DATE: 25 SEP 2009

RE: LETTER OF AMENDMENT #1 FOR HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors

Final Version 2.0, 16 September 2008
IND # 73,797

THE FOLLOWING INFORMATION IMPACTS THE HPTN 058 STUDY AND MUST BE FORWARDED TO ALL RESPONSIBLE INSTITUTIONAL REVIEW BOARDS (IRB)/ETHICS COMMITTEES (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS LETTER OF AMENDMENT MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE MODIFICATIONS IN THIS LETTER OF AMENDMENT RESULTS IN A CHANGE TO THE INFORMED CONSENT FORMS. THEREFORE, SUBJECTS WHO PREVIOUSLY PROVIDED INFORMED CONSENT AND ARE ENROLLED IN THE STUDY NEED TO BE RE-CONSENTED ONCE THE REVISED INFORMED CONSENTS ARE APPROVED BY THE IRB/EC.

THIS LETTER OF AMENDMENT AND ANY IRB/EC CORRESPONDENCE MUST BE FILED IN THE SITE REGULATORY FILE AND IN OTHER PERTINENT FILES. SUBMISSION OF THESE DOCUMENTS TO THE DAIDS/RCC PROTOCOL REGISTRATION OFFICE THROUGH THE HPTN CORE IS NOT REQUIRED UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FORM FOR THE SITE.

Section 1: Summary of Revisions and Rationale

1. Intervention Acceptability Assessment
   Each participant should complete an intervention acceptability assessment at the end of the fourth week for the participants enrolled during the Safety Phase and for all participants at Weeks 26 and 52. The type of staff that are recommended to conduct these assessments is not clearly defined in the protocol. The intent is to obtain an objective, unbiased assessment. This is best accomplished by recommending that those site staff members not directly involved with the treatment or counseling of the participant complete the assessment whenever possible.
2. Hepatitis C testing is added at Weeks 52, 78, 104, 130, 156 for those that previously tested negative in order to estimate incidence during the trial.
3. Adverse Event reporting post Week 52
   The protocol is clarified that post Week 52 all deaths and any serious adverse drug reactions that are at least possibly related to the study drug must be reported as an EAE/SAE.
4. Change in burden of Protocol Safety Review Team (PSRT) consultation for study drug resumption.
5. Plasma for storage.
   The protocol is clarified on the need to store plasma for quality control purposes at all visits that require HIV testing.
6. Short Term Medication Assisted Treatment vs. Long Term Medication Assisted Treatment
   The terms “Detoxification Treatment” and “Substitution Treatment” are replaced with “Short Term Medication Assisted Treatment (ST-MAT)” and “Long Term Medication Assisted Treatment (LT-MAT)” respectively. The latter terms more accurately describe the protocol treatment arms and are more consistent with current medical terminology.

Section 2: Implementation of the Protocol Modifications
The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

1. Intervention Acceptability Assessments

   - *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 fourth week of the study. **Whenever possible, it is recommended that** ~~S~~study staff **that are** not involved in **the** ~~delivery of the~~ counseling or drug intervention components **for that participant** will administer these assessments.

   - *Section 5.5.1, 26 and 52 Week Visits*
     Whenever possible, it is recommended that study staff that are not involved in the counseling or drug intervention components for that participant administer the assessment.

2. Hepatitis C Testing at Weeks 52, 78, 104, 130, 156

   - PROTOCOL SCHEMA
     Secondary Objectives:
     6. To estimate Hepatitis C incidence in the two study arms

   - Section 2.2 Secondary Objectives
     6. To estimate Hepatitis C incidence in the two study arms

   - Assessments During Full Study
     5.5.1 26 and 52 Week Visits
     - Hepatitis testing (**Hepatitis B at** Week 26 **if appropriate). Hepatitis C at Weeks 26 and 52 if appropriate).**

     5.5.2 78, 104, 130, and 156 Week Visits
     - **Hepatitis C if appropriate**

   - Section 7.2.2 Secondary Endpoints
     7. Estimate of Hepatitis C incidence in the two study arms

   - Section 7.7.2 Secondary Analyses
     6. To estimate Hepatitis C incidence in the two study arms

- 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	Wks 27-51	Wk 52	Wk 78	Wk 104	Wk[1] 130	Wk[1] 156
Hepatitis B[6] ~~and C[6]~~	X					X[11]						
Hepatitis C[6]	**X**					**X[12]**		**X[12]**	**X [12]**	**X [12]**	**X [12]**	**X [12]**

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

[11] Hepatitis B if appropriate.
[12] Hepatitis C testing if appropriate.

- APPENDIX III-B: Sample Enrollment Consent for Participants Enrolled during the Safety Phase
  Follow-up Visits:
  At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. We will send some of your blood to the laboratory to test your liver, kidneys and general health, **including tests for Hepatitis B at Week 26 and C at Weeks 26 and 52 if appropriate.** You will be told the results of your tests as soon as they are ready, usually about a week.

  Every six months thereafter (Weeks 78, 104, 130, and 156) we will draw approximately 5 mL of blood in order to test you for HIV in addition to Hepatitis C.

  If at any time you test positive for Hepatitis B or C, we will discuss with you the meaning of the test results and refer you for further evaluation, if needed.

- APPENDIX III-D: Sample Enrollment Consent for Participants Enrolled during the Full Study
  Follow-up Visits:
  At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health. The study staff will draw about 14 mL of blood (about 3 teaspoons *or local equivalent*). Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. We will send some of your blood to the laboratory to test your liver, kidneys and general health, **including tests for Hepatitis B at Week 26 and C at Weeks 26 and 52 if appropriate.** You will be told the results of your tests as soon as they are ready, usually about a week.

  Every six months thereafter (Weeks 78, 104, 130, and 156) we will draw approximately 5 mL of blood in order to test you for HIV in addition to Hepatitis C.

  If at any time you test positive for Hepatitis B or C, we will discuss with you the meaning of the test results and refer you for further evaluation, if needed.

3. Adverse Event reporting post Week 52
   - Section 6.2 Adverse Event Reporting Requirements
     There will be no active reporting of adverse events after the period specified above (52 weeks of follow-up); however**, all deaths as well as any** unexpected, serious adverse drug reactions **that are**

at least possibly related to study drug must be reported if the study site staff become aware of the events**.**

4. PSRT Consultations for Study Drug resumption.
   - Section 3.5.1 Missed Treatment Visits
     Participants in the substitution treatment arm will be evaluated for resumption of BUP/NX treatment upon return to the study site and may resume study drug dosing based on clinical judgment ~~and after consultation with the PSRT~~ but may need to repeat BUP/NX induction. No participant will receive BUP/NX beyond 52 weeks from the time of enrollment.

   - Section 4.4.1 Criteria for Adjusting or Discontinuing Study Drug
     Decisions regarding resumption of study drug following discontinuation **due to clinician's judgment** will be made in consultation with the PSRT. **Participants who discontinue study drug either due to their request or missed study visits may resume treatment based on the judgment of the study clinician.** If drug interruption occurs for two weeks or longer, induction may need to be repeated. Further details regarding discontinuing or adjusting study drug will be specified in the treatment manual.

5. Plasma for storage

   - 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	Wks 27-51	Wk 52	Wk 78	Wk 104	Wk [1] 130	Wk[1] 156
Laboratory Tests												
Plasma for storage	**X**					**X**		**X**	**X**	**X**	**X**	**X**

   - APPENDIX III-A: Sample Screening Consent for Participants Screened during the Safety Phase
     - What will happen if you agree to the study screening?

       Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. Some of your blood will be tested for HIV**. Some of your left over blood will be stored temporarily in the event that any additional protocol related testing is needed. If you agree, any other left over blood samples will be kept and used for future HIV-related research. A separate Informed Consent Form must be signed for this purpose.** We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes.

   - APPENDIX III-B: Sample Enrollment Consent for Participants Enrolled during the Safety Phase
     Follow-up Visits:
     At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health…

     Every six months thereafter (Weeks 78, 104, 130, and 156) we will draw approximately 5 mL of blood in order to test you for HIV in addition to Hepatitis C. Some of the blood will be used immediately for these protocol tests and some will be stored temporarily for protocol specified tests.

If you agree, any other left over blood samples will be kept and used for future HIV-related research. A separate Informed Consent Form must be signed for this purpose.

- APPENDIX III-C: Sample Screening Consent for Participants Screened during the Full Study
  - What will happen if you agree to the study screening?

    Your blood sample will be stored at a local laboratory. Your name will not be linked to the sample. Some of your blood will be tested for HIV**. Some of your left over blood will be stored temporarily in the event that any additional protocol related testing is needed. If you agree, any other left over blood samples will be kept and used for future HIV-related research. A separate Informed Consent Form must be signed for this purpose.** We will use rapid HIV tests, so your results should be ready in about 20 to 40 minutes.

- APPENDIX III-D: Sample Enrollment Consent for Participants Enrolled during the Full Study
  Follow-up Visits:
  At the six (Week 26) and twelve (Week 52) month visits only, the doctor will conduct a physical exam and talk with you about your health.

  Every six months thereafter (Weeks 78, 104, 130, and 156) we will draw approximately 5 mL of blood in order to test you for HIV in addition to Hepatitis C. Some of the blood will be used immediately for these protocol tests and some will be stored temporarily for protocol specified tests.

  If you agree, any other left over blood samples will be kept and used for future HIV-related research. A separate Informed Consent Form must be signed for this purpose.

6. Short Term Medication Assisted Treatment vs. Long Term Medication Assisted Treatment
   Throughout the protocol and Informed Consent Forms, the term "~~Detoxification Treatment~~" is replaced with "**Short Term Medication Assisted Treatment**" and the term "~~Substitution Treatment"~~ is replaced with "**Long Term Medication Assisted Treatment**".