

## HIV Prevention Trials Network

### 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 2.0, DATED 22 MAY 2005**

**Clarification Memo Date: 26 January 2006**

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

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1. To correct an inconsistency in the protocol, the units describing the target nevirapine concentration levels “micrograms” (mcg) is replaced by “nanograms” (ng). The majority of references to the concentration level throughout the protocol include the correct unit.
  2. The definition of infant age has been clarified to provide guidance for the time points at which infants can receive study medication based on the Infant Dosing Regimen Table in the Schema and Section 6.2. Age will be defined using a rounding rule, similar to those used for weight, specifying that infants will be considered to be the appropriate age for a dose adjustment if they are no more than one week below the target age, **except** at two weeks of age when the dose is escalated. Infants will be eligible for the two week dose escalation at only two days prior to the target age. There are no safety concerns associated with adjusting the dose of infants who are one week under the target age from a PK standpoint, particularly given the fact that there will be much variation in weight, and after the 2-week dose escalation the doses are adjusted for growth with the goal of keeping the dose per kg relatively constant. The dose adjustments are very small and the concentrations are much lower than therapeutic doses.
  3. To clarify the administration of study drug and syringes to mothers and to provide for the safe follow-up of infants, Section 6.2 has been modified to specify the maximum amount of study drug and syringes that may be dispensed at one time.
  4. To ensure consistency throughout the Sample Study Enrollment Consent Form, a single reference to “nevirapine” in one section is changed to “study syrup.”
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#### **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 #1 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. Nevirapine Concentration Level Units:

- List of Abbreviations and Acronyms

MTCT	mother-to-child HIV transmission
<b>ng</b>	<b>nanogram</b>
NIAID	(United States) National Institute of Allergy and Infectious Diseases

- The terms “micrograms” or “mcg” have been replaced by “ng” in the following sections:
  - Section 1.2, Rationale for Extended Regimen of Infant NVP to Prevent MTCT, third paragraph, second sentence
  - Section 1.3.1, Pharmacokinetics of Intrapartum/Neonatal NVP, first paragraph, first sentence and second paragraph, last sentence
  - Section 1.5, HIVNET 023: Safety and Pharmacokinetics of Extended NVP Regimen, first paragraph, second sentence

## 2. Infant Age

The following note has been added below the infant dosing regimen table in the schema and section 6.2:

**Note: Infants will be considered to be the appropriate age for dose adjustment if they are no more than one week below the target age, except at two weeks of age. Infants will be eligible for the two week dose escalation at only two days prior to the target age.**

## 3. Dosing Quantity

The following wording has been added after sentence four of Section 6.2:

Mothers will receive syringes and instructions for dosing the oral suspension to their infants. **Mothers will receive at least enough study drug and syringes to dose their infant until the next scheduled visit. Clinic staff may request additional study drug and syringes in the event that the mother cannot return to the clinic on the infant’s scheduled visit date but will still be returning within the infant’s visit window. Site staff may not authorize dispensation of any additional supply of study drugs or oral syringes that would be used in the event of a missed visit window because infants need to be seen to be properly evaluated for possible toxicities. Details of this distribution can be found in the SSP.** The study drug regimen will be based on infant age...

## 4. Study Syrup:

Appendix IIA, Sample Study Enrollment Consent

Weaning

You will be encouraged by the study staff to stop breastfeeding at the end of 6 months or earlier if you choose. Your baby's last dose of nevirapine study syrup will be given at 6-months or soon after you stop breastfeeding, whichever comes first.