

**SUMMARY OF CHANGES
INCLUDED IN THE
FULL PROTOCOL AMENDMENT TO:**

**HIVNET 024: PHASE III TRIAL OF ANTIBIOTICS TO REDUCE
CHORIOAMNIONITIS-RELATED PERINATAL HIV TRANSMISSION,
VERSION 4.0, DATED FEBRUARY 13, 2002**

**THE AMENDED PROTOCOL IS IDENTIFIED AS
VERSION 5.0 AND DATED 6 AUGUST 2003**

SUMMARY OF REVISIONS AND RATIONALE

On February 18, 2003, the NIAID Division of AIDS (DAIDS) Data and Safety Monitoring Board (DSMB) reviewed the interim study data available through December 20, 2002 and recommended that further enrollment be halted and that follow-up continue. The study sponsor (DAIDS) concurred with this recommendation. Consequently, accrual to HIVNET 024 – and administration of the initial course of antibiotics/placebos -- was halted on February 21, 2003. As of March 5th, dispensing of the second (labor) course of study antibiotics/placebos was halted, and sites began retrieving study antibiotics/placebos under the instruction of the DAIDS Pharmacy Affairs Branch. The Institutional Review Boards/Ethics Committees overseeing the research at each of the study sites were informed of all of these changes.

The changes included in this protocol amendment are summarized briefly below and detailed in the following “implementation” section:

- 1) The recommendations of the DSMB have been incorporated. Specifically:
 - Study enrollment is eliminated
 - Distribution of study antibiotics/placebos is eliminated
- 2) The study follow-up period has been shortened from one year after delivery/birth to three months after delivery/birth as study endpoints will have been reached by that time. For enrolled mother/infant pairs who return for a scheduled follow-up visit three months or more following delivery, that visit will represent the final study encounter.
- 3) The schedules of evaluations have been updated and are included in the appendices.
- 4) Four new sample informed consents reflective of the above changes have been included as appendices.
- 5) The modifications included in previously approved Letters of Amendment 1 and 2 to Version 4.0 (dated July 3, 2002, and January 6, 2003, respectively) have been incorporated into Version 5.0 of the protocol.
- 6) Further collection of CBCs from the infants born to women enrolled as HIV uninfected has been discontinued. These samples were not being collected for safety purposes and were no longer of clinical or statistical significance.

- 6) Minor additional changes (such as updating of the team roster) have been incorporated throughout; these are detailed below.

The section that has undergone the most revisions is “4.0 Clinical and Laboratory Evaluations.” While no new laboratory assessments have been added, shortening the duration of follow up has necessitated creating a final visit schema that can be applied to all HIV-infected women and their babies who return for follow up at or after the three-month visit.

IMPLEMENTATION

Protocol Team Roster

- The address and contact information of Dr. Jeffrey Stringer has been updated
- Contact information for the Investigator of Record of the Blantyre, Malawi site – Dr George Kafulafula – has been added
- The contact information for 2 former 024 Study Coordinators – Allison Nowlin in Lusaka, Zambia, and Gretchen Antelman in Dar es Salaam, Tanzania – have been deleted
- Contact information for Dr. Elizabeth Brown, Protocol Statistician with SCHARP, has been added
- Fax and email information for Lynda Emel have been corrected
- Corrections have been made to contact information for Scharla Estep

Signature Page of the Study Site Investigator of Record

- The term “Protocol Co-Chair” in the first sentence and in the signature line have been replaced with the more accurate term “Site Investigator of Record”

Table of Contents

- The Table of Contents has been updated to reflect the changes incorporated into Version 5.0 of the protocol

Schema

- “HIVNET 024” has been added to the title line

Section 1.0 INTRODUCTION

- A 3-paragraph introduction now precedes the original protocol and provides a background for the changes in this amended version.

Section 2.0 STUDY OBJECTIVES

- The following sentence now precedes the original section on Study Objectives:

“While the primary study objective was answered during the interim data analysis, the protocol team will pursue answers to the remaining objectives with the data collected.”

Section 3.0 STUDY DESIGN

- The following sentence now precedes the original section on Study Design:

“The original study design is described below. All active participants in HIVNET 024 must be re-consented to participate in the follow-up of this protocol. Sample informed consents for the follow-up are in the appendices; there is a separate consent for those women who were HIV infected at enrollment and those women who were HIV uninfected at enrollment. The original target accrual was 3120 HIV-infected and 600 HIV-uninfected women. At the time that accrual was halted, the trial was approximately 70% enrolled.”

Section 4.0 CLINICAL AND LABORATORY EVALUATIONS

- The following introduction now precedes section 4.1:

“The shortened duration of follow-up has not increased the number or type of clinical or laboratory evaluations to be collected from participants. All evaluations following enrollment through 3 months are unchanged with the exception that:

 - no study antibiotics/placebos are to be dispensed and
 - the 3-month visit (or the 6-, 9-, or 12-month visit for those mother/infant pairs already beyond the 3-month visit) has become a final visit.

In those rare cases that study antibiotics/placebos were not retrieved from the participant, the site is obligated to complete all documentation relevant to maternal study antibiotics/placebos adherence and to assess for adverse events after the first dose and for 2 weeks following the last dose.

In sections 4.1 through 4.3 are the expected clinical and laboratory evaluations for the HIV-infected and HIV-uninfected cohorts and their infants for pregnancy and until three months after delivery/birth; for HIV-infected and HIV-uninfected women and their infants who return for a final follow-up visit at 3, 6, or 9 months after delivery/birth; and for HIV-infected and HIV-uninfected women and their infants who return for a final follow-up visit at 12 months after delivery/birth. Sections 4.4 through 4.8 are from the original protocol and are included for comparison and to provide necessary background information.

Appropriate post-test counseling, as well as infant feeding counseling, should be provided to mothers of all HIV-exposed infants who undergo diagnostic testing for HIV infection. All infants identified as HIV-infected should be referred for specialized care, if available. Mothers of breastfeeding infants with negative HIV diagnostic test results should be counseled about the continued risk of MTCT of HIV through breast milk, and should be cautioned that a negative test result while

the infant is breastfeeding does not guarantee that the infant will remain HIV-uninfected.”

- Section 4.1: “Maternal and Infant Evaluations through 3 months” has been added
- Section 4.2: “Maternal and Infant Final Visit(s): 3, 6 and 9 months” has been added
- Section 4.3: “Maternal and Infant Final Visit(s): 12 months” has been added
- This sentence precedes section 4.4:

“The following sections -- 4.4 through 4.7 -- are essentially the instructions for evaluations in the protocol as originally designed. There have been minor modifications made to section 4.4 (“Pre-entry Evaluations”) to clarify that women of known HIV status would be exempt from the 024 screening process; to section 4.5 (“Evaluations During Pregnancy and Labor”) to clarify methods for determining gestational age; and to the title of section 4.5.1 (“Adherence to Study Antibiotics/Placebos”) to clarify that, because this is a blinded study, strategies for determining adherence applied to both the study antibiotics and to the placebos. All of these changes are highlighted.”

- The original section 4.1 has been renumbered as 4.4
- The following phrase (in bold) has been added to the second sentence of section 4.4 to clarify and acknowledge that women may have been screened for HIV independent of HIVNET 024 (this is a further clarification of the intent of Clarification Memo #2 to Version 3.0, dated July 5, 2001):

“Women **who had not already undergone VCT through another mechanism** and who agree to be HIV tested will sign a screening informed consent form.”

- The following phrase (in bold) has been added to the fifth sentence of section 4.4 to clarify and acknowledge that not all participants may have undergone counseling and screening through HIVNET 024 and that only those who had would have been required to undergo post-test counseling at the study clinic (this is a further clarification of the intent of Clarification Memo #2 to Version 3.0, dated July 5, 2001):

“All women **who underwent pre-test counseling and testing** will receive post-test counseling upon return to the clinic.”

- The following 2nd sentence has been added to the 3rd paragraph of section 4.7:

“Ultrasound examinations are rarely performed at these sites; therefore estimating gestational age by this criterion will not be routinely available. However, in the event that an ultrasound examination is performed, the gestational age from that assessment should be used.”

- The following 4th sentence has been added to the 3rd paragraph of section 4.5:

“The Ballard must be done within 48 hours of delivery to be considered valid.”

- “Placebos” has been added to the title of section 4.5.1: “Adherence to Study Antibiotics/Placebos”
- As noted in Letter of Amendment #2 to Version 4.0 of HIVNET 024 dated January 6, 2003, collection of DBS at 3 months has been added to Table 5 of section 4.5
- As noted in Letter of Amendment #1 to Version 4.0 of HIVNET 024 dated July 3, 2002, reference to the collection of breast milk has been deleted from section 4.7.

Section 6.0 STUDY TREATMENT

- “Placebos” has been added to the title of section 6.1.1: “Antibiotics/Placebos”
- The following introductory paragraph has been added to precede section 6.1.1:

“As per the recommendations of the DSMB following the interim analysis, no study antibiotics/placebos are to be dispensed. Any study antibiotics/placebos that have been dispensed are to be retrieved. The remainder of this section (6.1.1) describes the original design of the protocol with respect to the study antibiotics/placebos.”

- Section 6.2 was corrected from the following:

“The active antibiotics will be acquired through the Pharmaceutical Affairs Branch (PAB)/Division of AIDS contract with the University of Maryland. The same contractor will make the placebos.

The multivitamins will be purchased from Tishcon Corporation of Baltimore, MD.”

To

“The active antibiotics **were** acquired through the Division of AIDS contract with SRI. The same contractor will make the placebos.

The multivitamins **were manufactured by** Tishcon Corporation.”

Section 7.0 STATISTICAL CONSIDERATIONS

- As noted in Letter of Amendment #1 to Version 4.0 of HIVNET 024 dated July 3, 2002, reference to plasma serum zinc and vitamin levels has been deleted from section 7.5 (“Monitoring and Analysis”)

Appendix I SCHEDULE OF EVALUATIONS

- The following schedules of evaluations have been added:
 - “A. Evaluations for HIV-infected and HIV-uninfected women from pregnancy through 3 months”
 - “B. Evaluations for HIV-exposed and HIV-unexposed infants from birth through 3 months”

- “C. Evaluations for women/infant pairs who return for final follow up at 3, 6 or 9 months post delivery”
- “D. Evaluations for women/infant pairs who return for final follow up at 12 months post delivery”
- The former schedule of evaluations (maternal and neonate) is now labeled as:

“E: ORIGINAL SCHEDULE OF EVALUATIONS”
- As noted in Letter of Amendment #2 to Version 4.0 of HIVNET 024 dated January 6, 2003, collection of DBS at 3 months has been added to the neonate schedule of evaluations.

Appendix II SAMPLE OF INFORMED CONSENTS

- Four new informed sample informed consents have been written to reflect the changes in the amended protocol and are included as:
 - 1.0 Follow-Up Informed Consent for Pregnant HIV-Infected Participants
 - 2.0 Follow-Up Informed Consent for Pregnant HIV-Uninfected Participants
 - 3.0 Follow-Up Informed Consent for Postpartum HIV-Infected Participant
 - 4.0 Follow-Up Informed Consent for Postpartum HIV-Uninfected Participant
- The screening and enrollment informed consents have been renamed and included as:
 - 5.0 Original Screening Informed Consent
 - 6.0 Original Enrollment Informed Consent for Sites Enrolling HIV-Infected and HIV-Uninfected Participants
 - 7.0 Original Enrollment Informed Consent for Sites Enrolling HIV-Infected Participants Only