

HIV Prevention Trials Network

Protocol Clarification Memorandum #2 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 2.0, DATED 22 MAY 2005

Clarification Memo Date: 9 May 2007

Summary of Revisions and Rationale

1. The instructions for initiation of study drug on Day 5 after birth (± 2 days) have been clarified and instructions to consult the Protocol Safety Review Team (PSRT) with any concerns or questions about introduction or resumption of study drug dosing have been added.
2. It is clarified that normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered reportable adverse events as defined in Section 7.0; examples include clinical findings such as milia, miliaria and newborn peeling and laboratory findings such as slightly elevated or low monocyte, basophil or MCH counts, or elevated platelet, neutrophil or lymphocyte counts, as these are not toxicities.
3. Grade 3-A2 of the *Supplemental Table for Grading the Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever* which describes skin rash, is modified from “fever, $>39^{\circ}\text{C}$ ” to “Grade 2 fever.” This clarification allows for the original intent of this constitutional finding regardless of how the temperature is measured (axillary or rectal).

Implementation

The procedures clarified in this memorandum have been approved by the NIAID and NICHD Medical Officers and are to be implemented immediately upon issuance. IRB approval of Protocol Clarification Memorandum #2 for HPTN 046 Protocol Version 2.0 is not required by the sponsor; however sites may submit the Clarification Memo to the responsible IRBs/ECs for their information.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in bold will be added.

1. Dose Initiation and Breastfeeding

Section 6.2.1, Conditions for Exclusion from Initial Study Drug Dosing, the Note modifies as follows:

Note: Mothers will be instructed to begin administration of the study drug to the infant on Day 5 after birth (± 2 days), with the day of birth considered Day 0. If at a subsequent study visit, the study staff learn that administration of the study drug was not begun within this timeframe and the infant continues to meet the dosing criteria specified above **and has been exposed to breast milk within the last 30 days**, the procedures below will be followed:

- If within four weeks (≤ 28 days) of the Day 5 target: The mother will be instructed to begin dosing as soon as possible at the appropriate level for the infant's age.
- If more than four weeks (> 28 days) after the Day 5 target: The mother will be instructed to begin dosing as soon as possible at the appropriate level for the infant's age *only if* an HIV DNA PCR result from a specimen drawn at the current visit or within the previous two weeks is negative. (Note: Quantitative HIV-1 RNA PCR may be used if HIV-1 DNA PCR is not available.)

Note: Concerns or questions about introduction or resumption of study drug dosing in unusual cases should be directed to the PSRT, which will determine how the situation is to be handled.

2. Normal Variations

Section 7.0, Safety Monitoring and Adverse Event Reporting, the first paragraph will amend as follows:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which may or may not have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Study participants will be instructed to contact the study clinician to report any AEs their infants may experience. **Normal variations in typical neonatal conditions that are not regarded as unfavorable are not considered adverse events as defined above; examples include clinical conditions such as milia, miliaria and newborn peeling and laboratory findings, which are not gradable events per the DAIDS Toxicity Table, such as slightly elevated or low monocyte, basophil or MCH counts, or elevated platelet, neutrophil or lymphocyte counts.**

3. **Grade 3-A2 Skin Rash**

Appendix III, Supplemental Table for Grading the Severity of Cutaneous/Skin Rash/Dermatitis, Malnutrition and Fever, Grade 3 column amends as follows:

A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to the drug:

1. 5 x ULN AST, ALT or 2 x baseline if baseline > ULN
2. ~~fever, >39°C~~ **Grade 2 fever**
3. blistering and/or vesiculation of cutaneous eruptions
4. any site of mucosal lesions; OR