

## **Letter of Amendment #2 for:**

### **HPTN 046: A PHASE III TRIAL TO DETERMINE THE EFFICACY AND SAFETY OF AN EXTENDED REGIMEN OF NEVIRAPINE IN INFANTS BORN TO HIV-INFECTED WOMEN TO PREVENT VERTICAL HIV TRANSMISSION DURING BREAST-FEEDING, VERSION 3.0, DATED 26 SEPTMEBER 2007**

**IND 72,592**

**DAIDS Document ID 10142**

**Letter of Amendment Date: 4 March 2009**

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#### ***Instructions to the Study Sites from the Sponsor (US NIH/NIAID/DAIDS)***

The following information impacts the HPTN 046 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible. This Letter of Amendment must be approved by your IRBs/ECs prior to implementation.

This Letter of Amendment (LoA) includes changes to the informed consent form for participants enrolled under Version 3.0 of the protocol. Participants enrolled prior to IRB/EC approval of this LoA need not be re-consented with the modified consent form, unless you are otherwise instructed by your IRBs/ECs; however, the new information contained therein must be provided to these participants as they return for follow-up, and this process must be documented. Your IRBs/ECs are responsible for determining how study participants are to be informed of the contents of this Letter of Amendment.

This LoA and all related IRB/EC correspondence must be retained in the site regulatory file and in other pertinent files. Protocol registration approval is not required by DAIDS for Letters of Amendment.

If the HPTN 046 protocol undergoes a full amendment in the future, the changes in this Letter of Amendment will be incorporated into the next version of the protocol.

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#### ***Summary of Revisions and Rationale***

This Letter of Amendment includes no changes in participation requirements (e.g., volume or number of blood draws) or study procedures. The change included in Clarification Memorandum # 2, dated 20 February 2009, to Protocol HPTN 046 Version 3.0, dated 26 September 2007, has been included in this LoA.

The modifications are summarized briefly below and detailed in the 'implementation' section that follows.

1. As recommended by the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB), the informed consent form for participants enrolled under Version 3.0 of the protocol has been modified to include new information from other studies regarding the use of nevirapine for prevention of HIV transmission through breastfeeding.
2. It is clarified that the laboratory parameters on which infant enrollment criteria are based (ALT, hemoglobin, absolute neutrophil count and platelet count) can be re-assessed prior to final eligibility determination/enrollment if initial testing reveals exclusionary abnormalities in an infant otherwise likely to be eligible for study participation. The “birth specimen” is considered the final blood sample obtained on or before Day 7 of life that is used to confirm eligibility for enrollment. While this was the original intent and represents no change in study procedures, it was not explicitly stated in the current version of the protocol.

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### **Implementation**

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) Modifications to Informed Consent Form: Appendix II A, Sample Study Consent Form for Initial Enrollment Under Protocol Version 3.0 – *The affected sections are specified below.*

Purpose of the Study, paragraphs 4 and 5

A ~~recent~~ study conducted in Ethiopia, India and Uganda found that giving 6 weeks of the drug nevirapine once a day until the baby was 6 weeks old lowered the chance of passing HIV to the baby through breastfeeding. Because of these results, all babies who join this study will receive nevirapine once a day until the baby is 6 weeks old, even if this is not standard practice yet in this country. The study showed that using nevirapine until age 6 weeks reduces but does not completely prevent the chance of a mother passing the HIV virus to her baby. ~~It is not known if giving nevirapine to babies for a longer time would be even better in cutting the chance of passing HIV to the baby while breastfeeding.~~

We do not know **for certain** if nevirapine or any other drug given to the baby every day for more than six weeks is safe or if it will prevent a baby from getting infected with HIV while breastfeeding. **Other studies suggest that breastfeeding babies have some protection from HIV infection from breastfeeding while they are taking nevirapine. Thus, there is some suggestion that breastfeeding babies who take nevirapine for 6 months might be at lower risk of getting HIV from breastfeeding than they would be if they stopped taking nevirapine at 6 weeks of age. However, no one yet knows how long is best for breastfeeding babies to take nevirapine or any other drug to prevent transmission of HIV through breastfeeding.** This study will help find that out. Currently, the only certain way to prevent passing HIV through breastfeeding is not to breastfeed. As the counselors have discussed with you, there are health risks and benefits to both breastfeeding and not breastfeeding.

Risks and/or Discomforts, paragraph 1

**One half of the babies in this study will stop taking nevirapine after 6 weeks, while the other half will continue nevirapine until they are 6 months old. Other studies suggest that breastfeeding babies have some protection against HIV infection from breast milk while they are taking nevirapine. Thus, there is some suggestion that breastfeeding babies who take nevirapine for 6 months might be at lower risk of getting HIV from breast milk than if they stopped taking nevirapine at 6 weeks of age. However, no one yet knows how long is best for breastfeeding babies to take nevirapine, including how easy it will be to make sure that all babies in this country and other countries can get the right amount of nevirapine while they are breastfeeding. This study and others are trying to get enough information to help decide what is best for all babies in all countries.**

Alternatives to Participation, paragraph 1

You do not have to be in this study if you do not want to. The only known way to completely prevent passing HIV from a mother to her baby during breastfeeding is not to breastfeed. The clinic and study staff will explain the risks and benefits of breastfeeding to you and about safe alternatives. You will be provided information about where formula may be obtained. **If programs providing nevirapine or other drugs for prevention of HIV through breastfeeding become available in this area, the study staff will inform you.** The study staff will also refer you to HIV treatment programs that are available in your area. If you decide not to participate in the study, you will not lose the benefits of your standard medical care. You have a right to consider all options available to you and your baby.

- 2) Clarification Regarding Assessment of Infant Eligibility: *The following text (in bold) will be added after the last bullet:*

Section 4.2 Infant Enrollment Criteria

Infants who meet any of the following criteria will be excluded from enrollment into the study:

- ALT from birth specimen is Grade 2 or higher.
- Hemoglobin, absolute neutrophil count or platelet count from birth specimen is Grade 3 or higher
- Skin rash grade 2B (urticaria) or skin rash grade 3 or above
- Confirmed or suspected clinical hepatitis, defined as clinical signs and symptoms of clinical hepatic dysfunction including but not necessarily limited to enlarged liver (>4 cm below right costal margin), hepatic tenderness and/or ascites.
- Serious illness or condition that would prohibit compliance with study procedures as judged by site clinician

**Note: Abnormal laboratory results as specified above (ALT, hemoglobin, absolute neutrophil count and platelet count) may be re-assessed as necessary on or before Day 7, and if the infant meets all the eligibility criteria, s/he can be enrolled. The “birth specimen” is considered the final specimen obtained on or before Day 7 of life that is used to confirm eligibility for enrollment.**