

LETTER OF AMENDMENT # 1 TO:

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 breastfeeding, Version 1.0, dated 10 October 2003

FINAL Version: 6 July 2004

The following information impacts the HPTN 046 study and must be forwarded to your institutional review board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Please file this letter and any IRB/EC correspondence in your regulatory file and other pertinent files. You are NOT required to submit these documents to the Protocol Registration Office unless the changes result in a change to the informed consent for your site.

If the HPTN 046 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

Summary of Revisions and Rationale

The study sponsor, the Division of AIDS, US National Institute of Allergy and Infectious Diseases, has requested that its new 'Manual for Expedited Reporting of Adverse Events to DAIDS' be employed in HPTN 046. Specifically, the 'standard' level of reporting defined in the Manual will be applied.

The definitions of adverse events and serious adverse events remain unchanged. The effective differences between the adverse experience reporting requirements specified in Version 1.0 of the study protocol and the new Manual are two:

- **Deaths** judged to be **not related** are now to be reported to the DAIDS Safety Reporting Office in an expedited manner
- **Persistent or significant disabilities/incapacities** judged to be **not related** are now to be reported to the DAIDS Safety Reporting Office in an expedited manner.

In Version 1.0 of the protocol, all AEs and SAEs, regardless of relatedness or severity grade, were to be reported on DataFax case report forms for entry into the study database; all SAEs except those judged to be definitely not related were to be reported to the DAIDS Safety Reporting Office in an expedited manner. The new Manual introduces a new relationship category, 'probably not related'. In version 1.0 of the protocol, such events would have been considered 'possibly related' and reported accordingly, therefore there are no effective changes in the types of AEs that would be reported in an expedited manner to DAIDS, with the two exceptions bulleted above for events deemed *not related* to the study drug.

The sponsor has also requested the following protocol-specific reporting requirement: In addition to those specified in the 'Manual for Expedited Reporting of Adverse Events to DAIDS', the following adverse events will also be reported in an expedited manner to DAIDS: **all grade 3 and 4 skin rashes and alanine aminotransferase (ALT) levels** that otherwise do not meet the criteria for reporting specified in the Manual.

In addition, the sponsor requested that the reference to the specific DAIDS Toxicity Tables used for grading the severity of AEs be broadened to allow for transition to the new version of these standard tables when finalized and available.

Implementation

The following specific changes will be incorporated into the body of the protocol document with the next full amendment. Deleted text is noted by strike-through; added text is in bold.

- 1) Section 7.0, paragraph 3: The first and second sentences have been moved to the end of the paragraph for clarity; only changed text is noted below in bold or strike-through.

Throughout the entire 18 month follow-up period, **the Manual for Expedited Reporting of Adverse Events to DAIDS will be followed; specifically the 'standard' level of reporting specified therein will be applied. In addition, as a protocol-specific requirement, all grade 3 and 4 rashes and alanine aminotransferase (ALT) levels, regardless of seriousness or relatedness, will be reported in an expedited manner to DAIDS. Adverse events that meet the criteria for expedited reporting as specified in the Manual or in this protocol** ~~SAEs that are judged by the on-site study clinician to be possibly, probably or definitely related to the study drug, or for which a relationship cannot be determined will also be reported on the DAIDS SAE Expedited Adverse Event Report Form and sent within three business days of site awareness to the DAIDS Safety Adverse Experience Reporting AER Office.~~ Information on all non-serious and serious AEs in infants through 8 months of life (8 weeks after maximum study dosing duration) - regardless of relatedness - will be recorded in the participant source records and on standard Datafax AE case report forms (CRFs) for entry into the study database. After 8 months of life, information on all concurrent illnesses will be recorded in the participant source records, but only SAEs **and any other grade 3 and 4 skin rashes and ALTs** will be reported on standard Datafax AE CRFs for entry into the study database.

- 2) Section 7.1, paragraph 1, sentence 1:

Severity of all AEs will be graded according to the **current** standard DAIDS Toxicity Tables ~~for infants <3 months and children >3 months of age~~