

## AMENDMENT TO:

### Version 1.0 of HIVNET 012

**ORIGINALLY TITLED "A PHASE III PLACEBO CONTROLLED TRIAL TO DETERMINE THE EFFICACY OF ORAL AZT AND THE EFFICACY OF ORAL NEVIRAPINE FOR THE PREVENTION OF VERTICAL TRANSMISSION OF HIV-1 INFECTION IN PREGNANT UGANDAN WOMEN AND THEIR NEONATES" AND DATED 5 JUNE 1997**

**THE AMENDED PROTOCOL IS REFERRED TO AS  
VERSION 2.0 AND DATED 14 MAY 2003**

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### SUMMARY OF REVISIONS

At the specific request of the sponsor, this amendment incorporates into a single document, referred to below as Version 2.0, two significant modifications to HIVNET 012 Version 1.0 previously approved by the JHU and Uganda Institutional Review Boards/Ethics Committees:

- Elimination of the placebo control and continued randomization of subjects into a two-arm open label trial (by Letter of Amendment dated 9 March 1998). The attendant sample informed consent form for participation in the primary 18-month study used from March 1998 through June 1999 is also incorporated into this version of the protocol.
- Extension of follow-up of all children participating in the primary 18-month study and mothers in the NVP arm from 18 months postpartum to five years postpartum (Amendment dated 21 February 2000). The attendant informed consent form for long-term follow-up is also incorporated into this version of the protocol.

In addition, Version 2.0 includes modifications throughout where additional detail or clarification was needed. These are modifications detailed below. None of these changes affect or necessitate a change to the text of the informed consent forms mentioned above.

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### APPROACH

As this amended protocol has been prepared retrospectively at the request of the sponsor, it is important to explain the approach used by the protocol team. The rationale presented in the document for the significant changes referred in the two bullets above, reflects the verbatim arguments on which approval of the IRBs was sought and granted at the time these changes were made. Therefore, even where additional data are currently available, these data are not incorporated into Version 2.0, as they were not available at the time decisions were made to eliminate the placebo control and subsequently to extend follow-up to 5 years post birth. The protocol team believes that it is important for the information included in Version 2.0 of the protocol to be consistent with the information on which the earlier decisions were based.

The most significant change to Version 1.0 of the protocol was elimination of the placebo control just after the February 1998 CDC announcement that a 300 BID dose of AZT given to mothers in Thailand at 36 weeks gestation through labor was able to significantly reduce the rate of vertical HIV transmission from 18.6% to 9.2%. At that time, the protocol team planned to redesign the efficacy

trial with an appropriate control, which was assumed would be one of the regimens included in the UNAIDS-sponsored PETRA study which was then also ongoing. Because an appropriate comparison arm would be a regimen tested in the same study population with established efficacy (neither the AZT nor NVP regimen in HIVNET 012 had been tested previously), the team intended to wait for the PETRA results, which were expected within a few months. As presented to the IRBs at the time, the study team wanted to continue accrual in the active agent (NVP and AZT) arms of the study as an interim measure to gain preliminary efficacy data on the two short course antiretroviral regimens to guide a decision about which of the two should be included in the re-designed efficacy trial. In fact, a full revised protocol was indeed developed and underwent initial HIVNET review with finalization pending release of the PETRA results, as planned. Because of the magnitude of the protective effect demonstrated in the HIVNET 012 interim analyses presented to the DAIDS DSMB, it was concluded that pursuit of the subsequent planned efficacy trial was unnecessary. Instead, efforts were focused on extending the follow up of children in HIVNET 012 and mothers in the NVP arm for long-term safety monitoring.

Version 2.0 is divided into two parts. Part I is the initial 18-month follow-up component to evaluate the primary study endpoints (Sections 1.0-9.0, Appendices I and II). Part II is the long-term follow-up study to monitor safety in all children participating in Part I and mothers in the Nevirapine arm through 5 years post birth (Sections 10.0-14.0, Appendices III, IV and V). The remaining sections apply to both Part I and Part II.

As noted above, Version 2.0 also includes modifications throughout only where the protocol team believed that additional detail or clarification to the original text was needed.

## **MODIFICATIONS AND RATIONALE**

Modifications to the protocol and the rationale for each are presented below generally in the order in which they appear in the protocol. As noted below, some changes were made in multiple places where relevant throughout the protocol. To avoid redundancy, such changes are specifically noted below only in the first place that they appear. In Version 2.0, changes made to the original text are highlighted throughout; deletions are noted below.

- 1) Elimination of the placebo control: All references to the placebo control were eliminated throughout the title, schema, body of the protocol and the informed consent (Appendix II). The purpose of the study was changed to reflect the basis on which IRB approval was sought and obtained for elimination of the placebo control and continued accrual into the active agent arms of the study, as described above, to guide a decision about which regimen would be selected for inclusion in a planned re-designed efficacy trial. The statistical section (8.0) includes the calculations originally presented to the IRBs showing the range of power expected depending on the number of mother/infant pairs enrolled during the interim accrual period.
- 2) Extension of follow-up for mothers in the NVP arm and all children participating in the primary 18-month follow-up study: The text of the previously approved amendment, dated 21 February 2000, has been included as Part II of Version 2.0 of HIVNET 012 along with the schedule of evaluations and the informed consent form used for this component of the study. This consent form included a separate section and signature box for specimen storage. Version 2.0 includes a new consent form for participation in the long-term follow-up study the content of which is unchanged from the original approved long-term follow-up informed consent form with the exception of the version number and date.
- 3) The title of the protocol was changed to reflect elimination of the placebo control and the fact that the trial was no longer considered a Phase III study.

- 4) The DAIDS Medical Officer was updated to reflect current DAIDS staff: Samuel Adeniyi-Jones replaced Mary Glenn Fowler.
- 5) The protocol team roster was updated with current contact information and, as noted above, the current DAIDS Medical Officer was added.
- 6) The table of contents was updated with the new section titles and numbering. **NOTE that the section numbers for Version 2.0 do not correspond with the same sections in Version 1.0, as a new Introduction section was added to Version 2.0 as stated below.**
- 7) The study schema was updated to include the purpose of the interim study and to reflect a two-arm open label design with target interim accrual of approximately 400-600 mother-infants pairs and incorporates long-term follow-up of subjects under “study duration”.
- 8) Section 1.0 of Version 2.0 (Introduction) was revised to incorporate the purpose of the study after the placebo control was eliminated and to outline the remaining sections of the protocol, including the division into two parts.
- 9) Section 2.0 of Version 2.0 (Background), the background for the primary 18-month follow-up study was revised only slightly to reflect that it pertains specifically to Part I. This text remains almost completely unchanged with the exception of places in which data were referred to as “recent”. The descriptions of these data remain unchanged but references to them as “recent” were deleted.
- 10) Section 3.0 of Version 2.0 (Rationale), was revised to acknowledge the change to Version 1.0 of the protocol (elimination of the placebo control) necessitated by the February 1998 CDC announcement that a 300 BID dose of AZT given to mothers in Thailand at 36 weeks gestation through labor was able to significantly reduce the rate of vertical HIV transmission from 18.6% to 9.2% and to state the purpose of the study after elimination of the placebo control.
- 11) Section 5.0 of Version 2.0 (Study Design), was revised to reflect that it pertains specifically to Part I (the primary 18-month follow-up study) and to describe the two-arm open label design used after the placebo control was eliminated. It was also clarified in this section and throughout the following sections, where appropriate, that randomization and enrollment took place at  $\geq 36$  weeks gestation to clarify that 36 weeks was the minimum gestational age as originally intended.
- 12) Section 6.0 of Version 2.0 (Study Population): In the second paragraph, the sentence regarding duration of infant follow-up, Version 1.0 of the protocol erroneously referred to determining HIV status at 6 months of age; this is the only place in the protocol that this was mentioned and no assessment of HIV at 6 months was included in the schedule of evaluations. Therefore, to eliminate this inconsistency, the time point referred to was changed to “14 weeks” rather than six months. To also clarify that assignment of the study identification number corresponding with a study drug kit was the effective point of randomization, the third paragraph was modified as follows: “If they agree to participate, they will be given a study-specific identification number corresponding with a pre labeled study drug kit. At that point, they will be considered randomized and given the study drug to take home for self-administration.”
- 13) The “note” at the end of Section 5.21 (Study Exclusion Criteria) in Version 1.0 related to study drug dosing rather than to study inclusion criteria and was therefore confusing in this location. Because dosing criteria are detailed in Section 9.0 of Version 2.0 (Section 8.0 of Version 1.0), the note was deleted. Likewise, in the same section (5.21 of Version 1.0) under “Disallowed Medications”, reference to exclusion of mothers from dosing was eliminated as this is covered more clearly in the section on Study Treatment (9.0 of Version 2.0).
- 14) Sections 7.11, 7.21 and 7.22 of Version 2.0 (Evaluations During/After Treatment): A note was added to the bullets for maternal and neonatal RNA PCR to clarify that direct detection of HIV RNA includes sequencing of the virus.

- 15) Section 7.22 of Version 2.0 (Neonatal Evaluations): This section was modified to accurately reflect the fact that hematology had to be done when CD4 counts were done, therefore the 14 week time point was added to the bullet for hematology as were the 12 and 18 months time points for infected children. These changes are also reflected in the Schedule of Evaluations (Appendix I).
- 16) Section 7.3 of Version 2.0 (Post Study Evaluations): Where appropriate, it was specified that this section applies to Part I of the study only.
- 17) Section 8.3 of Version 2.0 (Adverse Experience Reporting): The following specifics regarding the reporting of non-serious adverse experiences included in the study procedures manual were added to Version 2.0: “All AEs in mothers and infants through 6 weeks post birth, regardless of seriousness or relatedness, will be recorded on case report forms for entry into the study data base. After six weeks post birth, only serious adverse experiences in infants will be recorded on case report forms for entry into the study database. (Note: Mothers are not routinely followed after 6 weeks post birth in Part I of the study.)”
- 18) Section 9.11 of Version 2.0 (Dosing procedures): This section was modified throughout to reflect elimination of the placebo control. In the fourth bullet, it was clarified that if a women in the NVP arm was dosed during false labor, she was to receive an additional dose at onset of active labor if more than 48 hours (rather than 24 hours as specified in Version 1.0) had passed since initial dosing. The original reference to 24 hours was an error. The case reports forms and other documents consistently referred to 48 hours.
- 19) Section 9.121 of Version 2.0 (Maternal Exclusion Criteria for Study Dosing/Study Continuation): Paragraph 2 was modified to eliminate reference to randomization as this is covered in section 3.0 and to clarify that the following list of conditions apply to mothers not already dosed prior to arrival at the hospital.
- 20) Section 9.122 of Version 2.0 (Neonatal Exclusion Criteria for Study Dosing/Study Continuation): In the second paragraph and in the 5<sup>th</sup> bullet, it was clarified that laboratory results were not required prior to dosing. This makes more explicit what was implied in Version 1.0 by the use of the term “documented” lab results.
- 21) Section 9.4 of Version 2.0 (Concomitant Medications): To eliminate any misconception that medications needed to treat conditions unrelated to the study drug were withheld due to study participation, it was clarified that the medications listed in Sections 6.21 and 9.122 could be given after study drug dosing *if needed for medical care* as judged by the on-site clinician. (Specific permission of the PI was not required).
- 22) Section 9.6 of Version 2.0 (Criteria for Treatment Discontinuation): The corresponding Section (8.6) in Version 1.0 of the protocol indicated that study drug was to be withheld “until confirmation laboratory results” in the case of a grade 3 or 4 adverse event. Because not all grade 3 or 4 adverse events are associated with a laboratory abnormality or possibly related to the study drug, this statement was not clear and was therefore changed to read as follows: “Subjects experiencing a Grade 3 or 4 adverse event as noted in the appropriate Toxicity table will be followed closely. Study drug may be withheld or discontinued permanently if the AE is thought to be possibly related to the study drug, as judged by the on-site clinician.”
- 23) Section 10.0 of Version 2.0 (Statistical Considerations): This section was changed throughout to reflect elimination of the placebo control and continued randomization to the two active agent arms of the study as noted above. The calculations and related text and tables originally presented to the IRBs when the placebo was eliminated have been incorporated into this section (10.4) and replaced the original text where appropriate nearly verbatim showing the range of power to be achieved depending on the number of subjects enrolled in the interim accrual period and the guidelines to be used for selecting a regimen for the planned re-designed efficacy trial.

- 24) Section 10.3 of Version 2.0 (Randomization and Blinding) was revised to reflect the procedures followed after the placebo control was eliminated, including assignment of a pre-labeled study drug kit upon enrollment, which is the effective point of randomization.
- 25) Footnote #1 in Appendix I (Schedule of Maternal Evaluations) was modified as follows to eliminate an internal inconsistency with the text in Sections 5 and 6 (and throughout the protocol) which clearly indicate that screening was to begin between 32 weeks gestation and enrollment: “Hematology and serum chemistries must be obtained between 32 weeks gestation and 21 days prior to study entry.”
- 26) As noted above, the text of the previously approved amendment (dated 21 February 2000) to extend follow-up of all children participating in the primary 18 month follow-up study and mothers in the NVP arm was incorporated nearly verbatim into Sections 11.0-15.0 of the Version 2.0. In the original amendment under “Maternal Evaluations”, a meaningless phrase was erroneously included at the end of the second bullet for specimens obtained for assessment of NVP resistance as follows “and at 12 months the mother if has not reached that time point in the protocol”. This has been deleted. Also, the adverse experience reporting section for Part II (Section 14.0 of Version 2.0) has been changed to reflect that any SAE meeting the criteria specified in the protocol for expedited reporting would be sent to the DAIDS Regulatory Operations Center rather than to FHI.
- 27) In the Procedures section of Part II (Section 13.0 of Version 2.0), the following underlined phrase has been added in the second paragraph to clarify that resistance testing is not performed in real time: “A blood specimen will be obtained yearly (at every other child visit) from mothers randomized to the Nevirapine arm for assessment of resistance, which will be performed after the mother has completed study follow-up, if indicated by interim history or subsequent exposure to NVP.” There was never any intent to perform resistance testing in real time and the protocol did not specify this, therefore this does not reflect a procedural modification.
- 28) A footnote was added to Appendix IV (the Schedule of Evaluations for Part II) to clarify that the safety assessments specified at each time point can be completed up to 1 month before the next scheduled visit if the mother does not present on time and that, likewise, assessments specified at each time point may be completed up to one month before if the mother presents to the clinic then. Also, the superscripts corresponding with footnotes 1 and 2 correctly appear in the relevant heading in the first column of the table. Therefore, to eliminate internal inconsistency, the superscripts appearing in the top row of the table were deleted.
- 29) Section 19 of Version 2.0 (References): This section incorporates the references cited in the amendment to extend follow-up from 18 months to 5 years as numbers 26-28.
- 30) As noted above, the informed consent forms used in the primary 18-month follow-up study after the placebo control was eliminated and in the long term follow-up study have been incorporated into the of Version 2.0 of the protocol (Appendices II and III). Version 2.0 includes a new consent form (Appendix V) for participation in the long-term follow-up study the text of which is unchanged from the original approved long-term follow-up consent; only the version number and date will change.