SUMMARY OF CHANGES
INCLUDED IN THE
FULL PROTOCOL AMENDMENT TO:

HPTN 058: A PHASE III RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE EFFICACY OF DRUG TREATMENT IN PREVENTION OF HIV INFECTION AMONG OPIATE DEPENDENT INJECTORS,
VERSION 1.0, DATED 7 OCTOBER 2005

THE AMENDED PROTOCOL IS IDENTIFIED AS
FINAL VERSION 2.0 AND DATED 16 September 2008

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the rationale are summarized briefly below and detailed in the 'implementation' section that follows. The modifications are presented generally in order of their first appearance in the study protocol.

With this amendment, the additional information included in Clarification Memo #1 to Version 1.0, dated 21 December 2005, Clarification Memo #2 to Version 1.0, dated 23 June 2006, Clarification Memo #3 to Version 1.0, dated 6 July 2007, and Letter of Amendment #1 to Version 1.0, dated 6 December 2006 are formally incorporated into the protocol document.

HPTN 058 study investigators will submit this Summary of Changes and the corresponding protocol Version 2.0 to all relevant regulatory authorities and Institutional Review Boards/Ethics Committees (IRBs/ECs) for approval. Upon completion of protocol registration procedures with the DAIDS Regulatory Compliance Center, Version 2.0 of the protocol may be implemented.

1. The primary objective of the study will now be to measure long-term (104 weeks) reduction in death as well as cumulative HIV incidence in the BUP/NX substitution arm compared to the short-term BUP/NX detoxification arm. Reduction in average HIV incidence and death overall and at 52 and 156 weeks has been listed as one of the secondary objectives. HIV incidence rates and death rates are also listed separately as secondary endpoints. This change ensued after protocol team discussion of an FDA comment, noting that assuming censoring due to death was non-informative would possibly lead to bias in the Kaplan-Meier estimates of HIV infection rates. The protocol team recognizes the very real potential for a substantial treatment effect on death outcomes in addition to HIV infection, given that a significant cause of death among injection drug users is related to injection drug behaviors, e.g. overdose. Thus it was concluded it was appropriate to include death in the primary endpoint for the intervention evaluated in this trial. Since death will now be a primary endpoint, information on death must be obtained from external sources such as death certificates or other documentation of death.

2. The team roster has been updated to reflect changes in contact information and personnel.

3. The sample size has been slightly increased from 1460 (730 in each arm) to 1500 (750 in each arm) as a result of the change in the primary objective combined with a slight decrease in the expected HIV seroincidence rate. The sample size target for each site will be based on estimated seroincidence and feasibility of enrolling the study population. 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.

4. The name of "booster sessions" has been changed to "monthly counseling sessions." This change is to reflect that these sessions are a key part of the core intervention and are not just auxiliary to the intervention. Additionally, these sessions must occur with individual participants and can no longer be conducted in groups.

5. The duration of the safety phase has been increased to 30 weeks (26 weeks for enrollment, plus four weeks follow-up of last enrolled participant) to allow for a more gradual scale up of monthly enrollment rates at the start of the study. Additionally, language has been updated regarding the primary purpose of the safety phase.

6. Specific references to the study sites being only in China and Thailand have been deleted throughout to allow for the future addition of study sites.

7. The description of the study design (Section 2.3) specifies that participants will have routine urine testing for opiates and other commonly abused drugs. The protocol has been modified throughout to indicate that urine testing will not be solely for opiates.

8. The criteria that a participant in the detoxification arm must meet in order to qualify for a second round of Suboxone detoxification have been clarified in Section 2.3 to include only the criteria for opiate dependence and no contraindications for study drug usage as indicated in other sections of the protocol. Additionally, women who complete a second round of detoxification will have another pregnancy test approximately 4 weeks after the first dose of the detoxification.

9. An evaluation of the informed consent participant comprehension quiz has been added after the signing of the enrollment informed consent. The objectives of this evaluation are 1) to evaluate the acceptability of the quiz as a tool for judging the quality of informed consent in internationally collaborative HIV prevention research; 2) to measure participants' opinions about the quiz and the overall informed consent process; and 3) to assess the relationship of these metrics to participants' socio-demographic characteristics, reported drug use, enrollment outcomes, and participant retention. In addition, by using data collected during the comprehension quiz and evaluation it will be possible to pinpoint which concepts are NOT being successfully explained to study participants during the informed consent process and to use this information to refine or enhance the process of obtaining informed consent in the trial if necessary.

10. Version 1.0 of the protocol specified that acceptability assessments would be completed at weeks 2 and 4 during the safety phase of the study. This has been modified to include acceptability assessments at week 4 only to allow participants more time to reflect on their experience with study participation.

11. The screening and follow-up HIV testing algorithms have been revised. When performing HIV testing at screening and follow-up, sites will be required to perform two rapid HIV tests and confirm all positive or discordant results. Changes to the algorithms will result in greater confidence in screening and endpoint determination. Additionally, the requirement that rapid tests be performed on venous blood has been removed to allow greater flexibility for screening.

12. Four exclusion criteria have been re-worded to clarify meaning, to be more specific and/or to improve operationalization. Specifically, to prevent individuals from leaving another treatment program just to enroll in the study, the exclusion criterion related to treatment for opioid dependence has been elaborated to indicate that participants cannot currently be receiving treatment guided by a clinician or have received treatment within the last twelve weeks. Also, the criterion related to dependence on alcohol and benzodiazepines has been strengthened because of safety concerns related to use of Suboxone in participants who are dependent on these substances.

13. The protocol has been clarified to allow for potential participants to be re-screened for the study only once after 30 days from the initial screening blood draw.

14. An HIV assay to screen individuals for evidence of recent infection (BED and other assays) will be performed at sites participating in evaluation of HIV incidence for individuals who have a positive confirmatory HIV test at screening. Samples from individuals with positive BED and other assay results will be shipped to the HPTN Network Laboratory for additional testing with other assays. The assays for HIV incidence, which will be performed on batched specimens, will give a cross-sectional estimate of incidence within the IDU population. This early incidence information will give guidance to the HPTN in determining the feasibility of conducting the trial at the existing study sites, and the impact on sample size. Only those HIV-positive patients who consent to screening will be included in the extra testing. Since assays for estimating recent infection are not approved for clinical use, results will not be provided to participants.

15. The language in section 3.5.1 that indicated that participants who are absent from study visits for more than 12 weeks could not resume study drug dosing or counseling has been removed. The protocol team would like participants to be exposed to as much of the intervention as possible for clinical benefit and given the intent to treat analysis.

16. The definition of how adherence will be measured has been clarified. Additionally, per regulations in each participating country, only those authorized to dispense medications will be allowed to do so; therefore, redundant language has been removed.

17. To allow for greater flexibility in scheduling, it has been clarified that monthly counseling sessions and urine testing for opiates and pregnancy will be conducted approximately every four weeks and are not required to occur at the same time as counseling visits.

18. Several changes have been made to the drug dosing guidelines. Drug dosing at induction has been revised to comply with Treatment Improvement Protocol 40 (TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction), which is the US standard for training of Suboxone practitioners. All participants will begin with a 4 mg dose of BUP/NX. The dosing regimen has been clarified to give flexibility to site clinicians when determining daily dosing schedules and to make criteria for eligibility for a second detoxification at six months less restrictive. Additionally, the term “permanent” has been removed when referring to discontinuation of the study drug to allow participants in the substitution arm to restart the drug following a discontinuation in use if they continue to have a demonstrated need for treatment.

19. To allow for greater flexibility at the sites, it has been clarified that the order of screening procedures should be followed as written in the protocol but can be modified if needed. Additionally, the Enrollment/ Randomization Procedures have been clarified.

20. The protocol is clarified throughout to allow for site specific choice for HCV testing. For study purposes Hepatitis C infection may be diagnosed by two different reactive HCV antibody enzyme

immunoassays, a positive HCV RNA assay, or a positive HCV recombinant immunoblot assay (RIBA).

21. ALT and bilirubin tests have been specified to occur at weeks 12 and 40 in addition to tests conducted at the weeks 26 and 52 follow-up visits. It has also been clarified that the liver function tests are not required to occur at the same time as a counseling visit, although this is preferable to reduce participant and staff burden and improve compliance.

22. To eliminate an internal inconsistency, the protocol has been corrected to reflect that social harms will be actively monitored only at follow-up visits every six months, as well as weekly for the first four weeks for participants in the safety phase. 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 to the study database.

23. Plans for interim analysis have been modified and expanded based on recommendations from the study DSMB.

24. A discrepancy in the secondary analysis related to measurement of the frequency of drug use has been corrected.

25. The specimen storage requirements identified in the protocol are clarified to require storage of blood specimens only. The protocol does not require storage of urine specimens.

26. The protocol has been modified to indicate that protocol registration will be handled in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual and will not be handled via the HPTN CORE.

27. The distribution of the Study Specific Procedures (SSP) Manual has been specified and the website address where it can be accessed has been added.

28. Discrepancies in the enrollment informed consent forms for the safety phase and full study have been corrected.

29. A table summarizing the adverse event reporting and documentation requirements has been added as Appendix VI.

30. Substitution Treatment Arm Dosing has been clarified to specify that daily dosing will take place up to 21 days (until dose stabilization).

31. Detoxification Treatment Arm Dosing has been clarified to specify that dosing will take place up to 18 days.

32. The Schedule of Procedures and Evaluations in Appendix IA for the Full Study has been updated reflecting all changes between protocol versions 1.0 and 2.0.

33. Minor clarifications to the Informed Consent Forms including information regarding local regulations for HIV and STI reporting, pregnancy testing, and referrals.

34. Clarification that Hepatitis testing will take place at Week 26, but does not have to take place at Week 52.

35. Minor wording changes and modifications, such as correcting inaccurate references to section numbers, adding the IND number (73,797) and DAIDS Document ID (10144)**,** deleting US National Institute of Mental Health as a sponsor, adding Office of Human Research Protection (OHRP) to the List of Abbreviations and Acronyms, and changing the name of the Central Laboratory to Network Laboratory, have been incorporated throughout.

Implementation of Modifications

The following changes have been incorporated into the text of DRAFT Regulatory Version 1.9 of HPTN 058, dated 26 August 2008). Deletions in the protocol text are indicated by strikethrough and additions are indicated in **bold**.

1. Study Objectives:

- The study title has been changed throughout to:

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

- *Protocol Schema, Purpose:* To determine the efficacy of a drug treatment ~~program~~ **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.

- *Protocol Schema and Section 2.1, 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.

- *Protocol Schema and Section 2.2, 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 ~~increases~~ **decreases** average HIV ~~free survival~~ **incidence** compared to detoxification treatment; and HIV ~~free survival~~ **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…

- *Section 7.1, Study Design, first paragraph:* 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 BUP/NX detoxification and counseling.

- *Section 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**.

- *Section 7.2.1, Primary Endpoint:* HIV-1 infection **or death by** ~~at~~ the 104 week visit

- *Section 7.4, Sample Size, Effect Size, and Accrual:*

  The combined targeted event rate (HIV infections and Death) in the detoxification arm at 104 week 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, ~~the current observed~~ **projected** annual seroincidence rates among injectors per 100 person years are ~~8~~**3**.0 in ~~Thailand~~ **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.** ~~Assuming equal enrollment at all three sites, the mean annual seroincidence rate would be 6.0~~

  ~~In the substitution treatment arm, where risk reduction counseling is combined with BUP/NX, 60% effectiveness is expected, i.e., a mean annual seroincidence rate of 2.40 is expected. In the detoxification arm, the detoxification and r~~**R**isk reduction counseling ~~are~~ **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 $1 - (1- 0.0541*0.8)^2 = 0.085$.** ~~i.e., a mean annual seroincidence rate of 4.7 is expected.~~ This 20% **overall** reduction also ~~includes~~ **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.

  ~~Over the course of the 24 months of follow-up, the projected proportion of seroconverters in the detoxification arm is therefore 9.4%. BUP/NX and counseling for 52 weeks is projected to reduce the proportion of seroconverters in the substitution treatment arm to 4.8% over 2 years.~~

  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] ~~In the event that death is not independent of HIV seroincidence, a~~ **A**nalysis of the efficacy endpoint of HIV-free survival ~~would be~~ **is** free of the bias induced by the ~~resulting~~ informative censoring **that would result if HIV incidence were the primary endpoint and deaths were censored**. Thus HIV free survival is ~~an important secondary~~ **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. ~~A similar effect size is hypothesized for HIV-free survival. At the Thailand site, 14 deaths have been observed in 300 IDUs followed for 2 years in the OUR study, giving a mortality rate of about 2.33 per 100 person years. In HPTN 033, 8 deaths were observed in Xinjiang and 2 in Guangxi over a one year follow-up period. Based on this, we anticipate rates of HIV-free survival in the range of 86-90% in the two years of follow-up.~~

- *Section 7.4.2, Effect Size, last paragraph:* The data from these protocols support the effect size estimates of 50% **reduction in HIV infection at 2 years** used in HPTN 058~~, where assuming a baseline rate of 6/100 person years, we project the proportion of seroconverters at 104 weeks to be 4.7% in the substitution treatment arm compared to 9.4% in the detoxification arm~~.

- *Section 7.~~7~~6.1, Primary Analysis, first paragraph, last sentence:* Endpoints will be compared between treatment arms using Kaplan Meier estimates of the proportion uninfected **and living** ~~after~~ **by** the 104-week visit~~, and~~ with variances estimated by Greenwood's formula.

- *Section 7.~~7~~6.2, 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 substitution treatment ~~increases~~ **decreases** average HIV~~-free survival~~ **incidence** compared to detoxification treatment; and **decreases** HIV~~-free survival~~ **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.

- *Appendix III- A,B,C,D Sample Consents, Introduction, first paragraph, second sentence:* The research study will test whether a drug treatment program can reduce the ~~spread of HIV~~ **number of deaths and HIV infections** in injection drug users by reducing drug use and other risky behavior.

- *Appendix III-A,B,C,D, Sample Consents, Why is this research being done, first paragraph, first sentence:* The purpose of the research is to compare how well two different treatments help ~~prevent the spread of HIV~~ **reduce the number of deaths and HIV infections** among injection drug users by reducing drug use and other risky behavior.

2. Personnel:

The protocol title page and team roster have updated to reflect the following:

- Shao Yiming, MD has been added as a Protocol Co-Chair
- Apinun Aramrattana, MD, PhD has been named as a Protocol Co-Chair
- Monica Ruiz, PhD, MPH has been deleted as the DAIDS Program Officer.
- Jack Blaine, MD has been changed from the NIDA Medical Officer to a Protocol Consultant.
- Liping Fu has replaced Yuanzhi Zhang as a China investigator.
- Huguette Redinger has replaced Tom Perdue as the SDMC Project Manager.
- Deborah Hilgenberg has been removed as a CORE Protocol Specialist, Scott Mitchell Rose has replaced Bethany Freeman, and Nirupama Sista, Philip Andrew, and Bonnie Dye have been added.
- Paul Richardson, MSc and William Clarke have replaced Hua Shan as Network Lab Representatives.

- Paul Fudala, PhD has been removed as a Pharmaceutical Liaison.
- Xiaofang Yu has been removed as a Johns Hopkins Representative.
- Bariatu Smith and Lynnea Ladouceur have been added as OCSO Representatives.
- The contact information for Katie Shin, Liu Wei, and Deborah Donnell has been updated.

3. Sample Size:

- *Protocol Schema, Study Size:* ~~1460~~ **1500** opiate dependent injection drug users.

- *Protocol Schema, Treatment Regimen, first column of table:* Substitution Treatment Arm n = ~~730~~**750**; Detoxification Treatment Arm n = ~~730~~**750**

- *Overview of Study Design and Randomization Schema:* The boxes indicating the number randomized into each arm have been updated to 750 from 730.

- *Section 3.0, Study Population, the following paragraph will be added at the end of the section:* **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.**

- *Section 3.4, Screening and Enrollment Process, first sentence:* A total of ~~1460 total~~ **1500** participants will be enrolled in the study across all of the participating sites.

- *Section 7.1, Study Design, second paragraph, last sentence:* A total of ~~1460~~ **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.

- *Section 7.1, Study Design, first column of table:* Substitution Arm n = ~~730~~**750**; Detoxification Arm n = ~~730~~**750**

- *Section 7.4.1, Sample Size:* To achieve 90% power for ~~50%~~ reduction in the probability of **HIV** infection **or death** at 104 weeks from ~~9.4~~ **12.5**% to ~~4.7~~ **7.25**% requires a total of ~~1236~~ **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**~~5~~%, a projected total enrollment of ~~1460~~ **1500** (~~730~~**750** participants per arm) is required.

  A total enrollment of ~~1460~~ **1500** will yield an approximate sample of 1290 for the HIV-free survival endpoint, assuming **an additional** 4% ~~of the 15%~~ loss to follow-up ~~is~~ attributable to censoring due to death. The power for ~~this composite~~ **the HIV infection** endpoint is given below for a range of potential rates for HIV infection ~~or death~~, assuming 50% efficacy as for the HIV infection endpoint.

Power for the HIV infection ~~or Death~~ Endpoint.		
Substitution Arm	Detoxification arm	Power
~~5~~**3**.5%	~~10.9~~ **7.0**%	~~94.4~~ **92.8**
~~6.3~~ **4.25**%	~~12.4~~ **8.5**%	~~96.7~~ **88.0**
~~7.1~~ **5.0**%	~~13.9~~ **10.0**%	~~98.1~~ **80.7**

- *Section 7.4.3, Accrual:* Each site is expected to enroll 50 participants in approximately ~~three~~ **the first six** months during the safety phase of the study. The remaining ~~1310~~ participants will be enrolled over approximately 24 months. The actual number accrued at each site ~~is expected to be approximately equal~~ **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.

- *Section 7.5, Random Assignment, first sentence:* Participants will be randomized in a 1:1 ratio, with ~~730~~**750** participants in each arm.

- *Section 7.~~6~~**7.1, Primary Analysis, third paragraph, first sentence:* 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 ~~5~~**10**% at two years.

- *Appendix III- A,B,C,D Sample Consents, Why is this research being done, third paragraph, second sentence:* A total of about ~~1460~~ **1500** people will participate in the study in ~~these two countries~~ **[the study countries**]. **About [approximate site-specific accrual target] people will be in the study here in [study site].**

4. Monthly Counseling Sessions

- *Protocol Schema, Treatment Regimen, second column of table, Substitution and Detoxification Arms, second bullet:* Weekly individual drug- and risk-reduction counseling for twelve weeks, followed thereafter by ~~booster~~ **monthly counseling** sessions every four weeks through week 52.

- *Overview of Study Design and Randomization Schema:* The boxes indicating the counseling sessions that will occur following the first 12 weeks of the study have been updated as follows: ~~Booster~~ **Monthly** counseling sessions every 4 weeks through week 52

- *Section 2.3, Study Design, first paragraph, first bullet:* "Substitution Treatment" Arm – sublingual BUP/NX administered three times per week for 52 weeks in addition to weekly drug- and risk-reduction counseling for twelve weeks followed by ~~booster~~ **monthly counseling** sessions every four weeks through week 52;

- *Section 2.3, Study Design, first paragraph, second bullet, first sentence:* "Detoxification Treatment" Arm – short-term BUP/NX detoxification in addition to weekly drug- and risk-reduction counseling alone for twelve weeks followed by ~~booster~~ **monthly counseling** sessions every four weeks through week 52.

- *Section 3.5.1, Missed Treatment Visits, first paragraph, first sentence:* Participants in either study arm who miss study visits for more than two weeks ~~but less than twelve~~ weeks may resume weekly counseling sessions (during the first twelve weeks of study participation) and ~~booster~~ **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** ~~No participant will receive BUP/NX beyond 52 weeks from the time of enrollment. Individuals who miss two or more consecutive days of study medication~~ may need to repeat BUP/NX induction. **No participant will receive BUP/NX beyond 52 weeks from the time of enrollment.**

- *Section 3.5.1, Missed Treatment Visits, second paragraph, last sentence:* These participants may continue counseling visits, ~~booster~~ **monthly counseling** sessions, and follow-up visits as regularly scheduled.

- *Section 3.5.1, Missed Treatment Visits, third paragraph, first sentence:* 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 ~~booster~~ **monthly counseling sessions** and follow-up visits as originally scheduled unless otherwise specified.

- *Section 4.2, Description of the Counseling Intervention, last paragraph, first sentence:* These counseling services will be delivered weekly for 12 weeks followed by ~~booster~~ **monthly counseling** sessions every four weeks through week 52.

- *Section 4.2.2, ~~Booster~~ **Monthly Counseling** Sessions:*

  The **monthly** counseling ~~booster~~ sessions, beginning during ~~the fourth month~~ **Week 16** and continuing through the end of ~~month~~ **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. ~~At the site's discretion, booster sessions can be conducted with individual participants or in groups separated by study arm, that is, substitution treatment arm participants will attend booster sessions only with other substitution treatment arm participants and the same will apply to detoxification participants.~~

- *Section 5.3.3, ~~Booster~~ **Monthly Counseling** Sessions, last sentence:* ~~Booster~~ **Monthly counseling** sessions can be combined with dispensing and follow-up visits.

- *Section 5.5, Assessments during Full Study, last sentence:* Follow-up visits can be combined with ~~booster~~ **monthly counseling** sessions and BUP/NX dispensing visits.

- *Section 7.1, Study Design, second column of table, Substitution and Detoxification Arms:* Weekly individual drug- and risk-reduction counseling for 12 weeks, followed thereafter by ~~booster~~ **monthly counseling** sessions every 4 weeks through week 52.

- *Appendix I-A: Schedule of Procedures and Evaluations – Full Study, item 26:* ~~Booster~~ **Monthly counseling** sessions every four weeks

5. Safety Phase:

- *Protocol Schema, Study Duration, second sentence:* The initial safety and feasibility phase will take approximately **30**~~16~~ weeks **at each site, with 26 weeks to enroll the targeted 50 participants plus four weeks to complete the last safety phase visit.**

- *Section 2.3, Study Design, second paragraph:* The total duration of the study will be approximately four and a half years. The initial safety and feasibility phase will take approximately **30**~~16~~ weeks…

- *Section 2.3.1, Safety and Feasibility Phase, first sentence:* The study will begin with a safety phase during which each site will enroll 50 participants over a period of approximately ~~three~~ **six** months.

- *Section 2.3.1, Safety and Feasibility Phase, second sentence:* The primary purpose of this initial phase is to collect detailed safety data that ~~may be required by the Chinese authorities to allow importation of BUP/NX for the full study. These data~~ will ~~also~~ 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.

- *Section 7.1, Study Design, second paragraph:* The study will be a phase III, multi-site, two-arm, randomized trial. **In** an initial safety phase**,** ~~will include~~ the first 50 study participants at each site~~, who~~ will undergo randomization and ~~one~~ **in their first** month ~~of~~ **receive more** intensive monitoring, ~~followed by standard study procedures and~~ **before reverting to the standard study monitoring schedule. These first 50 participants** will therefore contribute to the full study analysis.

- *Section 7.4.3, Accrual, first sentence:* Each site is expected to enroll 50 participants in approximately ~~three~~ **the first six** months during the safety phase of the study.

6. Study Sites:

- *Protocol Schema, Study Sites:* The study will be conducted at **a minimum in** HPTN sites in Guangxi and Xinjiang, China and Chiang Mai, Thailand.

- *Section 1.2, Rationale, second paragraph:* 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 ~~(see Section 3.3)~~, 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 lower incidence rates among this population than seen in the NIDA Prevalence Study.

Importantly, existing drug treatment strategies in ~~each of these settings~~ **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.

- *Section 1.2.1, Expanded Treatment Options, first paragraph, second sentence:* Methadone (and buprenorphine to a lesser extent) is available ~~in both China and Thailand~~ **at the study sites** on a very limited basis.

- *Section 2.3, Study Design, first paragraph, first sentence:* This is a phase III, multi-site, two-arm, randomized, controlled trial to be conducted **at a minimum** in China and Thailand.

- *Section 3.0, Study Population, second paragraph:* Participants will be enrolled at **a minimum in** HPTN sites in China and Thailand. **Additional sites may be added in the future.**

- *Section 3.2.1, Women and Contraception, third sentence:* Available contraception in ~~China and Thailand~~ **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.

- *Section 3.3, Recruitment ~~Setting and~~ Process:* ~~In China and Thailand,~~ 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 ~~the~~ HPTN 033 **and 037** ~~study in which the China sites participated and in HPTN 037 in which Thailand is participating~~. 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 heath 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.

~~Chiang Mai, Thailand~~

~~IDUs in Thailand will be recruited using primarily street outreach and respondent-driven sampling in Chiang Mai and nearby provinces in upper northern Thailand. The site will also collaborate with the Chiang Mai Drug Dependence Treatment Center (CDTC), which services Chiang Mai and nearby provinces including Lampang, Lamphun, Payao and Chiang Rai, and with the Outpatient Psychiatric Clinic of the Chiang Mai University Hospital. The CDTC has both inpatient facilities in Chiang Mai and outpatient facilities in Chiang Mai and Lampang. It is operated by the Department of Medical Services, Ministry of Public Health. Patients are admitted for a maximum stay of 45 days; approximately 25% of patients leave against medical advice. It is estimated that the relapse rate among injection drug users is 90% within one year and, based on re-admission data, is over 50% within the first three months following discharge.[133] The clinic at Chiang Mai University Hospital is operated by academic psychiatrists within the Faculty of Medicine and provides both short- and long-term methadone treatment programs for a small number of patients. Given the high rate of relapse, patients will be given a study brochure upon release from treatment and told to contact the study in the future if they are interested.~~

~~Chiang Mai began recruiting IDUs for HPTN 037, a behavioral study of drug users and their sex and/or drug sharing partners, in March 2004. As of November 16, 2004, the site had successfully recruited 234 participants from both rural and urban areas of Chiang Mai. Attendance at the education sessions has been approximately 93%. During screening, HIV prevalence has been 16%; no incidence data is available yet.~~

~~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. In Chiang Mai, HIV-positives can receive ART, but the cost is high. The current universal insurance scheme does cover the ART under a special program called NAPHA; however, to date, few IDUs have actually used the service perhaps because of the fear of exposing themselves as drug users.~~

~~Urumqi, Xinjiang Province, and Guangxi Province, China~~

~~The Chinese Ministry of Health estimates that there were approximately 840,000 cases of HIV at the end of 2003 in China. Although only about 5% of HIV/AIDS cases are reported in China, available HIV prevalence data indicate 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.~~

~~HPTN 033 enrolled 1009 HIV-negative injecting drug users in Urumqi, Xinjiang and Heng County, Guangxi within six months using street outreach and community based, respondent driven sampling. The prevalence of HIV among those screened for the study was 29% in Xinjiang and 25% in Guangxi. Retention in Xinjiang was 93% at twelve months, and was slightly lower in Guangxi (87%), largely due to migration to the neighboring province. The seroincidence was 8.8 and 3.1 per 100 person years in Xinjiang and Guangxi, respectively. As in HPTN 033, IDUs in Guangxi and Xinjiang will be recruited using primarily street outreach and respondent-driven sampling during 058. These HPTN sites have well-developed infrastructure and could, if needed, quickly expand enrollment locations to nearby cities if recruitment and retention prove inadequate in Urumqi and Heng County.~~

~~The Guangxi Province, in the southwest of China, has 46.8 million people and shares a border with Vietnam. Nanning is a city of about two million people and contains the CDC laboratory and data management facilities. In 2003, 3132 cases of HIV were reported in Guangxi; 80.4% were in IDUs.[128] Enrollment sites in Guangxi Province for HPTN 058 will be in Heng County where HPTN 033 was conducted, and possibly one other location in the province, the most likely being in Ningming, a city of 400,000 close to the Vietnam border. Given the central location of Nanning, other recruitment sites are feasible within the province if enrollment is slower than anticipated in Heng County. Medecins sans Frontiers provides free comprehensive care and ART to Nanning and Heng county residents, and ART is also available at several hospitals and clinics in Nanning, though patients need to pay for testing and other services. China Comprehensive AIDS Response (CARES) sites are expanding in Guangxi province, including Heng County.~~

~~Xinjiang province's capital, Urumqi, is a large industrial city in the northwest of China, with a population of two million people. There are approximately 10,000 registered (i.e., known to the police) drug users, though this is thought to be a serious underestimate. Another possible enrollment site is in Yili, about an hour from Urumqi, where drug use and HIV prevalence are very high. Xinjiang province is 47% Uighur (ethnic minority); in HPTN 033, 59% of the sero-conversions were within the Uighur population. Free ART medication is available in Urumqi. However, like in Guangxi, patients must pay for testing, physician consultations, and treatment for opportunistic infections. China CARES is expected to begin in 2005; local public hospitals and CDC clinics can provide basic health care and treat opportunistic infections.~~

- *Section 6.1, Safety Monitoring, first paragraph, second sentence:* There is no *a priori* expectation that the safety profile will differ in the HPTN 058 study population ~~in China and Thailand~~; nonetheless, close safety monitoring is planned.

- *Section 8.4, Benefits, first paragraph, fourth sentence:* 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 ~~in China and Thailand~~ planned for this study.

- *Appendix III- A,B,C,D Sample Consents, Why is this research being done, third paragraph:* ~~This study will take place in China and Thailand.~~ A total of about ~~1460~~ **1500** people will participate in the study in ~~these two countries~~ **[the study countries**].

7. Testing for Opiates and Other Drugs:

- *Overview of Study Design and Randomization Schema, box following initial eligibility screening:* Baseline HIV Risk Survey; ~~Opiate~~ **Drug** and Pregnancy testing

- *Section 2.3.2, Assessments during the Safety and Feasibility Phase, sixth bullet:* Urine tests for ~~opiate~~ **drug** use

- *Section 3.4, Screening and Enrollment Process, Screening Visit, first paragraph, seventh sentence:* A urine specimen for testing for pregnancy (for all women) and opiates **and other drugs** will be collected.

- *Section 5.1, Screening Visit, first bulleted section, fourth bullet:* Urine collection (pregnancy and ~~opiate~~ **drug** tests)

- *Section 5.3.2, Drug and Risk-Reduction Counseling Visits, first paragraph, second sentence:* …participants will be asked to provide urine for ~~opiate~~ **drug** testing …

- *Section 5.3.3, ~~Booster~~ **Monthly** Counseling Sessions, second sentence:* At each of these sessions, participants will be asked to update their locator information and provide urine for ~~opiate~~ **drug** and pregnancy testing (for women in the substitution treatment arm only).

- *Section 5.4, Assessments during Safety Phase, sixth bullet:* Urine tests for ~~opiate~~ **drug** use

- *Section 5.5, Assessments during Full Study, first paragraph, first sentence:* 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**.

- *Section 5.5.1, 26 and 52 Week Visits, seventh bullet:* Urine testing for opiates **and other drugs**

- *Section 5.5.1, 26 and 52 Week Visits, eighth bullet:* Pregnancy urine test for women in substitution arm **and women in the detoxification arm who are undergoing a second induction**

- *Section 5.5.2, 78, 104, 130, and 156 Week Visits, third bullet:* Urine testing for opiates **and other drugs**

- *Section 9.1, first paragraph, first sentence:* 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 ~~opiate~~ **drug** and pregnancy testing.

- *Appendix I-A and I-B: Schedules of Procedures and Evaluations, Item 22:* Urine Test for Opiates **and Other Drugs**

- *Appendix III-A and C: Sample Screening Consents, What will happen if you agree to the study screening, first paragraph, fifth sentence:* You will be asked to provide a urine sample to test for opiates **and other drugs**.

- *Appendix III-B: Sample Enrollment Consent for Safety Phase, What will happen if you agree to take part in this study, Treatment Visits, second paragraph, sixth sentence:* We will also test your urine for opiates **and other drugs**.

- *Appendix III-B: Sample Enrollment Consent for Safety Phase, What will happen if you agree to take part in this study, Treatment Visits, fourth paragraph, last sentence:* All participants will have a urine test for opiates **and other drugs** ~~once a month~~ **every four weeks** for a year.

- *Appendix III-D: Sample Enrollment Consent for Full Study, What will happen if you agree to take part in this study, Treatment Visits, third paragraph, sixth sentence:* All participants will have a urine test for opiates **and other drugs every four weeks** ~~once a month~~ for a year.

8. Detoxification Criteria:

- *Section 2.3, Study Design, second bullet, second sentence:* The detoxification regimen may be repeated at the 26 week visit if the participant meets the same ~~eligibility~~ criteria **for opiate dependence** as at screening **and has no contraindications for short-term study drug use**. **Women who receive a second detoxification regimen will have another pregnancy test on the day of the first treatment dose and approximately four weeks later.**

- *Section 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~~., the following will be repeated to determine eligibility for second detoxification:~~

  ~~o Interviewer-administered eligibility questionnaire, including DSM-IV diagnosis~~
  ~~o Hepatitis B surface antigen and hepatitis C antibody testing if needed~~

9. Informed Consent Evaluation:

- *Section 2.3, Study Design:* The following paragraph will be added to the end of the section:

  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.

- *Section 3.4, Screening and Enrollment Process, 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 quiz after signing the consent form.** Those who are hepatitis B (HBV) negative will be offered the first dose of the HBV vaccine…

- *Section 5.2, Enrollment/Randomization, first paragraph:* 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…

- *Section 8.2, Informed Consent, third paragraph:* 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.** ~~Each site will be responsible for implementing procedures to ensure that participants understand the study and for writing these procedures in an SOP prior to activation. This could entail a "consent quiz" or open-ended questions that will be documented in chart notes.~~

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

- *Appendix III-B and D: Sample Enrollment Consents, What will happen if you agree to take part in this study, first paragraph:* 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 ~~fully~~ 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…

10. Acceptability Assessments

- *Section 2.3.2, Assessments during the Safety and Feasibility Phase, last bullet:*
  - Acceptability assessment at week~~s 2 and~~ 4
- *Section 2.3.2, Assessments during the Safety and Feasibility Phase, next to last paragraph:* Each participant will complete an intervention acceptability assessment at the completion of the ~~second week of the study, and again at completion of the~~ fourth week **of the study**.

- *Section 5.4, Assessments during Safety Phase, last bullet:*
  - Acceptability assessment at week~~s 2 and~~ 4

- *Appendix I-B: Schedule of Procedures and Evaluations—Safety Phase:* Under "Intervention Acceptability Assessment" remove X in Week 2 column.

11. HIV Testing

- *Overview of Study Design and Randomization Schema:*

HIV- **(as evidenced by two rapid tests)**

- *Section 3.1, Inclusion Criteria, third bullet:*

    - HIV-uninfected **as evidenced by two different rapid tests** on specimen obtained within 28 days of enrollment

- *Section 3.4, Screening and Enrollment Process, third paragraph:* Participants will be given their **rapid** HIV test result**s** and post-test counseling the same day if possible. Individuals ~~with positive HIV test results~~ **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…**

- *Section 5.1 Screening Visit, beginning after second paragraph:*

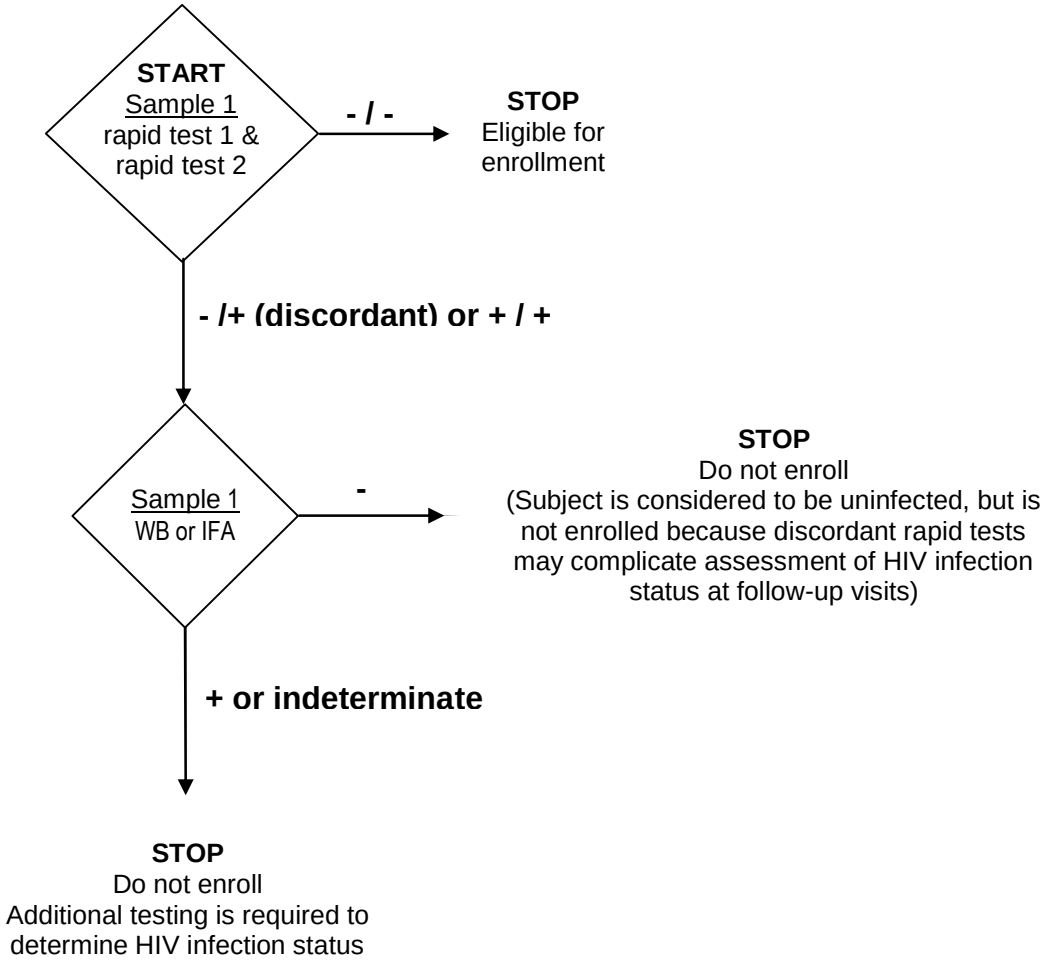
    - Pre-test HIV counseling
    - Blood draw for the following laboratory tests:
        - ~~Rapid~~ HIV test**ing**
        - Hematology (CBC and platelet count)
        - Hepatitis B surface antigen and hepatitis C antibody testing
        - Blood chemistry (creatinine)
        - Liver function tests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

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

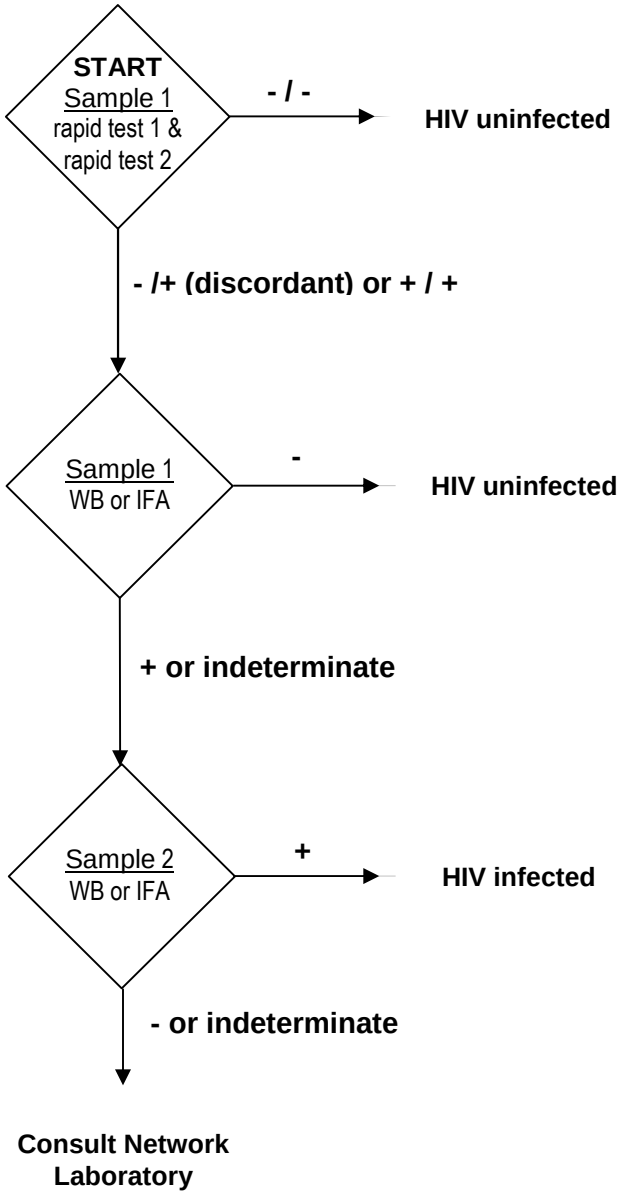
    When results of the HIV **rapid** test**s** are available (approximately 20-40 minutes later for most volunteers), participants will receive HIV post-test counseling. Individuals **who require confirmatory testing are not eligible for the study but** ~~whose initial rapid test is positive~~ will be asked to return to the clinic in about a week to receive **their** results ~~of the WB or IFA and other lab tests;~~ **however, they may be rescreened according to protocol requirements if the Western blot result proves negative**. Individuals who ~~test positive on the second test~~ **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**...**

- Appendix II-A and II-B, HIV testing algorithms have been replaced entirely with the following algorithms:

APPENDIX II-A: HIV Antibody Testing Algorithm – Screening



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



- *Appendix III-A and III-C, Screening consents, What will happen if you agree to the study screening, second paragraph, fifth sentence:* We will use ~~a~~ rapid HIV test**s**, so your results should be ready in about 20 to 40 minutes…

- *Appendix III-A and III-C, Screening consents, What will happen if you agree to the study screening, third paragraph: If your ~~first~~ HIV test shows you* ***~~are~~ 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. ~~If this second test shows that you are infected with HIV, you are not eligible for the study and screening will stop.~~ 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…

- *Appendix III-A and III-C, Screening consents, What will happen if you agree to the study screening, fourth paragraph:* **If you agree, ~~Y~~y**our blood specimen will be stored and tested later to look for additional evidence of infection with HIV…

- *Appendix III-B and D, What will happen if you agree to take part in this study, Follow-up Visits, second paragraph:* You will receive HIV counseling and testing at every follow-up visit. We will use ~~a~~ rapid HIV test**s**, so your results should be ready in about 20 to 40 minutes…

12. Exclusion Criteria

*Section 3.2 Exclusion Criteria***:**

- Current **or recent (within the last 12 weeks) clinician-guided** treatment **for opioid dependence** with methadone, ~~morphine,~~ LAAM, **buprenorphine,** naltrexone, or nalmefene, according to self-report
- Current enrollment in another HIV prevention or drug use intervention study
- Known ~~hypersensitivity~~ **clinically-diagnosed allergy** to buprenorphine or naloxone, according to self-report
- ~~Requiring immediate medical attention~~ **Meets DSM-IV criteria** for dependence on alcohol~~,~~ **or** benzodiazepines ~~or~~**; requiring immediate medical attention for dependence on** other substances (except tobacco), as judged by study clinician.
- Currently injecting substances other than opiates more than twice ~~per month~~ **in the last 28 days**, according to self-report

13. Re-screening:

- *Section 3.4, Screening and Enrollment Process:* The following sentence has been added to the end of the first paragraph: **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.**

- *Section 5.*1, *Screening Visit: The following has been clarified in the fourth paragraph:* 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 the protocol requirements if the Western blot result proves negative**.

14. Testing for Recent HIV Infection:

- *Overview of Study Design and Randomization Schema:* A new box has been added indicating that additional testing will be performed on samples from individuals confirmed to be HIV infected at screening to **screen individuals for evidence of recent infection (BED and other assays).**

- *Section 3.4, Screening and Enrollment Process, Screening Visit:* The following paragraph will be added to the end of the section:

  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.

- *Section 9.1, Local Laboratory Specimens:* The following paragraph will be added after the first paragraph: **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.**

- *Section 9.2, ~~Central~~ **Network** Laboratory Specimens, first paragraph:* None of the routine laboratory tests for this study will be conducted at the HPTN ~~Central~~ **Network** Laboratory (~~CL~~ **NL**). However, a sample of specimens will be retested by the ~~Central~~ **Network** Laboratory at the site or at the HPTN ~~Central~~ **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.**

- *Appendix III-A and C: Sample Screening Consents, What will happen if you agree to the study screening, third paragraph, last sentence:* Your blood specimen will be ~~discarded~~ **stored and tested later to look for additional evidence of infection with HIV. We will not contact you with the results from 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.**

15. Missed Treatment Visits:

- *Section 3.5.1, Missed Treatment Visits, first paragraph, first sentence:* Participants in either study arm who miss study visits for more than two weeks ~~but less than twelve weeks~~ may resume weekly counseling sessions…

- *Section 3.5.1, Missed Treatment Visits, first paragraph, last sentence:* Individuals who miss ~~three~~ **two** or more consecutive ~~days~~ **weeks** of study medication may need to repeat BUP/NX induction.

- *Section 3.5.1, Missed Treatment Visits, third paragraph:* ~~If a participant in either arm is absent from study visits for more than twelve weeks, s/he will be considered a treatment failure and~~

~~cannot resume counseling visits or BUP/NX dosing.~~ 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…

- *Section 4.4.1, Criteria for Adjusting or Discontinuing ~~Temporarily Withholding or Adjusting~~ Study Drug, second paragraph, second sentence:* If drug interruption occurs for ~~three days~~ **two weeks** or longer, induction may need to be repeated.

16. Adherence Monitoring:

- *Section 4.1, Adherence, first paragraph, third sentence:* Adherence will be ~~measured based on the percentage of completed counseling and BUP/NX dispensing visits in each arm~~ **monitored using attendance at counseling visits and dispensing of BUP/NX.**

- ***Section 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. ~~Staff with appropriate credentials in their country will be responsible for dispensing the study drug to participants.~~

17. Urine Test and Monthly Counseling Session Timing:

- *Section 4.2, Description of the Counseling Intervention, fifth paragraph, first sentence:* These counseling services will be delivered weekly for 12 weeks followed by ~~booster~~ **monthly counseling** sessions **approximately** every four weeks through week 52.

- *Section 4.4.2~~3~~, Considerations for Women who Become Pregnant during the Study, second paragraph, first sentence:* Urine pregnancy tests will be performed **approximately** every four weeks during BUP/NX treatment.

- *Section 5.3.2, Drug and Risk-Reduction Counseling Visits, first paragraph:* 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 ~~opiate~~ **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.

- *Section 5.3.3, ~~Booster~~ **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…

- *Appendix I-A: Schedule of Procedures and Evaluations – Full Study, Footnote #3:* **Approximately** every four weeks

- *Appendix III-B: Sample Enrollment Consent for Safety Phase, What will happen if you agree to take part in this study, Treatment Visits, third paragraph:* 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.

- *Appendix III-B and D: Sample Enrollment Consents, Are there risks related to pregnancy, first paragraph, third sentence:* Women must have a pregnancy test before entering this study **and every month while taking Suboxone.**

- *Appendix III-D: Sample Enrollment Consent for Full study, What will happen if you agree to take part in this study, Treatment Visits, third paragraph:* You will talk with a counselor every week for 12 weeks for about 45 minutes. After the first 12 weeks, you will return ~~once a month~~ **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.

18. Dosing Guidelines

- *Section 4.3.3 Treatment Dose and Administration, Detoxification Treatment Arm first paragraph:* 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 ~~or 8~~ mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total ~~minimum~~ first day's dosage of 8 mg. ~~Patients may receive an additional dose (or doses) up to a maximum, total first-day dosage of 16 mg.~~ Up to ~~32~~**16** mg may be given on Day~~s~~ 2 **and 32 mg on Day** 3 depending on individual response.[135]

- *Section 4.3.3, Treatment Dose and Administration, Detoxification Treatment Arm second paragraph, first sentence:* 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.

- *Section 4.3.3 Treatment Dose and Administration, Substitution Treatment Arm first paragraph:* 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 ~~or 8~~ mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a ~~minimum~~ total first day's dosage of 8 mg. ~~Patients may receive an additional dose (or doses) up to a maximum, total first-day dosage of 16 mg.~~ **On Day 2, up to 16 mg may be given.** Up to 32 mg may be given on Day ~~2~~**3** and thereafter until three-times-weekly dosing begins…

- *Section 4.4, Toxicity Management, last sentence:* The PSRT will also participate in the decision-making regarding study drug ~~interruption~~, **discontinuation and** resumption ~~and permanent discontinuation~~.

- *Section 4.4.1:*

4.4.1 Criteria for **Adjusting or Discontinuing** ~~Temporarily Withholding or Adjusting~~ 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 ~~withheld~~ **discontinued** with appropriate dose tapering ~~pending further evaluation by the study clinician~~.

- 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 ~~**temporarily**~~ contraindicated for any reason, as judged by the study clinician and/or PSRT (e.g. elevated ALT)

Decisions regarding resumption of study drug following ~~withholding~~ **discontinuation** will be made in consultation with the PSRT ~~as required~~. If drug interruption occurs for ~~three days~~ **two weeks** or longer, induction may need to be repeated. Further details regarding ~~withholding~~ **discontinuing** or adjusting study drug will be specified in the treatment manual ~~and Study Specific Procedures Manual (SSP)~~.

~~4.4.2 Criteria for Permanent Discontinuation of Study Drug~~

~~Decisions regarding permanent discontinuation of study drug should be made in consultation with the PSRT. The study drug will be permanently discontinued with appropriate dose tapering in participants who meet one or more of the following criteria:~~

- ~~Pregnant~~
- ~~Continued dosing is contraindicated for safety reasons, as judged by the study clinician and/or PSRT~~
- ~~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~~

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. ~~Further details regarding permanent discontinuation of study drug will be specified in the treatment manual and the SSP Manual.~~

Those participants that were previously permanently discontinued from the study treatment under protocol version 1.0 will be eligible to re-start medications 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.~~3~~**2** Considerations for Women who Become Pregnant during the Study

- *Section 6.1, Safety Monitoring, second paragraph, last sentence:* In addition to the routine safety data reviews, the PSRT will participate in the decision-making regarding ~~permanent~~ discontinuation **and resumption** of study drug ~~and resumption following withholding of BUP/NX~~.

19. Order of Screening Procedures and clarification of Enrollment/ Randomization Procedures

Section 5.1, Screening Visit, first paragraph: 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:

- ~~Screening Informed Consent~~

Section 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.

Section 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.

Section 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.

Section 5.3.3 ~~Booster~~ 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.

Section 5.4 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.

Section 5.4.1 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.

Section 5.4.2 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 ideally during the counseling visits for the first year of enrollment. Women will have pregnancy testing approximately every four weeks ideally 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.

ALT and bilirubin testing also will be performed at weeks 12 and 40 (+/- 2 weeks) for all participants during the first year of study participation (in addition to tests completed at regularly scheduled follow-up visits); ideally, 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.

Section 5.4.3 Booster 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 ideally 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.

Section 5.5 Follow-Up Visits

Section 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** ~~**opiate**~~ use
- Assessment of social harms
- Acceptability assessment at week~~s 2 and~~ 4

Section 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 ~~booster~~ **monthly counseling** sessions and BUP/NX dispensing visits.

ALT and bilirubin testing also will be performed at weeks 12 and 40 for all participants ~~**during the first year of study participation**~~ **(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.

Section 5.5.1 ***26 and 52 Week Visits***

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.

20. Hepatitis C Testing:

- *Section 5.1, Screening Visit, next to last paragraph:* 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. ~~Reactive HCV antibody tests will be confirmed by HCV RIBA or HCV RNA.~~ 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.

- *Appendix I-A, Footnote #6:* After screening, hepatitis testing may be performed at any point during first year of participation if clinically indicated. ~~Reactive HCV antibody tests will be confirmed by RIBA or RNA test.~~ Hepatitis B vaccine will be offered to randomized participants if appropriate

- *Appendix I-A,* Under "Laboratory Tests, Hepatitis B and C," superscript 9 has been removed from the Wk 26 column.

- *Appendix I-B, Footnote #3:* ~~Reactive HCV antibody tests will be confirmed by RIBA or RNA test.~~ Hep B vaccine will be offered to randomized participants if appropriate.

21. Liver Function Test Timing

- *Section 5.5, Assessments during Full Study, second paragraph, first sentence:* ALT and bilirubin testing also will be performed **at weeks 12 and 40 every** ~~twelve weeks during the first year of study participation~~ for all participants during the first year of study participation **(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.

- *Section 9.1, Local Laboratory Specimens, first paragraph:* 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 ~~opiate~~ **drug** and pregnancy testing. ~~Specimens will also be collected for bilirubin and ALT testing every 12 weeks during the first year of study participation for all participants.~~ 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**. ~~Participants in the Safety Phase will have blood drawn weekly during the first four weeks of the study. Blood will be drawn for HIV testing at the 78, 104, 130, and 156 week visits.~~

- *Appendix I-A: Schedule of Procedures and Evaluations – Full Study, Footnote #7:* Completed **at weeks 12 and 40** ~~every twelve weeks~~

- *Appendix III-B and III-D: Sample Enrollment Consents, What will happen if you agree to take part in this study, Treatment visits, fourth paragraph:* **About** every **3 months** ~~12 weeks during your regularly scheduled visit~~, the staff will draw about 4 ml of blood (about 1 teaspoon *or local equivalent*) to make sure your liver is healthy.

22. Social Harms

- *Section 5.3.3, ~~Booster~~ **Monthly** Counseling Sessions:* 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 ~~opiate~~ **drug** and pregnancy testing (for women in the substitution treatment arm only). ~~Participants will also be asked about social harms they may have experienced~~…

- *Section 5.5, Assessments during Full Study, third paragraph, first sentence:* Locator information ~~and social harms~~ will also be assessed at four-week intervals.

- *Section 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.** When**ever** problems are identified, additional data regarding the severity and resolution will be described and recorded on a ~~separate~~ 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.

- *Appendix I-A, Schedule of Procedures and Evaluations—Full Study, Social Harms Assessment:* Remove X^3 in both "Intervention Visits" columns.

23. Interim Analysis:

- *Section 7.1, Study Design, last paragraph:* Behavioral and serologic assessments will take place at baseline and at six-month intervals throughout the study period. ~~Since it is expected that the study will achieve maximal benefit in HIV incidence at 52 weeks of study participation, the study will use one-sided stopping rules, where the protocol will be stopped before 12 months only on evidence of insufficient benefit or sufficient harm. 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.~~

- *A new section has been added following Section 7.5. All subsequent section numbers have been updated. The following will be added:*

  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 ¼, ½, ¾ and all of the primary events have been collected (i.e. when ¼, ½, ¾, 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.

- *Section 7.~~7~~.~~6~~.1, Primary Analysis:* The second paragraph has been deleted as follows: ~~Analyses of safety and formal interim analyses of efficacy will be performed at intervals as determined by the charter of the DAIDS DSMB during the remainder of the projected 36-month study duration. Recommendations for early termination of positive or negative results will be guided by an adaptation of the O'Brien-Fleming stopping boundaries, where interim monitoring through at least 52 weeks will be one-sided for lack of benefit. Recommendations regarding trial continuation and modification of study conduct will be based on safety as well as efficacy considerations.~~

24. Secondary Analysis Discrepancy

Section 7.~~7~~.~~6~~.2, Secondary Analyses, Number 5: To compare the frequency of drug use measured by **self-report and by** urinalysis in the two study arms.

25. Protocol Registration

- *Section 8.1, Ethical Review, second paragraph, last sentence:* Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office~~, via the HPTN CORE,~~ in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

- *Section 10.1, Study Activation, first paragraph, second sentence:* CORE staff will work with study site staff ~~and~~ **to** complete DAIDS protocol registration in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

26. Specimen Storage:

Section 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** ~~all leftover~~ specimens ~~collected in this study through the end of the study and~~

should not be destroyed until notification from the HPTN SDMC and ~~CL~~**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…

27. Study Specific Procedures Manual

Section 10.2, Study Coordination, second paragraph: 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.**

28. Informed Consent Discrepancies:

- *Appendix III-A: Sample Screening Consent during the Safety Phase:*
  What are your rights as a research participant?
  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.**

  What will happen if you agree to the study screening?
  The study staff will draw **about ~~no more than~~** 14 mL…

  You will be offered HIV counseling and testing whether or not you are eligible to join the study. The study staff will draw about **~~than~~** 14 mL of blood (about 3 teaspoons *or local equivalent*). **If you agree, ~~Y~~y**our blood specimen will be stored…

  What other choices do you have besides this study?
  The staff will talk with you about other ~~treatment~~ 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*).**

- Appendix III-C: Sample Screening Consent for Participants Screened during the Full Study:
  What will happen if you agree to the study screening?
  If your ~~first~~ HIV test shows you are 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…. Your blood specimen will be ~~discarded~~ **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.**

  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.

~~**All participants in the study will return for HIV testing and interviews every six months. There will be four to six follow-up visits depending on when you enroll in the study. Each follow-up visit will last about one to two hours. If you enroll in the study, the staff will tell you the details of the follow-up visits.**~~
~~**Your urine will be tested for opiates and other drugs every four weeks. For all female participants, you will have a pregnancy test at week 4.**~~

~~***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. 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.~~

~~***If you are in the Substitution Treatment group***, you will take Suboxone medicine for one year and attend counseling as described above. In the beginning of the study, you will be asked to come to the clinic every day to take your medicine for up to three weeks. After this, you will need to return to the clinic at least three times per week for a year. For this group, pregnancy testing will be performed every four weeks in the first year of study participation.~~

- *Appendix III-B and D: Sample Enrollment Consents, Statement of Consent, first paragraph:* I have read (or someone has read and explained to me) this consent form. I understand the purpose of the ~~screening~~ **study**, 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~~ **join this** drug treatment research study.

- *Appendix III-B and D: Sample Enrollment Consents, Statement of Consent, second paragraph:* <u>For staff:</u> I have explained the ~~purpose of the screening~~ **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 ~~screening~~.

- *Appendix III-B and D: Sample Enrollment Consents, Statement of Consent, third paragraph:* <u>For witnesses for illiterate volunteers</u>: 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~~.

- *Appendix III-D: Sample Enrollment Consent for Full study, What are the risks/discomforts of this study, third paragraph, third sentence:* The most common side effects are ~~cold or flu-like symptoms,~~ headaches, **pain,** sweating, **nausea,** sleeping ~~difficulties~~ **problems, and constipation** ~~stomach pains and mood swings~~.

- *Appendix III-D: Sample Enrollment Consent for Full study, What are the risks/discomforts of this study, fourth paragraph, last sentence:* We will check your liver**, kidneys, and blood** to make sure it is healthy while you are taking Suboxone.

- *Appendix III-A,B,C, and D, Sample Consents, What about confidentiality, last sentence:* 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 ~~screening~~ **study-related** records.

29. Addition of AE Reporting Table:

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.

30. Substitution Treatment Arm Dosing has been clarified to specify that daily dosing will take place up to 21 days (until dose stabilization).

Protocol Schema:

STUDY ARM	**Intervention**
Substitution Treatment Arm n=750	• 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.

2.3 Study Design

- "Substitution Treatment" Arm- sublingual BUP/NX administered **daily up to 21 days (until dose stabilization) and then** three times per week for 52 weeks…

7.1 Study Design

STUDY ARM	**Intervention**
Substitution Treatment Arm n=750	• 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.

31. Detoxification Treatment Arm Dosing has been clarified to specify that dosing will take place up to 18 days.

Protocol Schema:

Detoxification Treatment Arm n=750	• 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.

2.3 Study Design:

- "Detoxification Treatment" Arm – short-term BUP/NX detoxification **for 18 days maximum** in addition to weekly

7.1 Study Design:

Detoxification Treatment Arm n=750	• 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.

32. APPENDIX I-A: Schedule of Procedures and Evaluations- Full Study; the table has been replaced.

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

Procedures/ Evaluations	Screening Visit	Enrollment/ Randomization Visit	Intervention Visits		Follow-Up Visits					
			Weeks 0-12	Weeks 16-52	Wk 26	Wk 52	Wk 78	Wk 104	Wk[1] 130	Wk[1] 156
Screening Informed Consent	X									
Enrollment Informed Consent[2]		X								
Demographics	X									
Locator Information	X	X	X[3]	X[3]	X	X	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	X
Social Harms Assessment			X[3]	X[3]	X	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	X
Hepatitis B and C[6]	X				X[9]					
Platelet count	X				X	X				
CBC	X				X	X				
Bilirubin	X		X[7]	X[7]	X	X				
Creatinine	X				X	X				
ALT	X		X[7]	X[7]	X	X				
Urine Test for Opiates	X		X[3]	X[3]	X	X	X	X	X	X
Urine Test for Pregnancy[8]	X	X	X[3]	X[3]	X	X				
Pre- and Post-test HIV Counseling	X				X	X	X	X	X	X
Weekly Counseling Visits			X							
Booster Sessions every four weeks				X						
BUP/NX Dispensing Visits		X	X[9]	X[9]	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] Every four weeks

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

[5] If 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. Reactive HCV antibody tests will be confirmed by RIBA or RNA test. Hepatitis B vaccine will be offered to randomized participants if appropriate

[7] Completed every twelve weeks

[8] For female participants in both arms at screening and week 4 only; thereafter, in the substitution treatment arm only

[9] Completed daily for up to the first three weeks of dosing in both arms, and three times per week thereafter in the substitution treatment arm only

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	Wk[1] 156
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	X
Eligibility Interview (incl. DSM-IV Diagnosis)	X					X[4]						
Behavioral Risk Assessment (drug use & sexual risk)	X					X		X	X	X	X	X
Social Harms Assessment						X		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	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	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	X
Weekly Counseling Visits			X									
Monthly Counseling Sessions					X[3]		X[3]	X				
BUP/NX Dispensing Visit[9]		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
[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 visit are combined.

33. Informed Consent Clarifications

- *Appendix III-A: Sample Screening Consent during the Safety Phase: If your HIV test shows that you may be infected with HIV, second paragraph:*

1. What will happen if you agree to the study screening?

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.**

2. **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.*]**

3. 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. ~~You will be in this study about 3 years.~~
~~During the first four weeks, you will have blood tests and exams each week. These visits will take about 1 to 2 hours.~~

~~You will also talk with a counselor~~ every week for 12 weeks ~~for about 45 minutes. After the first 12 weeks, you will return every four weeks for 10 more counseling sessions. Each of these visits will last about 45 minutes.~~

~~***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. After this time, you will not receive any more Suboxone, but you will continue to come to the clinic for counseling visits and exams 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.~~

~~***If you are in the Substitution Treatment group***, you will take Suboxone medicine for one year and attend counseling visits as described above. In the beginning of the study, you will be asked to come to the clinic every day to take your medicine for up to three weeks. After this, you will need to return to the clinic~~ at least three times per week for a year~~.~~

~~All participants in the study will return for HIV testing and interviews every six months. There will be 6 of these follow-up visits. Each follow-up visit will last about one to two hours. If you enroll in the study, the staff will tell you the details of the follow-up visits.~~

4. **What are the risks/discomforts of this screening?**

~~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, and constipation. If you join the study, the doctor will explain more about the drug and how to take it correctly~~

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.

5. **Are there risks related to pregnancy?**

~~We do not know if Suboxone will harm unborn babies.~~ 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.** ~~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~~

6. **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 ~~treatment~~ 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*).**

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

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

If you are a woman, we will do another pregnancy test on your urine **and you will be given the results.**

2. Treatment Visits:

All participants will have a urine test for opiates **and other drugs every four weeks** for a year.

3. If you are in the Substitution Treatment group

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.**

4. Follow-up Visits:

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.

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.]

5. 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).
- ~~You are not able to attend the visits or follow the procedures required by the study.~~

6. What are the risks/discomforts of this study?

If **people think that** you are infected with HIV, you may have problems finding or keeping a job.

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.

We will check your liver, kidneys, and blood to make sure ~~it is~~ **they are** healthy while you are taking Suboxone.

7. 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.

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

1. What will happen if you agree to the study screening?

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.**

2. **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.*]**

3. 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.**

~~You will talk with a counselor every week for 12 weeks for about 45 minutes. After the first 12 weeks, you will return every four weeks for 10 more counseling sessions. Each of these visits will last about 45 minutes.~~

~~All participants in the study will return for HIV testing and interviews every six months. There will be 4 to 6 follow-up visits depending on when you enroll in the study. Each follow-up visit will last about one to two hours. If you enroll in the study, the staff will tell you the details of the follow-up visits.~~

~~Your urine will be tested for opiates and other durgs every four weeks. For all female participants, you will have a pregnancy test at week 4.~~

~~***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. 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.~~

~~***If you are in the Substitution Treatment group***, you will take Suboxone medicine for one year and attend counseling as described above. In the beginning of the study, you will be asked to come to the clinic every day to take your medicine for up to three weeks. After this, you will need to return to the clinic at least three times per week for a year. For this group, pregnancy testing will be performed every four weeks in the first year of study participation.~~

4. What are the risks/discomforts of study screening?

~~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, and constipation. If you join the study, the doctor will explain more about the drug and how to take it correctly.~~

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.

5. **Are there risks related to pregnancy?**

~~We do not know if Suboxone will harm unborn babies.~~ 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.** ~~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:~~

~~7. Hormonal methods, like birth control pills, shots, patches, implants or vaginal rings~~
~~8. Male or female condoms~~
~~9. Diaphragm or cervical cap with a cream or gel that kills sperm~~
~~10. Intrauterine device (IUD)~~
~~11. Complete abstinence from sex~~

6. 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.***]*

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

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

If you are a woman, we will do another pregnancy test on your urine **and you will be given the results.**

2. **Treatment Visits:**
   All participants will have a urine test for opiates **and other drugs every four weeks** for a year.

3. **If you are in the Substitution Treatment group**
   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.**

4. **Follow-up Visits:**
   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.

   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.]

5. **What are the risks/discomforts of this study?**
   If **people think that** you are infected with HIV, you may have problems finding or keeping a job.
   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.
   We will check your liver, kidneys, and blood to make sure ~~it is~~ **they are** healthy while you are taking Suboxone.

6. **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).
   - ~~You are not able to attend the visits or follow the procedures required by the study.~~

7. **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.

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

.

1. **Title update: 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**

2. **<u>What are my rights?</u>**
   Your samples will then not be used and will be destroyed according to local regulations

34. Clarification of Hepatitis testing at Weeks 26 and 52
    5.5.1 26 and 52 Week Visits
    - Hepatitis testing (Week 26)