DATE: July 19, 2011

TO: Protocol HPTN 058 Principal Investigators, Study Coordinators and Study Staff

FROM: HPTN 058 Protocol Team

SUBJECT: Letter of Amendment #3 to Protocol HPTN 058, Version 2.0 dated 16 September 2008 (IND # 73,797), entitled ***A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors***

The following information impacts the HPTN 058 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

I. *A Sub-Study is added to the protocol as Appendix VII in Xinjiang, China, in order to characterize the withdrawal effects of rapid, immediate discontinuation of Buprenorphine/ Naloxone in Xinjiang, China*
II. *The Protocol Team Roster is updated*
III. *The overall Follow-up Period is clarified. Study participants will be followed for approximately 104 Weeks in China and approximately 156 Weeks in Thailand. This decision reflects the protocol team's desire to devote all available resources to the collection of data necessary to answer the primary and secondary objectives with as much power as possible. Additional time is being allowed at the Chiang Mai site given the early end of enrollment and will increase opportunities to identify incident cases.*
IV. *Information from Clarification Memo #1 dated 17 March 2011 is incorporated into this Letter of Amendment.*
V. *The Secondary Objectives of the Protocol are clarified in order to provide greater scientific impact and clarity.*

Additions are noted as **bolded** text. Deletions are noted as ~~strikethrough.~~The information belowwill be incorporated into the next version of the protocol at a later time if it is amended.

I. APPENDIX VII

HPTN 058 Sub-Study A: Withdrawal effects of rapid, immediate discontinuation of Buprenorphine/Naloxone in Xinjiang, China

Protocol Chair: Yiming Shao
Protocol Co-Chairs: Ray Chen, Yuhua Ruan, David Metzger, Scott Rose

Background:
Long-term buprenorphine/naloxone (BUP/NX) use is associated with dependence and discontinuation should be done gradually. The discontinuation effects of rapid, immediate withdrawal of BUP/NX have not been well characterized outside of laboratory settings.

Purpose/objectives:
Tocollect and categorize data on the withdrawal experience of study participants who abruptly stopped receipt of BUP/NX due to arrest.

Rationale:
The recent spate of incarcerations among HPTN 058 study participants in Xinjiang resulted in the immediate withdrawal from BUP/NX of a number of long-term treatment participants, allowing for an exploration of the effects of immediate BUP/NX withdrawal.

Methods:
In order to assess the subjective effects of BUP/NX withdrawal, a retrospective questionnaire will be administered to study participants in the long-term treatment arm who self-report that they were detained/incarceratedand subsequently released and who provide informed consent to participate in this substudy. In addition, study participants who self-report that they were detained/arrested with immediate discontinuation of BUP/NX and subsequently released will be prospectively included if they likewise provide informed consent to participate in this substudy. The study will be conducted by the HPTN 058 staff in Xinjiang. The primary study will not be affected by the proposed investigation as no urine or blood will be collected. Information on drug use collected is proximal to the time of incarceration.

Analysis Plan:
Statistical description for each variable.
The total scores of withdrawal symptoms for burpenorphine, heroin and methadone will be calculated. Comparison of total scores among buprenorphine, heroin and methadone will be performed with Chi-square test (for categorical variables, such as low and high score) and ANOVA (for continuous variables). Analysis and

publication will not take place until the main study's primary objectives are published.

Inclusion criteria:

- **Current or former participant in HPTN 058 study in Xinjiang who was actively in the long-term treatment arm on stable maintenance dose of Suboxone when detained/arrested (last dose within 2 days of incarceration), resulting in immediate cessation of Suboxone without tapering**
- **Currently released from detention**
- **Willing to complete one-time questionnaire**
- **Willing to sign informed consent**

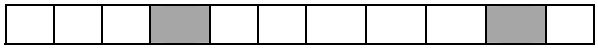
Exclusion criteria:

- **Any medical or psychiatric condition that, in the opinion of the investigator, would make participation in the study unsafe, or would otherwise interfere with the study objectives or interpretation**

An abbreviated SSP Manual will be created for site staff detailing study implementation, including use of the Chart Extraction Tool and ensuring that participants answer questions in the context of opiate withdrawal symptoms, and not related to feelings of incarceration, etc.

Chart Extraction tool
HPTN 058 Ancillary study on Suboxone withdrawal in Xinjiang incarcerated participants

1. **PTID**



2. **Form Completion Date: _____**

3. **Person completing form: _____**

4. **Participant's date of enrollment (randomization and first dose of Suboxone)? _____**

5. **During the participant's post-induction dosing of Suboxone, how many dosing visits was the participant scheduled to attend? _____**

6. **During the participant's post-induction dosing of Suboxone, how many dosing visits did the participant complete? _____**

7. **Prior to the participant's reported incarceration, had the participant missed one or more weeks of dosing?**
   - □ **Yes**
   - □ **No**

   - **If <u>yes</u>, what study weeks did the participant miss?**

   - **If <u>yes</u>, what was the stated reason for missing a dosing visit (check all that apply for all weeks missed)?**
     - □ **Reported incarceration**
     - □ **Verified incarceration**
     - □ **Participant refused**
     - □ **Illness/hospitalization**
     - □ **Relocation**
     - □ **Personal obligation**
     - □ **Unknown**
     - □ **Other**

8. **List the last six dosing dates and doses of Suboxone taken prior to their reported incarceration.**

Date	**Dose (mg) of Suboxone taken**

9. **Date of birth ___**

10. **Ethnicity**
    a. **Han**
    b. **Uighur**
    c. **Hui**
    d. **Other_____**

Questionnaire:

HPTN 058 study history

1. **What was your date of incarceration?**

A. <u>Withdrawal history- Buprenorphine</u>

1. **When you were incarcerated and not able to obtain buprenorphine, how long was it before you started feeling withdrawal symptoms? [hours] or [days]**
2. **What symptoms did you feel? For each of the 17symptomsbelow,please circlethe most severe (worst) feeling that youhadduring your incarceration.**

	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I felt anxious	0	1	2	3	4
2	I felt like yawning	0	1	2	3	4
3	I was perspiring	0	1	2	3	4
4	My eyes were teary	0	1	2	3	4
5	My nose was running	0	1	2	3	4
6	I had goosebumps	0	1	2	3	4
7	I was shaking	0	1	2	3	4
8	I had hot flushes	0	1	2	3	4
9	I had cold flushes	0	1	2	3	4
10	My bones and muscles ached	0	1	2	3	4
11	I felt restless	0	1	2	3	4
12	I felt nauseous	0	1	2	3	4

13	**I felt like vomiting**	**0**	**1**	**2**	**3**	**4**
14	**My muscles twitched**	**0**	**1**	**2**	**3**	**4**
15	**I had stomach cramps**	**0**	**1**	**2**	**3**	**4**
16	**I felt like using heroin**	**0**	**1**	**2**	**3**	**4**
17	**Others**	**0**	**1**	**2**	**3**	**4**

3. **How long did these symptoms last? [Hours] or [days]**
4. **How many days after these symptoms appeared didyou start feeling better?**

B. Withdrawal history (prior to participation in HPTN 058)- Heroin

1. **Have you ever been through heroin withdrawal before? If no, skip to Withdrawal history- Methadone (C).**
2. **How many times have you withdrawn from heroin before?**
3. **Did you take any medication to help reduce your withdrawal symptoms?**
4. **For each of the 17 symptoms below,please circle the most severe (worst) feeling that you had at the time of your first few days of heroin withdrawal.**

	SYMPTOM	**NOT AT ALL**	**A LITTLE**	**MODERATELY**	**QUITE A BIT**	**EXTREMELY**
1	**I felt anxious**	**0**	**1**	**2**	**3**	**4**
2	**I felt like yawning**	**0**	**1**	**2**	**3**	**4**
3	**I was perspiring**	**0**	**1**	**2**	**3**	**4**
4	**My eyes were teary**	**0**	**1**	**2**	**3**	**4**
5	**My nose was running**	**0**	**1**	**2**	**3**	**4**
6	**I had goosebumps**	**0**	**1**	**2**	**3**	**4**
7	**I was shaking**	**0**	**1**	**2**	**3**	**4**
8	**I had hot flushes**	**0**	**1**	**2**	**3**	**4**

9	**I had cold flushes**	**0**	**1**	**2**	**3**	**4**
10	**My bones and muscles ached**	**0**	**1**	**2**	**3**	**4**
11	**I felt restless**	**0**	**1**	**2**	**3**	**4**
12	**I felt nauseous**	**0**	**1**	**2**	**3**	**4**
13	**I felt like vomiting**	**0**	**1**	**2**	**3**	**4**
14	**My muscles twitched**	**0**	**1**	**2**	**3**	**4**
15	**I had stomach cramps**	**0**	**1**	**2**	**3**	**4**
16	**I felt like using heroin**	**0**	**1**	**2**	**3**	**4**
17	**Others**	**0**	**1**	**2**	**3**	**4**

4. **How long did these symptoms last [Hours] or [days]**
5. **How many days after these symptoms appeared didyou start feeling better?**

C. Withdrawal history (prior to participation in HPTN 058)- Methadone

1. **Have you ever been through methadone withdrawal before? If no, end of form.**
2. **How many times have you withdrawn from methadone before?**
3. **For each of the 17 symptoms below, please circle the most severe (worst) feeling that you had at the time of your first few days of methadone withdrawal.**

	SYMPTOM	**NOT AT ALL**	**A LITTLE**	**MODERATELY**	**QUITE A BIT**	**EXTREMELY**
1	**I felt anxious**	**0**	**1**	**2**	**3**	**4**
2	**I felt like yawning**	**0**	**1**	**2**	**3**	**4**
3	**I was perspiring**	**0**	**1**	**2**	**3**	**4**
4	**My eyes were teary**	**0**	**1**	**2**	**3**	**4**
5	**My nose was running**	**0**	**1**	**2**	**3**	**4**

6	**I had goosebumps**	**0**	**1**	**2**	**3**	**4**
7	**I was shaking**	**0**	**1**	**2**	**3**	**4**
8	**I had hot flushes**	**0**	**1**	**2**	**3**	**4**
9	**I had cold flushes**	**0**	**1**	**2**	**3**	**4**
10	**My bones and muscles ached**	**0**	**1**	**2**	**3**	**4**
11	**I felt restless**	**0**	**1**	**2**	**3**	**4**
12	**I felt nauseous**	**0**	**1**	**2**	**3**	**4**
13	**I felt like vomiting**	**0**	**1**	**2**	**3**	**4**
14	**My muscles twitched**	**0**	**1**	**2**	**3**	**4**
15	**I had stomach cramps**	**0**	**1**	**2**	**3**	**4**
16	**I felt like usingmetha done**	**0**	**1**	**2**	**3**	**4**
17	**Others**	**0**	**1**	**2**	**3**	**4**

4. **How long did these symptoms last [Hours] or [days]**
5. **How many days after these symptoms appeared didyou start feeling better?**

Sample Consent for HPTN 058 Substudy A Participants

HPTN 058 Ancillary Study: Withdrawal effects of rapid, immediate discontinuation of Buprenorphine/Naloxone in Xinjiang, China
11 July 2011

Principle Investigator: Liping Fu
Jianquan First Street 380,
Urumqi, Xinjiang 830002, China
Phone Number 2665552

<u>Introduction</u>
You are being asked to take part in a research study to help us better understand whether, upon your incarceration,you hadany withdrawal effects after rapid

andimmediate discontinuation of Suboxone that you were taking as a participant in the HPTN 058 study sponsored by the US National Institutes of Health.

This study is sponsored by the NationalCenter for AIDS/STD Control and Prevention and Xinjiang CDC.The person in charge of this study at this site is Dr. Liping Fu.

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

<u>What are your rights as a research participant?</u>

- **Your participation in the study is entirely voluntary.**
- **You may decide not to take part in the study or to leave at any time without losing the benefits of your standard medical care or other services. You will be treated the same no matter what you decide. Your participation in the main study, HPTN 058, will not be affected one way or another.**
- **If you decide not to participate in the study, you can still join another research study later, if one is available and you qualify. If you refuse to participate in this study, we will respect your rights and will not ask you again.**
- **We will tell you about new information from this or other studies that may affect your health, welfare or willingness to participate in this study.**

<u>Why is this research being done?</u>

The purpose of the research is to describe any withdrawal effects that you experienced when you immediately discontinued use of Suboxone upon your incarceration. There is no drug or counseling intervention in this study as in the main HPTN 058 study. We ask that you complete a short form which will ask you about your experiences of any potential withdrawal effects related to Suboxone use, as well as any previous withdrawal effects you may have had to methadone or heroin. The study is only taking place here in Urumqi.

We anticipate that 30-40 persons from the Long-Term Treatment Arm in HPTN 058whowere incarcerated, will participate in this study.

<u>What will happen if you agree to participate in the study?</u>

The visit may take 1-2 hours and may proceed today if you are willing. We will record information regarding your date of enrollment, race (ethnicity), date of birth, and dosing history from the main study. We will ask you questions about your health during your incarceration and about your drug use prior to your incarceration. If you are not willing to give us this information, you cannot be in

this study. You will not be asked to provide any urine or blood samples for this study. Your answers in this study will be linked to the confidential participant identifier information from the main HPTN 058 study.

We will contact you with the results from this study when available.

How long will you be in this study if you are eligible?
This sub-study consists of a single visit which you may complete today. You will need to complete a questionnaireabout any withdrawal symptoms you might have had while incarcerated as well as any drug use prior to your incarceration.

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

Are there risks related to pregnancy?
There are no risks related to pregnancy, as this is an observational study. There is no drug or counseling provided, and no specimens (blood or urine) will be collected from you.

Are there potential benefits to study participation?
There is no direct benefit to you from study participation.

What other choices do you have besides this study?
You do not have to agree to enroll in this research study. The staff will talk with you about other research studies if any are available now or in the future.

What about confidentiality?
All efforts will be made to keep your personal information confidential to the extent permitted by law, but we cannot promise complete confidentiality. On your records, a code will be used instead of your name. This code will be the same code that is used in the main study, HPTN 058. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the local Ministry of Health, the study sponsor(s) (the U.S. National Institutes of Health), the U.S. Food and Drug Administration, the company that manufactures the study drug (Reckitt Benckiser), the Institutional Review Board or Ethics Committee, and their authorized representatives will be allowed to inspect your study-related records.

What are the costs or payments to you?
There will be no cost to you for this visit. This study does not provide treatment for any conditions that are discovered during the course of the study. There are no

plans to give you money either through this institution, the company that manufactures the study drug (Reckitt Benckiser), or the U.S. National Institutes of Health if there is a research-related complication or injury.
You will be paid for your time and travel expenses for *RMB 20 Yuan per time.*

<u>What happens if you are injured during the study?</u>
Injuries are not anticipated as this is a one time survey. If you are injured as a result of answering questions during this study, you will be given immediate treatment for your injuries. You may have to pay for this care. If we find any illness or injury during the sub-study, we will tell you about medical care and other services available in the community. There are no plans to give you money if there is a research-related complication or injury. You will not be giving up any of your legal rights by signing this consent form.

<u>Who should you contact if you have problems or questions about the study?</u>

- ***Liping Fu***
  Jianquanyi Street No.380, Urumqi, Xinjiang 830002 China
  Phone Number:2665552

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

- ***Biao Liu, Chairperson of Xinjiang IRB***
  Beijing South Road No.48
  Phone Number:0991-3850327

STATEMENT OF CONSENT

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

Participant's Name (print)	**Participant's Signature or Thumbprint and Date**

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

Study Staff Conducting Consent Discussion (print)	**Study Staff Signature and Date**

<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 and has voluntarily accepted to participate in this study.

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

Witness' Name (print)	**Witness's Signature and Date**

II. PROTOCOL TEAM ROSTER

Ray Chen, MD, MPH
NIH Medical Officer
Unit 7300 Box 0076
DPO AP 96521-0076
Phone: 86-10-6318 7701 x807
Fax: 301-451-5492
rchen@niaid.nih.gov

Yiming Shao, MD
National Center for AIDS/STD Control and Prevention,
Chinese Center for Disease Control and Prevention
155 Changbai Road, Changping District,
Beijing, 102206,P.R.China
Phone: 86-10-58900981
Fax: 86-10-58900980
yshao@bbn.cn
~~National Center for AIDS Prevention and Control~~
~~27 Nanwei Road Xuanwu District~~
~~Beijing 100050 CHINA~~
~~Phone: 86-10-63166184~~
~~Fax: 86-10-63154638~~

III. CLARIFICATION OF FOLLOW-UP PERIOD

PROTOCOL SCHEMA
Study Duration:…Participants will be followed for ~~a minimum of~~**approximately** 104 weeks **in China**and ~~a maximum of~~ **approximately** 156 weeks**in Thailand**~~, depending on when they are enrolled~~. Behavioral and serologic assessments will take place at baseline and at 26 week intervals throughout the follow-up period.

2.3 Study Design
…Participants will be followed for ~~a minimum of~~**approximately**104 weeks **in China** and ~~a maximum of~~**approximately**156 weeks **in Thailand**~~, depending on when they are enrolled~~.

…Participants will be followed after enrollment for ~~a minimum of~~**approximately**104 weeks **in China** and ~~a maximum of~~**approximately**156 weeks **in Thailand**~~, depending on when they are enrolled in the study~~.

2.3.1 Safety and Feasibility Phase

…All participants will be followed for ~~a minimum of~~**approximately**104 weeks **in China** and ~~a maximum of~~ **approximately**156 weeks **in Thailand,** ~~depending on when they are~~

~~enrolled, with those enrolled earlier accumulating a longer duration of follow-up than those enrolled later in the study~~.

3.5 Participant Retention

Once a participant enrolls in the study, the study site will make every effort to retain him/her for the full study period (104 to 156 weeks~~, depending on when s/he is enrolled)~~ to minimize possible bias associated with loss-to-follow-up.

APPENDIX I-A: Schedule of Procedures and Evaluations – Full Study
Participants will be followed for **approximately**~~a minimum of~~ 24 months **in China** and **approximately**~~a maximum of~~ 36 months **in Thailand.**~~, depending on when they are enrolled~~

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

How long will you be in this study if you are eligible?
You will be in this study ***(sites to specify: approximately 2 years in China and approximately 3 years in Thailand)***~~about 2 to 3 years depending on when you begin.~~

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

Treatment Visits:
The treatment part of this study will last one year. Then we will continue to do HIV tests for another ~~*one-two years*~~***(sites to specify: approximately 1 year in China and approximately 2 years in Thailand)*** *after the treatment ends. Altogether, you will be in the study for two****(China)*** *to three* ***(Thailand)****years.*

Follow-up Visits:
All participants in the study will return to the clinic every six months for HIV testing and interviews. There will be **(sites to specify: 4 visits in China and 6 in Thailand).**~~between 4 and 6 follow-up visits over 2 to 3 years depending on when you start participating.~~

IV. INFORMATION FROM PROTOCOL VERSION 2.0 CLARIFICATION MEMO #1

4.3.3 Treatment Dose and Administration

Substitution Treatment Arm

Dosing will begin with a titration over a period of two to three days under supervision in the study clinic using the COWS as described above. On the first day of treatment, patients will initially receive a 4 mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total first

day's dosage of 8 mg. On Day 2, up to 16 mg may be given. Up to 32 mg may be given on Day 3 and thereafter until three-times-weekly dosing begins. The induction strategy is primarily dependent on three factors: 1) time since last opiate use; 2) type of opiate (e.g., long or short-acting) used; and 3) degree of physical dependence. Therefore, each dosing schedule will be tailored to the individual participant.

Individuals randomized to the substitution treatment arm will come to the study site daily for direct observation of dosing until they have stabilized (for up to three weeks). Participants may be given a double dose or a take-home dose for days that the site is not staffed for dosing. After induction and stabilization, participants will be asked to come to the site for dosing three-times-weekly. **For example,**T**t**he target dosage schedule for individuals whose daily dose was 16 to 24 mg/day **or more** is expected to be 32/32/48 mg administered on a three-times-weekly schedule (e.g., M/W/F); this is also the maximum three-times-weekly dosage.~~On rare occasions, for individuals who require more than 24 mg/day (i.e., 26, 28, 30, or 32 mg/day), it is unlikely that.~~ **In some individuals,** the 32/32/48 mg **three-times-weekly** dosage schedule **may not** be adequate. For **such** individuals, as well as forothers who received 24 mg or less per day but for whom the 32/32/48 mg three-times- weekly schedule is not adequate, dosing may be continued on a daily basis through Week 52 of the study, with take-home doses administered for those days on which in-clinic dosing is not possible (e.g., 32 mg on M/Tu/W/Th/F/Sat with a take-home 32 mg dose on Sun). **Dosing may be observed in the clinic 4-times to 7-times per week during the maintenance phase as required for optimal treatment response. The maximum dose that may be administered at one time (i.e., to cover > 1 day) is 48 mg.** Participants receiving daily doses may also be given alternative day take home doses, which would conform to the visit schedule of those participants on three-times weekly dosing, at the discretion of the local investigators.

V. CLARIFICATION OF SECONDARY OBJECTIVES

PROTOCOL SCHEMA

Secondary Objectives:

1. **To determine if assignment to the long term treatment arm reduces HIV risk taking as measured by self-report of injected drugs and occurrence of positive opiate urine tests compared to the short term treatment arm.**

2. **To determine if assignment to the long term treatment arm reduces the frequency of other HIV risk behaviors (injection-related and sexual) as measured by self-reported needle sharing, injection with others, reuse of needles, number of sexual partners, and unprotected sexual acts compared to the short term treatment arm.**

3. **To determine if assignment to the long term treatment arm results in fewer arrests and higher rates of employment compared to the short term treatment arm.**

4. **To determine if assignment to the long term treatment arm increases enrollment in any type of drug treatment program following Week 52 relative to the short term treatment arm.**

5. **To determine if assignment to the long term treatment arm results in fewer infections with the following biological endpoints: Hepatitis B; Hepatitis C; HIV; Death (both all cause and restricted to drug-related) relative to the short term treatment arm. Analyses stratified by at-risk populations for Hepatitis endpoints at enrollment.**

6. **Determine if assignment to long-term treatment affects the occurrence of liver toxicity events (grade 3 or higher ALT or bilirubin) compared to assignment to short-term treatment.**

Analyses will include data from Thailand at Weeks 130 and 156 where appropriate.

~~**Secondary Objectives:**~~

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

2.2 SECONDARY OBJECTIVES

1. **To determine if assignment to the long term treatment arm reduces HIV risk taking as measured by self-report of injected drugs and occurrence of positive opiate urine tests compared to the short term treatment arm.**

2. **To determine if assignment to the long term treatment arm reduces the frequency of other HIV risk behaviors (injection-related and sexual) as measured by self-reported needle sharing, injection with others, reuse of needles, number of sexual partners, and unprotected sexual acts compared to the short term treatment arm.**

3. **To determine if assignment to the long term treatment arm results in fewer arrests and higher rates of employment compared to the short term treatment arm.**

4. **To determine if assignment to the long term treatment arm increases enrollment in any type of drug treatment program following Week 52 relative to the short term treatment arm.**

5. **To determine if assignment to the long term treatment arm results in fewer infections with the following biological endpoints: Hepatitis B; Hepatitis C; HIV; Death (both all cause and restricted to drug-related)) relative to the short term treatment arm. Analyses stratified by at-risk populations for Hepatitis endpoints at enrollment.**

6. **Determine if assignment to long-term treatment affects the occurrence of liver toxicity events (grade 3 or higher ALT or bilirubin) compared to assignment to short-term treatment.**

Analyses will include data from Thailand at Weeks 130 and 156 where appropriate.

~~**Secondary Objectives:**~~

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

~~7.2.2 Secondary Endpoints~~

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

- ~~HIV-1 infection every six months at scheduled study follow-up visits~~
- ~~Mortality~~

- ~~Continued opiate use as measured by self-report and urinalysis~~
- ~~Self reported frequency of injection~~
- ~~Self reported frequency of injection with previously used injection equipment (needles, syringes, cookers, cottons, and rinse water).~~
- ~~Self-reported frequency of unprotected sex or sex sold/traded for drugs~~

7.7.2 Secondary Analyses

1. To determine if assignment to the long term treatment arm reduces HIV risk taking as measured by self-report of injected drugs and occurrence of positive opiate urine tests compared to the short term treatment arm.

Endpoints:

- **Self-report of continued injection opiate use**
- **Urinalysis results positive for opiates**

Repeated measure of self reported injection opiate use and repeated assessment of urine positive for opiates will be analyzed using logistic regression with generalized estimating equations techniques for repeated measures to assess difference in odds of use between the two study arms.

2. To determine if assignment to the long term treatment arm reduces the frequency of other HIV risk behaviors (injection-related and sexual) as measured by self-reported needle sharing, injection with others, reuse of needles, number of sexual partners, and unprotected sexual acts compared to the short term treatment arm.

Endpoints:

- **Self reported frequency of injection**
- **Self reported frequency of injection with previously used injection equipment (needles, syringes, cookers, cottons, and rinse water).**
- **Self-reported frequency of unprotected sex or sex sold/traded for drugs**

Repeated measure of self reported injection behaviors and repeated assessment of sexual behaviors will be analyzed using logistic regression with generalized estimating equations techniques for repeated measures of binary outcomes to assess difference in odds of use between the two study arms. Measures of frequency will use mixed models to assess differences in mean frequency between the two study arms.

3. **To determine if assignment to the long term treatment arm results in fewer arrests and higher rates of employment compared to the short term treatment arm.**

   Endpoints:

   - **Self-report of number of days employed in past month**
   - **Self-report of incarceration, detention and jail.**
   - **Study site confirmed report of incarceration, detention and jail**

Analysis of employment will used mixed model methods to assess difference in number of days employed per month between study arms, using repeated measure methods. Analysis of incarceration, detention and jail (both self report and site confirmed) will examine time to first incarceration using survival methods, stratified by site. Repeated events methods will be used if multiple detentions are observed or reported.

4. **To determine if assignment to the long term treatment arm increases enrollment in any type of drug treatment program following Week 52 relative to the short term treatment arm.**

   Endpoints:

   - **Self-report of enrollment into drug treatment programs at the 78 and 104 week visits.**

   Repeated measure of enrollment into drug treatment programs will be analyzed using logistic regression with generalized estimating equations techniques for repeated measures of binary outcomes to assess difference in odds of use between the two study arms

5. **To determine if assignment to the long term treatment arm results in fewer infections with the following biological endpoints:Hepatitis B; Hepatitis C; HIV; Death (both all cause and restricted to drug-related)) relative to the short term treatment arm.**

   Endpoints:

   - **Incident Hepatitis C infections**
   - **Incident Hepatitis B infections**
   - **Incidence HIV infections**
   - **Death**

Analysis of incident infections and death will use survival methods to compare hazard of first infection or death between study arms. Analysis will initially examine hazards within different baseline populations (e,g,. those Hep-B negative, HIV negative at enrollment, or those Hep-B, Hep-C and HIV-negative).

6. Determine if assignment to long-term treatment affects the occurrence of liver toxicity events (grade 3 or higher ALT or bilirubin) compared to assignment to short-term treatment.

Endpoints:

- **ALT toxicity grades**
- **Bilirubin toxicity grades**
- **ALT lab values**
- **Bilirubin lab vales**

Repeated measure of ALT and/or bilirubin Grade 3 or higher toxicities will be analyzed using logistic regression with generalized estimating equations techniques for repeated measures of binary outcomes to assess difference in odds of occurrence between the two study arms. Analysis of shift in mean lab values for each of ALT and bilirubin will use mixed models to assess differences in mean between the two study arms over the course of the study.

~~1. To determine if the substitution treatment reduces average HIV incidence and death compared to the detoxification arm; and reduces HIV incidence and death at 52 weeks and 156 weeks.~~

~~2. To determine if the substitution treatment decreases average HIV incidence compared to the detoxification treatment; and decreases HIV incidence at 52, 104, and 156 weeks.~~

~~3. To compare the average rates of deaths between the two arms; and the rates of death at 52, 104, and 156 weeks.~~

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

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

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

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

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