

AMENDMENT II

Extended Mother and Child Follow-up

HIVNET 012: Phase IIB trial to evaluate the efficacy of oral Nevirapine and the efficacy of oral AZT in infants born to HIV-infected mothers in Uganda for prevention of vertical HIV transmission

21 February 2000

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SUMMARY OF REVISIONS

- Follow-up of participating mothers and children will be extended from 18 months to 5 years.
- Resistance to Nevirapine will be evaluated yearly in mothers randomized to that treatment arm.
- Separate informed consent will be obtained.

RATIONALE

Recently, Blanche and colleagues reported that, of 1754 infants of HIV infected mothers exposed perinatally to AZT or AZT + 3TC, eight HIV uninfected children had evidence of mitochondrial toxicity (1). Five of these eight children presented with delayed neurological symptoms and two died. The other three were symptom-free but had severe biological or neurological abnormalities. Although the symptoms in these patients were quite variable, four of eight children had repeated seizures and five of eight had persistent lactic acidosis. All children had abnormally low absolute or relative activities of respiratory chain complexes I, IV, V, or both, months or years after the end of antiretroviral treatment. These findings suggest that AZT may be linked to mitochondrial toxicity. On the other hand, long term follow-up of greater than 15,000 perinatally exposed infants in United States studies revealed no excess of deaths before 5 years of age that might represent mitochondrial toxicity (2). Nevertheless, this possible, but seemingly rare toxicity, is cause for concern as are other unknown toxicities of antiretrovirals in the long term. In the Uganda setting, specific diagnosis of mitochondrial toxicity is not feasible. However, it is prudent to extend follow-up of children in the HIVNET 012 study who were exposed perinatally to either NVP or AZT from 18 months of age to 5 years of age to assess the occurrence of serious adverse experiences and mortality.

Preliminary data from the Uganda Phase I/II trial of nevirapine (HIVNET 006) suggest evidence of a single genotypic resistance mutation (K103N) associated with nevirapine found six weeks postpartum in 3 of 15 women given the 200 mg single dose of nevirapine in labor (3). Follow-up of women who received NVP in HIVNET 012 to assess the presence and persistence of this mutation is important in determining whether there is any possibility that

this mutation could limit the efficacy of nevirapine for prevention of vertical HIV transmission in future pregnancies or for treatment of HIV infection in these mothers.

PROCEDURES

Informed consent (Appendix A) will be sought from all women who participated in HIVNET 012 to extend study follow-up from 18 months to five years. Children will be followed at the study clinic every six months. At 24 months postpartum and at each subsequent visit, the child's history since the last visit will be reviewed and s/he will undergo a physical exam. Information on all serious adverse experiences in children will be recorded. Those children continuing to be breastfed will be tested for HIV every six months. (The average duration of breastfeeding in Uganda is approximately 14 months with over 95% discontinuing by two years.) Disease progression and viral load will be assessed in all HIV-infected children.

A blood specimen will be obtained yearly (at every other child visit) from mothers randomized to the Nevirapine arm for assessment of resistance.

Location/contact information will be updated at each visit. Mothers will be asked to notify the study staff if they foresee a prolonged absence or permanent move out of the area.

NOTE: Enrolled mothers and children may receive any therapy and/or enter any other trial but will be asked to continue follow-up in this study as scheduled.

CLINICAL AND LABORATORY EVALUATIONS

Clinical and laboratory evaluations (Appendix B) will proceed after written informed consent has been obtained for extended follow-up of mothers and infants.

Pediatric Evaluations

Evaluations for all children

- ◇ History since last visit [general, breastfeeding status, SAEs, medications)
- 24, 30, 36, 42, 48, 54, 60 months
- ◇ Physical exam (including growth, neurologic assessment, neurodevelopment (Denver developmental))
- 24, 30, 36, 42, 48, 54, 60 months

Evaluations for HIV-uninfected children only

- ◇ HIV Ab EIA; if positive, confirmed by Western blot
- 24, 30, 36, 42, 48, 54, 60 months (*for breastfeeding children only - through six months post cessation*)

Evaluations for HIV-infected children only

- ◇ HIV-related history and AIDS-defining symptoms
- 24, 30, 36, 42, 48, 54, 60 months
- ◇ Hematology (CBC with differential and platelet count, CD4 count)
- ◇ HIV RNA PCR quantitative (Stored plasma)

Because of the difficulty of evaluating clinical disease progression in Uganda, evaluation of clinical/immunologic disease progression in children will primarily be based on mortality and CD4 cell counts at multiple time points using the following criteria from the U.S. CDC definitions of immune suppression. If the CD4 absolute count and the CD4% result in different categories, the more severe category will be used.

No evidence of suppression	CD4 \geq 1000/uL or \geq 25%
Moderate suppression	CD4 = 500-999/uL or 15-24%
Severe suppression	CD4 < 500/uL or <15%

Maternal Evaluations

Evaluations for mothers in NVP arm only

- ◇ Interim history (receipt of any antiretrovirals)
- ◇ Specimen obtained for assessment of NVP resistance
 - 24, 36, 48, 60 months and at 12 months the mother if has not reached that timepoint in the protocol

ADVERSE EVENT REPORTING

Information on all serious adverse events (SAEs) in children, regardless of relatedness, will be reported on a standard AE/Illness form and transmitted to the data center. SAEs that are judged by the on-site clinician as possibly, probably or definitely related to the study drugs will also be reported on the standard DAIDS SAE form and sent within three days of site awareness to Family Health International (FHI). FHI will forward these reports to the DAIDS Safety Specialist and Medical Officer and will prepare a safety report for submission to the FDA, if indicated. A serious adverse event (SAE) is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening condition, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or an important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require intervention to prevent one of the outcomes listed above (21 CFR 312.32(a), April, 1998). Any adverse experience otherwise judged as serious by the on-site clinician should be reported as a serious AE.

The severity of adverse experiences (the clinician's evaluation of the *intensity* of the AE) will be graded using the Division of AIDS Tables for Grading Severity of Adverse Experiences and the Supplemental Table for Grading of Cutaneous/Skin Rashes/Dermatitis. Grading of severity is determined by comparing observed symptoms and/or laboratory values to those included in the standard toxicity tables.

Management of any adverse event will be according to the best clinical practice available and the judgment of the site investigator.

REFERENCES

1. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;354:1084-1089.
2. Smith ME. Ongoing nucleoside safety review of HIV exposed children in US studies. Abstract 96; 2nd Conference on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants. Montreal, September 1999.
3. Becker-Pergola G, Guay L, Mmiro F, et al. Selection of K103N Nevirapine (NVP) Resistance Mutation in Ugandan Women Receiving NVP Prophylaxis to Prevent HIV-1 Vertical Transmission (HIVNET 006). Abstract 658; International Conference on Retroviruses. San Francisco, January 2000.

APPENDIX A
SAMPLE INFORMED CONSENT FORM

**HIVNET 012: Phase IIb Trial to Determine the Efficacy of Two Regimens of
Oral Nevirapine for the Prevention of Vertical HIV-1 Transmission in Pregnant Ugandan
Women and Their Neonates**
Extended Follow-up of Mothers and Children

REMINDER TO CLINICAL SITES: DO NOT USE PREAMBLE IN LOCAL CONSENTS

NOTE FROM OPRR (OFFICE OF PROTECTION AGAINST RESEARCH RISKS) TO SITES ENROLLING SUBJECTS IN THIS STUDY:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB WITH A COPY OF THIS SAMPLE CONSENT ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBS ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OF SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB, AND NOTED IN THE IRB MINUTES. JUSTIFICATION AND IRB APPROVAL OF SUCH CHANGES MUST BE DOCUMENTED FOR ANY NIH-SPONSORED TRIAL. SPONSOR-APPROVED CHANGES IN A DAIDS PROTOCOL MUST BE APPROVED BY THE LOCAL IRB BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB MAY OTHERWISE ADDITIONALLY REQUIRE.

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Introduction:

Since you and your child participated in the study named above, you are being asked to extend your participation from 18 months of follow-up to five years. Before you decide if you want to participate in the extended follow-up study, we would like to explain the purpose, the risks and benefits of participating, and what is expected of you and your child.

This informed consent form gives you information about the extended follow-up study. This information will also be discussed with you. After the extended follow-up study has been explained and you have been given a chance to ask questions, if you agree that you and your child can take part, you will be asked to sign this consent form or make your mark in front of a witness. You will receive a copy of this form to keep. Please note that your decision to participate in this research is entirely voluntary. You may decide that you do not want to take part or to withdraw from the study at any time without losing the benefits of your standard medical care. If the father of your child is available, the extended follow-up study will be explained to him and he will also be asked to sign the consent form.

Purpose of the Study:

The purpose of the extended follow-up study is to see whether there are any long-term effects of the study drugs in children and what affect the study drugs may have on the ability of mothers to respond to treatment with Nevirapine in the future. So far, the dosages of the drugs given in this study have been shown to be safe. Nevirapine has been given to over 800 infants in the U.S. and Uganda with

no significant safety concerns. Likewise, AZT has been given to more than 15,000 infants in studies in the United States and other countries with no significant safety concerns. Both of the study drugs are licensed in the U.S. for treatment of HIV infected adults and children in much higher doses than those given in this study. However, there may be long term side effects of the study drugs that we do not yet know about.

Your Part in the Research Study:

You will be asked to bring your child to the clinic for about seven extra visits – once every six months beginning when your child is 2 years of age until s/he is five years of age. At each visit, you will be asked about your child's health and any symptoms or illnesses that s/he has had since the last clinic visit. Your child will have a physical exam. You will be asked about whether you are still breastfeeding your child. At most or all of these visits, a sample of your child's blood will be taken. The amount of blood will never be more than 1 teaspoon. If your child was found to be HIV uninfected at the previous study visit and you are continuing to breastfeed, the blood sample will be tested for HIV (as many as seven times during the follow-up period). If at any time, your child is found to be HIV-infected, the study staff will tell you in person as soon as possible. If your child is found to be HIV-infected anytime during the follow-up period, the blood taken at the remaining study follow-up visits will be tested to see how much of the virus it contains. Any information related to your or your child's health will be given to you and explained to you. If your child is HIV infected or has other health problems, you may be asked to bring him/her to the clinic for additional tests and care.

In addition, some mothers (those who received Nevirapine in the study) will also be asked to give a sample of blood once a year – at about every other child visit (4-5 times during the five year follow-up period). The amount of blood taken from the mothers at each of these visits will be about two teaspoons. The study staff will answer any questions you may have and will refer you and your baby for additional care, if necessary.

A home visitor may come to your home with you at the time you agree that your child can participate in the extended follow-up study. Then the home visitor will know where you live and can help remind you of clinic appointments.

Possible Risks and Benefits

Drawing of blood can cause discomfort or slight pain. You or your child may have a bruise or swelling where the blood is drawn.

The additional follow-up visits in this study may be of no direct benefit to you or your child, however the information learned from the study may help others in Uganda and other countries the future.

New Findings:

The study doctors or staff will tell you any new information learned during the study that may affect your willingness to continue participating in the study. The study staff will also tell you when the study results will be available and how to learn about them.

Confidentiality:

The study doctors and staff will protect information about you and your child and your participation in this study to the best of their ability. On study records, a code will be used instead of your name or your child's name. Only the study staff will know this code. The study staff will not give out any information that identifies you or your child without your written consent. However, agencies that oversee the research including the Ugandan Ministry of Health, the U.S. Food and Drug Administration, the study sponsor (the U.S. National Institutes of Health) or their agents will be

allowed to inspect your and your child's study records. Your family's privacy will be respected. Neither you nor your child will be personally identified in any publication or presentation about this research study.

Costs or Payments to You:

The study clinic visits, examinations, and laboratory tests required in this study will be provided free of charge. You will be reimbursed only for the actual cost of transportation to the clinic for scheduled visits, if necessary.

Policy Regarding Research-related Injuries:

Medical care will be provided for illness or injury directly related to this study at no cost to you. Care or appropriate referral will be provided for any illness or injury that occurs during the study that is not directly related to the study, but you may have to pay for this care. There are no plans to give you money if there is a research-related complication or injury.

Reasons for Withdrawal from the Study Without Your Consent:

You may be withdrawn from the study before completion if your baby's father is available and objects to your baby being in the study or if the study is canceled by the study sponsor, the Ugandan Ministry of Health, or the U.S. Food and Drug Administration, or the Institutional Review Boards that oversee the research.

Persons to Contact with Problems or Questions :

If you ever have questions about this research or need more information or if you or your child is injured in the study, you should contact the study investigators, Professor Francis Mmiro at the Department of Obstetrics and Gynecology, Mulago Hospital or Dr. Phillipa Musoke at the Department of Pediatrics, Mulago Hospital. You may ring either Professor Mmiro or Dr. Musoke at 541044. If you have questions about your child's rights as a research volunteer, you may contact Dr. Edward Mbidde at the Uganda Cancer Institute across from the TB Ward at Mulago Hospital or you may ring him at 540410. Dr. Mmidde is a member of the Uganda Ministry of Health's AIDS Research Subcommittee, the committee that oversees the conduct of HIV/AIDS research in Uganda.

Statement of Consent:

I have read this consent form or had it read to me and it has been explained to me. I understand the purpose of the extended follow-up study, the procedures to be followed, and the risks and benefits as described in this written summary. I voluntarily agree to participate and to allow my baby to participate in this study.

Volunteer's Name (print) Volunteer's Signature or mark Date

Father's Name (print) Father's Signature or mark Date
(If he is reasonably available)

Witness' Name (print) Witness' Signature Date

I have explained the purpose of this study to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits of this study.

Investigator's or Designee's Name Investigator's or Designee's Signature Date
(print)

APPENDIX B (Amendment II)
SCHEDULE OF EVALUATIONS

	Baseline (24 months)	30 months	36 months	42 months post-birth¹	48 months post-birth	54 months post-birth²	60 months post-birth
Evaluations of all children							
Interim hx (general, breastfeeding status, SAEs, medications)	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X
Evaluations of HIV-uninfected children							
HIV ELISA; if positive, confirmed by WB ¹	X	X	X	X	X	X	X
Evaluations of HIV –infected children²							
Hematology (CBC with differential and platelet count)	X	X	X	X	X	X	X
CD4 count	X	X	X	X	X	X	X
HIV RNA PCR quantitative – stored plasma	X	X	X	X	X	X	X
Evaluations of all mothers in the NVP arm							
Interim history (receipt of any antiretrovirals)	X		X		X		X
10 ml of blood for resistance testing	X		X		X		X

¹ For breastfeeding infants only – through six months post complete cessation

² These evaluations will begin at the next scheduled visit following positive HIV diagnosis (at 24 months for infants indentified as HIV infected prior to enrollment in HIVNET 012A).

HIVNET 012

**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**

A Study of the HIVNET Group

**Sponsored by:
The National Institute of Allergy
and Infectious Diseases**

IND #49,991

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SCHEMA

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

Design: The study will be a four-arm, randomized, placebo-controlled trial.

Population: Mothers: HIV-1 infected Ugandan pregnant women > 32 weeks gestation;
Neonates: Born to HIV-1 infected mothers

Sample Size: 1500

Treatment Regimen*		
<i>Treatment</i>	<i>Mother Dosing Regimen</i>	<i>Infant Dosing Regimen</i>
Nevirapine (n= 500) -----OR----- NVP Placebo (n = 250)	Single dose (SD) of 200 mg NVP at onset of labor ----- Single dose (SD) of placebo at onset of labor	SD 2 mg/kg NVP at 48-72 hrs post-delivery, or discharge ----- SD of placebo at 48-72 hrs post-delivery, or discharge
AZT (n= 500) -----OR----- AZT placebo (n= 250)	600 mg AZT po bolus at onset of labor, then 300 mg po q3h until delivery ----- placebo po bolus at onset of labor, then po q3h until delivery	4 mg/kg AZT po BID for 7 days ----- placebo po BID for 7 days

* Volunteers will first be randomized to a NVP or AZT arm and then randomized to receive either the active agent or a placebo.

Study Duration: Enrollment: 18 months
Follow-up: neonates - 18 months post-delivery, mothers - 6-8 weeks post-partum

Primary Endpoints:

- Rate of HIV-1 infection in infants born to study participants in each arm of the study as determined by a positive qualitative plasma HIV-1 RNA result confirmed at the next visit by a positive culture or quantitative plasma RNA level on a different specimen for infants < 18 months of age. Infants 18 months of age will be considered infected if the EIA and Western blot are positive.
- Proportion of infants who are alive and free of HIV at 18 months of age
- Safety/tolerance of oral NVP and AZT given to pregnant Ugandan women during labor and their neonates during the first week of life

Secondary Endpoints:

- Rates of disease progression in the infected infants in each arm
- Infant survival in each arm (mortality, regardless of HIV infection)
- Relationship of maternal plasma RNA levels at delivery with risk of perinatal transmission
- The rate of infant death or HIV-1 infection

1.0 INTRODUCTION

The increase in pediatric HIV infection has a substantial impact on childhood mortality in both the U.S. and in the developing world. The majority of cases of pediatric HIV infection are due to maternal-to-infant transmission. The frequency of transmission of HIV-1 from an infected mother to her infant is estimated to be in the range of 15-40% (1-3). Recent evidence suggests that three modes of transmission occur: *in utero*, intrapartum, and postpartum through breast milk (4-11). A number of studies applying early diagnostic techniques of culture and PCR suggest that as many as half or more of maternal-infant HIV-1 transmission in the developed countries occurs late in pregnancy or during labor and delivery (1-12).

1.1 General Background

1.11 Nevirapine

Nevirapine (NVP) is a non-nucleoside benzodiazepine derivative which is a potent inhibitor of HIV-1 reverse transcriptase with an IC_{50} of 40 nM (10 ng/ml) and a high therapeutic index (13). The HIV-1 antiviral activity is rapid with significant reduction in plasma virus occurring within a few days of drug administration. Development of viral resistance to nevirapine occurs rapidly, with resistance observed in all subjects studied by 4 weeks. Potent antiviral effects usually persist for 1-2 weeks followed by an increase in plasma virus with the development of viral resistance. Nevirapine is well-tolerated with excellent oral absorption and bioavailability. Pharmacokinetic characteristics of nevirapine are appropriate for once-daily dosing.

1.12 AZT

Zidovudine (AZT) is a nucleoside analogue that interferes with the HIV RNA dependent DNA polymerase (reverse transcriptase) by premature chain termination. The AZT triphosphate also inhibits cellular DNA polymerases, but at concentrations 100-fold higher than those required to inhibit reverse transcriptase. AZT has been licensed for the treatment of HIV-1 infected adults with evidence of impaired immunity since 1987 and in the last two years for the treatment of HIV-1 infected pregnant women for the prevention of vertical transmission.

1.2 Treatment Activity

1.21 NVP - Activity

Nevirapine is currently in Phase I/II evaluation and when used in adults and children (3 months of age and older) at doses of 12.5 mg to 200 mg per day, the drug was well tolerated and produced a rapid rise in CD4 T-cell counts and a reduction in HIV p24 antigen (14,15). Antiviral responses were transient with p24 antigen returning to baseline values after 4 weeks of therapy. The loss of antiviral activity was associated with the emergence of isolates of HIV with greater than 100-fold reduction in drug susceptibility. Higher doses of nevirapine (400-600 mg/day) are now being examined to determine if higher plasma levels of drug can sustain antiviral activity against resistant virus. Preliminary results

suggest that nevirapine doses at 400 mg or greater per day result in plasma drug levels above the IC₅₀ of resistant virus with resultant sustained antiviral responses (15).

1.22 AZT - Activity

The results of ACTG 076, a multicenter international placebo-controlled study sponsored by the NIAID showed that giving zidovudine (AZT) to relatively healthy HIV-1 infected pregnant women prenatally from as early as the 14th week, continuously throughout labor and delivery, and to their neonates for the first six weeks of life, significantly reduced the rate of HIV-1 vertical transmission. The rates of vertical transmission were 24.9% in the placebo group and 7.9% in the group receiving AZT (16). AZT treatment was well-tolerated among women and infants, with no clinically significant toxicity observed. Reported adverse events were evenly distributed between the two randomized groups with the exception that hemoglobin levels were lower among the infants in the AZT group. During therapy, the maximum difference in the mean hemoglobin levels between the AZT group and the placebo group was 1 gm/dl. The AZT treatment regimen used in ACTG 076 consisted of 100 mg of oral AZT administered five times daily until onset of labor. During labor and delivery, the women received an IV infusion loading dose of 2 mg/kg given over one hour followed by continuous constant-rate IV infusion of 1 mg/kg/hour until delivery. Neonates then received oral AZT syrup doses of 2 mg/kg every six hours for the first six weeks of life. The AZT treatment regimen used in ACTG 076 has been adopted as the guideline for the use of antiretroviral therapy to prevent maternal-infant transmission during pregnancy (17). Recently, concern has been raised by the NIH announcement of data suggesting that AZT may have a transplacental carcinogenic effect which is dose dependent. A study by intramural NCI investigators demonstrated an increase in the incidence of tumors in the offspring of mice given very high doses of AZT early in gestation. Another recent study by Glaxo-Wellcome scientists showed no increase in risk of tumors in the offspring of mice given a variety of regimens of AZT. While experts acknowledge that the NCI data warrant consideration, they have agreed that, at this time, these findings do not alter the known safety profile of AZT.

Maternal-infant HIV transmission appears to be multi-factorial. There is increasing evidence that maternal viral load at the time of delivery is associated with vertical transmission (18-23). However, the ACTG 076 data suggest that reduction in maternal viral load during pregnancy with AZT was poorly correlated with transmission and suggests that neonatal prophylaxis with AZT may be providing the effective outcome. In addition, the AZT regimen used in ACTG 076 is neither practical nor affordable in many developing countries. Therefore, a simple and inexpensive AZT regimen that prophylaxes the infant during labor, delivery and the first week of life, during exposure to colostrum, may be effective in reducing perinatal transmission.

Administration of AZT by infusion, as used in ACTG 076 during labor and delivery, is not practical worldwide. However, it is not known whether systemic drug exposure achieved with oral administration of AZT during labor will provide similar protection against vertical transmission as seen in ACTG 076. Available pharmacokinetic data, however, support selection of oral dosing regimens for investigation.

1.3 Pharmacokinetics

1.31 NVP - Pharmacokinetics

Peak plasma nevirapine concentrations are reached between 2.6 and 4.6 hours after oral administration (14,15). Mean trough levels of nevirapine are 0.23, 1.10, and 1.90 **ng**/ml for the 12.5 mg, 50 mg, and 200 mg per day doses, respectively. These levels represent 8 times, 37 times, and 63 times the IC₅₀ [40 nM (10 ng/ml)] of subject isolates, respectively. Plasma half-life was 44 hours for the 12.5 mg and 50 mg/day doses, and 20 hours for the 200 mg/day dose. Data for children are accumulating from Boehringer-Ingelheim (BIPI) trials 882/892. Nevirapine is highly soluble at pH <3, and solubility decreases to approximately 0.1 mg/ml at neutral pH. Studies in pregnant animals suggest that the pharmacokinetics may be altered such that higher peak concentrations are achieved antepartum. To date, a trend towards a 50% higher clearance of NVP has been seen in children < 9 years of age.

Initial Data Summary - ACTG 250, Cohort 1A and 1B

The AIDS Clinical Trials Group (ACTG) has conducted a Phase I study (ACTG 250) of NVP in pregnant women and their newborns in the United States. Ten mother-infant pairs have been enrolled in the study, 4 in Cohort 1A and 6 in Cohort 1B. Cohort 1A involved administration of a single 100 mg oral dose of nevirapine (NVP) to the mother in active labor, followed by pharmacokinetic sampling of the mother and the newborn. Cohort 1B was identical except the dose of NVP was increased to 200 mg. In these initial cohorts, no NVP doses were administered to the infants. All study mothers were HIV-infected and all received AZT during the pregnancy. The mean age of the mothers was 25.9 + 2.8 years, and their mean weight at delivery was 80.8 + 27.7 kg. Seven of the mothers were Hispanic, two were black, and one was white.

There was a large amount of variability with a few extreme outliers for some of the study population pharmacokinetic parameters. The pharmacokinetic data are presented as medians with the range in parentheses in order to most accurately represent the data. Mothers in Cohort 1A (100 mg dose NVP) delivered at a median of 5.3 hours (range 3.5-6.0 hours) after NVP dosing with a median serum NVP concentration at delivery of 725 ng/ml (range: 273-964 ng/ml). Mothers in Cohort 1B (200 mg dose NVP) delivered at a median of 6.7 hours (range: 0.9-10.5 hours) after NVP dosing with a median serum NVP concentration at delivery of 714 ng/ml (range: 80-1678 ng/ml). The infants (5 female, 5 male) were all born at term with birth weight averaging 3341 + 553 grams. Nevirapine crossed the placenta well in both groups, and for the entire population (both cohorts combined) the median ratio of cord blood NVP concentration to the maternal serum NVP concentration at the time of delivery was 99% (range: 74%-123%). No maternal or infant drug related toxicity was noted. Median breast milk NVP concentration (4 samples from 3 women) during the first week of life was 76% (54%-104%) of maternal serum concentration. Maternal and infant pharmacokinetic parameters presented as median (range) are included in Table 1.

Table 1. ACTG 250 maternal and infant pharmacokinetic data

	Tmax (hrs)	Cmax (ng/ml)		AUC (ng*hr/ml)		Cl/F (ml/k/hr)	Vd/F (l/kg)	t 1/2 (hrs)
		100 mg	200 mg	100 mg	200 mg			
Mothers	3 (1-8)	1002 (312-422)	1663 (447-2639)	53665 (17516-301901)	90872 (36214-119027)	29.3 (4.7-90.5)	0.96 (0.53-6.85)	65.7 (22.7-279.2)
Infants	10 (0-12)	862 (257-1031)		-----	-----	-----	-----	45.4 (35.4-330.7)

These data demonstrate that NVP can be safely administered to laboring women and that it readily crosses the placenta, achieving therapeutic concentrations in the fetus. In Cohort 1A (single maternal dose of 100 mg) all 4 infants maintained serum concentrations above 100 ng/ml for the first 36 hours of life, and 3 remained above the target concentration for 72 hours. In Cohort 1B, one mother received NVP less than 1 hour before delivery. She did not achieve a serum concentration of 100 ng/ml by the time of delivery and her infant never achieved a serum concentration above 100 ng/ml. All other infants in Cohort 1B maintained serum concentrations above 100 ng/ml for at least 72 hours after birth, but not above 25 ng/ml at day 7 after delivery. These data suggest that maternal doses of 200 mg, if given several hours before delivery, should result in adequate transfer of NVP to the fetus to maintain the newborn serum concentration above 100 ng/ml for at least 72 hours [Protocol ACTG 250, Ver. 2.0].

1.32 AZT - Pharmacokinetics

Preliminary pharmacokinetic data from the use of oral AZT given to four HIV-infected pregnant women during labor in Haiti are available (personal communication from Dr. Andrea Ruff). In that study, each of the four women (average weight = 60 kg) received 200 mg AZT po every four hours during labor. Pharmacokinetic data were obtained after the initial oral dose. The peak serum concentrations of AZT ranged from 755 to 2323 ng/mL (mean 1247 + 724 ng/mL). The time to peak concentration ranged from 0.5 to 1.0 hours (mean 0.6 + 0.2 hours). The area under the concentration-time curve ranged from 1178 to 1975 hr ng/mL (mean 1561 + 425 hr ng/mL). The ratio of umbilical cord to maternal serum AZT concentrations (2 participants) was estimated to be 1.22 and 1.28. Oral AZT was well tolerated. The pharmacokinetics of oral AZT given during labor in this study was similar to that previously observed in women earlier in pregnancy in ACTG 082. In this small study, labor did not appear to affect the pharmacokinetics of AZT.

To aid in considerations of oral AZT dosing during labor, computer simulations were conducted by Burroughs Wellcome Co. Assuming an average body weight of 65 kg in late pregnancy and an average AZT oral bioavailability of 65%, then systemic drug delivery comparable to the 1 mg/kg/hr continuous infusion regimen used in ACTG 076 would require oral AZT administration at a rate of 100mg/hour. The assumption of an average body weight of 65 Kg was considered reasonable for women in the developing world where access to IV administration is considered most problematic. The 100mg/hr rate of oral AZT administration (i.e. 100 mg every hour, 200 mg every 2 hours, 300 mg every three

hours, etc.) would theoretically result in the same average steady-state plasma concentration as the ACTG 076 regimen. Making use of the above assumptions and average pharmacokinetic parameter estimates from oral AZT dosing in ACTG 082, the predicted peak concentration and predicted average steady-state concentration representative of the 300 mg q3hr oral dosing regimen are approximately 1 ug/mL and 0.6 ug/mL, respectively. However, based on simulations from data in ACTG 082 and the data from Dr. Ruff, steady-state peak concentrations of AZT from about 0.6 to 2 ug/mL and trough levels from approximately 0.1 to 0.4 ug/mL are anticipated. Steady state average plasma AZT concentrations over a 3-hour dosing interval can be expected to range from approximately 0.4 to 1.0 ug/mL.

Preliminary data - Oral AZT

The intrapartum IV dosing regimen of AZT used on ACTG 076 was based on information obtained from the Phase I investigation of AZT during pregnancy in ACTG 082 (24). This study included an initial investigation of 200 mg oral AZT administration prior to labor and intermittent IV dosing of 140 mg (about 2 mg/kg) every four hours during labor and delivery in eight women (weight range 60-110 kg). Results indicated that the average pharmacokinetics of AZT in pregnant women were similar to that in other non-pregnant adults, although there was considerable variability. Peak plasma AZT concentrations after the initial oral dose ranged from 0.33 to 2.04 ug/mL (mean 0.86 ± 0.59 ug/mL) and area under the concentration-time curve ranged from 0.66 to 1.79 hr*ug/mL (mean 1.10 ± 0.44 hr*ug/mL). The average oral bioavailability of AZT (62%) was similar to that historically observed in other adults. From the intermittent IV dosing during labor, drug concentrations in umbilical cord and in neonatal plasma at the time of delivery were comparable to simultaneous determinations in maternal plasma, suggesting passive transplacental drug transport. However, these concentrations were highly variable and dependent on time of birth relative to the most recent time of AZT administration. Subsequent concerns about adequate protection against HIV-1 transmission to the newborn led to a protocol amendment to investigate administration of AZT by continuous IV infusion during labor and delivery. The IV regimen used during labor and delivery in the ACTG 082 amendment consisted of an initial 2 mg/kg 1-hour loading infusion followed by a continuous constant-rate infusion of 1 mg/kg/hr until delivery. The median AZT plasma concentration at the time of delivery was 0.59 ug/mL (N=9) and ranged from 0.41 to 1.32 ug/mL (mean=0.82 ug/mL; SD = 0.61). The average neonatal plasma AZT concentration at birth was 0.75 ug/mL. This regimen was well-tolerated and was subsequently utilized in ACTG 076.

The infant dose proposed in this trial is the same total dose as that used in the ACTG 076 trial except the dosing interval is 4 mg/kg BID vs. 2 mg/kg QID in the ACTG 076 trial. In addition, a recent study reported that the steady state intracellular concentrations of the active moiety AZT-TP were not significantly different when given to adults at doses of either 100 mg three times per day or 300 mg two times per day, suggesting that the relevant intracellular AZT-TP concentration will be maintained with this dosing (25). This AZT dosing interval was chosen to enhance compliance and is the same AZT regimen being used in the WHO-sponsored PETRA study.

A Phase I/II study of AZT given to HIV-1 infected pregnant Ugandan women at 38 weeks gestation through labor and delivery was recently completed. Women were treated with 300mg AZT orally BID starting at 38 weeks gestation until onset of labor. During labor, women received a 600 mg oral bolus of

AZT followed by 300 mg orally every three hours until delivery. Eighteen women completed this regimen with no clinical adverse events attributed to AZT, including vomiting. The mean AZT plasma level at the time of delivery in this group was 462 ng/mL (median 225 ng/mL, range 0-1770 ng/mL) with all but one mother having detectable AZT levels at delivery. The median cord blood level was 306 ng/mL (range 26.5-1240 ng/ml).

1.4 Product Safety

1.41 NVP - Safety

A sedative effect, described as either somnolence or fatigue, is the most commonly reported event, followed by headache, diarrhea, nausea, fever, and skin rash (14,15,26). Somnolence or fatigue occurred as often at the 12.5 mg/day dose as at the 200 mg/day dose, usually 1-2 hours post-dosing, and was transient. These symptoms were considered to be nevirapine-related in 30-40% of total subjects. Additionally, enzyme elevations in ALT (SGPT), AST (SGOT), or alkaline phosphatase have been observed in participants receiving nevirapine. GGT was elevated as a result of the anticipated induction of liver enzymes. It was not used in defining liver toxicity because it reflects a physiological response to NVP (26).

The overall incidence of significant liver function test (LFT) elevations (i.e., >Grade 3) in unblinded studies was 7%. There does not appear to be a gender-specific risk for increased LFTs. The rate of clinically significant LFT abnormalities in healthy volunteer studies is low, except for an unexplained cluster of 3 female volunteers in a Phase I chronic dosing study. There have been no gender differences seen in the kinetics of NVP.

In the first multiple-dosing studies of NVP monotherapy, skin rash emerged as a dose-limiting toxicity. Of the 21 subjects who have received 200 mg/day dosing, 3 developed skin rash; 2 of the 3 subjects were also receiving Augmentin, which is now avoided as a concomitant therapy. Later studies used a lower priming NVP dose for a 2-4 week "lead-in" period. A total of 139 participants in Boehringer-Ingelheim sponsored trials have received a 200 mg/day lead-in period; of these participants, 13 (9%) reported rash during this period and 8 participants permanently discontinued drug prior to receiving the higher NVP dose (6 due to rash). For participants receiving 400 mg/day of NVP, the use of the lead-in period reduced the number of rashes at the higher doses from 57% of participants receiving 400 mg/day de novo to 18% of participants receiving 400 mg/day following the lead-in.

The temporal pattern of rashes appears to be bimodal, with the majority (81%) occurring within 28 days after starting the highest dose of NVP. A total of 31 severe (DAIDS severity Grade 3 or 4) cases have been reported in trials sponsored by Boehringer-Ingelheim or in adult ACTG trials (out of approximately 550 total participants receiving multiple doses). Two confirmed cases of Stevens-Johnson Syndrome (SJS) have been reported. Approximately 3% of participants on ACTG 241, a double-blind, randomized trial with a total of 199 participants receiving NVP at 400 mg/day, preceded by a 14-day lead-in period with 200 mg/day, and approximately 5% (1 out of 21) participants on ACTG 180, a pediatric multiple-dosing Phase I trial, permanently discontinued treatment due to rash. No serious toxicities have been seen in the single dosing Phase I pharmacokinetic studies of NVP in children.

1.42 AZT - Safety

Anemia and neutropenia are the most common serious adverse events associated with longterm use of AZT. However, because of the short duration of use in both the mother and the infant in the proposed trial, neither of these events should be an issue unless anemia or neutropenia are present at baseline. Headache and nausea are also commonly reported symptoms with ingestion of AZT, although these symptoms were not significant in the Phase I/II trial of AZT in Uganda.

2.0 RATIONALE

The goal of this perinatal prevention efficacy trial is to interrupt transmission of HIV-1 from pregnant Ugandan women to their infants. The proposed trial will specifically test the hypothesis that chemoprophylaxis of the fetus/neonate during labor and delivery and the first week of life may significantly reduce the risk of perinatal HIV-1 transmission. It is hypothesized that treatment of the mother during active labor will result in therapeutic levels of NVP or AZT in the neonate at the time of exposure to HIV-1 during parturition, decreasing the neonate's risk of infection. The frequency of vertical HIV-1 transmission is estimated to be 25%. There is an urgent need to find a safe, effective means of preventing mother-to-infant transmission that would also be applicable and affordable in developing-country settings.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- 3.11 To determine the rate of HIV-1 infection in infants born to study participants in each arm of the study as determined by a positive qualitative plasma HIV-1 RNA result confirmed at the next visit by a positive culture or quantitative plasma RNA level on a different specimen for infants < 18 months of age. Infants 18 months of age or older will be considered infected if the EIA and Western blot are positive.
- 3.12 To determine the proportion of infants who are alive and free of HIV at 18 months.
- 3.13 To evaluate the safety/tolerance of oral NVP and oral AZT given to pregnant Ugandan women during labor and their neonates during the first week of life.

3.2 Secondary Objectives

- 3.21 To compare immunologic disease progression through assessment of CD4 cell counts in the infected infants in each arm.

- 3.22 To compare infant survival in each arm (mortality, regardless of HIV-1 infection).
- 3.23 To determine the relationship of maternal plasma RNA levels at delivery with rate of perinatal transmission.
- 3.24 To compare the rate in each arm of infant death or HIV-1 infection.

4.0 STUDY DESIGN

This study will be a four-arm, randomized, placebo-controlled trial of the use of oral AZT and the use of oral NVP for prevention of vertical HIV-1 transmission in Uganda. A total of 1500 eligible HIV-1 infected pregnant women will be randomized to one of four study arms (500 in each active agent arm and 250 in each placebo arm). Randomization will be performed at 36 weeks gestation. Participants will first be randomized in an unblinded fashion to a NVP or AZT arm. A second blinded randomization will be carried out to determine whether the participant will receive the active agent or a placebo. After initial screening and enrollment, mothers will be followed during labor and delivery, and at 7 days and 6-8 weeks post-partum. Infants born to study mothers will receive a regimen of the same treatment (AZT, NVP or placebo) given to the mother. History, physical exams, and laboratory parameters will be followed to determine toxicity, evidence of HIV-1 infection, and clinical disease progression. Infants will be followed through the first week and at 6, 10 and 14 weeks and 6, 9, 12, and 18 months post-delivery.

The placebo arm of the study enables determination of effect of the intervention on the rate of vertical transmission as a comparison group. Neither AZT nor NVP is available as intervention in Uganda; the current standard of care involves no antiretroviral therapy. It is not known whether the regimens being studied will have any impact on vertical HIV-1 transmission. Ethically, therefore, this study will not deny women access to a proven therapy to which they would otherwise have access. If the short regimen of AZT and/or NVP is effective in preventing vertical transmission, the costs of the drugs would be affordable by many in Uganda and could be subsidized by donor agencies for others. Providing the drugs to mothers for therapy would be problematic due to toxicity monitoring issues and the questionable value of monotherapy in asymptomatic participants.

Evaluation of clinical/immunologic disease progression in infants will be based on mortality and CD4 cell counts at multiple time points using the following criteria from the CDC definitions of immune suppression. If the CD4 absolute count and the CD4% result in different categories, the more severe category will be used.

For infants <12 months of age:

No evidence of suppression	CD4 \geq 1500/uL or \geq 25%
Moderate suppression	CD4 = 750-1499/uL or 15-24%
Severe suppression	CD4 < 750/uL or <15%

For infants 12 or more months of age:

No evidence of suppression	CD4 \geq 1000/uL or \geq 25%
Moderate suppression	CD4 = 500-999/uL or 15-24%
Severe suppression	CD4 < 500/uL or <15%

NVP regimen: Mothers randomized to the NVP (active agent) arm will self-administer a single dose of 200 mg of NVP upon onset of active labor, and their infants will receive a single dose of 2.0 mg/kg of NVP at approximately 48-72 hours post-delivery, unless discharge occurs earlier, at which time the drug will be administered. The timing of the dose and the amount of the dose is currently based on the ACTG 250 data (see above). The initial PK data from cohort 1 of HIVNET 006 showed that even with a single maternal dose in labor of 200 mg (approximately 3 mg/kg), the infant plasma NVP level was greater than 100 ng/mL at day 7 or 10 times the IC₅₀ of NVP.

The proposed infant dose was derived by dividing the 200 mg adult dose by a presumed average adult weight of 70 kg, for an average adult per kilogram dose of 2.86 mg/kg. We then rounded down for safety to 2.0 mg/kg due to the long half-life of NVP in neonates and the added contribution of NVP through breast milk. Recently completed pediatric phase I studies of Nevirapine (ACTG 165 and ACTG 180) demonstrated that single doses of 120 mg/m² in infants and children are safe and result in plasma concentration equivalent to those seen in adults receiving 200 mg doses. Assuming a body surface area of 0.22 m² for an average 3.3 kg baby, 120 mg/m² of Nevirapine results in dose of 26.4 mg, or 8 mg/kg, compared to a dose of 6.6 mg based on 2.0 mg/kg. Neonates have a higher surface area to weight ratio than older children, and body surface area is generally not used in drug or fluid calculations in infants less than 10 kg. We have chosen to use the mg/kg dosing approach, which results in a smaller dose than body surface area dosing, in order to maximize participant safety. Due to the fact that mothers will be receiving only single doses of nevirapine, minimal pre-dosing laboratory evaluation results will be required before the mother is given the drug to take home for self administration. Mothers randomized to the NVP Placebo arm and their infants will receive a placebo using the same regimen as for the active agent.

AZT regimen: Mothers randomized to the AZT (active agent) arm will self-administer a 600 mg oral bolus of AZT upon onset of active labor, followed by 300 mg po q3h until delivery. Their infants will receive a 4 mg/kg AZT oral syrup dose twice a day for seven days after delivery, beginning as soon as they can tolerate liquids by mouth, within 24 hours of birth. Mothers randomized to the AZT Placebo arm and their infants will receive a placebo using the same regimen as for the active agent.

5.0 STUDY POPULATION - Participant Selection & Enrollment

With 21,000 deliveries annually and an HIV-1 seroprevalence of over 20%, more than 4200 HIV-1 infected pregnant women deliver at Mulago Hospital each year and over 16,000 seek antenatal care at the hospital facilities. Mean lag time from presentation to delivery is five hours with over 80% of the women in labor at the hospital for more than two hours. The lag time could be increased if women were asked to come to the hospital immediately at onset of labor. It is anticipated that 80-85 women could be enrolled in the study per month, leading to completion of data collection in approximately 36 months.

The HIV-1 vertical transmission rate in this population was found to be 25% in over 800 HIV-1 infected women evaluated in natural cohort studies. Infant mortality was found to be 9.7% and 18% by

6 and 18 months of age, respectively. Half of these infants were unevaluable for definitive infection status. Experience with previous prospective HIV studies has shown that minimal loss to follow-up rates (6.5% over two years) can be maintained with extensive home visiting and the clinic systems that are currently in place.

Breastfeeding will be encouraged for all women according to the WHO recommendations for HIV-infected women in developing countries. The average duration of breastfeeding in Uganda is 14 months with over 95% discontinuing by two years. The proposed study will examine the effect of AZT and NVP use during labor and delivery and in the early period of colostrum feeding. Although early diagnostic methods will be used to determine the HIV status of infants at six months of age, the infants will continue to be followed for 18 months for repeat assessment of their HIV status to determine overall transmission in this breast-fed cohort.

Women presenting for antenatal care who live within 15 km of the hospital will be counseled and offered HIV-1 antibody testing by a trained nurse/counselor or physician. Those who agree to be tested, to receive their test results and to be counseled after informed consent will be further screened for study eligibility by a nurse or counselor. Women found to be HIV positive who meet all other eligibility criteria will be offered the opportunity to enroll in the study at 36 weeks gestation. If they agree to participate, they will be given a study-specific identification number. At this visit, they will be randomized and given the study drug to take home for self administration. They will be carefully instructed when and how the study drug should be taken. A health visitor will take each woman home to document her location. Recruitment, screening, and follow-up procedures will be detailed in the study manual of operations.

5.1 Study Inclusion Criteria

5.11 Mother

- Pregnant women of at least 18 years of age with estimated gestational age >32 weeks by menstrual history, as confirmed either by medical examination or screening ultrasound.
- Evidence of HIV-1 infection, documented by an FDA licensed Western blot for HIV-1 antibody.
- A consent form for mother and neonate signed by either the mother or guardian. In compliance with U.S. Federal regulations, the father of the fetus, if available, must also provide written informed consent.
- Residence within 15 km of Mulago Hospital, the study site.

5.12 Neonate

- Neonates born to enrolled HIV-1 infected women who have been randomized to receive study drug

5.2 Study Exclusion Criteria

5.21 Mother

- Active serious infection other than HIV or other potentially serious illnesses
- Hemoglobin < 7.5 gm/dl, ALT (SGPT) value > 3 times the upper limit of normal, or a serum creatinine value of > 1.5 mg/dl
- Concurrent receipt of any antiretroviral therapy
- Participation during current pregnancy in any other therapeutic or vaccine perinatal trial
- Receipt of nevirapine or AZT within the last 6 months
- Known hypersensitivity to any benzodiazepine
- Current use of illicit substances and/or active chronic alcohol use
- Uncontrolled hypertension, as judged by examining clinician
- Disallowed Medications: Mothers will be excluded from randomization and dosing if they have received any of the following medications in the last two weeks before randomization or delivery:
 - Anticoagulants
 - Benzodiazepines other than study drug
 - Magnesium sulfate

NOTE: Mothers who have *not* already self-administered the study drug upon arrival at the hospital will be excluded from dosing with a study drug at the time of active labor for any of the conditions listed below:

- Admission to the hospital in the second stage of labor
- Pregnancy-induced hypertension requiring intrapartum magnesium sulfate
- Severe maternal infection with sequelae of shock (e.g., ARDS, hypotension) or other potentially serious illness at time of presentation to hospital
- Intrapartum complication requiring anticoagulation therapy
- Intrapartum seizure(s)
- Immediate life-threatening condition.

5.22 Neonate

- Mother excluded prior to randomization for any reason.

6.0 CLINICAL AND LABORATORY EVALUATIONS

See Appendix I, Schedule of Evaluations.

NOTE: At each blood draw for mothers and infants, approximately 25 microliters of whole blood will be transferred to filter paper in the laboratory for possible future technical assessment.

6.1 Pre-Entry Evaluations (Mother)

6.11 Pre-Entry

Informed consent must be obtained and maternal pre-entry evaluations, except where noted below, must be completed between 32 weeks gestation and enrollment at 36 weeks gestation, when the mother will be randomized and given the study drug given to take home for self-administration.

Clinical evaluations

- ◇ History [general, potential drug reaction]
- ◇ HIV-related history and AIDS-defining symptoms (if applicable)
- ◇ Physical exam

Laboratory evaluations

- ◇ Hematology (CBC with differential and platelet count, CD4 count)
- ◇ Serum chemistries [ALT (SGPT), bilirubin, creatinine]
- ◇ HIV EIA/WB
- ◇ HIV RNA PCR (Stored plasma samples for later assay: 0.5 ml, frozen at -70°C)

6.12 Enrollment (36 weeks gestation)

Clinical evaluations

- ◇ History [general, potential drug reaction]
- ◇ HIV-related history and AIDS-defining symptoms (if applicable)
- ◇ Physical exam

6.2 Evaluations During/After Treatment

6.21 Mother

Clinical evaluations

- ◇ History (general, potential drug reaction):
 - active labor and delivery (within 24 hours)
 - 24-48 hours post-partum,
 - 7 days (± 24 hours) post-partum,
 - 6 weeks post-partum
- ◇ HIV-related history and/or AIDS-defining symptoms (if applicable):
 - active labor and delivery (within 24 hours)
 - 6 weeks post-partum
- ◇ Physical exam:
 - active labor and delivery (within 24 hours)
 - 7 days (± 24 hours) post-partum,
 - 6 weeks post-partum

Laboratory evaluations

- ◇ Hematology (CBC with differential and platelet count):
 - 24-48 hours post-partum
- ◇ Serum chemistries [ALT (SGPT), bilirubin, creatinine]: *NOTE: This test may be dropped if tests results from first 100 participants indicate that it is unnecessary.*
 - 7 days (± 24 hours) post-partum
 - 6 weeks post-partum (*only if Day 7 chemistries show abnormalities*)
- ◇ HIV RNA PCR (stored plasma samples for later assay)
 - active labor and delivery (within 24 hours)
 - 24-48 hours post-partum
 - 7 days (± 24 hours) post-partum
 - 6 weeks post-partum
- ◇ Malaria smear, if fever present. Concomitant use of antimalarials will be recorded, but will not be an exclusion criterion.
 - active labor and delivery (within 24 hours)

6.22 Neonate

Clinical evaluations

- ◇ History:
 - birth (labor & delivery history recorded),

- 7 days (± 24 hours) post-birth,
- 6, 10 and 14 weeks post-birth,
- 6, 9, 12, 18 months post-birth

◇ Physical exam:

- birth,
- 7 days (± 24 hours) post-birth,
- 6, 10 and 14 weeks post-birth,
- 6, 9, 12, 18 months post-birth

Laboratory evaluations

◇ Hematology (CBC with differential and platelet count):

- 24 hours post-birth,
- 7 days (± 24 hours) post-birth,
- 6 weeks post-birth

◇ CD4 count:

- 24 hours post-birth,
- 14 weeks post-birth.

For HIV-infected infants only:

- 12 months post birth,
- 18 months post-birth

◇ Serum chemistries [ALT (SGPT), bilirubin, creatinine]:

- 24 hours post-birth ,
- 7 days (± 24 hours) post-birth,
- 6 weeks post-birth

◇ HIV RNA PCR (qualitative) - *If positive, both culture and quantitative RNA PCR will be done on a specimen obtained at the next visit, and quantitative RNA PCR will be repeated for each subsequent scheduled blood draw, including 12 and 18 months post birth:*

- 24 hours post-birth,
- 6 and 14 weeks post-birth,

◇ HIV Ab EIA; if positive, confirmed by Western blot:

- 18 months post-birth

6.3 Post-Study Evaluations

6.31 Mother

6.311 For mothers completing the study as scheduled

All mothers completing the 6 week evaluation (see Appendix I) will be considered to have fulfilled the maternal clinical and laboratory evaluation requirements for HIVNET 012.

6.312 For mothers prematurely discontinued from the study

Mothers prematurely discontinued from the study at any time post-randomization will have the following clinical and laboratory evaluations performed:

- ◇ History (general, potential drug reaction)
- ◇ HIV-related history and AIDS-defining symptoms
- ◇ Physical exam
- ◇ Plasma sample for storage (0.5 ml, frozen at -70°C and stored on-site)

These women will continue to be followed for 6 weeks post-partum for safety and toxicity monitoring.

6.32 Neonate

6.321 For neonates completing the study as scheduled

All neonates completing the 18-month evaluation schedule (see Appendix I) will be considered to have fulfilled the neonate clinical and laboratory evaluation requirements for HIVNET 012.

6.322 For neonates prematurely discontinued from the study

Neonates prematurely discontinued from the study at any time after birth and before the 6 week evaluation (see Appendix I) will have the following clinical and laboratory evaluations performed:

- ◇ History
- ◇ Physical exam
- ◇ Hematology: CBC, differential and platelets
- ◇ Serum chemistries [ALT (SGPT), bilirubin, creatinine]
- ◇ Qualitative HIV RNA PCR, HIV culture

Neonates prematurely discontinued from the study at any time after the 6-8 week evaluation (see Appendix I) will have the following clinical and laboratory evaluations performed:

- ◇ History
- ◇ Physical exam
- ◇ Qualitative HIV RNA PCR, HIV culture

NOTE: Should a neonate become HIV-positive at any time during the study, they may continue in HIVNET 012, or they may go off-study, receive any therapy and/or enter any

other trial. If a subject discontinues from HIVNET 012 for becoming HIV-positive after the 6 week evaluation schedule and enters another trial, the subject does not need to complete the evaluations specified above. Evaluations will be completed in a subset of these infants, if possible, at 6, 12 and/or 18 months post birth.

7.0 DATA COLLECTION, MONITORING, AND ADVERSE EVENT REPORTING

7.1 Records to be Kept

Case Report Forms (CRF) will be completed for each subject. Study participants must not be identified by name on any study documents. Subjects will be identified by the Study Identification Number (SID) provided by the HIVNET Statistical and Data Coordinating Center upon enrollment.

All data on the CRF must be legibly recorded in black ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or a designated, qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained.

7.11 Documentation guidelines (keyed/non-keyed)

Instructions concerning the recording of study data or the entry of such data into the computerized data base will be provided by the HIVNET Statistical and Data Coordinating Center and included in the Manual of Operations.

7.2 Regional Monitoring

Site visits by study monitors will be made in accordance with HIVNET policy to monitor the quality of data collected in the research records, the accuracy of the data entered in the database, and to determine that all regulatory requirements surrounding the trial are met. The investigator will allow the monitors, the FDA, and the Uganda Ministry of Health to inspect study documents (e.g., consent forms, drug distribution forms, case report forms) and pertinent hospital or clinic records for confirmation of the study data.

7.3 Adverse Experience Reporting

An adverse event (AE) is defined as any health-related reaction, effect, toxicity or abnormal laboratory result that a participant experiences during the course of a study irrespective of relationship to study treatment. This includes changes in a participant's condition or laboratory results which have or could have a deleterious effect on a participant's health or well-being. Information concerning the type of event, duration of the adverse experience, severity, action taken, outcome and causality will be recorded for all adverse experiences. The severity of adverse experiences will be graded using standardized study toxicity tables, to be included in the Manual of Study Operations. Adverse

experiences will be reported on case report forms and entered into the database. Adverse experience management and reporting requirements will be detailed in the Manual of Study Operations.

A serious adverse event is defined as any experience that is fatal or life-threatening, permanently disabling, requires in-patient hospitalization, is a congenital anomaly, cancer or overdose or is otherwise judged to be serious by the on-site clinician. Reporting procedures for serious AEs will be detailed in the Manual of Study Operations. All serious AEs will be reported by the on-site clinician to the Principal Investigator via fax and e-mail immediately. The PI will assess the relatedness of the AE to the study product. If the AE is judged to be definitely unrelated to the study drug, the PI will instruct the on-site clinician to document this in participant's files and on the appropriate case report form. If the AE is judged to be possibly, probably or definitely related to the study drug or the relationship cannot be determined, the Principal Investigator will prepare an AE Abstract and forward it to FHI and the DAIDS Medical Officer via fax and e-mail within 24 hours of receipt of notification from the site. If the AE is judged to be serious, unexpected, *and* possibly, probably or definitely related to the study product or the relationship cannot be determined, an FDA Safety Report and submission package will be prepared by FHI and sent to the DAIDS Pharmaceutical Regulatory Affairs Branch (PRAB) by Day 7 for signature. PRAB will send an original and two copies to the FDA by Day 10, with a copy to FHI. FHI will forward copies of the Safety Report package to the PI and drug manufacturer. In addition, if the AE is *fatal or life-threatening*, unexpected, *and* possibly, probably or definitely related to the study product or the relationship cannot be determined, the PI will notify the FDA by telephone within 3 days of receipt of notification. Information on all adverse events will be included in the annual IND report to the FDA. Adverse events will be reported to the Uganda and U.S. IRBs and the DAIDS DSMB according to their individual requirements.

8.0 STUDY TREATMENT

8.1 Drug Regimen, Administration and Duration

8.11 Dosing Procedures

Mothers will be dosed with the study drug at the onset of active labor according to the procedures below. At Mulago Hospital, the mean time between arrival of mother to the hospital and delivery is five hours with 80% arriving two hours before delivery. Participants will be given their initial dose to take home at the time of randomization at 36 weeks gestation. Participants will be instructed to take the drug at onset of active labor and then to report immediately to the hospital. It is preferable to have the drug administered prior to the second stage of labor, as it will be difficult to predict when delivery will actually occur.

- ◇ For a non-elective and/or emergency Cesarean section procedure, dosing with the study drug will be given as soon as possible after arrival to labor and delivery.
- ◇ For an elective Cesarean section, dosing with the study drug will begin 4 hours before the scheduled procedure.

- ◇ Women who have a Cesarean section *after* dosing with the study drug will be monitored closely throughout the procedure and data will be collected on the timing, type and amount of additional medications received.
- ◇ Women who are determined to be in false labor after dosing with study drug may have the initial dose readministered dependant upon the amount of time between false labor and active labor. If a woman in the NVP arm is dosed during false labor, she will receive an additional dose at onset of active labor if more than 24 hours have passed since initial dosing. If a woman in the AZT arm is given the initial dose of 600 mg oral bolus during false labor, she will be given the 600 mg dose again at onset of active labor if more than 6 hours have passed since initial dosing. If six hours have not passed between initial dosing and onset of active labor, the woman will be given the 300 mg dose of AZT every three hours, as scheduled.
- ◇ Mothers who vomit within 30 minutes of dosing will start the assigned drug regimen again upon arrival at the hospital. Women randomized to the NVP arm will receive a second 200 mg dose of the drug. Women randomized to the AZT arm will receive a second 600 mg bolus dose of the study drug. Mothers who vomit 30 minutes or more after dosing will not re-start the drug regimen.

Infants in the AZT arm will receive 4mg/kg of AZT or AZT-Placebo every 12 hours for seven days beginning when they can tolerate liquids by mouth, within 24 hours of birth. Mothers will be instructed to administer the study drug to the infant after discharge from the hospital. Post-discharge compliance will be assessed by interview and observation of the remaining study product during the scheduled Day 7 evaluation. Infants in the NVP arm will receive 2 mg/kg NVP or NVP-Placebo 48-72 hours post-delivery, unless discharge occurs earlier, at which time the dose will be administered. For infants born to mothers who are randomized but not dosed for some reason or who deliver within one hour of dosing, the drug regimen will be started as soon after birth as the infant can tolerate liquids by mouth.

8.12 Exclusion Criteria for Study Dosing/Study Continuation

8.121 Maternal

Mothers discontinued from the study after randomization will have all of the evaluations listed in Section 6.312 performed. For those who are discontinued prior to randomization, the reason will be documented, but no additional evaluations will be performed.

Mothers who gave informed consent at screening will be excluded from randomization and/or study drug dosing for any of the conditions listed below.

- ◇ Admission to the hospital in the second stage of labor without prior self-administration of study drug
- ◇ Pregnancy-induced hypertension requiring intrapartum magnesium sulfate
- ◇ Severe maternal infection with sequelae of shock (e.g., ARDS, hypotension)

- ◇ Uncontrolled hypertension
- ◇ Intrapartum complication requiring anticoagulation therapy
- ◇ Intrapartum seizure(s)
- ◇ Condition whereby mother is unable to tolerate oral study drug
- ◇ Active serious infection other than HIV or other serious illness at time of labor

8.122 Neonate

Neonates born to mothers who have been randomized will remain in the study and follow all study procedures including dosing with the study drug, whether or not dosing of the mother occurred. Neonates born to mothers who are excluded before randomization will not be followed.

Neonates will be excluded from study drug dosing if any of the following conditions are present at birth or develop prior to dosing. Any neonate who has been exposed to study drug and is discontinued from dosing will have toxicity monitoring and clinical follow-up as listed in Section 6.322.

- ◇ Known severe congenital malformations or other condition(s) not compatible with life
- ◇ Known severe anemia or hypovolemia requiring volume replacement and/or blood product therapy
- ◇ Known severe hyperbilirubinemia necessitating transfusion or volume replacement. Neonates receiving phototherapy are allowed to receive study drug
- ◇ Documented or suspected serious infectious, cardiac, respiratory, or metabolic illness, or other immediate life-threatening condition
- ◇ Any of the following documented laboratory findings:
 - Hemoglobin < 12.0 gm/dl
 - Platelet count < 100,000/uL
 - Bilirubin > 10mg/dl
 - Creatinine > 2.0 mg/dl
- ◇ Receipt of the following medications:
 - Anticoagulants
 - Benzodiazepines other than study drug
 - Magnesium sulfate

8.2 Drug Formulation

Nevirapine will be obtained from Boehringer-Ingelheim Pharmaceuticals, Inc. as 200 mg tablets and as a 10 mg/ml oral suspension. Both products should be stored at room temperature between 15 and 30°C (between 59 and 86°F). AZT will be obtained from Glaxo-Wellcome; 300 mg tablets or capsules will be used for adult dose. Placebos will be made to look identical to active agents.

8.3 Drug Supply, Distribution and Pharmacy

8.31 Investigational Agent Accountability

The on-site study investigators are required to maintain complete records of all study agents received from Boehringer-Ingelheim Pharmaceuticals, Inc. and from Glaxo Wellcome and subsequently dispensed. All unused study agents must be returned to the manufacturer or destroyed according to their specifications after the study is completed or terminated.

8.4 Concomitant Medications

Any concomitant medication, with the exception of those listed in Section 5.21 for mothers and in Section 8.122 for neonates, will be permitted for either the mother or the neonate while on-study. Concomitant medications listed in these sections may be given after dosing with the study drug with the permission of the Principal Investigator or the on-site study investigator.

8.5 Toxicity Management

8.51 Dose modification

The dose will not be modified within a treatment group. The drug will either be discontinued, or continued at full dose.

8.52 Criteria for Subject Management

8.521 General

Criteria for toxicity are based upon the DAIDS Toxicity Tables for neonates, children and adults.

8.522 Management of Adverse Events (Mother and Neonate)

8.5221 Management of the adverse event will be according to the best clinical practice and the judgment of the site investigator.

8.5222 Abnormal clinical and laboratory evaluations at Grades 1 and 2 will be repeated within 48 hours and if value remains at Grade 1 or 2, the subject will continue to receive study drug if required.

8.5223 Abnormal evaluations reaching Grade 3 or 4 will be followed. (See 8.6 for treatment guidelines.)

8.523 Management and Grading for Cutaneous/Skin Rash/Dermatitis Adverse Experiences (Mother and Neonate)

These grading criteria supersede any criteria listed in the standard DAIDS Toxicity Tables (to be included in the Manual of Study Operations). The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Experiences in the Manual of Study Operations and the text below are to be followed instead.

A prodromal syndrome of new onset consisting of clinical symptom complex manifested as fever ($> 39^{\circ}\text{C}$), malaise, cough, lymphadenopathy, edema, myalgia, and/or arthralgia may occur prior to the development of cutaneous manifestations of Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or the SJS/TEN Overlap Syndrome. If these symptoms occur during the study, the subject will be managed as stated below.

Grade 1

- ⇒ Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications.
- ⇒ Study drug is continued if applicable.

Grade 2

- ⇒ Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications.

Grade 2A cutaneous eruptions

- ⇒ Study drug is continued if applicable.

Grade 2B urticaria

- ⇒ Study drug is continued if applicable.

*Grade 3**

- ⇒ Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications.
- ⇒ Study drug is permanently discontinued.

*Grade 4**

- ⇒ Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications.

⇒ Study drug is permanently discontinued.

*All Grade 3 and 4 skin rashes will be reported to the principal investigator within 48 hours of the event. An adverse experience report will be sent to the principal investigator within 48 hours of the event and the appropriate case report form will be keyed into the database. The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Experiences MUST be used for grading these toxicities.

8.6 Criteria for Treatment Discontinuation (Mother and Neonate)

Subjects experiencing a Grade 3 or 4 adverse event as noted in the appropriate Toxicity table will have laboratory values confirmed by a second test done within 24 hours of the first abnormal value. Study drug will be withheld until the confirmatory laboratory results have been verified.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary objective of this placebo-controlled Phase III trial is to evaluate the safety and efficacy of oral NVP and oral AZT administered to pregnant women during labor and to their neonates during the first week of life to interrupt vertical transmission of HIV.

Volunteers will be randomized to one of four treatment arms, NVP, NVP Placebo, AZT, AZT Placebo, in a ratio of 2:1:2:1. Randomization of volunteers will occur over the 18-month period of enrollment. Follow-up will continue for 18 months after the last volunteer is enrolled or until sufficient events accrue to provide adequate power for the primary endpoint.

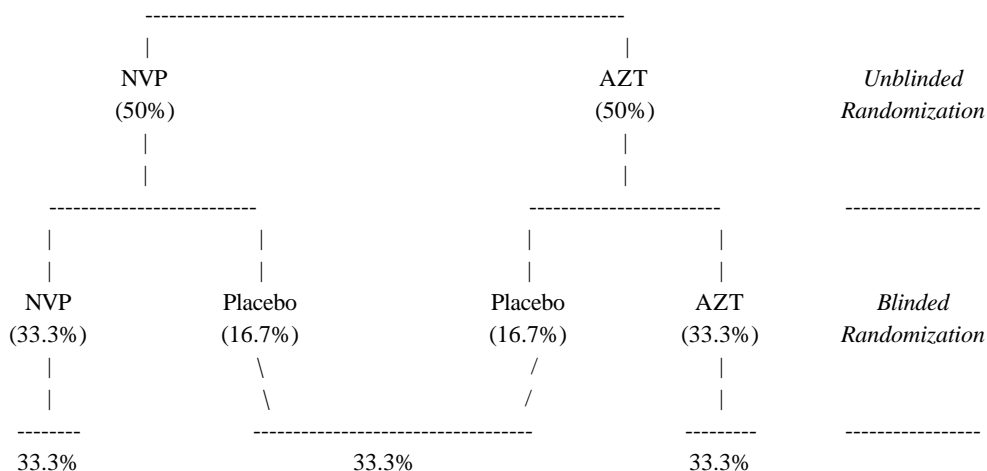
9.2 Primary Study Endpoints

- 9.21 Rate of HIV-1 infection in neonates born to study participants in each arm of the study as determined by a positive qualitative plasma HIV-1 RNA result confirmed at the next visit by a positive culture or quantitative plasma RNA level on a different specimen for infants < 18 months of age. Infants 18 months of age or older will be considered infected if the EIA and Western blot are positive.
- 9.22 Proportion of infants who are alive and free of HIV at 18 months
- 9.23 Safety/tolerance of oral NVP and oral AZT given to pregnant Ugandan women during labor and their neonates in the first week of life.

9.3 Randomization and Blinding

Randomization will be performed at 36 weeks gestation. Participants will be randomized initially in an unblinded fashion to receive either NVP or NVP Placebo vs AZT or AZT placebo. A second double-blinded randomization will then carried out to determine whether the participant will receive the active agent (NVP or AZT) or placebo. Randomization will follow the schema shown in Figure 1. Randomization will employ permuted block algorithms with randomized block size. These procedures will be coordinated with the HIVNET Statistical Center and detailed in the Manual of Operations.

Figure 1: Study Design Schematic



9.4 Sample Size

The rate of HIV-1 transmission is a primary endpoint of this study. The placebo arm transmission probability is estimated to be 25%, with most events expected to be detected in the first 6 months after delivery. For a one-sided 0.025-level log rank (or Cox regression) statistic to provide 90% power to detect a 33% reduction (25% on Placebo vs. 16.67% on AZT; or similarly 25% on Placebo vs. 16.67% on NVP) in vertical transmission, 202 HIV infection events are required for each pairwise comparison. In turn, 485 participants are needed in each study arm (AZT, NVP and the combined placebo arms). The 33% reduction represents a highly relevant public health benefit and, due to *in utero* transmission and transmission by breastfeeding after the first week of life, is much more plausible than the 67% reduction observed in ACTG 076.

If 10% of the women receive dosing during the last hour of labor and delivery and in turn achieve only one-half of the intervention-induced reduction in risk of HIV infection, the overall reduction in the transmission probability (25% on Placebo vs. 17.09% on AZT or NVP) will be detected with 86% power.

To ensure quality study results, intensive follow-up procedures will be implemented. It is projected that only 3% of infants will be lost-to-follow-up on an annual basis. Although bias induced by loss-to-

follow-up cannot be eliminated, the study will enroll 500 participants per arm to remove the increase in variability.

The HIV-free survival rate is also a primary endpoint of the study. To approximate the power for each pairwise comparison, we assume the 9.7% death rate observed during the first six months of life is independent of HIV infection, while the deaths occurring during the next 18-24 months are predominantly due to HIV infection. With earlier assumptions for the rate of HIV infection, a 33% reduction in HIV vertical transmission would result in a six-month difference in HIV-free survival of 75.2% vs. 67.7% for each pairwise comparison. A one-sided 0.025 level logrank statistic would have 61% power to detect this effect of the intervention.

9.5 Data Monitoring and Analysis

Close collaboration between the protocol chair, study statistician, data managers and study investigators will be necessary to evaluate and respond to occurrences of toxicity in a timely manner. Accrual and loss-to-follow-up rates as well as toxicities/adverse events will be monitored closely by the study team and if unexpected concerns arise, they will be dealt with according to DAIDS standard operating procedures for Phase III clinical trials.

Information on number of women screened, number found to be eligible, number enrolled, and rate of follow-up, along with interim safety data, will be monitored by the DAIDS Data Safety and Monitoring Board (DSMB) on a six- to twelve-month basis.

Formal interim analyses of the primary efficacy endpoints will be performed approximately annually during the projected three-year study duration. Recommendations for early termination of positive or negative results will be guided by the symmetric group sequential O'Brien-Fleming boundary. The O'Brien-Fleming design allows for early termination if extreme initial results are seen, while essentially allowing one to employ the standard single stage one-sided 0.025-level logrank statistic at the final analysis if it is reached. This enables one to maintain the power of the single-stage design in the presence of interim monitoring without having to increase the maximum sample size. The Lan-DeMets implementation of the O'Brien-Fleming use function will be employed to define proper significance levels at the time of each formal interim analysis by the DSMB.

Infants will be followed through 18 months post-birth unless no efficacy of the drugs is demonstrated by the HIV transmission rates at 14 weeks of age. If analysis shows a lack of efficacy of both interventions, the study would be concluded and infants would not be followed after the next scheduled visit, at which time plasma would be obtained for appropriate diagnosis of HIV infection. If interim analysis reveals that the differences in transmission rates rule out benefit, the study may be concluded earlier. The Data and Safety Monitoring Board should recommend an increase in sample size to restore power if the actual transmission probability in the placebo arm of the trial is less than the protocol specified rate of 25%. Recommended increases in sample size should be limited to 25%, and should be made as soon as sufficient data are available to estimate the actual placebo event rate. This recommendation should not be influenced by the relative efficacy and relative safety data available at that time.

Infants who test positive for plasma HIV-1 RNA within 48 hours of birth will be considered to have been infected in utero. Those infants who test negative for plasma HIV-1 RNA within 48 hours of birth and positive at six weeks of age will be considered to have been infected intrapartum or through breastmilk. Infants who test negative at 48 hours and six weeks post birth, but positive at 14 weeks will be considered to have been infected through breastmilk.

9.6 Toxicities

Suspected drug-related toxicities will be recorded on the case report forms and through the adverse experience reporting mechanism described in this protocol. Toxicity measurements will be analyzed in conjunction with clinical stage of disease, age, concomitant medications, and other study parameters in an attempt to elucidate the toxicity profile of nevirapine and AZT.

10.0 PROTECTION OF HUMAN SUBJECTS

10.1 Institutional Review and Informed Consent

This protocol and the informed consent document (Appendix II) and any subsequent modifications will be reviewed and approved by the Institutional Review Boards or Ethics Committees responsible for oversight of the study. Written informed consent will be obtained from the subject (or parent or legal guardian of subjects who cannot consent for themselves, e.g., infants). The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

10.2 Subject Confidentiality

All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only, to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records. All local databases must be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information must be stored in a separate, locked file in an area with limited access.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring by the International Master Contractor, the Statistical and Clinical Coordinating Center, the Food and Drug Administration, the pharmaceutical sponsors, the National Institute of Allergy and Infectious Diseases, and/or the Ugandan Ministry of Health.

10.3 Study Discontinuation

The study may be discontinued at any time by NIAID, the pharmaceutical sponsor, the FDA, or the Ugandan government.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by DAIDS policies. Any presentation, abstract, or manuscript will be made available by the U.S. and Ugandan investigators to the Ugandan Director of Medical Services, DAIDS and the pharmaceutical co-sponsors for review prior to submission.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control.

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APPENDICES

- I. SCHEDULES OF EVALUATIONS
- II. SAMPLE INFORMED CONSENT

APPENDIX I
SCHEDULE OF EVALUATIONS
MATERNAL EVALUATIONS

Evaluation	Pre-Entry	Enrollmen t (36 weeks gestation)	Labor & Delivery (within 24 hrs)	24 to 48 Hours Post- Partum	7 Days Post-Partum (± 24 hours)	6 to 8 Weeks Post-Partum²
Informed Consent	x					
History (general, potential drug reaction)	x	x	x	x	x	x
HIV-related history and AIDS-defining symptoms, if applicable	x	x	x			x
Physical examination	x	x	x		x	x
Hematology (CBC with differential and platelet count)	x ¹			x		
CD4 cell count	x					
Serum chemistries [ALT (SGPT), bilirubin, creatinine]	x ¹				x	x ³
HIV-1 EIA/WB	x					
Plasma for storage (four 0.5 ml aliquots, frozen at -70°C for HIV RNA PCR)	x		x	x	x	x
Malaria smear, if fever present			x			

NOTE: At each blood draw, approximately 25 microliters of whole blood will transferred to filter paper in the laboratory for possible future technical assessment.

¹ Hematology and serum chemistries must be obtained within 21 days prior to study entry.

² These evaluations must be obtained if the mother is prematurely discontinued from the study (serum chemistries not included).

³ Only if Day 7 chemistries reveal abnormalities.

APPENDIX I
SCHEDULE OF EVALUATIONS
NEONATE EVALUATIONS

Evaluation	Birth	24 hours post-birth	7 days post-birth (± 24 hours)	6 weeks post-birth¹	10 weeks post-birth	14 weeks post-birth²	6 months post-birth	9 months post-birth	12 months post-birth	18 months post-birth
History	x (L&D hx)		x	x	x	x	x	x	x	x
Physical Examination	x		x	x	x	x	x	x	x	x
Hematology (CBC with differential and plateletcount)		x	x	x						
Serum chemistries [ALT (SGPT), bilirubin, creatinine]		x	x	x						
CD4 count		x				x			x ⁴	x ⁴
HIV RNA PCR (qualitative) ³	plasma from cord blood stored	x ³		x ³		x ³				
HIV ELISA; if positive, confirmed by WB										x

NOTE: At each blood draw, approximately 25 microliters of whole blood will transferred to filter paper in the laboratory for possible future technical assessment.

¹ These evaluations and HIV culture must be obtained if the subject is prematurely discontinued from the study after dosing and before this visit.

² These evaluations and HIV culture must be obtained if the subject is prematurely discontinued from the study after the 6-8 week post-birth visit.

³ If positive, both culture and quantitative RNA PCR will be done on a specimen collected at the next visit, and quantitative RNA PCR will be repeated for each subsequent scheduled blood draw, including 12 and 18 months post-birth.

⁴ For HIV-infected infants only.

Appendix II

Sample Informed Consent for: A Phase III Placebo-Controlled Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical HIV-1 Transmission in Pregnant Ugandan Women and Their Neonates

Introduction:

This consent form gives you information about this research study. To be sure that you have all the facts about being in this research study, you should read this form. You can have someone read and explain it to you, too. If you agree that your baby and you can take part in the research study, you will sign and date this form. If you cannot sign, you will make your mark in front of a witness. If the father of your baby is available, he also will be given this form to read and sign. You will receive a copy of this form to keep.

Reason for the Research Study:

Since you are HIV positive and pregnant, you are being asked to take part in a research study aimed at preventing transmission of HIV from mother to baby. This study involves two drugs, Nevirapine (NVP) and Zidovudine (AZT). These drugs have been developed for use against HIV, the virus that causes AIDS. These drugs have been tested in adults and children. They have been shown to decrease the amount of HIV in the blood. In addition, in the US, when AZT was given to mothers starting early in pregnancy up through labor and delivery and then to the baby for six weeks after birth, this intensive treatment significantly reduced the risk of the mother passing the HIV virus to her baby. Uganda, like many other developing countries, does not currently have the resources or capabilities to offer this complicated therapy to pregnant women. There is a need to find simpler treatments that work which could be used in Uganda. Therefore, the purpose of this research study is to compare a placebo with NVP or AZT given, in pill form, to mothers ONLY during labor and delivery and to their babies during the first week of life to see if NVP or AZT can decrease HIV transmission from mother to baby. (A placebo is not a drug. It is an inactive pill made to look like the drug being tested. It has no effect on HIV.) In this research study, 500 pregnant women in labor will receive NVP, 500 will receive AZT, and 500 will receive placebo.

About two or three of every ten babies born to HIV positive mothers are also infected with HIV. The study doctors do not know if NVP or AZT will reduce the chance of your baby getting infected with HIV. Also, the study doctors do not know if these drugs will be useful in treating HIV infections in either you or your baby.

Your Part in the Research Study:

Before you enter the research study, you will have some routine blood tests. A nurse or doctor will draw about 1 tablespoon of blood from you using a needle. These tests will show if you qualify for the

study. A home visitor will come to your home with you at the time you enroll in the research study. Then the home visitor will know where you live and can help remind you of clinic appointments.

If you agree to take part in the research study, you will be in one of two groups. One group will get either NVP or a placebo. The other group will receive either AZT or placebo. A placebo does not have any drug in it. If you are in the NVP group, you will take NVP or placebo in pill form by mouth when you start labor. After your baby is born, the baby will be examined by the doctor. The doctor or nurse will draw about 1 teaspoon of blood from your baby for some tests. Three days after birth or when you are discharged from the hospital (whichever comes first), your baby will be given one dose of NVP or placebo in a syrup.

If you are in the AZT group, you will take AZT or placebo in pill form when you start labor. You will take AZT or placebo every three hours until delivery. After your baby is born, the baby will be examined by the doctor. The doctor or nurse will draw about 1 teaspoon of blood from your baby for some tests. For one week after birth, your baby will receive either AZT or placebo in a syrup twice a day.

Unless there are problems, your baby and you will stay in the hospital for 1-2 days after delivery and have needed blood tests at no cost to you. Then you both will be taken home. Your baby and you will return to the hospital again for tests 7 days and 6-8 weeks after the baby is born. At each visit, about 2 teaspoons of blood will be collected from you. At each visit, the doctors will draw about one teaspoon of blood from your baby. During the whole study you and your baby will each have blood drawn using a needle about six times. Your baby will have a follow-up medical exam and blood tests at about 6 months and a final visit at 18 months after birth. Your baby will have blood drawn to check for HIV infection. You understand that your baby's HIV test results will be offered to you.

Possible Risks and Benefits:

Because NVP has only been given to a few pregnant women or children less than three months of age, the long-term and short-term risks to you and your baby are not fully known. As of March 1996, NVP has been licensed in the United States for treatment of HIV infection in adults.

There are some risks to taking NVP. However because you and your baby will be taking NVP for only a few days these risks are much less likely. Life threatening rash has been reported in several patients taking nevirapine, but not in patients who have received only a single dose. The most common side effects of a short course of Nevirapine are drowsiness, nausea, and headache, although most patients do not experience any of the above symptoms.

In one research study, 18 pregnant women and 8 of their babies in the United States each received a single dose of NVP and showed no side effects. In addition, eight pregnant women in Uganda have received NVP in labor with no serious side effects attributable to the drug in either the mothers or their infants.

AZT has been widely tested and has been approved for use in pregnant women and infants in the United States and other countries. Women and infants who were given AZT did not have any serious side effects. Infants who were given AZT did have lower hemoglobin levels in their blood. In laboratory mice given high doses of AZT during the last third of pregnancy, a significant number of their adult offspring developed tumors. In another mouse study using a lower dose of AZT during pregnancy, similar to the daily dose you may receive, no increase in unexpected tumors was seen in the offspring. It is not known at this time what this observation in laboratory mice means for human infants.

There are some risks to taking AZT. However, because you and your baby will be taking AZT for only a few days these risks are not as great as those taking AZT for longer periods of time. Side effects of AZT taken for one week or less include nausea, vomiting, diarrhea, headache, and/or fatigue. However, the majority of patients experience none of the above symptoms. The study doctors and nurses will give you medical care if you need it.

The study doctors do not know if being in this study will reduce the risk of your baby becoming infected with HIV. Your baby and you may or may not benefit directly from this study. However, the results of this research study may help the doctors understand more about the effect of NVP and AZT in HIV-infected mothers, and may help others with HIV in the future. The study doctors do not know what the long-term side effects for you or your baby will be.

The study doctors will provide the care and closely watch the medical condition of your baby and you during the study. If you get a rash after taking the drug, you will tell the doctor right away. If your baby or you have any serious reactions to NVP or AZT, you will be treated. The hospital will give your baby and you a medical exam and laboratory tests. The same study doctors will be able to tell you any new information learned from this study. This will help you decide if your baby and you should stay in this research study.

Alternative Treatment

There are currently no drugs available in Uganda to prevent HIV transmission from mother to baby. As part of their participation in studies like this one, some women have received drugs that are being tested for this purpose, including the drugs being tested in this study.

If You Decide Not to be in the Research Study:

If you do not want to volunteer to be in this research study, that is okay. The doctors will still treat your baby and you for all problems and you can continue to receive health care at the hospital. If you choose to participate, you can withdraw from the research study when you want to. If you choose not to participate or if you withdraw, there will be no penalty.

Confidentiality:

The study workers will protect information about you and your taking part in this study to the best of their ability. On your study records, a code will be used instead of your name or your baby's name. Only the study workers will know this code. The study workers will not give out any information about you or your file, or about your baby without your written consent. However, the Ugandan Ministry of

Health, the U.S. Food and Drug Administration, the study sponsor and the companies that supply the drugs will be allowed to inspect your baby's and your study records without your consent. The study records will be kept separate from your medical records. Your family's privacy will be respected. Your baby and you will not be personally identified in any publication or presentation about this research study.

Costs or Payments to You:

There is no cost to you for the study drug, study clinic visits, examinations, or for the laboratory tests required in this study. Any medical care and costs for your baby and you will be provided by Mulago Hospital in accordance with Ugandan Ministry of Health policy. These costs include care provided to you during your pregnancy, delivery of your baby, and the time your baby and you spend in the hospital. Neither your baby nor you will receive any money for being in this study, except for transport allowance if necessary.

Policy About Research Related Injuries

Medical care will be provided for illness or injury directly related to this study at no cost to you. Care or appropriate referral will be provided for any illness or injury that occurs during the study that is not directly related to the study. There are no plans to give you money if there is a research related complication or injury.

Reasons for Withdrawal from the Study:

Your baby and you will not be allowed to remain in the research study if:

- Your doctor or the baby's doctor decides that continuing in the research study would be harmful to you or your baby;
- Your baby or you need a medicine not allowed on this study;
- You have a serious reaction to the study drug;
- Your baby's father objects to your baby being in the research study;
- The research study is canceled by the study sponsor, the Ugandan Ministry of Health, or the U.S. government.

Problems or Questions:

If you need any more information about the research or if you become injured in the research study, you can contact Professor Francis Mmiro or Dr. Phillipa Musoke at 541-044. If you have questions about your rights or your baby's rights as a volunteer or about research related injuries, you can contact Dr. Edward Mbidde, Chairman of the Uganda AIDS Research Subcommittee at 559-622.

Statement of Consent:

I have read (or have had explained to me) this consent form. I understand the purpose of the research study, the clinical and research procedures to be followed and which ones are extra, and the risks and benefits as described in this written summary. I voluntarily agree to join this research study and allow my baby to join this research study.

Volunteer's Name (print)

Volunteer's Signature or mark Date

Father's Name (print)
(If he is reasonably available)

Father's Signature or mark Date

Witness' Name (print)

Witness' Signature Date

I have explained the purpose of this study to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits of this study.

Investigator's Name Investigator's Signature
(Type or print)

Date