this trial were derived in part from two published placebo controlled randomized trials, one examining the effectiveness of buprenorphine and the other the effectiveness of methadone for treatment of opiate dependence.

A randomized, placebo controlled trial of one year of buprenorphine was conducted amongst 40 volunteers in Sweden, in 2000-1.¹³⁹ In the buprenorphine treatment arm, only one out of 20 people had no negative test results when testing for continued opiate use (i.e., never stopped using opiates). Of the remaining 19, about 80% of their samples were negative for opiates. In the control arm, 13 out of 20 had no negative samples, and of the remaining seven, about 50% of their samples were negative for opiates.¹⁴⁰ Assuming reduction in injection translates directly to reduction in HIV infection, we estimate HIV infection rates after 1 year in the HPTN 058 study as:

$$rate_{drug} = \frac{1}{20} \times rate_0 + \frac{19}{20} \times rate_0 \times 0.20$$

$$rate_{ctl} = \frac{13}{20} \times rate_0 + \frac{7}{20} \times rate_0 \times 0.50$$

In addition, we require for the substitution intervention to be considered effective that after a year off BUP/NX, it remains at least half as effective as when on BUP/NX. The detoxification arm is assumed to remain equally effective to provide the most conservative basis for comparison.

In the table below, one and two year cumulative HIV infection rates are presented based on these effectiveness assumptions derived from the Swedish study for baseline infection rates of 5 to 8 per 100 person years.

Annual infection rate	Proportion HIV Infected at 1 year		Proportion HIV Infected at 2 years		% reduction in infection compared to baseline at 2 years	
	Substitution	Detox	Substitution	Detox	Substitution	Detox
8	1.9	6.6	6.1	12.8	60.3	16.9
7	1.7	5.8	5.3	11.2	60.4	17.0
6	1.4	5.0	4.6	9.7	60.6	17.1
5	1.2	4.1	3.8	8.1	60.7	17.1

A randomized controlled trial of long-term methadone treatment was conducted among 100 volunteers in Hong Kong in 1972-5.¹⁴¹ In the methadone study, after 3 years 5/50 subjects (10%) on methadone had 6 consecutive positive urine tests for morphine (the

condition for termination from study), while 31/50 subjects (61%) on placebo had 6 consecutive positive urine tests for morphine. After 32 weeks, 5 of the controls were still on placebo, whereas 38/50 (76%) remained on methadone treatment. At three years, 1/50 of control were still on placebo, and 28/56 (56%) on treatment, i.e., 49/50 no longer on placebo; 22/50 no longer on methadone. Among those on methadone, about 35% had at least one positive urine each month, and in those who were positive on a given month, about 10-20% of their daily urines were positive.

Using the results from this study, we derive the following estimates of potential effectiveness. For those on substitution treatment, 25% will fail to stay on treatment throughout the year, however their injection risk is still reduced by 50% during the year. The remaining 75% remain on treatment, with an average reduction in risk of 93%. For those receiving detoxification, we assume 10% reduce their risk by 100%, but among the remaining 90%, their injection risk is reduced by 10%. As above, we further assume that reduction in injection risk translates to reduction in HIV infection risk, and that the effectiveness of the first year continues in the detoxification arm, but is reduced by half in the substitution arm after weaning from BUP/NX.

The table below estimates 52 and 104 week cumulative HIV infection rates based on the effectiveness assumptions above derived from the methadone study for baseline infection rates of 5 to 8 per 100 person years.

Annual infection rate	Proportion HIV Infected at 52 weeks		Proportion HIV Infected at 104 weeks		% reduction in infection compared to baseline at 104 weeks	
	Substitution	Detox	Substitution	Detox	Substitution	Detox
8	1.4	6.5	5.3	12.5	65.4	18.4
7	1.2	5.7	4.7	11.0	65.5	18.4
6	1.1	4.9	4.0	9.5	65.7	18.5
5	0.9	4.1	3.3	7.9	65.8	18.6

The data from these protocols support the effect size estimates of 50% reduction in HIV infection at 2 years used in HPTN 058.

7.4.3 Accrual

Each site is expected to enroll 50 participants in approximately the first six months during the safety phase of the study. The remaining participants will be enrolled over approximately 24 months. The actual number accrued at each site will be higher at sites anticipated to have higher HIV seroincidence rates, with each site expected to accrue between 200 and 600 participants to achieve the total sample size of 1500. Site accrual targets will be closely monitored and adjusted as needed in response to site performance, while balancing the need to achieve targeted event rates.

Approximately every three months during the accrual period and at the recommendation of protocol team members, the HPTN SMC or the DSMB, the protocol team will review performance data from each study site — including accrual rates, retention rates, protocol adherence measures, data quality measures, and HIV incidence rates — to determine whether enrollment slots should be shifted across sites to achieve the study objectives most efficiently.

7.5 Random Assignment

Participants will be randomized in a 1:1 ratio, with 750 participants in each arm. In an unblinded trial, special care needs to be taken to assure that the study staff cannot control or guess assignment to arm. Techniques such as large block size, and/or dynamic allocation between sites may be used. The HPTN Statistical and Data Management Center will coordinate these procedures, which will be specified in the SSP manual.

7.6 Interim Analysis

In this study, the drug BUP/NX in the substitution arm is discontinued at 52 weeks, but the primary efficacy endpoint is defined as 104 weeks to allow the evaluation of the long-term effect of the intervention. This change in treatment during the follow-up requires careful consideration in the interim monitoring strategy. First, given discontinuation of the drug at 52 weeks, it is possible that the hazards of infection will not be proportional between the arms throughout the evaluation. Second, it is plausible that risk of HIV infection will increase in the substitution arm after cessation of BUP/NX at 52 weeks, even perhaps that risk of infection will temporarily exceed that in the control arm. Finally, it is likely that the study will achieve maximal difference in cumulative infection between the arms at 52 weeks of study participation. The potential for departure from proportional hazards, and even for crossing hazards, are carefully considered in the monitoring of this trial.

Briefly, we propose to use a stopping boundary for insufficient benefit that take into consideration the accumulated evidence from events in both arms at both 52 weeks and 104 weeks. The stopping boundary for benefit will only consider the 104 week outcomes. Interim analyses will occur four times during the trial, when $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$ and all of the primary events have been collected (i.e. when $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, all of the participants have attained their 104 week primary outcome). At each interim visit, we will use the O'Brien-Fleming boundaries on the difference in accumulated survival probability endpoint by the 104 week visit to assess stopping early for proven benefit. The protocol may be stopped early for insufficient benefit if interim analyses indicate that the data are not consistent with the hypothesized long-term benefit at 104 weeks. Since the benefit of BUP/NX must occur primarily in the first 52 weeks, data that are not consistent with substantial benefit at 52 weeks would support discontinuing the study.

Detailed monitoring plans, specifying the boundary conditions for discontinuation will be developed in a separate interim monitoring plan. As in any interim monitoring, a decision to stop the trial will take into consideration the totality of the data including evidence of mortality and social harms, in addition to HIV incidence and death.

7.7 Data Analysis

7.7.1 Primary Analysis

An intent-to-treat analysis will be conducted using the entire sample from all sites. The incidence of HIV-1 and mortality rates will be determined among participants in each study arm. Endpoints will be compared between treatment arms using Kaplan Meier estimates of the proportion uninfected and living by the 104-week visit, with variances estimated by Greenwood's formula.

Since significant loss-to-follow-up results in a risk of bias in the efficacy analysis, our intention is to make considerable efforts to achieve rates of loss-to-follow up that are no more than 10% at two years. In addition, to more fully assess the potential impact of individuals lost-to-follow-up, we plan to conduct a sensitivity analysis where, for each individual in the drug and counseling group who is lost, we will use an imputation of subsequent risk of infection that is based in the estimated subsequent risk of infection in the control arm. This will allow us to gain insight into the potentially optimistic estimation of the efficacy based on imputing risk of infection of those lost to follow-up in the treatment arm with the estimated subsequent risk of those remaining on treatment in the treatment arm.

7.7.2 Secondary Analyses

1. To determine if the substitution treatment reduces average HIV incidence and death compared to the detoxification arm; and reduces HIV incidence and death at 52 weeks and 156 weeks.
2. To determine if the substitution treatment decreases average HIV incidence compared to the detoxification treatment; and decreases HIV incidence at 52, 104, and 156 weeks.
3. To compare the average rates of deaths between the two arms; and the rates of death at 52, 104, and 156 weeks.

For each of the above three endpoints, “average” rates will be compared between treatment arms using a log-rank test, which utilizes all the event information accumulated in the trial. Rates will then also be compared for the specified time points using Kaplan Meier estimates of the proportion uninfected after the 52, 104 and 156 week visits, and with variances estimated by Greenwood’s formula.

4. To compare the self-reported frequency of injection, drug and sex-related HIV risk behaviors in the two study arms.

Self reported behaviors will be analyzed using generalized estimating equations techniques for repeated measures of behavior to assess difference in frequency of use between the two study arms.

5. To compare the frequency of drug use measured by self-report and by urinalysis in the two study arms.

Urinalysis results will be compared between arms using simple cross sectional summaries at each time point, in addition to generalized estimating equation approaches for repeated measures. In addition, comparison between urinalysis and self-reported injection frequency will be used to assess validity of self reported data.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Serious adverse events and social harms will be reported to the IRBs/ECs according to their individual requirements. In addition, all DSMB review summaries will be provided to the IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

Written informed consent for study screening and for study enrollment will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendix III that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the consents into local languages and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness (further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS Standard Operating Procedure for Source Documentation). Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

An assessment of comprehension will be done with each participant prior to signing the enrollment consent. A standardized comprehension quiz will be used at each site. Interim analyses of aggregate data will be used to monitor the effectiveness and efficiency of the informed consent process. Steps to improve the process will be implemented if the interim analyses reveal topical areas that are frequently misunderstood by participants.

Participants will be offered a copy of their informed consent forms to keep.

The specimen storage consent (see Appendix III-E) is for storage and testing of samples that are not required by the study protocol. Participants do not have to provide consent for specimen storage to be enrolled. Storage of specimens not required by the study protocol is optional for study sites. Consent for storage and possible future testing may be obtained at any point during

the participant's enrollment in the study. Future use of blood samples approved for post-study testing/use of stored specimens must be approved by the relevant IRBs/ECs.

8.3 Risks

The risks associated with use of BUP/NX for treatment of opiate dependency are described in the package insert/patient information sheet. Commonly reported adverse events have included headache, pain, problems sleeping, nausea, sweating, stomach pain, and constipation, although the frequency of these and other events have sometimes been less, or apparently not clinically different from that observed with placebo. Like other opioids, BUP/NX has been associated with respiratory depression, especially when combined with other respiratory and/or CNS depressants. BUP/NX is controlled under Schedule III of the US Controlled Substances Act. Chronic administration of BUP/NX produces dependence of the opioid type.

By participating in the study, participants run the risk of social harm as described in Section 6.3. This could include discriminatory treatment and violence associated with possible disclosure of participants' drug or sex-related behaviors or of their HIV serostatus. Participants also may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become anxious while waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Prisoners will not be recruited or enrolled in HPTN 058. Nor will any study related visits be conducted in prisons or jails with study participants.

8.4 Benefits

Participants in this study will be offered free HIV testing and counseling for HIV risk reduction. They will have physical examinations and will be provided with the results of any tests or other findings related to their health. They will be referred for care as appropriate. All participants will receive individual counseling for a year. Participants enrolled in the study will receive a drug shown to be safe and effective in the treatment of opiate dependence in the US and Europe; however, this drug has not been tested among the study populations planned for this study. No differences in safety and efficacy are expected in the study population, but there is no guarantee.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective intervention that helps prevent HIV infection by reducing high risk behaviors where treatment options are very limited.

Appendix V provides a table summarizing efficacy rates for key outcomes described in the available literature and the risks and benefits to participants and communities.

8.5 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study. Site-specific reimbursement amounts will be specified in the study informed consent forms or otherwise approved by the IRB/EC.

8.6 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored securely in areas with access limited to study staff. To maintain participant confidentiality, a coded number will identify all study specific laboratory specimens, reports, study data collection, process, and administrative forms. Study-specific laboratory specimens, case report forms or documents that are transferred or transmitted off-site for processing will be identified only by a coded number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate area with limited access. The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; the manufacturer of the study drug; representatives of the HPTN CORE, SDMC, and/or Network Laboratory (NL); the US FDA, other government and regulatory authorities, and/or local IRBs/ECs.

8.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

8.8 Study Discontinuation

The study may be discontinued at any time by the sponsor (NIAID), the HPTN, the study drug manufacturer, NIDA, Office of Human Research Protection (OHRP), and/or the US FDA, local government or regulatory authorities, and/or site IRBs/ECs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (LL): serum or plasma for HIV testing, HBV and HCV; EDTA whole blood for hematology, serum for creatinine and liver function tests; urine for drug and pregnancy testing. A maximum of 14 mL of blood will be collected from each participant at screening, and at the 26 and 52 week visits. Refer to Section 5.5 and Appendix I-A for specimen collection schedule).

At selected sites, exploratory testing will be conducted on specimens from individuals who are confirmed to be HIV-infected at screening. Samples may be tested on-site. Samples that test positive for incident infection will be shipped to the HPTN NL for additional testing with other assays. A portion of non-incident samples will also be sent to the HPTN NL as controls. The

STD/Microbiology Core of the HPTN NL will retest those samples using the same assay and related assays for confirmation of incident HIV-1 infection.

Each study site will adhere to standards of good laboratory practice, the HPTN Network Laboratory Manual, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

HPTN guidelines require that the Network Lab certify each local laboratory for all protocol-specified testing, and that the HIV testing algorithms be validated. FDA approved rapid HIV test kits should be used if available in country. If FDA approved kits are not available or easily imported, the site must provide information regarding available kits prior to study activation and in the event that the kit changes during the study. Only non-FDA approved rapid test kits that have been validated by the local laboratory and approved by the Network Laboratory can be used. FDA approved Western blot kits must be used to confirm HIV status.

9.2 Network Laboratory Specimens

None of the routine laboratory tests for this study will be conducted at the HPTN Network Laboratory (NL). However, a sample of specimens will be retested by the Network Laboratory at the site or at the HPTN Network Laboratory for quality assurance purposes. Testing for recent infection on specimens from individuals who are confirmed to be HIV-infected at screening will also be conducted at the HPTN NL as described in section 9.1 or at the study site if necessary.

HPTN guidelines require that the HPTN Network Lab certify each local laboratory for all protocol-specified testing, and that the rapid tests algorithms be validated. The NL will work with each site to assure that this is completed prior to study initiation.

Each study site will adhere to standards of good laboratory practice and the HPTN Network Laboratory Manual for proper collection, processing, labeling, and transport of specimens. If specimens are shipped, this will be done in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the study-specific procedures manual.

9.3 Quality Control and Quality Assurance Procedures

The HPTN NL has established a proficiency-testing program at each study site. NL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. NL staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

Approximately every six months, baseline plasma/serum samples from 50 or ten percent (whichever is greater) of randomly selected enrolled adult subjects at each site will be retested for HIV antibody by the HPTN NL using FDA licensed tests either at the site or at the HPTN NL. Samples from all subjects will be retested if there are less than 50 total trial subjects. In the event of a false positive or false negative result that changes the infection status of the subject, an additional 100 or 20% of samples (whichever is greater) from enrolled subjects will be retested.

All HIV incidence cases (their baseline and seroconversion samples) will be retested and an equal number of randomly selected samples from uninfected subjects will be tested.

The SDMC and NL will inform site staff of the samples selected for QA testing. The NL will test the specimens for HIV antibody and compare the results of their tests with the results obtained by the local labs. NL staff will follow-up directly with site staff to resolve any QA problems identified through this process.

9.4 Specimen Storage and Possible Future Research Testing

Study site staff will store plasma samples from selected visits; this will be indicated in the Study Specific Procedures Manual. These specimens should not be destroyed until notification from the HPTN SDMC and NL that all outstanding results have been received and all quality assurance testing has been completed. Consent will be sought to store leftover blood specimens post-study for future HIV-related testing. (Appendix III-E—Sample Consent for Storage and Future Use of Blood Samples) Participants who choose to participate in the study do not have to provide consent for possible future testing to be enrolled. Storage of specimens not required by the study protocol is optional for study sites. Consent for storage and possible future testing may be obtained at any point during the participant's enrollment in the study. Future use of blood samples approved for post-study testing/use of stored specimens must be approved by the relevant IRBs/ECs.

9.5 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 United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

10.0 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the study-specific procedures manual — to the HPTN CORE. CORE staff will work with study site staff to complete DAIDS protocol registration in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual. Included in this step will be CORE and DAIDS review of each site-specific study informed consent form.

Pending successful protocol registration and submission of all required documents, HPTN CORE staff will issue an 'activation notice' to the site, after which they may begin study operations.

10.2 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study. Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to Reckitt Benckiser Pharmaceuticals, Inc. for cross-referencing with the company's other INDs and NDAs for the study product. Assignment of all responsibilities for this study will be specified in a Clinical Trials Agreement executed between DAIDS as the study sponsor and Reckitt Benckiser Pharmaceuticals, Inc.

This protocol as well as the SSP Manual will direct study implementation. The SSP Manual — which will contain reference copies of the DAIDS SOPs for Source Documentation and Essential Documents, as well as the Manual for Expedited Reporting of Adverse Events to DAIDS and the standard DAIDS Toxicity Tables — will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. The SSP Manual will be submitted to the sponsor prior to implementation of the study, will be posted on the following website: <http://www.HPTN.org>, and will be made available in hard copy to the IRBs/ECs, the US FDA and other regulatory authorities upon request.

The study team and HPTN SDMC will develop study case report forms. Data will be transferred to the HPTN SDMC, entered, and cleaned using the SDMC DataFax data management system. Quality control reports and queries will be generated and routinely distributed to the study sites for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The protocol team, as well as the HPTN Study Monitoring Committee, will monitor rates of accrual, adherence, follow-up, and AE incidence closely. The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, and CORE Protocol Specialist will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. As described previously, a Protocol Safety Review Team will closely oversee safety aspects of the study on an ongoing basis. In addition, the NIAID Data and Safety Monitoring Board will monitor the study.

10.3 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NL, NIAID, Reckitt Benckiser Pharmaceuticals, Inc., and US and in-country government and regulatory authorities including the US FDA. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol and consent form(s) will not be amended without prior written approval by the sponsor and the IRBs/ECs. All proposed protocol amendments must be submitted to and approved by the relevant DAIDS regulatory authorities prior to submission to local IRBs.

10.5 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with federal regulations, for the study drug being tested, the Investigator will retain all study records for at least two years following the date of approval of any labeling change for this licensed product. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.6 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. The Investigator will submit any presentation, abstract, or manuscript to the HPTN Manuscript Review Committee, DAIDS, and Reckitt Benckiser Pharmaceuticals, Inc. for review prior to submission.

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APPENDICES

- I Schedule of Evaluations
- II HIV Testing Algorithms
- III Sample Informed Consent Form(s)
- IV Referral Information for Site
- V Equipoise in HPTN 058: Comparisons between the Two Study Arms
- VI Adverse Event Reporting and Documentation Requirements

APPENDIX I-A: Schedule of Procedures and Evaluations – Full Study

Procedures/Evaluations	Screening	Enroll/ Randomization	Intervention and Follow-up					Follow-up				
			Day 1 of Wk 1	Wks 1-12	Wks 13-15	Wks 16-25	Wk 26 ¹⁰	Wks 27-51	Wk 52	Wk 78	Wk 104	Wk ¹ 130
Screening Informed Consent	X											
Enrollment Informed Consent ²		X										
Demographics	X											
Locator Information	X	X	X ³			X ³	X	X ³	X	X	X	X
Eligibility Interview (incl. DSM-IV Diagnosis)	X					X ⁴						
Behavioral Risk Assessment (drug use & sexual risk)	X					X			X	X	X	X
Social Harms Assessment						X			X	X	X	X
Physical Examination for HIV negative pts.	X											
Symptom-directed Physical Exam						X			X			
Intervention Acceptability Assessment						X			X			
Targeted Medical History for HIV negative pts.	X											
Interim Medical History						X			X			
Randomization		X										
Laboratory Tests												
Rapid HIV testing ⁵	X					X			X	X	X	X
Hepatitis B and C ⁶	X					X						
Platelet count	X					X			X			
CBC	X					X			X			
Bilirubin	X		X ⁷			X	X ⁷		X			
Creatinine	X					X			X			
ALT	X		X ⁷			X	X ⁷		X			
Urine Test for Opiates and Other Drugs	X		X ³			X ³	X	X ³	X	X	X	X
Urine Test for Pregnancy ⁸	X	X	X			X	X	X	X			
Pre- and Post-test HIV Counseling	X					X			X	X	X	X
Weekly Counseling Visits			X									
Monthly Counseling Sessions every four weeks						X ³			X ³			
BUP/NX Dispensing Visit ⁹		X	X	X	X	X	X	X	X			

1 Participants will be followed for a minimum of 24 months and a maximum of 36 months, depending on when they are enrolled

2 Participants will provide consent for study enrollment on or before the visit at which they are randomized

3 Perform approximately every four weeks

4 Repeated if needed for Detoxification Treatment arm participants to determine eligibility for second detoxification

5 If Rapid HIV test is positive, confirmatory testing to be performed according to one of the algorithms in Appendix II; if confirmed, subsequent HIV tests not performed

6 After screening, hepatitis testing may be performed at any point during first year of participation if clinically indicated. Hepatitis B vaccine will be offered to randomized participants if appropriate

7 Bilirubin and ALT tests completed at weeks 12 and 40, in addition to the scheduled follow-up visits at weeks 26 and 52

8 For female participants perform Pregnancy Test, in both arms, at screening, enrollment and week 4 only. Then, approximately every four weeks through week 52 in the substitution treatment arm only. Pregnancy tests should be repeated for female participants in the Detoxification arm eligible for a second detoxification at week 26

9 Completed daily for up to the first three weeks of dosing in both arms, then, three times per week through week 52 in the substitution treatment arm only

10 The week 24 counseling visit and the week 26 follow-up may be combined into one visit to reduce participant visit burden. There should be no duplication of any laboratory tests or the collection of any other study information if the visits are combined.

APPENDIX I-B: Schedule of Procedures and Evaluations – Safety Phase*

Procedures/Evaluations	Screening Visit	Enrollment/ Randomization Visit	Week 1	Week 2	Week 3	Week 4
Screening Informed Consent	X					
Enrollment Informed Consent ¹		X				
Demographics	X					
Locator Information	X	X				X
Eligibility Interview (incl. DSM-IV diagnosis)	X					
Behavioral Risk Assessment (drug use and sexual risk)	X					
Social Harms Assessment			X	X	X	X
Physical Examination for HIV negative pts.	X					
Symptom-directed Physical Exam			X	X	X	X
Intervention Acceptability Assessment						X
Targeted Medical history for HIV negative pts.	X					
Interim Medical History			X	X	X	X
Randomization		X				
Laboratory Tests						
Rapid HIV testing ²	X					
Hepatitis B & C ³	X					
Platelet count	X		X	X	X	X
CBC	X		X	X	X	X
Bilirubin	X		X	X	X	X
Creatinine	X		X	X	X	X
ALT	X		X	X	X	X
Urine Test for Opiates and other drugs	X		X	X	X	X
Urine Test for Pregnancy ⁴	X	X				X
Pre- and Post-test HIV Counseling	X					
Counseling Visits			X	X	X	X
BUP/NX Dispensing Visits ⁵		X	X	X	X	X

¹Participants will provide consent for study enrollment on or before the visit at which they are randomized.

²If positive, confirmatory testing to be performed according to the algorithm in Appendix II-A.

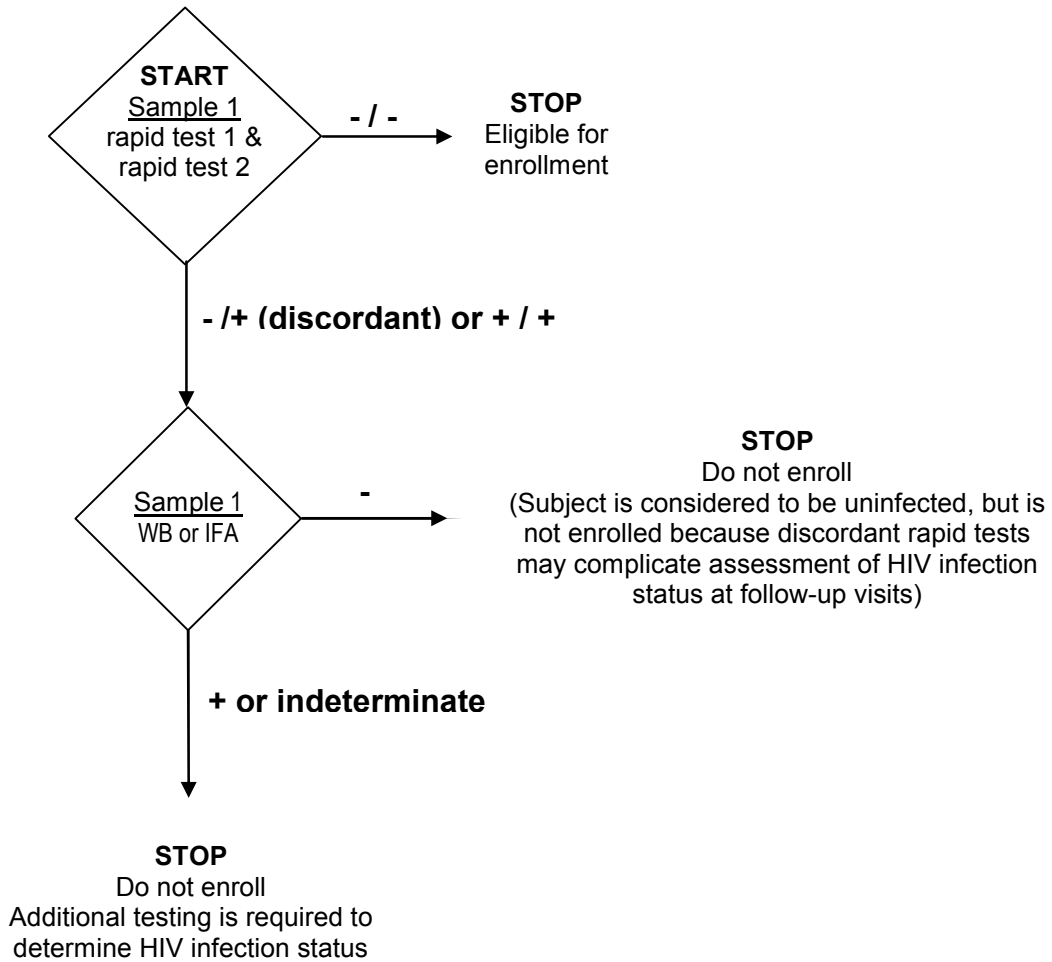
³After screening, hepatitis testing may be performed at any point during first year of participation if clinically indicated. Hep B vaccine will be offered to randomized participants if appropriate.

⁴For female participants only.

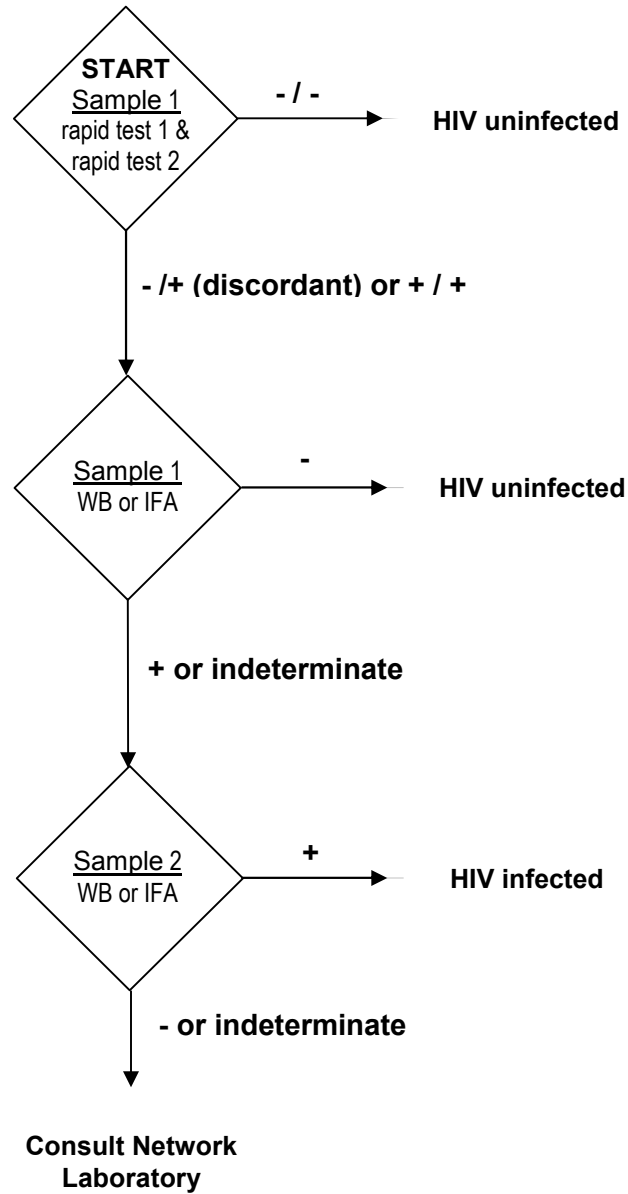
⁵Completed daily for up to the first three weeks of dosing in both arms, and three times per week thereafter in the substitution arm.

NOTE: The first 50 participants enrolled at each site will undergo the same screening and randomization procedures as participants enrolled later in the study; however, more safety data will be collected during the first month of enrollment. These participants will continue on the same schedule of activities after the first month as all other enrollees, as described in Appendix I-A.

APPENDIX II-A: HIV Antibody Testing Algorithm – Screening



APPENDIX II-B: HIV Antibody Testing Algorithm – Follow-up



APPENDIX III-A: Sample Screening Consent for Participants Screened during the Safety Phase

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and deaths among opiate dependent injectors Final Version 2.0, 16 September 2008

Principle Investigators: [Name and Contact Info]

Introduction

You are being asked to take part in a screening process to find out if you are eligible to take part in the research study named above. The research study will test whether a drug treatment program can reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behavior. HIV is the virus that causes AIDS. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is (*Name of Principal Investigator*).

Before you decide if you want to be a part of this screening, we want you to know about the study. This consent form will give you information about the screening process. The study staff will discuss the screening with you. You are free to ask any questions. After the screening has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the screening, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

What are your rights as a research participant?

- Your participation in the screening is entirely voluntary.
- You may decide not to take part in the screening tests or to leave at any time without losing the benefits of your standard medical care or other services. You will be treated the same no matter what you decide.
- If you decide not to participate in the screening, you cannot participate in this research study, but you can still join another research study later, if one is available and you qualify.
- Even if you agree to participate in the screening, it does not mean you have agreed to participate in the research study.
- We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

Why is this research being done?

The purpose of the research is to compare how well two different treatments help reduce the number of deaths and HIV infections among injection drug users by reducing drug use and other risky behavior. One treatment includes a medicine called Suboxone® (a combination of two drugs, buprenorphine and naloxone) and counseling for one year; we call this the “substitution treatment” group. The other treatment uses Suboxone for short term detoxification and counseling for one year. We call this the “detoxification treatment” group. Suboxone is a drug that has been approved for treating drug users in the US. Suboxone does not prevent or treat HIV. The counseling used in this study has also been used in the US to help drug users reduce their drug use and their risk for HIV infection. It is not known if either of these treatments will prevent you from getting HIV.

Half of the people in this study will receive the substitution treatment; half will receive the detoxification treatment. Neither you nor the study staff will be able to choose which treatment you receive. The treatment you are given will be decided by chance, like flipping a coin (*insert local equivalent phrase*).

Both treatment groups are important to help us find ways of preventing HIV. After all the screening activities are done (about one week for most people), the staff will tell you which treatment group you are in.

A total of about 1500 people will participate in the study in [the study countries]. About [approximate site-specific accrual target] people will be in the study here in [study site].

The first part of this study will collect information about the safety of Suboxone and how well people like the two different treatments in this study. Even though these treatments have been used safely in people in the US, we want to see if the same is true for people in China and Thailand. We call this the “Safety Phase.” The first 50 people at each location will be part of the “Safety Phase.” The information we learn during this phase will help us plan the rest of the study.

What will happen if you agree to the study screening?

The screening visit may take 2 to 4 hours and may proceed today if you are willing. We will ask you questions about your health, drug use, and about your sexual activity. We will also ask you to tell us where you live and how we can find you. If you are not willing to give us this information, you should not agree to be in this study. You will be asked to provide a urine sample for a test for opiates and other drugs. If you are a woman, we will also do a pregnancy test on your urine. You will be given the result of the pregnancy test during this visit. You are not eligible if you are pregnant or breastfeeding. These screening questions and tests are the first step in determining if you will be able to join the study. Some people will not be eligible because of information learned during screening.

You will be offered HIV counseling and testing whether or not you are eligible to join the study. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. Some of your blood will be tested for HIV. We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes. When your HIV test results are ready, you will talk with the counselor about the meaning of your result. You must receive your HIV test result to be eligible for the research study.

If your HIV test shows that you may be infected with HIV, you will not be eligible for the study and screening will stop. However, we will do another test to confirm your results that will take about a week. The staff will talk with you about what this means. You will be given information about where you can go for additional testing and counseling. This study will not provide treatment if you are infected with HIV.

If you agree, your blood specimen will be stored and tested later to look for additional evidence of infection with HIV. We will not contact you with the results from the tests done on the stored samples. This is because research tests are often done with experimental procedures, so the results from these tests are not useful for making decisions on managing your health. If during the course of these screening tests, we find out that you have HIV or (*list communicable diseases which require reporting*), we must report this to [*insert the name(s) of the local health authorities and amend this paragraph to reflect the local requirements. If there are no local requirements to report HIV or other communicable diseases, delete this paragraph.*]

If your HIV test shows that you are not infected with HIV, you will then have a physical exam and the doctor will ask about your health history. We will also send some of your blood to a laboratory to test your kidneys, liver, and general health. These tests will take about one week to complete. We will give you the results of the tests when you return for the next visit.

We will also test some of your blood for the liver diseases hepatitis B and C. If you test positive for either of these infections, we will give you information about where you can go for additional testing and treatment. You may still be eligible to join this study if you have hepatitis. If you are not infected with hepatitis B, the staff will talk with you about getting the vaccine to protect you against hepatitis B.

If all screening activities show that you may be able to join the study, more detailed information about the study will be given to you at your next visit. You will be able to decide if you want to join the study or not. After the study has been fully explained to you, and you have asked all of your questions, the study staff will ask you some questions about the study to be sure that you understand. If you agree to participate in the study, you will be asked to sign another consent form that explains all study activities to you. If you agree to join the study, the first treatment visit will begin the same day and will last up to eight hours.

How long will you be in this study if you are eligible?

You will be in this study about 2 to 3 years depending on when you begin. Should you be eligible, you will be asked to sign an additional Informed Consent form which will describe the study visits and procedures in greater detail. You should feel free to ask the study site staff should you have any questions regarding the length of the study and your involvement.

What are the risks/discomforts of this screening?

Taking blood may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this screening. However, it is possible that you could have problems if people learn that you are here for this screening. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If people think that you are infected with HIV, you may have problems finding or keeping a job. Others may treat you unfairly, including your family and community.

Are there risks related to pregnancy?

You must have a pregnancy test before you enter this study. You are not eligible for this study if you are pregnant or breastfeeding. If you are found to be currently pregnant, there are no risks to having had the screening procedures.

Are there potential benefits to screening?

These screening tests may or may not be of direct benefit to you. If you take part in this screening, you will learn information about HIV and your HIV status. You will have a physical exam and other tests of your health.

What other choices do you have besides this study?

You do not have to agree to be screened for this research study. The staff will talk with you about other options for HIV counseling and testing, treatment for drug use, or research studies that may be available in your community (*site to add other treatment or research options for IDUs depending on local situation including access to counseling and HIV testing*). Please talk to the study staff about these and other choices that may be available to you. You do not have to receive any treatment. If you do not agree to the screening, you will not be able to join this study but you may be eligible for other studies in the future.

What about confidentiality?

All efforts will be made to keep your personal information confidential to the extent permitted by law, but we cannot promise complete confidentiality. On your screening records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the local Ministry of Health, the U.S. Food and Drug Administration, the company that makes the study drug, the Institutional Review Board or Ethics Committee, the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your study-related records.

What are the costs or payments to you?

There will be no cost to you for these visits, physical examinations, laboratory tests or other procedures. This study does not provide treatment for any conditions that are discovered during the course of the screening or study.

You will be paid for your time and travel expenses *[Schedule and amount to be specified in site specific consent.]*

What happens if you are injured during the screening?

If you are injured as a result of being in this screening, you will be given immediate treatment for your injuries. You may have to pay for this care. If we find any illness or injury during the screening that is not related to the screening, we will tell you about medical care and other services available in the community. There are no plans to give you money either through this institution or the U.S. National Institutes of Health (NIH) if there is a research-related complication or injury. You will not be giving up any of your legal rights by signing this consent form.

What should you do if you have problems or questions about the screening?

For questions about this study or a research-related injury, contact:

- *[Name, physical address, phone number of the investigator or other study staff]*

For questions about your rights as a research subject, contact:

- *[Name, title, and contact information of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*

STATEMENT OF CONSENT

I have read (or someone has read and explained to me) this consent form. I understand the purpose of the screening, the procedures to be followed, and the risks and benefits as described in this consent form. I voluntarily agree to be screened for my potential participation in the drug treatment research study.

Participant's Name (print)

Participant's Signature or Thumbprint and Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study screening.

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study screening and has voluntarily accepted to participate in this screening.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

Witness' Name (print)

Witness's Signature and Date

APPENDIX III-B: Sample Enrollment Consent for Participants Enrolled during the Safety Phase

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and deaths among opiate dependent injectors, Final Version 2.0, 16 September 2008

Principle Investigators: [Name and Contact Info]

Introduction

You are being asked to take part in the research study named above. The research study will test whether a drug treatment program can reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behavior. HIV is the virus that causes AIDS. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is (*Name of Principal Investigator*).

Before you decide if you want to be a part of this research, you need to know the purpose of the study, the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form will give you information about the research study. The study staff will also discuss the study with you. They will answer any questions that you have. After the study has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to take part in the study, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

What are your rights as a research participant?

- Your participation in the study is entirely voluntary.
- You may decide not to take part in the study or to leave at any time without losing the benefits of your standard medical care or other services. You will be treated the same no matter what you decide.
- If you decide not to participate in the study, you can still join another research study later, if one is available and you are eligible.

Why is this research being done?

The purpose of the research is to compare how well two different treatments help reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behaviors. One treatment includes a medicine called Suboxone® (a combination of two drugs, buprenorphine and naloxone) and counseling for one year; we call this “substitution treatment.” The other treatment uses Suboxone for short term detoxification and counseling for one year. We call this the “detoxification treatment” group. Suboxone has been approved for treating drug users in the US. Suboxone does not prevent or treat HIV. The counseling used in this study has also been used in the US to help drug users reduce their drug use and their risk for HIV infection. It is not known if either of these treatments will prevent you from getting HIV. This study will not provide treatment for HIV.

Half of the people in this study will receive detoxification; half will receive the substitution treatment. Both groups will receive HIV tests every 6 months. Neither you nor the study staff will be able to choose which treatment you receive. The treatment you are given will be decided by chance, like flipping a coin (*or insert local equivalent phrase*). Both treatment groups are important to help us find ways of preventing HIV.

A total of about 1500 people will participate in the study in [the study countries]. About [approximate site-specific accrual target] people will be in the study here in [study site].

The first part of this study will test how people react to Suboxone and how well they like the two different treatments in this study. Even though these treatments have been used safely in people in the US, we want to see if the same is true for people in China and Thailand. We call this the “Safety Phase.” The first 50 people at each location will be part of the “Safety Phase.” The information we learn during this phase will help us plan the rest of the study.

What will happen if you agree to take part in this study?

Since the results of your screening tests show that you are eligible, you are being asked to agree to participate in the drug treatment research study. The study staff will explain the study to you and answer any questions you have. You will be asked some questions about the study to be sure that you understand what is involved. If you agree to take part in the study, you will be asked to sign this consent form. We will also ask you how you felt when answering questions about the study, but you do not have to answer if you don't want to. We will make sure your contact information is the same. If you are a woman, we will do another pregnancy test on your urine and you will be given the results. We will also make sure that you will be available to stay at the clinic for up to eight hours today. When these steps are done, you will be told which treatment group you are in. Your visit today will last up to 8 hours.

Treatment Visits:

The treatment part of this study will last one year. Then we will continue to do HIV tests for another two years after the treatment ends. Altogether, you will be in the study for three years.

During each of the first four weeks that you are in the study, we will perform a physical exam and urine and blood tests. We will ask you about your health and take about 14 mL of blood (about 3 teaspoons *or local equivalent*). This blood will be sent to the laboratory to test your kidneys, liver, and general health. Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. We will also test your urine for opiates and other drugs. We will tell you the results from the lab tests when we receive them. These visits could take about 1 to 2 hours.

You will talk with a counselor for about 45 minutes every week for 12 weeks. After the first 12 weeks, you will return about every four weeks for 10 more counseling sessions. The counselor will talk with you about ways to reduce your drug use and to protect yourself from HIV and other diseases.

About every three months, the staff will draw about 4 mL of blood (about 1 teaspoon *or local equivalent*) to make sure your liver is healthy. If your test is not normal, the staff will contact you. All participants will have a urine test for opiates and other drugs every four weeks for a year.

If you are in the Detoxification Treatment group, you will be asked to come to the clinic every day for two to three weeks to take the Suboxone medicine. During the first three days, the amount of Suboxone you will receive will be enough to relieve withdrawal symptoms. Then the amount will be reduced every day until you are no longer receiving any Suboxone. This usually takes 10 to 15 days; some people will take a few days less, some more. After this time, you will not receive any more Suboxone, but you will continue to come to the clinic for counseling visits as described above.

At the six-month visit, the doctor will decide if you need another detoxification treatment. If you have detoxification again, the procedures will be the same as above.

If you are in this treatment group, you will have about 45 to 60 visits in the first year of the study.

If you are in the Substitution Treatment group, you will take the Suboxone medicine for one year and also receive counseling as described above. During the first one to three weeks that you are taking Suboxone, you will have to come to the clinic every day to take your medicine until we find the right dose for you. After we are sure that you are doing well, you will need to return to the clinic three times a week for a year to receive this medicine. We will try to combine your medication and counseling visits so they happen on the same day. At about the 47th week, the dose of Suboxone will be gradually reduced each week so that you are no longer receiving any medicine by the end of week 52.

If you are a woman and you are taking Suboxone, we will do a pregnancy test every month. You will be given the results of these tests.

If you are in this treatment group, you will have about 155 visits in the first year of the study.

Follow-up Visits:

All participants in the study will return to the clinic every six months for HIV testing and interviews. There will be 6 follow-up visits over three years.

You will receive HIV counseling and testing at every follow-up visit. We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes. You will talk with a counselor before and after your HIV test. We will also ask you questions about your drug use and sexual behavior and test your urine for opiates and other drugs at each visit. We will ask how being in the study has affected your life. If your HIV test shows that you are infected with HIV, you will be given information about where you can go for additional testing and counseling. This study will not provide treatment for HIV.

If during the course of these screening tests, we find out that you have HIV or other (*list communicable diseases that require reporting*), we must report this to [*insert the name(s) of the local health authorities and amend this paragraph to reflect the local requirements*]. *If there are no local requirements to report HIV or communicable diseases, delete this paragraph.*]

At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. We will send some of your blood to the laboratory to test your liver, kidneys and general health. You will be told the results of your tests as soon as they are ready, usually about a week.

Follow-up visits will last about 1 to 2 hours. We will try to combine your follow-up visits with counseling visits so they happen on the same day during the first year you are in the study.

How will study staff keep in contact with you during the study?

You will be asked to provide your address, phone number, and places where you are likely to be found. The staff will ask you for names of people who will always know how to find you. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

What are the risks/discomforts of this study?

Blood drawing may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might

make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are here for this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If people think that you are infected with HIV, you may have problems finding or keeping a job. Others may treat you unfairly, including your family and community.

It is also possible that others may find out that you have been screened for this study and assume that you are an injection drug user. This could cause you problems finding or keeping a job. Others may treat you unfairly, including your family and community.

The doctor will give you complete instructions about how to take Suboxone. It is important to follow the instructions to avoid an overdose or withdrawal symptoms. Because the medicine must be dissolved under your tongue, it may cause some mild irritation or leave a bad taste in your mouth. The most common side effects are headaches, pain, sweating, nausea, sleeping problems, stomach pains and constipation. Suboxone may impair mental and physical abilities involved in activities such as driving or operating machinery; therefore you should not do these activities until you know how the medicine will affect you.

Suboxone can cause breathing difficulties especially when mixed with other drugs like alcohol or benzodiazepines/tranquilizers (*insert local equivalents for commonly used depressants*). Do not drink alcohol or take tranquilizers or sedatives (*insert local equivalent slang*) while you are taking Suboxone. Some people have had allergic reactions to buprenorphine such as itching or rashes. Suboxone has been linked with liver problems in some people. We will check your liver, kidneys and blood to make sure it is healthy while you are taking Suboxone.

It is very important that you do not inject (*insert local equivalent slang*) Suboxone or mix it with other drugs. Some people have died when they have injected buprenorphine (one of the drugs in Suboxone) or used it at the same time with benzodiazepines (such as diazepam), other opiates (such as heroin, opium, or morphine), or drugs that are depressants like sleeping pills, alcohol, or tranquilizers (*insert local equivalents*). If you do use these other drugs at the same time you are taking Suboxone, the doctor may decide to stop your doses of Suboxone.

It is possible that the doctor may decide it is not safe for you to continue using Suboxone. For example, if your blood tests show that your liver is not healthy, your medicine may be stopped or adjusted. If this happens, you will still be asked to continue to come to the clinic for other scheduled visits during the full study period.

Suboxone can cause drug dependence, which means that withdrawal symptoms may occur when you stop using the medicine. Everyone in this study will be taken off Suboxone very gradually to avoid withdrawal symptoms. However, there is the risk that you might have withdrawal symptoms or relapse during or after this withdrawal period.

Are there risks related to pregnancy?

We do not know if Suboxone could harm unborn babies. Suboxone passes through breast milk, so you should not breastfeed while taking Suboxone. Women must have a pregnancy test before entering this study and every month while taking Suboxone. Pregnant or breastfeeding women are not eligible for this study. If you can become pregnant, you must agree to use an acceptable birth control method during the first 12 months that you are enrolled in the study, such as:

1. Hormonal methods, like birth control pills, shots, patches, implants or vaginal rings
2. Male or female condoms
3. Diaphragm or cervical cap with a cream or gel that kills sperm
4. Intrauterine device (IUD)
5. Complete abstinence from sex

If you become pregnant while you are taking Suboxone, it is important that you tell the study staff immediately. We will counsel you about treatment during pregnancy and give you referrals. Your dose of Suboxone will be slowly cut down and stopped, but you can still continue with counseling sessions and follow-up visits. After your baby is born, we will talk with you about your baby's health. If you leave the study or the study ends before you deliver the baby, we will ask to contact you to know the outcome of the pregnancy.

Are there potential benefits to taking part in this study?

There may be no direct benefit to you from this study. However, information learned from this study may help in the future to develop ways to prevent the spread of HIV. If you take part in this study, you will learn information about HIV and your HIV status. You will receive information about your health from the study examinations and laboratory tests. You will be able to talk to counselors about your health and feelings. You will also receive free condoms throughout the entire course of the study.

What if the researchers learn something new?

The study staff will tell you about new information learned during this or other studies that may affect your health, welfare or willingness to stay in this study. Near the end of the study, you will be told when the study results will be available and how to learn about them.

Why would your participation in the study be stopped early?

The study staff may need to end your participation in the study early without your permission if:

- The study is canceled by the U.S. Food and Drug Administration (FDA), the U.S. National Institutes of Health (NIH), the drug company giving the medicine for this study, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (an IRB or Ethics Committee is a committee that watches over the safety and rights of research subjects).
- The Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (a DSMB is an outside group of experts who monitor the study).
- The study staff believe that it is unsafe for you or the staff to stay in the study for any reason. For example, if you are disruptive at the clinic, the staff may withdraw you from the study.
- Other administrative reasons.

What other choices do you have besides this study?

You do not have to agree to join this study. The staff will talk with you about other treatment or research studies that may be available in your community. (*Add other treatment options for IDUs depending on local situation.*) You do not have to receive any treatment. Please talk to the study staff about these and other choices that may be available to you.

What about confidentiality?

All efforts will be made to keep your personal information confidential to the extent permitted by law, but we cannot promise complete confidentiality. On your research records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that

identifies you without your written consent. However, the local Ministry of Health, the U.S. Food and Drug Administration, the company that makes the study drug, the Institutional Review Board or Ethics Committee, the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your study-related records.

What are the costs or payments to you?

There will be no cost to you for these visits, physical examinations, the study drug (Suboxone), laboratory tests or other procedures. This study does not provide treatment for any conditions that are discovered during the course of the study.

You will be paid for your time and travel expenses *[Schedule and amount to be specified in site specific consent.]*

What happens if you are injured during the study?

If you are injured as a result of being in this research study, you will be given immediate treatment for your injuries. You may have to pay for this care. If we find any illness or injury during the study that is not related to the study, we will tell you about medical care and other services available in the community. There are no plans to give you money either through this institution or the U.S. National Institutes of Health (NIH) if there is a research-related complication or injury. You will not be giving up any of your legal rights by signing this consent form.

What should you do if you have problems or questions about the study?

For questions about this study or a research-related injury, contact:

- *[Name, physical address, and phone number of the investigator or other study staff]*

For questions about your rights as a research subject, contact:

- *[Name, title, and contact information of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*

STATEMENT OF CONSENT

I have read (or someone has read and explained to me) this consent form. I understand the purpose of the study, the procedures to be followed, and the risks and benefits as described in this consent form. I voluntarily agree to join this drug treatment research study.

Participant's Name (print)

Participant's Signature or Thumbprint and Date

For staff: I have explained the study to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

Witness' Name (print)

Witness's Signature and Date

APPENDIX III-C: Sample Screening Consent for Participants Screened during the Full Study

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and deaths among opiate dependent injectors, Final Version 2.0, 16 September 2008

Principle Investigators: [Name and Contact Info]

Introduction

You are being asked to take part in a screening process to find out if you are eligible to take part in the research study named above. The research study will test whether a drug treatment program can reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behavior. HIV is the virus that causes AIDS. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is (*Name of Principal Investigator*).

Before you decide if you want to be a part of this screening, we want you to know about the study. This consent form will give you information about the screening process. The study staff will discuss the screening with you. You are free to ask any questions. After the screening has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the screening, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

What are your rights as a research participant?

- Your participation in the screening is entirely voluntary.
- You may decide not to take part in the screening tests or to leave at any time without losing the benefits of your standard medical care or other services. You will be treated the same no matter what you decide.
- If you decide not to participate in the screening, you cannot participate in this research study, but you can still join another research study later, if one is available and you qualify.
- Even if you agree to participate in the screening, it does not mean you have agreed to participate in the research study.
- We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

Why is this research being done?

The purpose of the research is to compare how well two different treatments help reduce the number of deaths and HIV infections among injection drug users by reducing drug use and other risky behavior. One treatment includes a medicine called Suboxone® (a combination of two drugs, buprenorphine and naloxone) and counseling for one year; we call this the “substitution treatment” group. The other treatment uses Suboxone for short term detoxification and counseling for one year. We call this the “detoxification treatment” group. Suboxone is a drug that has been approved for treating drug users in the US. Suboxone does not prevent or treat HIV. The counseling used in this study has also been used in the US to help drug users reduce their drug use and their risk for HIV infection. It is not known if either of these treatments will prevent you from getting HIV.

Half of the people in this study will receive the substitution treatment; half will receive the detoxification treatment. Neither you nor the study staff will be able to choose which treatment you receive. The treatment you are given will be decided by chance, like flipping a coin (*insert local equivalent phrase*). Both treatment groups are important to help us find ways of preventing HIV. After all the screening

activities are done (about one week for most people), the staff will tell you which treatment group you are in.

A total of about 1500 people will participate in the study in [the study countries]. About [approximate site-specific accrual target] people will be in the study here in [study site].

What will happen if you agree to the study screening?

The screening visit may take 2 to 4 hours and may proceed today if you are willing. We will ask you questions about your health, drug use, and about your sexual activity. We will also ask you to tell us where you live and how we can find you. If you are not willing to give us this information, you should not agree to be in this study. You will be asked to provide a urine sample for a test for opiates and other drugs. If you are a woman, we will also do a pregnancy test on your urine. You will be given the result of the pregnancy test during this visit. You are not eligible if you are pregnant or breastfeeding. These screening questions and tests are the first step in determining if you will be able to join the study. Some people will not be eligible because of information learned during screening.

You will be offered HIV counseling and testing whether or not you are eligible to join the study. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. Some of your blood will be tested for HIV. We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes. When your HIV test results are ready, you will talk with the counselor about the meaning of your results. You must receive your HIV test result to be eligible for the research study.

If your HIV test shows you may be infected with HIV, you will not be eligible for the study and screening will stop. However, we will do another test to confirm your results that will take about a week. The staff will talk with you about what this means. The staff will talk with you about what this means. You will be given information about where you can go for additional testing and counseling. This study will not provide treatment if you are infected with HIV.

If you agree, your blood specimen will be stored and tested later to look for additional evidence of infection with HIV. We will not contact you with the results from the tests done on the stored samples. This is because research tests are often done with experimental procedures, so the results from these tests are not useful for making decisions on managing your health. If during the course of these screening tests, we find out that you have HIV or (*list communicable diseases to be reported*), we must report this to [*insert the name(s) of the local health authorities and amend this paragraph to reflect the local requirements. If there are no local requirements to report HIV or communicable diseases, delete this paragraph.*]

If your HIV test shows that you are not infected with HIV, you will then have a physical exam and the doctor will ask about your health history. We will also send some of your blood to a laboratory to test your kidneys, liver, and general health. These tests will take about one week to complete. We will give you the results of the tests when you return for the next visit.

We will also test some of your blood for the liver diseases hepatitis B and C. If you test positive for either of these infections, we will give you information about where you can go for additional testing and treatment. You may still be eligible to join this study if you have hepatitis. If you are not infected with hepatitis B, the staff will talk with you about getting the vaccine to protect you against hepatitis B.

If all screening activities show that you may be able to join the study, more detailed information about the study will be given to you at your next visit. You will be able to decide if you want to join the study or

not. After the study has been fully explained to you, and you have asked all of your questions, the study staff will ask you some questions about the study to be sure that you understand. If you agree to participate in the study, you will be asked to sign another consent form that explains all study activities to you. If you agree to join the study, the first treatment visit will begin the same day and will last up to eight hours.

How long will you be in this study if you are eligible?

You will be in this study about 2 to 3 years depending on when you begin. Should you be eligible, you will be asked to sign an additional Informed Consent form which will describe the study visits and procedures in greater detail. You should feel free to ask the study site staff should you have any questions regarding the length of the study and your involvement.

What are the risks/discomforts of study screening?

Taking blood may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this screening. However, it is possible that you could have problems if people learn that you are here for this screening. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If people think that you are infected with HIV, you may have problems finding or keeping a job. Others may treat you unfairly, including your family and community.

Are there risks related to pregnancy?

You must have a pregnancy test before you enter this study. You are not eligible for this study if you are pregnant or breastfeeding. If you are found to be currently pregnant, there are no risks to having had the screening procedures.

Are there potential benefits to study screening?

These screening tests may or may not be of direct benefit to you. If you take part in this screening, you will learn information about HIV and your HIV status. You will have a physical exam and other tests of your health.

What other choices do you have besides this study?

You do not have to agree to be screened for this research study. The staff will talk with you about other options for HIV counseling and testing, treatment options for drug use, or research studies that may be available in your community. *[Add other treatment or research options for IDUs depending on local situation including access to counseling and HIV testing.]* Please talk to the study staff about these and other choices that may be available to you. You do not have to receive any treatment. If you do not agree to the screening, you will not be able to join this study but you may be able to join another study in the future if you are eligible.

What about confidentiality?

All efforts will be made to keep your personal information confidential to the extent permitted by law, but we cannot promise complete confidentiality. On your screening records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the local Ministry of Health, the U.S. Food and Drug Administration, the company that makes the study drug, the Institutional Review Board or Ethics Committee,

the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your study-related records.

What are the costs or payments to you?

There will be no cost to you for these visits, physical examinations, laboratory tests or other procedures. This study does not provide treatment for any conditions that are discovered during the course of the screening or study.

You will be paid for your time and travel expenses for *[Schedule and amount to be specified in site specific consent.]*

What happens if you are injured during the screening?

If you are injured as a result of being in this screening, you will be given immediate treatment for your injuries. You may have to pay for this care. If we find any illness or injury during the screening that is not related to the screening, we will tell you about medical care and other services available in the community. There are no plans to give you money either through this institution or the U.S. National Institutes of Health (NIH) if there is a research-related complication or injury. You will not be giving up any of your legal rights by signing this consent form.

What should you do if you have problems or questions about the screening?

For questions about this study or a research-related injury, contact:

- *[Name, physical address, and phone of the investigator or other study staff]*

For questions about your rights as a research subject, contact:

- *[Name, title, and contact information of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*

STATEMENT OF CONSENT

I have read (or someone has read and explained to me) this consent form. I understand the purpose of the screening, the procedures to be followed, and the risks and benefits as described in this consent form. I voluntarily agree to be screened for my potential participation in the drug treatment research study.

Participant's Name (print)

Participant's Signature or Thumbprint and Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study screening.

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study screening and has voluntarily accepted to participate in this screening.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

Witness' Name (print)

Witness's Signature and Date

APPENDIX III-D: Sample Enrollment Consent for Participants Enrolled during the Full Study

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and deaths among opiate dependent injectors, Final Version 2.0, 16 September 2008

Principle Investigators: [Name and Contact Info]

Introduction

You are being asked to take part in the research study named above. The research study will test whether a drug treatment program can reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behavior. HIV is the virus that causes AIDS. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is (*Name of Principal Investigator*).

Before you decide if you want to be a part of this research, you need to know the purpose of the study, the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form will give you information about the research study. The study staff will also discuss the study with you. They will answer any questions that you have. After the study has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to take part in the study, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

What are your rights as a research participant?

- Your participation in the study is entirely voluntary.
- You may decide not to take part in the study or to leave at any time without losing the benefits of your standard medical care or other services. You will be treated the same no matter what you decide.
- If you decide not to participate in the study, you can still join another research study later if one is available and you are eligible.

Why is this research being done?

The purpose of the research is to compare how well two different treatments help reduce the number of deaths and HIV infections in injection drug users by reducing drug use and other risky behavior. One treatment includes a medicine called Suboxone® (a combination of two drugs, buprenorphine and naloxone) and counseling for one year; we call this “substitution treatment.” The other treatment uses Suboxone for short term detoxification and counseling for one year. We call this the “detoxification treatment” group. Suboxone has been approved for treating drug users in the US. Suboxone does not prevent or treat HIV. The counseling used in this study has also been used in the US to help drug users reduce their drug use and their risk for HIV infection. It is not known if either of these treatments will prevent you from getting HIV. This study will not provide treatment for HIV.

Half of the people in this study will receive detoxification; half will receive the substitution treatment. Both groups will receive HIV tests every 6 months. Neither you nor the study staff will be able to choose which treatment you receive. The treatment you are given will be decided by chance, like flipping a coin (*or insert local equivalent phrase*). Both treatment groups are important to help us find ways of preventing HIV.

A total of about 1500 people will participate in the study in [the study countries]. About [approximate site-specific accrual target] people will be in the study here in [study site].

What will happen if you agree to take part in this study?

Since the results of your screening tests show that you are eligible, you are being asked to agree to participate in the drug treatment research study. The study staff will explain the study to you and answer any questions you have. You will be asked some questions about the study to be sure that you understand what is involved. If you agree to take part in the study, you will be asked to sign this consent form. We will also ask you how you felt when answering questions about the study, but you do not have to answer if you don't want to. We will make sure your contact information is the same. If you are a woman, we will do another pregnancy test on your urine and you will be given the results. We will also make sure that you will be available to stay at the clinic for up to eight hours today. Once these steps are done, you will be told which treatment group you are in. Your visit today will last up to 8 hours

Treatment Visits:

The treatment part of this study will last one year. Then we will continue to do HIV tests for another one-two years after the treatment ends. Altogether, you will be in the study for two to three years.

You will talk with a counselor every week for 12 weeks for about 45 minutes. After the first 12 weeks, you will return about every four weeks for 10 more counseling sessions. The counselor will talk with you about ways to reduce your drug use and to protect yourself from HIV and other diseases.

About every three months, the staff will draw about 4 mL of blood (about 1 teaspoon *or local equivalent*) to make sure your liver is healthy. If your test is not normal, the staff will contact you. All participants will have a urine test for opiates and other drugs every four weeks for a year.

If you are in the Detoxification Treatment group, you will be asked to come to the clinic every day for two to three weeks to take Suboxone medicine. During the first three days, the amount of Suboxone you will receive will be enough to relieve withdrawal symptoms. Then the amount will be reduced every day until you are no longer receiving any Suboxone. This usually takes 10-15 days; some people will take a few days less, some more. After this time, you will not receive any more Suboxone, but you will continue to come to the clinic for counseling visits as described above.

At the six-month visit, the doctor will decide if you need another detoxification treatment. If you have detoxification again, the procedures will be the same as above.

If you are in this treatment group, you will have about 45 to 60 visits in the first year of the study.

If you are in the Substitution Treatment group, you will take Suboxone medicine for one year and also receive counseling as described above. During the first one to three weeks that you are taking Suboxone, you will have to come to the clinic every day to take your medicine until we find the right dose for you. After we are sure that you are doing well, you will need to return to the clinic three times a week for a year to receive this medicine. We will try to combine your medication and counseling visits so they happen on the same day. At about the 47th week, the dose of Suboxone will be gradually reduced each week so that you are no longer receiving any medicine by the end of week 52.

If you are a woman and you are taking Suboxone, we will do a pregnancy test every month. You will be given the results of all pregnancy tests.

If you are in this treatment group, you will have about 155 visits in the first year of the study.

Follow-up Visits:

All participants in the study will return to the clinic every six months for HIV testing and interviews. There will be between 4 and 6 follow-up visits over 2 to 3 years depending on when you start participating.

You will receive HIV counseling and testing at every follow-up visit. We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes. You will talk with a counselor before and after your HIV test. We will also ask you questions about your drug use and sexual behavior and test your urine for opiates and other drugs at each visit. We will ask how being in this study has affected your life. If your HIV test shows that you are infected with HIV, you will be given information about where you can go for additional testing and counseling. This study will not provide treatment for HIV.

If during the course of these screening tests, we find out that you have HIV or (*list communicable diseases to be reported*), we must report this to [*insert the name(s) of the local health authorities and amend this paragraph to reflect the local requirements. If there are no local requirements to report HIV or communicable diseases, delete this paragraph.*]

At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. We will send some of your blood to the laboratory to test your liver, kidneys and general health. You will be told the results of your tests as soon as they are ready, usually about a week.

Follow-up visits will last about 1 to 2 hours. We will try to combine your follow-up visits with counseling visits so they happen on the same day during the first year you are in the study.

How will study staff keep in contact with you during the study?

You will be asked to provide your address, phone number, and places where you are likely to be found. The staff will ask you for names of people who will always know how to find you. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

What are the risks/discomforts of this study?

Blood drawing may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are here for this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If people think that you are infected with HIV, you may have problems finding or keeping a job. Others may treat you unfairly, including your family and community.

It is also possible that others may find out that you have been screened for this study and assume that you are an injection drug user. This could cause you problems finding or keeping a job. Others may treat you unfairly, including your family and community.

The doctor will give you complete instructions about how to take Suboxone. It is important to follow the instructions to avoid an overdose or withdrawal symptoms. Because the medicine must be dissolved under your tongue, it may cause some mild irritation or leave a bad taste in your mouth. The most common side effects are headaches, pain, sweating, nausea, sleeping problems, stomach pains and constipation. Suboxone may impair mental and physical abilities involved in activities such as driving or operating machinery; therefore you should not do these activities until you know how the medicine will affect you.

Suboxone can cause breathing difficulties especially when mixed with other drugs like alcohol or benzodiazepines/ tranquilizers (*insert local equivalents for commonly used depressants*). Do not drink alcohol or take tranquilizers or sedatives (*insert local equivalent slang*) while you are taking Suboxone. Some people have had allergic reactions to buprenorphine such as itching or rashes. Suboxone has been linked with liver problems in some people. We will check your liver, kidneys, and blood to make sure they are healthy while you are taking Suboxone.

It is very important that you do not inject (*insert local equivalent slang*) Suboxone or mix it with other drugs. Some people have died when they have injected buprenorphine (one of the drugs in Suboxone) or used it at the same time with benzodiazepines (such as diazepam), other opiates (such as heroin, opium, or morphine), or drugs that are depressants like sleeping pills, alcohol, or tranquilizers (*insert local equivalents*). If you do use these other drugs at the same time you are taking Suboxone, the doctor may decide to stop your doses of Suboxone.

It is possible that the doctor may decide it is not safe for you to continue using Suboxone. For example, if your blood tests show that your liver is not healthy, your medicine may be stopped or adjusted. If this happens, you will still be asked to continue to come to the clinic for other scheduled visits during the full study period.

Suboxone can cause drug dependence, which means that withdrawal symptoms may occur when you stop using the medicine. Everyone in this study will be taken off Suboxone very gradually to avoid withdrawal symptoms. However, there is the risk that you might have withdrawal symptoms or relapse during or after this withdrawal period.

Are there risks related to pregnancy?

We do not know if Suboxone could harm unborn babies. Suboxone passes through breast milk so you should not breastfeed while taking Suboxone. Women must have a pregnancy test before entering this study and every month while taking Suboxone. Pregnant or breastfeeding women are not eligible for this study. If you can become pregnant, you must agree to use an acceptable birth control method during the first 12 months that you are enrolled in the study, such as:

1. Hormonal methods like birth control pills, shots, patches, implants or vaginal rings
2. Male or female condoms
3. Diaphragm or cervical cap with a cream or gel that kills sperm
4. Intrauterine device (IUD)
5. Complete abstinence from sex

If you become pregnant while you are taking Suboxone, it is important that you tell the study staff immediately. We will counsel you about treatment during pregnancy and give you referrals. Your dose of Suboxone will be slowly cut down and stopped, but you can still continue with counseling sessions and follow-up visits. After your baby is born, we will talk with you about your baby's health. If you leave

the study or the study ends before you deliver the baby, we will ask to contact you to know the outcome of the pregnancy.

Are there potential benefits to taking part in this study?

There may be no direct benefit to you from this study. However, information learned from this study may help in the future to develop ways to prevent the spread of HIV. If you take part in this study, you will learn information about HIV and your HIV status. You will receive information about your health from the study examinations and laboratory tests. You will be able to talk to counselors about your health and feelings. You will also receive free condoms throughout the entire course of the study.

What if the researchers learn something new?

The study staff will tell you about new information learned during this or other studies that may affect your health, welfare or willingness to stay in this study. Near the end of the study, you will be told when the study results will be available and how to learn about them.

Why would your participation in the study be stopped early?

The study staff may need to end your participation in the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), the U.S. National Institutes of Health (NIH), the drug company giving the medicine for this study, the local government or regulatory agency, or the Institutional Review Board (IRB) or Ethics Committee (an IRB or Ethics Committee is a committee that watches over the safety and rights of research subjects).
- The Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (a DSMB is an outside group of experts who monitor the study).
- The study staff believe that it is unsafe for you or the staff to stay in the study for any reason. For example, if you are disruptive at the clinic, the staff may withdraw you from the study.
- Other administrative reasons

What other choices do you have besides this study?

You do not have to agree to join this study. The staff will talk with you about other treatment or research studies that may be available in your community. (*Add other treatment options for IDUs depending on local situation.*) You do not have to receive any treatment. Please talk to the study staff about these and other choices that may be available to you.

What about confidentiality?

All efforts will be made to keep your personal information confidential to the extent permitted by law, but we cannot promise complete confidentiality. On your research records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the local Ministry of Health, the U.S. Food and Drug Administration, the company that makes the study drug, the Institutional Review Board or Ethics Committee, the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your study-related records.

What are the costs or payments to you?

There will be no cost to you for these visits, physical examinations, the study drug (Suboxone), laboratory tests or other procedures. This study does not provide treatment for any conditions that are discovered during the course of the screening or study.

You will be paid for your time and travel expenses for *[schedule and amount to be specified in site specific consent.]*

What happens if you are injured during the study?

If you are injured as a result of being in the research study, you will be given immediate treatment for your injuries. You may have to pay for this care. If we find any illness or injury during the study that is not related to the study, we will tell you about medical care and other services available in the community. There are no plans to give you money either through this institution or the U.S. National Institutes of Health (NIH) if there is a research-related complication or injury. You will not be giving up any of your legal rights by signing this consent form.

What should you do if you have problems or questions about the study?

For questions about this study or a research-related injury, contact:

- *[Name, physical address, and phone information of the investigator or other study staff]*

For questions about your rights as a research subject, contact:

- *[Name, title, and contact information of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*

STATEMENT OF CONSENT

I have read (or someone has read and explained to me) this consent form. I understand the purpose of the study, the procedures to be followed, and the risks and benefits as described in this consent form. I voluntarily agree to join this drug treatment research study.

Participant's Name (print)

Participant's Signature or Thumbprint and Date

For staff: I have explained the study to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

Witness' Name (print)

Witness's Signature and Date

APPENDIX III-E: Sample Consent for Storage and Future Use of Blood Samples

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors, Final Version 2.0, Dated 16 September 2008

Principal Investigators: [Insert name and contact information for the site PI]

Introduction

You have decided to take part in the study named above, which is sponsored by the US National Institutes of Health. While you are in this research study, there may be some blood samples taken from you that might be useful for future HIV-related research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask if you have any questions. If you agree to the storage of your samples, you will be asked to sign this consent form. You will be offered a copy to keep. You may participate in the study even if you do not agree to storage of your specimens.

How will you get the samples from me?

NO ADDITIONAL samples will be taken from you for storage. After all the tests are done for this research study, there may be some left over samples of blood. If you agree, left over samples will be kept and used for future HIV-related research.

How will you use my samples?

Your samples will only be used to look for additional evidence of infection with HIV or other agents, damage caused by infection, or your body's response to infection (such as examining cells, proteins, and other chemicals in your body). Tests may also include examining your genes (DNA), since they might affect your response to HIV disease in important ways. Your genes might make you more or less likely to become HIV infected, make your responses to HIV infection stronger or weaker, or make HIV progress more rapidly or slowly. No other kinds of genetic tests will be done by anyone on your stored specimens.

The researchers do not plan to contact you with any results from tests done on the stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are often not useful for making decisions about your health. Should a rare situation come up in which the researchers decide that a specific test result would provide important information for your health, the researchers will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number.

Your samples will not be sold or used directly to produce commercial products. Research studies using your samples will be reviewed by the sponsor of this study (the US National Institutes of Health) and a special committee at the researcher's institution (an Institutional Review Board).

How long will you keep my samples?

There is no time limit on how long your samples will be stored.

How will my samples be stored?

Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples.

Some employees of the storage facilities will need to have some access to your samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you.

Does storage of my samples benefit me?

There are no direct benefits to you. The benefit of doing research on stored samples includes learning more about HIV infection.

What are the risks?

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes), it could cause you problems with your family or problems getting a job or insurance.

What about confidentiality?

To keep your information private, your samples will be labeled with a code that can only be traced back to this research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

What are my rights?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study.

If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. **Your samples will then not be used and will be destroyed according to local regulations.**

What do I do if I have questions?

For questions about the storage of your samples, contact [*inset name of site investigator*] at [*inset telephone number*].

If you have questions about your rights as a research volunteer, contact [insert the name or title of person on the Institutional Review Board] at [insert telephone number].

STATEMENT OF CONSENT

Please carefully read the statements below or have them read to you and think about your choice. No matter what you decide it will not affect your care.

I agree to have my left over blood samples stored and tested for future research related to HIV infection.

_____ Yes

_____ No

Volunteer's Name (print)

Volunteer's Signature or mark

Date

Witness' Name (print)
(as appropriate for illiterate participant)

Witness' Signature

Date

I have explained the purpose of storing specimens from the study to the volunteer and have answered all of her/his questions. To the best of my knowledge, s/he understands the purpose, procedures, risks and benefits.

Printed name of Study Staff
Conducting Consent Discussion

Study Staff Signature

Date

APPENDIX IV: Referral Information for Sites

Please provide the requested information for each health care facility or organization that your site has used or will use for referrals for participants who are screened for or enrolled in the HPTN 058 protocol. Examples of organizations that you might use for referrals are support groups, emergency shelters, needle exchanges, medical care for HIV, and so on. This list should be updated at least every six months and will be monitored during site visits by sponsor representatives.

- a. Name of organization and contact person at this organization:

- b. Address and phone number of organization:

- c. Types of services/care provided at this organization and the cost of each:

- d. Approximate distance of organization from your research site:

- e. Days/hours when services are available:

- f. Typically, how long does it take to get an appointment at this organization?

- g. Has anyone from your research site visited this organization in the last six months?

- h. Has your research site or your research participants experienced any problems or challenges with this referral site? If yes, please describe.

Referral List for [name of site]

Organization	Address/Phone	Contact Person	Types of services offered and cost of each	Info last updated

This list will be used by HPTN staff when making referrals for participants who are screened for or enrolled in HPTN 058. This list should be updated regularly.

APPENDIX V: Equipoise in HPTN 058: Comparisons between the Two Study Arms

The following table is designed to summarize efficacy rates for key outcomes described in the available literature and individual and community level risks and benefits in each arm. As the table demonstrates, though efficacy for reduction in opiate use is not expected to be high in the detoxification treatment arm, efficacy for reduction in HIV incidence may be higher than hypothesized in the protocol given the available data demonstrating that behavioral interventions can dramatically reduce HIV risk behaviors. Additionally, the table illustrates that risks and benefits for participants in both arms are generally similar.

	Detoxification and Counseling Arm	Substitution and Counseling Arm
Efficacy information from available literature:		
HIV incidence	No studies have been conducted measuring HIV incidence among opiate dependent individuals following detoxification with or without counseling. A number of studies have demonstrated that when active drug users are engaged in behavioral risk reduction interventions, HIV risk behaviors are dramatically reduced. See Section 1.1.1 for greater detail.	No studies have been conducted examining HIV incidence during or following buprenorphine treatment. Observational studies of self-selected subjects have found significant associations between retention in methadone maintenance and lower rates of HIV incidence. See Section 1.1.1 for more information.
Opiate Use	Long-term outcomes and relapse rates from rapid opiate detoxification with buprenorphine followed by counseling have not been reported. It appears that buprenorphine is as effective as methadone for detoxification, though brief detoxification alone is unlikely to result in long-term abstinence from opiate use.	Several clinical trials have firmly established the efficacy of buprenorphine compared to placebo for reduction of opiate use. The percentage of participants in these trials with consistently opiate negative urine samples has ranged broadly based on length of treatment and dose. See Section 1.1.3 for more information about the efficacy of BUP/NX in the treatment of opiate use.
Needle Sharing	Studies show an average 27% reduction in needle sharing at 6-months among injectors exposed to behavioral interventions. See Section 1.1.1.	50-80% reduction based upon observational studies of methadone patients relative to untreated injectors.
Benefits to individuals screened for HPTN 058	<ul style="list-style-type: none"> • HIV, HBV, & HCV counseling and testing • Referral to available community health care for identified medical problems • If HIV positive, referral to available HIV services in the community • Referral to available drug treatment services in the community 	
Benefits to individuals enrolled in HPTN 058	<ul style="list-style-type: none"> • HIV counseling and testing every 6 months and on demand between assessment intervals • HBV and HCV testing as clinically indicated • Hepatitis B vaccine offered if appropriate • Outpatient BUP/NX detoxification during first 2-3 weeks of study • Weekly drug and risk reduction counseling during first 3 months of study • Monthly drug and risk counseling during months 4 through 12 of study • Referral to available community health care for identified medical problems • If HIV positive, referral to available HIV 	<ul style="list-style-type: none"> • HIV counseling and testing every 6 months and on demand between assessment intervals • HBV and HCV testing as clinically indicated • Hepatitis B vaccine offered if appropriate • Outpatient BUP/NX maintenance during first year of study • Weekly drug and risk reduction counseling during first 3 months of study • Monthly drug and risk counseling during months 4 through 12 of study • Referral to available community health care for identified medical problems • If HIV positive, referral to available HIV

	<p>services in the community</p> <ul style="list-style-type: none"> • Referral to available drug treatment services in the community • No potential interaction with other (e.g., HIV) drugs after detoxification phase 	<p>services in the community</p> <ul style="list-style-type: none"> • Referral to available drug treatment services in the community • Withdrawal easily tolerated during taper phase
Risks to individual participants	<ul style="list-style-type: none"> • Potential unwanted disclosure of drug use status as a result of participating in study procedures • Potential distress caused by discussions of drug use and related risks • Potential for rapid return to drug use following treatment phase • Treatment participation (weekly and monthly counseling sessions) may interfere with work or social activities • Discomfort during detoxification • Medication side effects during detoxification phase 	<ul style="list-style-type: none"> • Potential unwanted disclosure of drug use status as a result of participating in study procedures • Potential distress caused by discussions of drug use and related risks • Potential for rapid return to drug use following treatment phase • Treatment participation (3 times per week medication visits and counseling visits) may interfere with work or social activities • Discomfort during induction phase • Medication side effects during year of administration • Discomfort during taper (end of treatment titration) phase
Benefits/ advantages to community/ region	<ul style="list-style-type: none"> • Increased number of professionals able to deliver drug and risk-reduction counseling and train others • Increased number of physicians able to prescribe buprenorphine and train others • Improved data regarding HIV prevalence and incidence • Improved infrastructure (laboratory, pharmacy, etc) • Increased understanding of drug use and related HIV and HCV infection rates • Possible reduced spread of HIV to IDUs and other populations • Individual drug and risk counseling manuals (translated for use in Thailand and China and possibly others) • Buprenorphine administration manuals (translated for use in Thailand, and China and possibly others) • Data to inform policy makers on the impact of detoxification and counseling (low intensity) relative to one year of BUP/NX treatment (high intensity) • Increased opportunities for regional and international collaborations and networking 	
Risks/ disadvantages to community/ region	<ul style="list-style-type: none"> • More expensive than methadone • Small risk of BUP/NX diversion to street use • Study may prove inconclusive • May conflict with country policies 	

APPENDIX VI: HPTN 058 Adverse Event Reporting and Documentation Requirements*

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	Record event and grade in primary source documents	AE LOG (DataFax to SDMC)	EAE FORM (to DAIDS RCC within 3 business days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES	YES
	Is a congenital anomaly or birth defect or fetal loss	Regardless of relationship	YES	YES	YES
	Requires or prolongs hospitalization	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	Requires intervention to prevent significant incapacity/permanent disability or death	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	Is life-threatening (including all Grade 4 AEs)	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	All other SAEs	Not related to study product	YES	YES	NO (unless directly related to study participation)
Non-Serious Adverse Events	All non-serious AEs	Regardless of relationship	YES	NO	NO

* All AEs must be documented in the participant's source record, regardless of seriousness, severity or relatedness. AEs will only be documented and reported to the SDMC/DAIDS as appropriate for participants in both study arms through week 52 of follow-up.