

Protocol Clarification Memorandum #1 for:

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

DAIDS Document ID 10142

Clarification Memo Date: 26 February 2008

Summary of Revisions and Rationale

1. As clearly indicated throughout Version 3.0 of the protocol, the consent form included for participants enrolled under Version 2.0 (Appendix IIB) is intended for those being asked to continue in the study under Version 3.0. Those mother-infant pairs who were enrolled but not randomized under Version 2.0 are to be followed under Version 3.0 through the 3-month visit only; therefore, it is clarified that mother-infant pairs who are past the 3-month visit when the site implements Version 3.0 need not be re-consented because they are not being asked to undergo any further assessments or to continue in the study.
2. Section 4.3 specifies the infant randomization criteria and the timeframe for randomization. The target randomization day for infants is at the 6 week visit (Day 42); however, infants who meet the randomization criteria may be randomized at any time from 6 weeks (Day 42) through 8 weeks (Day 56) of life. The protocol states that abnormal lab results may be re-assessed and that if the infant meets the criteria before 8 weeks (Day 56), then the infant can be randomized. It is clarified that both abnormal lab results and clinical findings may be re-assessed within the specified timeframe to determine final eligibility for randomization. This clarification reflects no change in the eligibility criteria or time-frame for randomization.
3. Sections 6.2.2 and 6.2.3 provide instructions/criteria for resumption of dosing following a gap for open-label NVP and for study drug (blinded NVP or NVP placebo), respectively. It is clarified that, for both regimens, the instructions and criteria apply to gaps in dosing of ≥ 21 days.
4. For reporting purposes, it is clarified that a grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if the event is *immediately* life-threatening or otherwise meets the criteria for an SAE as defined in the protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS. This clarification reflects no change in reporting requirements but rather serves to highlight the distinction between immediately life-threatening events (participant was actually at risk of death as the AE

occurred) and potentially life-threatening events (participant may have been at risk of death *if* the condition had been worse). Note that this applies to infants enrolled under Version 2.0 or Version 3.0 of the protocol.

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer. IRB approval of this Clarification Memorandum is not required by the sponsor prior to implementation; however sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

The modifications included in this Clarification Memorandum will be incorporated into the next full protocol amendment.

- 1) Applicability of Consent Form for Participants Enrolled but Not Randomized under Version 2.0

Section 2.1, Maternal Screening, Enrollment and Follow-up, sub-section entitled "Version 2.0 Maternal Follow-up": The following text in bold will be added to last paragraph in this section:

Mothers of infants enrolled under Version 2.0 of the protocol and were not randomized (including those enrolled on or after 10 August 2007) that consent for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study. **Mothers of infants who were enrolled but not randomized under Version 2.0 and who are past the Month 3 visit when the site implements Version 3.0 need not be re-consented because they are not being asked to continue in the study. Instead, at the next visit, the study staff will explain to the mother that her and her infant's participation in the study is complete and document this in the participants' source records; no further assessments are to be undertaken.**

Section 2.3, Version 2.0 Infant Follow-up: The following text in bold will be added to last paragraph in this section:

Infants enrolled under Version 2.0 of the protocol who were not randomized (including those enrolled on or after 10 August 2007) and whose mothers consent for continued participation will be followed according to the study schedule described above through the Month 3 visit only and will then be terminated from the study. **Mothers of infants who were enrolled but not randomized under Version 2.0 and who are past the Month 3 visit when the site implements Version 3.0 need not be re-consented because they are not being asked to continue in the study. Instead, at the next visit, the study staff will explain to the mother that her and her infant's participation in the study is complete and document this in the participants' source records; no further assessments are to be undertaken.**

2) Randomization Criteria

Section 4.3 Infant Randomization Criteria: The following text in bold will be added and the text that is marked through will be removed from the first note following the criteria:

Note: Abnormal lab **and clinical results findings** as specified above may be reassessed and, if the infant meets all the criteria for randomization on or before 8 weeks (Day 56), the infant can be randomized.

3) Gaps in Dosing

Section 6.2.2, Conditions for Exclusion from Subsequent Doses of Open-Label NVP (through 6 weeks (42 days) of life): The text in bold will be added to the existing note.

Note: Infants with a gap in dosing **of 21 days or more** after initiation of open-label NVP until age 6 weeks must have a negative HIV DNA PCR result (or quantitative RNA PCR) on a specimen obtained at the study visit when the gap was identified or within the prior three weeks (≤ 21 days) **and** must have been exposed to breast milk within the last 30 days or dosing cannot be resumed. Resumption of open-label NVP 6-week regimen is to be at the dose appropriate for the infant's age.

Section 6.2.3, Initial and Subsequent Study Drug Dosing Following Randomization: The text in bold will be added to the existing note.

Note: Randomized infants who did not initiate study drug or with a gap in dosing **of 21 days or more** after initiation must have a negative HIV DNA PCR result (or quantitative RNA PCR) on a specimen obtained at the study visit when the non-initiation or gap was identified or within the prior three weeks (≤ 21 days) and must have been exposed to breast milk within the last 30 days or dosing cannot be started or resumed. Initiation or resumption of study drug is to be at the dose appropriate for the infant's age.

4) Reporting of Grade 4 Adverse Events

Appendix V, HPTN 046 Adverse Event Reporting and Documentation Requirements: The following note will be added after the footnotes to the table:

Note: A grade 4 asymptomatic laboratory adverse event is considered a serious adverse event (SAE) only if it is immediately life-threatening or otherwise meets the criteria for an SAE as defined in this protocol (Section 7.0) and the Manual for Expedited Adverse Event Reporting to DAIDS.