

HIVNET 024

**PHASE III TRIAL OF ANTIBIOTICS TO REDUCE
CHORIOAMNIONITIS-RELATED PERINATAL HIV TRANSMISSION**

A Study of the HIVNET Group

Sponsored by:

**The National Institute of Allergy and Infectious Diseases and
the National Institute of Child Health and Human Development**

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HIVNET 024

Phase III trial of antibiotics to reduce chorioamnionitis–related perinatal HIV transmission

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Sponsored by:

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the National Institute of Child Health and Human Development**

I, the Protocol Co-chair, agree to conduct this study in full accordance with the provisions of this protocol and will comply with all requirements regarding the obligations of clinical investigators as fully outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for a minimum of two years after FDA clearance or until Division of AIDS, NIAID/NIH and pharmaceutical co-sponsor advise that it is no longer necessary. Publication of the results of this study will be governed by DAIDS policies. Any presentation, abstract, or manuscript will be made available by the investigators to DAIDS and the pharmaceutical co-sponsors for review prior to submission.

I have read and understand the information in the Investigator's Brochure and Package Inserts, including the potential risks and side effects of the product under investigation and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Signature of Protocol Co-chair

Date

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TABLE OF CONTENTS

ACRONYMS	IX
SCHEMA	X
1.0	INTRODUCTION.....	1
1.1	<u>BACKGROUND</u>	1
1.2	<u>RATIONALE</u>	4
2.0	STUDY OBJECTIVES	5
2.1	<u>PRIMARY</u>	5
2.2	<u>SECONDARY</u>	5
3.0	STUDY DESIGN	7
3.1	<u>SELECTION AND ENROLLMENT OF SUBJECTS</u>	7
3.2	<u>CO-ENROLLMENT GUIDELINES</u>	8
4.0	CLINICAL AND LABORATORY EVALUATIONS.....	9
4.1	<u>PRE-ENTRY/ENTRY EVALUATIONS</u>	9
4.2	<u>EVALUATIONS DURING PREGNANCY AND LABOR</u>	9
4.3	<u>EVALUATIONS AT THE TIME OF PERMANENT TREATMENT DISCONTINUATION</u>	14
4.4	<u>POST-TREATMENT EVALUATIONS</u>	15
5.0	DATA COLLECTION AND MONITORING AND ADVERSE EXPERIENCE REPORTING.....	17
5.1	<u>RECORDS TO BE KEPT</u>	17
5.2	<u>DATA MANAGEMENT AND DOCUMENTATION GUIDELINES</u>	17
5.3	<u>REGIONAL MONITORING</u>	17
5.4	<u>ADVERSE EXPERIENCE REPORTING</u>	18
6.0	STUDY TREATMENT.....	18
6.1	<u>DRUG REGIMENS, ADMINISTRATION AND DURATION</u>	18
6.2	<u>DRUG FORMULATION</u>	19
6.3	<u>DRUG SUPPLY, DISTRIBUTION AND PHARMACY</u>	19
6.4	<u>CONCOMITANT MEDICATIONS</u>	20
6.5	<u>TOXICITY MANAGEMENT</u>	20
6.6	<u>CRITERIA FOR TREATMENT DISCONTINUATION</u>	21
6.7	<u>OTHER INFECTIONS</u>	21
7.0	STATISTICAL CONSIDERATIONS	21
7.1	<u>GENERAL DESIGN ISSUES</u>	21
7.2	<u>ENDPOINTS</u>	22
7.3	<u>RANDOMIZATION AND BLINDING PROCEDURES</u>	22
7.4	<u>SAMPLE SIZE AND ACCRUAL</u>	23
7.5	<u>MONITORING AND ANALYSIS</u>	23
8.0	HUMAN SUBJECTS	25
8.1	<u>INSTITUTIONAL REVIEW BOARD (IRB) REVIEW AND INFORMED CONSENT</u>	25
8.2	<u>SUBJECT CONFIDENTIALITY</u>	26
8.3	<u>STUDY DISCONTINUATION</u>	26
9.0	PUBLICATION OF RESEARCH FINDINGS	26
10.0	BIOHAZARD CONTAINMENT	26

11.0	REFERENCES	27
APPENDIX I	SCHEDULE OF EVALUATIONS	31
APPENDIX II.	SAMPLE INFORMED CONSENTS	33
APPENDIX III.	ADVERSE EXPERIENCE REPORTING REQUIREMENTS	45
APPENDIX IV.	DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES	52
APPENDIX V.	DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF PEDIATRIC ADVERSE EXPERIENCES	60

*The format for this protocol is that recommended by the HIVNET Perinatal Working Group.

ACRONYMS

AE	adverse experience
AIDS	Acquired Immune Deficiency Syndrome
AZT	zidovudine
BPM	beats per minute
BV	bacterial vaginosis
CRF	case report form
CRPMC	Clinical Research Products Management Center
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EIA	enzyme immunoassay
FFN	fetal fibronectin
FHI	Family Health International
GC	gonorrhea culture
HIV	human immunodeficiency virus
HIVNET	HIV Network for Prevention Trials
IRB	institutional review board
IU	international units
LCH	Lilongwe Central Hospital
LCR	ligase chain reaction
MCT	maternal-child transmission
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NVP	nevirapine
PAB	Pharmaceutical Affairs Branch, DAIDS
PAVE	Preparation for AIDS Vaccine Evaluation
PCR	polymerase chain reaction
PROM	premature rupture of membranes
QECH	Queen Elizabeth Central Hospital, Blantyre, Malawi
RAB	Regulatory Affairs Branch, DAIDS
RNA	ribonucleic acid
ROM	rupture of membranes
RPR	rapid plasma reagin (test for syphilis)
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse experience
STD	sexually transmitted disease
TID	three times a day
TPHA	<i>Treponema pallidum</i> hemagglutination
USAID	United States Agency for International Development

SCHEMA

PHASE III TRIAL OF ANTIBIOTICS TO REDUCE CHORIOAMNIONITIS-RELATED PERINATAL HIV TRANSMISSION

- DESIGN:** This will be a randomized, double-blinded, controlled Phase III trial of antibiotics to prevent chorioamnionitis-associated perinatal HIV transmission. Using a simple 2-arm design, half the subjects will receive two courses of antibiotics, with the control subjects receiving two courses of a placebo.
- SAMPLE SIZE:** Using a target of reduction in HIV transmission from 11% to 7.5% with 90% power, the sample size will be 3120 HIV-positive pregnant women. In order to prevent stigmatization and to investigate the impact of antibiotics on HIV-negative women in this setting, 600 additional HIV-negative women will be enrolled and treated indistinguishably from those who are HIV-positive.
- POPULATION:** This study will be conducted at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi and Lilongwe Central Hospital (LCH) in Lilongwe, Malawi. Women will be recruited from the antenatal clinics. After obtaining informed consent, HIV seropositive and seronegative women will be enrolled, followed during pregnancy, and requested to deliver in the hospital or clinics. Women and infants will attend postnatal follow-up visits in designated clinics at QECH and LCH.
- REGIMEN:** At 20 – 24 weeks, women randomized to receive antibiotics will receive metronidazole 250 mg three times a day (TID) and erythromycin 250 mg orally TID for 7 days. Women randomized to the control group will receive identically appearing placebos. With the onset of contractions and/or premature rupture of membranes (PROM), study participants will initiate a second oral course of antibiotics consisting of metronidazole 250 mg and ampicillin 500 mg or placebo every 4 hours, continuing after delivery TID until the course is completed. All HIV-infected women and their neonates will be offered the HIVNET 012 nevirapine (NVP) regimen. If the mother accepts the nevirapine for herself and her baby, she will be given one oral dose of 200 mg NVP at the 26-30 week antenatal visit to be taken at onset of labor, and her baby will receive one oral dose of 2mg/kg NVP suspension at 72 hours post-birth or discharge, whichever occurs earlier. If the mother refuses nevirapine or is uninfected, she will receive a matched placebo at the 26-30 week visit to preserve participant confidentiality.
- OBJECTIVE:** To determine if low-cost antibiotic treatment given twice during pregnancy (total cost less than \$5.00) aimed at reducing chronic and acute chorioamnionitis will reduce perinatal HIV transmission.

1.0 INTRODUCTION

1.1 Background

Obstetric risk factors for HIV maternal-child transmission (MCT) include preterm birth, prolonged rupture of the membranes, and both clinical and histologic chorioamnionitis. Each of these risk factors for HIV MCT may operate through a common pathway in which HIV-infected maternal white cells enter the amniotic fluid following bacterial infections of the placental membranes and result in both “histologic chorioamnionitis” and perinatal HIV transmission.

The relationship between chorioamnionitis and preterm birth has been investigated for a number of years.¹⁻¹⁰ Findings include the observation that a substantial number of preterm births are associated with and likely caused by chorioamnionitis, with this sub-clinical infection preceding labor or spontaneous rupture of membranes. The earlier the gestational age at onset of spontaneous labor, the more likely it is caused by chorioamnionitis, with histologic chorioamnionitis found in more than 80% of the spontaneous preterm births less than 30 weeks gestation. The organisms associated with this intrauterine infection in every population studied to date are of relatively low virulence and include *Ureaplasma*, *Mycoplasma*, *Bacteroides*, *Mobiluncus*, and *Gardnerella*.^{1,4}

Chorioamnionitis prior to delivery is asymptomatic, does not result in fever, chills or abdominal pain, and is not easy to diagnose. The location of the infection, in the choriodecidual space, is not amenable to culture. Treatment trials have therefore focused on suggestive evidence of this infection and included preterm contractions and the presence of bacterial vaginosis (BV). BV, an overgrowth of *Ureaplasma*, *Mycoplasma*, *Bacteroides*, *Mobiluncus*, and *Gardnerella* in the vagina, is associated with and probably a marker for chorioamnionitis. Treatment trials targeting these markers of infection in which metronidazole 250mg TID given orally for a week or more with or without ampicillin or erythromycin have often shown benefit in reducing prematurity, while treatment trials with other antibiotics, or metronidazole given in other dosing regimens, have not been effective. A randomized trial of antibiotics (metronidazole/erythromycin) in women at risk for spontaneous preterm birth who also had BV resulted in a substantial reduction in the rate of preterm birth in that population.⁷ Other studies have confirmed this result. In a mass antibiotic treatment trial of STDs in the Rakai district of Uganda using metronidazole in pregnant women, both low birthweight and preterm birth were significantly reduced (Gray RH, et al, unpublished data).

However, in a recently completed NICHD trial targeting vaginal *Trichomonas* infection, in which metronidazole was given as two 2gm oral doses 48 hours apart, and then repeated 4 weeks later, preterm birth increased – 19% versus 12% in the control group (p<0.001).¹¹ There are several possibilities for the apparent increase in preterm birth with metronidazole in women with *Trichomonas*. These

include: 1) chance, 2) metronidazole acting to stimulate contractions, or 3) the release of inflammatory products from the action of metronidazole on the *Trichomonas* organism. In all previous studies, metronidazole use has not been associated with an increase in preterm birth. Therefore, a direct labor-enhancing effect is unlikely. In the U.S., metronidazole is currently the treatment of choice for women with symptomatic *Trichomonas*, and to date, no one has suggested an increase in preterm birth in women with symptomatic *Trichomonas* infection treated with metronidazole. In a small study, its use in women with *Trichomonas* was not associated with an increase in preterm birth.⁸ This trial used metronidazole and erythromycin as is proposed in the 024 trial, not in doses used in the NICHD *Trichomonas* trial. The addition of erythromycin may also be significant, in that erythromycin is a macrolide antibiotic and has important anti-inflammatory properties in addition to its antibacterial properties. Therefore, even if a release of inflammatory products was the cause of the increase in preterm birth in the NICHD study, the addition of a macrolide antibiotic and the absence of bolus dosing make the 024 approach different. The protocol team believes that the risk of increasing prematurity by the use of the antibiotics in individual women is low, since the bulk of evidence suggests a reduction in preterm birth rather than an increase. Additionally, the populations are different, and as stated earlier, the dosing regimen proposed in this study is different. However, the team remains concerned about a possible interaction between metronidazole use and *Trichomonas* treatment leading to preterm birth, and will monitor outcomes closely for any such relationship.

A better predictor of spontaneous preterm birth than BV is fetal fibronectin (FFN), a placental membrane derived protein which when found in the vagina after 20 weeks gestation is the most potent predictor (odds ratio = 60) of spontaneous preterm birth yet described.¹² Fetal fibronectin, when found in the vagina at 20 to 24 weeks gestational age, is a strong predictor of neonatal sepsis (odds ratio = 6) and a very potent predictor of clinical chorioamnionitis (odds ratio of 20), and is nearly always associated with histologic chorioamnionitis at delivery.¹³ For reasons of both cost and practicality, it is not expected that fetal fibronectin testing will be used routinely in sub-Saharan Africa. However, if a positive fetal fibronectin result is strongly associated with HIV MCT, our understanding of the mechanism will be greatly increased.

The relationship between BV, preterm birth, histologic chorioamnionitis and perinatal transmission of HIV has been consistently demonstrated. Preliminary results from Malawi show a 2-fold increase (28% vs. 14%) in HIV MCT in BV positive vs. BV negative women.^{14,15} Perinatal HIV transmission is more common in preterm infants, and there is now evidence that sub-clinical chorioamnionitis is a substantial risk factor for MCT.^{16,17} For this study, the primary hypothesis is that early and appropriate treatment of sub-clinical chorioamnionitis prior to the onset of spontaneous preterm labor, and/or antibiotic treatment during labor to prevent PROM-associated-chorioamnionitis will reduce the risk of perinatal HIV transmission.¹⁸

In this study, a short-course of nevirapine will be offered to all HIV-infected women and their neonates. Among the non-nucleoside reverse transcriptase inhibitors, nevirapine is a non-nucleoside benzodiazepine derivative that is a potent inhibitor of HIV-1 replication with an IC₅₀ of 10 ng/ml, excellent oral absorption and bioavailability, with a high therapeutic index. Nevirapine is highly lipophilic and widely distributed throughout the body, and has been shown to penetrate cell-free HIV-1 and inactivate virion-associated reverse transcriptase in situ. Nevirapine prophylaxis has been shown to prevent infection in chimpanzees challenged with HIV-1.¹⁹ It has been used in adults, children, infants, and as a single dose in the first week of life in neonates.²⁰⁻²² The drug is well tolerated. Nevirapine is primarily metabolized by the liver. It is an inducer of hepatic cytochrome p450 metabolic enzymes, resulting in an “autoinduction” phenomenon characterized by an approximately 1.5 to 2 fold increase in apparent oral clearance and decrease in terminal half-life after 2-4 weeks of daily dosing in older children and adults. Because of liver metabolism, the half life of nevirapine in neonates is anticipated to be prolonged compared to older children; the half life of a single dose of nevirapine administered at age 48-72 hours in neonates was 36.8 hours (range 27.3-49.5 hours).²² The most frequently reported adverse events related to nevirapine are rash, fever, nausea, headache and abnormal liver function tests. The major clinical toxicity is rash, which can rarely be severe or life threatening (Stevens-Johnson Syndrome, occurring in 0.5% of 1752 adults patients exposed to nevirapine). Rashes are usually mild to moderate maculopapular erythematous cutaneous eruptions with or without pruritus and located on the trunk, face and extremities. The majority of severe rashes occur in the first 28 days of treatment. No rash toxicity was observed in the PACTG 250, in which infants received a single dose at 48-72 hours of age.²²

Results from HIVNET 012, *A Phase IIB randomized, controlled trial to evaluate the safety, tolerance, and HIV vertical transmission rates associated with short course nevirapine (NVP) vs. short course zidovudine (ZDV) in HIV infected pregnant women and their infants in Uganda*, were recently published.²³ An intrapartum/postpartum regimen of a 200 mg oral dose of NVP given to the mother at the onset of labor and a 2 mg/kg dose given to the infant within 72 hours of life reduced the risk of perinatal transmission among breastfeeding women by 48% at 14-16 weeks compared to an intrapartum/postpartum regimen of AZT (600 mg, then 300 mg every 3 hours during labor to mother, and 4mg/kg twice daily for one week to the infant). No serious drug-related toxicities were observed in the 626 women and babies who received either drug. In particular, the incidence of rash was similar between both treatment groups, and there were no cases of Stevens-Johnson syndrome. These data demonstrate the safety of a 2 dose NVP regimen, and the reduction in transmission with this NVP regimen persists to 14-16 weeks. This protocol is designed to include a single dose of NVP to the HIV-infected mothers and their infants, as in the HIVNET 012 regimen.

1.2 Rationale

This intervention to reduce HIV MCT is chosen for evaluation because:

1. It has biologic plausibility for reducing HIV MCT.
2. It is very low in cost compared to most antiretroviral therapies (i.e., a full course of metronidazole in Malawi is \$0.60, erythromycin \$1.50, and ampicillin \$2.50. The two courses of antibiotic treatment will be approximately \$4.60). As recommended in a recent meeting sponsored by the Pediatric AIDS Foundation and Emory University, "there is a need to evaluate simple and feasible interventions other than antiretroviral agents for their efficacy in diminishing HIV MCT in developing nations."
3. If, ultimately, antiretroviral agents are used only near delivery, it is not likely that they will reduce the portion of HIV MCT occurring earlier in pregnancy. Antibiotic treatment as described in this protocol has biologic plausibility for reducing antepartum as well as peripartum HIV MCT and for achieving additional reductions in HIV MCT over and above that achieved with short course antiretroviral therapy alone, if that treatment is available.

The specific antibiotics to be used prenatally include metronidazole and erythromycin. The rationale for choosing these two antibiotics includes: 1) the organisms discussed above are generally sensitive to one or both of these antibiotics; 2) only metronidazole and/or metronidazole and erythromycin have been shown to be associated with a reduction in spontaneous preterm birth; 3) metronidazole has been used during pregnancy in the United States and elsewhere for a number of years and is safe, especially in the second trimester. Erythromycin and ampicillin are also safe during pregnancy.

An initial treatment course of metronidazole and erythromycin will be given orally three times per day for seven days at 20-24 weeks gestation. This course was chosen for the following reasons: 1) in the second trimester women are being treated for an intrauterine infection and not solely bacterial vaginosis, and 2) the two trials in which a reduction in prematurity has been achieved used a prolonged course of antibiotics (one week or more) in the second trimester.

In labor and with ruptured membranes, since Group B Streptococcus is often the offending organism and rapid antibiotic entrance into the amniotic fluid is an important issue, metronidazole 250 mg in combination with ampicillin 500 mg will be administered orally every 4 hours to prevent the acute chorioamnionitis associated with membrane rupture. Both of these drugs achieve satisfactory serum and amniotic fluid levels within 1-2 hours after oral administration.

Organisms associated with both BV and chorioamnionitis have been similar whether studied in the U.S., Europe, Asia or South Africa, and have not differed substantially between black and white women in the U.S, Great Britain or South Africa.^{1,4,9} A randomized trial in South Africa showed a reduction in preterm birth in women in early preterm labor with intact membranes who used metronidazole

and ampicillin.⁹ Therefore, although most studies dealing with infection and preterm birth have been performed elsewhere, it is very likely that they are applicable to sub-Saharan Africa. Even if this study only demonstrates that the antibiotic strategy employed in this protocol reduces preterm births in sub-Saharan Africa, this result in itself will be of major importance to the women of these countries.

Currently, there is little consensus in the United States and other countries about the value of routinely screening for infection and treating pregnant women with antibiotics either prior to or during labor to prevent preterm birth. For example, while there is some evidence that treating women who had a previous preterm birth who were BV positive reduced preterm birth, there are several recent reports which suggest no benefit when large populations of women are screened and treated.²⁴ In fact, recently analyzed data from a large -scale NIH trial suggested no reduction in preterm birth using this approach.²⁵ In view of these findings, no major U.S. organization has yet made a recommendation for widespread screening for and treatment of bacterial vaginosis during pregnancy. Since this practice is not routine in the U.S. and in fact is under study in a number of U.S. locations, the investigators believe it is also appropriate to study antibiotic use during pregnancy using placebo controls in an African setting.

If antibiotic treatment aimed at reducing chorioamnionitis significantly reduces transmission, the study results as well as information regarding the cost of implementing the intervention will be provided to appropriate Ministry of Health officials and other policy makers in Malawi. Ministry of Health officials are aware of and are enthusiastic about this study because it offers the potential for a low-cost reduction in perinatal HIV transmission. While there are no formal guarantees of nationwide adoption, the introduction of this strategy will be evaluated. In addition, the investigators have already had discussions with USAID officials about funding the use of these medications in demonstration projects in Malawi, if the trial is successful.

2.0 STUDY OBJECTIVES

2.1 Primary

- To determine if antibiotic treatment aimed at reducing chronic and acute chorioamnionitis will reduce HIV MCT.

2.2 Secondary

- To determine if antibiotic treatment reduces preterm birth and maternal/infant morbidity and mortality.

- To determine if antibiotic treatment reduces HIV MCT in women with BV or a positive FFN.
- To determine if the reduction in HIV MCT potentially achieved by antibiotics is associated with a reduction in histologic chorioamnionitis, preterm birth, or vaginal viral load.
- In HIV-negative women, to determine if the antibiotic regimen employed in this study is associated with an improvement in birthweight and other perinatal outcomes.
- To determine the correlation between vaginal pH, the whiff test, a non-specific vaginal discharge and clue cells on a wet prep with a Gram stain diagnosis of BV, and to determine the sensitivity, specificity, positive and negative predictive values of these tests for diagnosing BV and predicting HIV MCT.

The secondary endpoints include preterm birth and infant and maternal morbidity and mortality. In developing countries, most preterm infants die. Even in term infants, mortality is often associated with infections acquired during childbirth. There are substantial data emerging from many sources that preterm birth is associated with a chronic but asymptomatic chorioamnionitis, and that chorioamnionitis at delivery is associated with neonatal infection, morbidity and mortality. It is, therefore, reasonable to hypothesize that antibiotic prophylaxis may reduce preterm birth and its associated morbidity and mortality, as well as the infectious morbidity and mortality associated with chorioamnionitis acquired near delivery. Maternal morbidity and mortality may also be reduced. This study will allow determination in both HIV positive and HIV negative women of whether perinatal morbidity and mortality may be reduced with prophylactic antibiotics.

The investigators are also interested in determining whether or not bacterial vaginosis and fetal fibronectin predict HIV MCT, and if women with these findings are more or less responsive to antibiotics for both the primary and secondary outcomes. The investigators expect the prevalence of BV in this population to be 30-50%. The prevalence of women testing positive for fetal fibronectin is expected to be 6-8%. Both of these "vaginal findings" have been linked to chorioamnionitis. Therefore, there is reason to believe that their presence may be related to both the primary and secondary outcomes. In this study, if antibiotics work to reduce HIV MCT, the cause of the reduction will be of interest. By obtaining the above information, examining the placenta for evidence of histologic chorioamnionitis in the treated women and controls, measuring vaginal viral load and determining if the antibiotics reduced the HIV MCT associated with preterm birth, a better understanding of the relationship between HIV MCT and antibiotics will be achieved.

Finally, although there is preliminary evidence that the presence of BV may be associated with HIV MCT, even this conclusion is uncertain. Furthermore, since BV may be diagnosed in many different ways, and it is not clear which, if any, of the many diagnostic tests predict HIV MCT, correlating this information with the

various outcomes may provide useful information about BV and HIV MCT.

3.0 STUDY DESIGN

This is a randomized, double blinded, controlled phase III clinical trial of antibiotics. The interventions will be conducted at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi, and Lilongwe Central Hospital (LCH) in Lilongwe, Malawi. Study participants will be randomized to receive either antibiotic treatment or placebo. All HIV-infected participants will be offered the HIVNET 012 nevirapine regimen. Enrollment will occur at a rate of approximately 100 mother/fetal pairs per month at QECH and LCH. Follow-up will continue until 12 months after the last woman delivers or until sufficient events accrue to provide adequate power for the primary endpoints.

In Blantyre, Malawi, several cohorts of pregnant women were recruited from the QECH during the ICAR, PAVE, birth canal washing and micronutrient supplementation studies. The HIV prevalence has been well-documented; it has risen from 2% in 1985 to 30% in 1997.²⁶ Approximately 1200 deliveries occur at QECH every month (during the HIVNET birth canal washing intervention, 6965 women gave birth at QECH during the six month duration of the study).²⁷ The investigators in Blantyre have routinely monitored antenatal clinic attendance at QECH over several years. On average, 520 women attend the antenatal clinic every month. Approximately 40-50% of the women attend hospital antenatal care by 23 weeks gestation. Of these women, approximately 80% agree to HIV testing and receive their results, with about 30% being positive. Therefore, about 56 HIV-positive women will be available for recruitment every month into the proposed clinical trial from the QECH alone, of which 50 will be enrolled. This is consistent with experience in the recruitment of the most recent cohort in 1995/96 where enrollment was initiated at 17 weeks gestation, in which a similar high proportion of women screened were enrolled. Based on the number of women attending antenatal care in 1998/99 at Lilongwe Central Hospital, approximately equal enrollment is anticipated. Therefore, enrollment between the two sites is expected at a rate of 100 HIV-positive women/month.

These data provide documentation that sufficient HIV-positive subjects are present in both locations. Each potential participant will be provided appropriate information about the study and her informed consent will be obtained prior to enrollment.

In each site about 300 HIV-negative women will be enrolled to conceal the HIV status and avoid stigmatization of participating women. This sample of HIV-negative women will also provide valuable information on the secondary objectives (see Section 3.2). Determination of whether the use of this regimen is associated with an improvement in birthweight, a reduction in preterm birth, and a reduction in maternal chorioamnionitis in HIV-negative women, as well as whether adherence to the treatment regimen and tolerance of the antibiotics are similar in the two cohorts, is of interest. Data from the HIV-positive and negative women will not be combined in the analysis.

3.1 Selection and Enrollment of Subjects

The inclusion and exclusion criteria refer to all prospective participants (both HIV positive and negative women with the exception of their HIV status).

3.1.1 Inclusion Criteria

- HIV positive at enrollment;
- 20-24 weeks gestation;
- Willing to give informed consent (for HIV testing and for enrollment into the study);
- Willing to take antibiotic treatment as scheduled;
- Planning to deliver at QECH or LCH;
- Willing to come back for follow-up visits for one year post-partum

3.1.2 Exclusion Criteria

- Have taken antibiotics, other than treatment for syphilis or gonorrhea, within the last two weeks;
- Are allergic to penicillin, ampicillin, erythromycin, or metronidazole;
- Have known major illnesses likely to influence pregnancy outcome including diabetes, severe renal or heart disease, or active tuberculosis, prior to randomization;
- Have known major obstetric problems such as placenta previa, ruptured membranes or multiple pregnancy prior to randomization;
- Have known central nervous system diseases, including seizures;
- Are taking anticoagulant drugs.

3.1.3 Enrollment Procedures

This study will be conducted at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi and Lilongwe Central Hospital (LCH) in Lilongwe, Malawi. Women will be recruited at 16-23 weeks gestation from the antenatal clinics. Informed consent for HIV counseling and testing, and screening for the study will take place. Women will return to the clinic in one to two weeks to receive their test results. If the woman is eligible for the study, an enrollment visit will be scheduled at 20-24 weeks gestation; the woman will be encouraged to bring the baby's father to the enrollment visit. At the enrollment visit, the study will be explained to the woman and her partner (if available) and informed consent will be obtained. After informed consent is obtained, the woman will be randomized. Randomization will employ permuted block algorithms with randomized block sizes. Randomization of HIV-positive women will be stratified only by site. A separate randomization stratification will occur for HIV-negative women (see section 3.2 below).

3.2 Co-enrollment Guidelines

A sample of 300 HIV-negative women will be included in the study from each site. These women will be randomized using a separate stratified randomization scheme and followed during pregnancy and postpartum (with their babies) in a manner indistinguishable from HIV-positive mother-infant dyads. Inclusion of

these HIV-negative women will allow avoidance of stigmatization associated with inclusion of only HIV-positive women from the antenatal clinics. Furthermore, with a sample of 300 women randomly selected from each site, the effect of antibiotic treatment on some of the secondary outcomes will be evaluable. For example, a study of a sample of 600 women will have more than 80% power to detect a reduction in low birth weight from 15% (the prevailing rate in Malawi) to 10% (a reduction of one third; alpha 0.05, one-sided test). Establishing a beneficial impact of the proposed treatments among HIV-negative women may justify recommending antibiotics to all women irrespective of their HIV status. There is also potential to study the effect of the antibiotics on early infant morbidity and mortality. Therefore, generalizability of the study findings will be possible.

A sample size of 300 is based on co-enrollment of one HIV-negative woman subsequent to every five HIV-positive women in each site. One HIV-negative woman will be requested to participate following the fifth successfully enrolled HIV-positive woman. If the selected participant refuses or is not eligible, the HIV-negative woman immediately succeeding her will be approached.

4.0 CLINICAL AND LABORATORY EVALUATIONS

4.1 Pre-entry Evaluations

Appropriate pretest HIV counseling by trained HIV counselors will be provided to all women attending the antenatal clinic on the day of screening. Women who agree to be HIV tested will sign a screening informed consent form. Screening for syphilis is part of the routine antenatal care in Malawi. For those tested, HIV and syphilis test results will be available within one week from the initial antenatal visit, and in general, women will be seen for a repeat counseling visit within two weeks of testing. All women will receive post-test counseling upon return to the clinic. HIV-positive women and a sample of HIV-negative women will be requested to participate in the study; an enrollment visit will be scheduled at 20-24 weeks gestation and women will be encouraged to bring the baby's father.

HIV testing: Blood will be collected from all consenting women for HIV testing. The Genetic Systems LAV EIA will be used for screening and the Wellcozyme HIV Recombinant EIA will be used for confirmation. These tests will be run on the same blood specimen to identify HIV seropositive women. HIV indeterminate results on EIA tests will be confirmed by western blot.

Syphilis testing: All women will have blood tested using RPR for screening and TPHA for confirmation. Women with a reactive syphilis test will receive treatment at no cost.

4.2 Evaluations During Pregnancy and Labor

At the enrollment visit the study procedures will be explained to the women and their babies' fathers, including the schedule of the follow-up visits. Women who

agree to participate in the trial will sign a separate enrollment consent form; signature of the baby's father will also be requested. HIV-infected women who enroll in the study will be offered the HIVNET 012 nevirapine regimen. Women who choose to accept the nevirapine will sign a separate signature line on the study enrollment consent; signature of the baby's father will also be requested.

Structured questionnaires will be used to collect the non-laboratory data described in the table below (Table 1). In addition, at the first antenatal visit (20-24 weeks) socio-demographic information including age, parity, maternal and paternal education, residence, socioeconomic status, marital status, and number of sexual partners will be collected on all women. The enrollment questionnaire will include symptoms of clinical AIDS (for HIV-positive women) and sexually transmitted diseases. A clinical examination form will also be completed. Table 1 summarizes these activities.

Gestational age will be determined based on patient recall of the last menstrual period, corroborated with uterine size. If uterine size is not consistent (within 2 weeks) with recall, uterine size will define the obstetric gestational age (ultrasound examinations are rarely performed at these sites; therefore estimating gestational age by this criterion will not be routinely available). In addition, at delivery, the babies will have a modified Ballard examination performed to allow for both an obstetric and pediatric estimation of gestational age. If the two are consistent within 2 weeks, the obstetric gestational age will be used; if not, the final study gestational age will be based on the Ballard examination. Staff at both locations will be trained to determine both the obstetric and pediatric gestational ages. However, this algorithm will result in a single project gestational age which will be used whenever a project gestational age is required as part of the protocol or as an outcome.

Table 1. Non-laboratory and laboratory evaluations during pregnancy and labor.

<u>Non-Laboratory Data</u>	<u>Labs</u>
<u>Enrollment (20-24 wks):</u> Maternal Demographics Obstetric History Medical History Sexual History Gestational Age Antibiotic Usage Other Medications	BV Status (Gram Stain, whiff test and pH) Wet mount for clue cells Candida, Trichomonas (2 wet mount slides) FFN Status (EIA) * Blood for CBC and CD4 Analysis? Plasma for Zinc/Vitamin *, Viral Load*? Cervical swab for HIV Load*? Cervical swab for Chlamydia EIA, Gonorrhea Culture, and STD LCR*
<u>Follow-up (26– 30 Wks)</u> Intervening Medical History Antibiotic Usage Other Medications Pill Counts/Adherence/Adverse Reactions	BV Status (Gram Stain, whiff test and pH) Wet mount for clue cells Candida, Trichomonas (2 wet mount slides) FFN Status (EIA) * Cervical swab for HIV Load*? Cervical swab for Gonorrhea Culture
<u>Follow-up (36 Wks)</u> Intervening Medical/OB History Antibiotic Usage Other Medications	Blood for CBC and CD4 Analysis? Plasma for Zinc/Vitamin *, Viral Load*?
<u>At Delivery</u> Length of Labor Length of ROM Clinical Chorioamnionitis Obstetric Interventions Infant Weight/Gestational Age Antibiotic Usage Adverse Reactions	Placenta, Membranes and Cord for Histology Colostrum for Viral Load?

* To be stored for later analyses

? To be run on all HIV-positive women; however, to maintain confidentiality, specimens will be collected from all women

4.2.1 Adherence

The prenatal antibiotics, metronidazole and erythromycin, and the peripartum antibiotics, metronidazole and ampicillin, and placebos will be packaged in blister packs to be given to each woman at appropriate visits. The initial dose of prenatal antibiotics or placebo will be taken at the enrollment visit under direct observation, and the participant will be asked to bring the blister packs with her to her next visit at 26-30 weeks gestation. Each woman will be given the peripartum antibiotics or placebo at the 26-30 week visit. She will take the antibiotics or placebo at onset of labor and throughout delivery and after delivery until the course is completed. If a woman vomits within one hour of dosing, she will be redosed. She will be asked to bring the blister packs with her to her next visit at 4-6 weeks post-partum. Adherence will be assessed by the number of pills missing from the blister packs at the follow-up visits. If the blister packs are not returned, reported use will be noted. Adherence to the

vitamin regimen will also be assessed through blood folate levels measured in a subset of women.

Erythromycin use is associated with various types of gastrointestinal complaints (but very few serious complications) and continued use is less than optimal for this reason. In an effort to enhance appropriate use of the drug, at randomization, each woman will be informed of the potential for mild but harmless gastrointestinal side-effects and will be encouraged to continue using the medications. If these side effects become intolerable, rather than discontinuing, the woman will be encouraged to reduce the dose, but take the medication over a longer time-period. The amount of each drug taken by the participants will be monitored.

Rarely, patients taking metronidazole and/or erythromycin have been reported to develop a peripheral neuropathy, seizures, or other CNS symptoms. For this reason, patients with central nervous system diseases, including seizures, will be excluded from participation, and any patient developing a neuropathy or other CNS sign or seizures during treatment will have the erythromycin and metronidazole or their placebos discontinued.

Since metronidazole may potentiate the action of certain anticoagulants, women taking any anticoagulant drug will also be excluded from participation.

4.2.2 Other STDs

Except for the intervention of study antibiotics (or placebo) and the addition of a vitamin/mineral supplement and the HIVNET 012 NVP regimen (to HIV-infected women and their infants), the women will receive regular prenatal care. In Malawi, women are generally screened for syphilis, and at times for gonorrhea. If reactive for syphilis or positive for gonorrhea, women are generally treated with a penicillin-like drug. Treatment of syphilis or gonorrhea with a penicillin-like drug should have little influence on the development of chorioamnionitis since the organisms involved, including *Gardnerella*, *Bacteroides*, *Mycoplasma* and *Ureaplasma*, are not generally susceptible to the penicillin-like antibiotics. For this reason, women who receive penicillin-like antibiotics or were treated for syphilis or gonorrhea within two weeks prior to randomization will not be excluded. Bacterial vaginosis is not usually screened for or treated in these settings, but if a woman complains of a symptomatic discharge, she will be appropriately treated. Candida, trichomonas and chlamydia are not routinely screened for, but occasionally are treated if symptomatic. In any case, for each woman, at the time of enrollment, during chart review and again at delivery, the study physicians will discern which antibiotics, if any, were used during the course of pregnancy and these will be recorded. It is important to nest this clinical

trial within the usual health care environment to assess its utility within the actual local medical practice. Other than the improved screening and treatment for syphilis and provision of multivitamin/mineral supplements and nevirapine, the usual standard of care in Malawi will be provided.

4.2.3 Evaluation of clinical and laboratory events

This study will investigate if BV and FFN are predictors of perinatal HIV transmission, and also if treatment of HIV-positive women with or without BV and/or FFN with the proposed antibiotic regimen results in a reduction in perinatal HIV transmission. Diagnosis of BV (or FFN positivity) will not influence the conduct of the treatment in this study. The diagnosis of BV will be determined based on a Gram stain (Nugent criteria) of vaginal fluid taken at the randomization visit. Since BV will not be used to direct therapy, the slides for Gram stain for BV will be evaluated in batch independent in time from the conduct of the trial. FFN testing is being done to answer a question related to the mechanism of HIV MCT; if MCT is more common in FFN-positive women, this would strongly suggest that chronic chorioamnionitis plays a significant role in this process.

The Gram staining method to diagnose BV requires expertise and training. Therefore, simple inexpensive methods to assess BV are desirable. Clinical criteria to diagnose BV have been developed (three of the following four criteria: vaginal pH >4.5, homogenous vaginal discharge, presence of $\geq 20\%$ clue cells, and a positive amine test), and are highly correlated with the Gram staining scoring method. In a recent study in Malawi, BV based on these clinical criteria was shown to be associated with HIV perinatal transmission¹⁵ and increased acquisition of HIV.¹⁴ Vaginal pH will be measured using pH paper on a vaginal swab obtained from lateral and posterior fornices. An amine (or whiff) test will be performed by mixing a few drops of 10% potassium hydroxide with vaginal fluid. These tests are simple and can be routinely performed in the hospital laboratories of Malawi. The presence of clue cells will be evaluated by mixing vaginal fluid with a drop of normal saline on a slide and examining under high power magnification. The presence of vaginal discharge will be determined by a speculum-aided pelvic exam conducted by trained nurses. The implications for low cost screening to identify candidate women for therapy in areas of the world with less resources are obvious; hence this nested evaluation of the sensitivity, specificity and predictive value of clinical criteria to diagnose BV is an important subproject within this clinical trial.

FFN is measured using an EIA assay from vaginal fluid collected using a Dacron swab which is placed in buffer and frozen for subsequent analysis. Adeza Biochemical, Sunnyvale, CA, has provided the investigators the EIA kits necessary to determine levels of fetal fibronectin and will make kits available for this study. If FFN identifies a group at substantially

increased risk for HIV MCT, this will enhance knowledge about the mechanism of MCT and it may allow future investigators the opportunity to target transmission in women at high risk for MCT.

At enrollment and approximately 4 weeks later, specimens will be collected to diagnose BV, and two wet mount slides will be prepared and examined for detection of candida and trichomonas. A swab in buffer for FFN and a cervical swab for GC and vaginal viral load evaluations will be collected. At enrollment, a cervical swab will also be collected for chlamydia EIA and STD LCR. Analysis of the Gram stains will be conducted for all women. FFN and STD DNA (chlamydia and gonorrhea) samples will be stored to be run in batch when feasible.

Blood samples will be collected from each woman at enrollment and the 36 week visit for a CBC. The blood from HIV-positive women only will be tested for CD4 counts and stored for viral load. The blood from each woman will be stored for future nutrient analyses to determine adherence with taking the vitamin/mineral supplement and for potential future studies relating MCT to nutritional status.

4.3 Evaluations at Delivery

At delivery, clinical chorioamnionitis will be defined by the presence of a temperature $>38^{\circ}\text{C}$ during labor in association with any of the following: 1) fetal tachycardia >160 BPM, 2) significant abdominal tenderness, 3) a purulent cervical discharge, or 4) a foul smelling infant or placenta.

After delivery, the placenta will be brought to the laboratory in a sealed plastic bucket containing 500 ml 10% formol saline and weighed. The membranes will be rolled in a standard fashion, and after fixation, two sections at least 2 cm apart will be evaluated. Two sections of the cord, one close to the placenta and the other near the fetus will be obtained, as will two representative sections of the placenta. The specimens will be fixed in 10% neutral buffered formalin, processed for routine paraffin embedding, embedded, cut at 5 μ micron thickness and stained by routine hemotoxylin-easin method.

Slides will be examined by the designated pathologist without knowledge of outcome or maternal HIV status.

Histologic chorioamnionitis will be based on qualitative assessment of the membranes, cord and placenta basalis, looking for mononuclear and polymorphonuclear white cells using a standard protocol. A grading system which divides the histologic chorioamnion evaluation into normal and mild, moderate and severe chorioamnionitis will be used. It will be noted if the predominant infiltrate is mononuclear or polymorphonuclear so that the chorioamnionitis may be divided into chronic or acute. The presence of findings suggestive of placental malarial infiltration will also be noted.²⁸⁻³⁰

Following delivery, mothers and infants will be evaluated for evidence of disease and adverse reactions to medications. Colostrum and breast milk will be collected from each woman; specimens from HIV-positive women will be frozen for later analysis, while specimens from HIV-negative women will be discarded. Placental tissue will be stored so that examination of the placenta by in situ and immunohistochemistry using a novel and highly sensitive method utilizing tyramide-fluorophors may be conducted.³¹ This method can simultaneously detect HIV RNA, HIV DNA, HIV proteins and cellular proteins and help delineate the role of chorioamnionitis and HIV expression. A section of the placenta will also be kept to examine for malaria parasites and histologic changes associated with malaria. Malaria is endemic in Malawi and is a known risk factor for preterm birth and low birthweight.³²

As described in the protocol, the investigators plan to obtain biologic specimens which have the potential to answer questions related to mechanisms of transmission, but are not crucial to answer the primary question about efficacy of antibiotics for reducing HIV MCT. These include the testing for BV; FFN; viral load in blood, vagina and breast milk; evidence of malaria in the placenta; blood for vitamin/mineral measurements, etc. If, during the initial enrollment period, it appears that obtaining any of these specimens will reduce the overall ability to carry out this study, the collection of these specimens will be deleted from the protocol.

4.4 Post-Delivery Evaluations (Table 2)

At 24-48 hours, 4-6 weeks and 3 months all infants will have a heelstick. At 24-48 hours and 4-6 weeks, the specimens from infants born to HIV-infected women will be tested for HIV RNA using PCR. Positive specimens will be confirmed by a second RNA PCR on a separate specimen no later than the next scheduled visit and sooner if possible. Infants who test positive on initial PCR testing but die or are lost to follow-up prior to a confirmation test on a separate specimen will be considered HIV-infected in the study analysis. The specimens collected at 3-months will be stored and tested for confirmation if necessary. Infants who are positive using the definition of an infected infant (section 7.51) will have reached the primary endpoint. Because a second primary endpoint includes being alive and free of disease at 1 year of age, infants of HIV-positive women who were not previously classified as HIV-infected will be tested for HIV RNA at 12 months, and all who are negative will be considered free of HIV. Infants who test positive at 12 months will have another PCR for HIV RNA performed and those positive using definitions in section 7.51 will be considered positive for this endpoint. If the recommendations are still current at the time study infants are born, each infant diagnosed as HIV-positive will be provided with prophylactic Bactrim or an equivalent medication during the course of the study. All infants will have a CBC performed on the blood specimens collected by heelstick at 24-48 hours, 4-6 weeks and 3 months, and by venous blood draw at 12 months. Specimens from

infants born to HIV-uninfected women will be stored for potential future approved studies.

To monitor the safety of nevirapine, infants who receive nevirapine will have an ALT at the 4-6 week visit. If the results from the ALT are a grade 1 or 2 abnormality, the test will be repeated at the 3 month visit. If the results are a grade 3 or 4 abnormality, the mother will be requested to return with her baby within one week of the test result for a repeat test. The ALT will be performed at the on-site laboratory.

Following delivery (24-48 hours), at 4-6 weeks, 3 months, 6 months, 9 months and one year of age, questions related to infant health, maternal health and breastfeeding practices will be asked. At each post-delivery visit, a clinical assessment form will be completed for the mother and the newborn, and a breastmilk specimen will be collected from the mother. These activities are summarized in Table 2.

Because there is concern that some antibiotic treatment may lead to an increase in neonatal sepsis with more virulent organisms, occurrence of neonatal sepsis prior to discharge from the hospital or at the 4-6 weeks evaluation will be monitored. The NIAID Vaccine and Prevention DSMB will evaluate mortality and severe morbidity in the treatment and placebo groups at 3 month intervals to ensure that the treatment is not causing harm.

Breast feeding is nearly universal in both sites. The investigators are aware of the risk associated with HIV transmission to the baby if breastfed. Currently, breastfeeding is encouraged in Malawi during the entire infancy since alternative safe measures are not generally available. However, women will be adequately counseled and the risks and benefits of breastfeeding will be explained thoroughly at each visit to help women make an informed decision. During the entire study period the research team will be guided by the advice and recommendations adopted in-country.

It is understood that some infants will likely become HIV infected due to breast feeding prior to evaluation at 4-6 weeks. There is no method available to allow distinction between infection occurring during the perinatal/peripartum period and secondary infection due to early breast feeding.

Table 2. Non-laboratory and laboratory evaluations during follow-up.

<u>Non-Laboratory Data</u>	<u>Labs</u>
<p>At 24-48 hours; 4 – 6 wks; 3, 6, and 9 month <u>1 year</u> Infant Viability and Health, Maternal Health Breast vs. Formula Feeding</p>	<p><u>24-48 hours, 4-6 weeks</u> Heelstick for Infant RNA PCR for HIV^D</p> <p><u>24-48 hours, 4-6 weeks, 3 months</u> Heelstick for CBC</p> <p><u>4-6 weeks</u> Heelstick for ALT</p> <p><u>12 months</u> Venous blood draw for Infant RNA PCR for HIV, CBC</p> <p><u>4-6 weeks; 3, 6, and 9 months; 1 year</u> Breast Milk collection*</p>

* Specimens from HIV-positive women will be stored for later analysis of viral load; specimens from HIV-negative women will be discarded.

^D To be run on infants of HIV-positive women. Positive specimens will be confirmed by a second RNA PCR on a separate specimen no later than the next scheduled visit and sooner if possible.

[?] In infants receiving nevirapine. If results indicate a grade 1 or 2 abnormality, the test will be repeated at the 3 month visit. If the results indicate a grade 3 or 4 abnormality, the test will be repeated within one week of the test result.

5.0 DATA COLLECTION AND MONITORING AND ADVERSE EXPERIENCE REPORTING

5.1 Records to Be Kept

Case Report Forms (CRF) will be provided for each subject. Subjects will not be identified by name on any study documents. Subjects will be identified by an identification number unique for each participant; this will be provided by the HIVNET Statistical Center upon randomization. At screening, all women will be provided a temporary screening ID to track clinical and laboratory results. The use of the screening ID will be discontinued upon randomization.

All data on the CRF must be legibly recorded in black ink. 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.

5.2 Data Management and Documentation Guidelines

Instructions concerning the recording of study data on case report forms, or the entry of data in the computerized database, will be provided by the HIVNET Statistical Center, who will coordinate data management for the trial.

5.3 Regional Monitoring

5.3.1 Site visits by FHI 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 compliance with all regulatory requirements associated with clinical trials.

5.3.2 Site visits will be made at the Blantyre and Lilongwe HIVNET sites at regular intervals.

5.3.3 The investigators will make study documents (e.g., consent forms, drug distribution forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the FHI site monitor, the FDA, Boehringer-Ingelheim staff and pertinent NIH staff for confirmation of the study data.

5.4 Adverse Experience Reporting

An adverse event is defined as any health related reaction, effect, toxicity or abnormal laboratory result that a patient experiences during the course of a study irrespective of relationship to study treatment.

Adverse experiences should be reported according to reporting requirements as described in Appendix III.

6.0 STUDY TREATMENT

6.1 Drug Regimens, Administration and Duration

6.1.1 Antibiotics

At 20–24 weeks, the women randomized to the treatment arm will receive metronidazole 250 mg TID and erythromycin 250 mg TID for 7 days. Women randomized to the control group will receive identically appearing placebos.

With the onset of labor and/or rupture of membranes, rapid antibiotic entrance into the amniotic fluid is important. Participants will be given metronidazole 250 mg and ampicillin 500 mg (or placebo) at the 26-30 week visit and will be instructed to take one of each pill at onset of labor. They will be asked to come to the hospital immediately after onset of labor, at which time the study staff will assume administration of the study antibiotics. These drugs were chosen to prevent the acute chorioamnionitis associated with membrane rupture. Both of these drugs achieve satisfactory serum and amniotic fluid levels within 1-2 hours after oral administration. Since the secondary outcomes include maternal infection and mortality, each woman will be asked to continue using the medications after delivery, three times per day, until the course is completed. Women randomized to the control group will receive identically appearing placebos.

6.1.2 Multivitamins

All women in both treatment and control arms will receive a standard vitamin/mineral preparation daily from enrollment in the study until delivery. This preparation will include 30 mg iron, 400 mcg folic acid, 5000 IU Vitamin A, 400 IU Vitamin D, 30 IU Vitamin E, 50 mg Vitamin C, 2 mg Vitamin B₁, 3 mg

Vitamin B₂, 3 mg Vitamin B₆, 5 mcg Vitamin B₁₂, 20 mg Niacin, 250 mg Calcium, 150 mcg Iodine, 100 mg Magnesium, and 15 mg Zinc.

6.1.3 Nevirapine

All HIV-infected women and their neonates will be offered the HIVNET 012 nevirapine (NVP) regimen. If the mother accepts the nevirapine for her and her baby, she will be given one oral dose of 200 mg NVP at the 26-30 week antenatal visit to be taken at onset of labor. If the mother does not deliver within 48 hours of taking the nevirapine pill, she will be redosed immediately, or at onset of active labor in the case of false labor.

If the mother delivers her baby more than one hour and less than 48 hours after taking nevirapine, her baby will receive one oral dose of 2mg/kg NVP suspension at 72 hours post-birth or discharge, whichever occurs earlier. If the mother delivers her baby less than one hour or more than 48 hours after taking nevirapine, the infant will be dosed as soon as possible. If the infant vomits within one hour of receiving nevirapine, the infant will be redosed once.

If the mother delivers somewhere other than the study hospital, she will be asked to return to the study clinic within seven days of delivery to allow infant dosing of nevirapine. Infants who are delivered elsewhere and do not present at the clinic within seven days will not be dosed.

All HIV-uninfected women and HIV-infected women who refuse nevirapine will be given a matched placebo at the 26-30 week visit to maintain participant confidentiality.

6.2 Drug Acquisition

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

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

The nevirapine and nevirapine placebo will be donated by Boehringer Ingelheim Pharmaceuticals.

6.3 Drug Supply, Distribution and Pharmacy

PAB will coordinate the packaging and shipping of the product through existing subcontracts with the Clinical Research Product Management Center (CRPMC). The antibiotics/placebos will be packaged in blister packs. The multivitamins will be packaged in bottles of 100. The nevirapine and nevirapine placebo will be packaged in bulk for distribution by the study pharmacist.

The protocol pharmacist is required to maintain complete records of all study agents received from the CRPMC of the Division of AIDS and subsequently dispensed.

6.4 Concomitant Medications

Any concomitant medication, if deemed medically necessary, will be permitted for either the mother or neonate while on-study; the administration of concomitant medication will be recorded on CRFs. Because of the reported interaction between metronidazole and alcohol, all women in the study will be asked to refrain from alcohol use during the trial, as reflected in the informed consent form.

6.5 Toxicity Management

Allergic reactions are possible with any drug. Severe anaphylactic types of reactions have been reported with penicillin use (1/50,000). Gastrointestinal side effects including nausea and vomiting and diarrhea have been reported with erythromycin use. If the toxicity appears to be a significant allergic reaction, both antibiotics will be stopped immediately. However, if the problem appears to be mild gastrointestinal discomfort associated with erythromycin use, the metronidazole will be continued at full dose. If necessary, the daily erythromycin dose may be reduced, but will not be discontinued unless the woman clearly cannot tolerate the medication. If there is nausea and vomiting or diarrhea, the women will be asked to decrease only the erythromycin, first to 2 tablets per day, and then, if necessary, to one per day until the symptoms abate. If a participant experiences wheezing or rash compatible with study drug reaction while on study drugs, the study drugs will be stopped and the participant will be asked to report to the study clinic immediately.

Extended nevirapine use has been associated with the occurrence of skin rashes. Nevirapine-related rashes are not expected in this protocol due to the abbreviated course of nevirapine that will be administered. This protocol will employ the short-course nevirapine regimen used in HIVNET 012, in which the occurrence of skin rashes was the same in the nevirapine and zidovudine arms. Despite the fact that nevirapine-related rashes are not expected, occurrence of skin rashes temporally related to nevirapine use will be recorded and reported as adverse events. The severity of skin rashes will be determined based on the Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Experiences located in Appendix V. Mothers will be instructed to return to the clinic if they or their baby experiences a rash. In addition to monitoring for skin rash, all infants who receive nevirapine will have an ALT at the 4-6 week visit. If the results are a grade 1 or 2 abnormality, the test will be repeated at the 3 month visit. If the results are a grade 3 or 4 abnormality, the mother will be requested to return with her baby within one week of the test result for a repeat test.

All mothers will agree to deliver at the study hospital when they enroll in the trial. Despite this fact, some mothers may deliver elsewhere. Mothers will be requested

to report to the clinic with their infants within 7 days after delivery if they do not deliver at the clinic. This will aid in toxicity management if any side effects are observed, as well as allow for infant dosing of nevirapine. As in the HIVNET 012 protocol, infants presented at the clinic within 7 days after birth will be given the infant nevirapine dose; if the mother presents with the infant after 7 days, no infant dose of nevirapine will be administered.

6.6 Criteria for Treatment Discontinuation

Study participants may be discontinued from treatment for the following reasons:

- The subject refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the subject's health or well-being.
- The subject experiences a severe allergic reaction to the study drugs.

6.7 Other Infections

A number of questions have arisen about the use of other treatments, especially the use of antibacterial agents that may obscure the results of this study. No appropriate treatment will be withheld because a woman is enrolled in this study. Therefore, if a woman has a symptomatic vaginal infection that would normally be treated in Malawi, appropriate treatment will be given. If it is standard treatment to use antibiotics in the face of ruptured membranes for more than 24 hours, or with maternal fever, they will be utilized. If newborns are normally treated with antibiotics following maternal chorioamnionitis they will be so treated. The individual treatments received by study subjects and the prevailing clinical practices that may influence MCT will be documented, but no attempt will be made to restrict what is considered routine medical care.

If during study drug administration a woman has a condition requiring antibiotic use, such as a urinary tract infection, chorioamnionitis or ruptured membranes of more than 24 hours, the woman will be treated with routine antibiotics in addition to the study drugs. Because the active arm of the study uses a relatively low dose of antibiotics, additional use of antibiotics should not place the woman at increased risk. The alternative option, unblinding the woman and providing antibiotics if she is on the placebo, would result in significant risk to bias the study. However, if the physician, because of severe allergic reaction or any other cause, feels it is necessary or in the patient's best interest to unblind the study products, the nature of the study drugs will be made available to the attending physician. The list will be kept by the in-country pharmacist, who will be the only person able to break the code.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

This is a randomized, double blinded, controlled Phase III clinical trial of antibiotics to reduce chorioamnionitis-associated perinatal HIV transmission. The

interventions will be administered to pregnant women during the second trimester of pregnancy and at onset of labor in order to interrupt vertical transmission of HIV.

7.2 Endpoints

7.2.1 Primary endpoints

- Infant HIV infection as determined by a positive RNA PCR on dried blood spots on filter paper taken at 4-6 weeks³³
- Composite of infant HIV infection and mortality at one year of age

7.2.2 Secondary endpoints

- Infant HIV infection at 24-48 hours and 12 months
- Rates of clinical and histologic chorioamnionitis
- Rates of neonatal/infant morbidity and mortality
- Rates of maternal morbidity and mortality
- Safety/tolerance of antibiotic treatment given to pregnant women from Malawi

7.2.3 Definition of gestational age is found in section 4.2. Preterm birth will be defined as <37 weeks, but evaluation of preterm birth at earlier gestational ages defined as <35 and <32 weeks will also be done. The definition of histologic chorioamnionitis is found in section 4.3. Infant mortality will be divided into neonatal, defined as <28 days, and post-neonatal, defined as 28 to 365 days. Evaluation of neonatal morbidity will include suspected or documented sepsis (based on physician examination or positive culture), pneumonia (based on physician examination or xray), and suspected or documented respiratory distress syndrome (based on examination or x-ray). The length of stay on initial hospitalization will be documented. Seizures and the presence of signs and symptoms of meningitis will be noted. Post-discharge medical problems such as seizures, pneumonia, meningitis, severe diarrhea, and all hospital readmissions and diagnoses will be noted. At each visit the infant will be weighed and the height and head circumference measured so that deviations from normal growth (<10th percentile for an African standard) may be determined. Medications used, such as any antibiotic treatment will be recorded.

Data on the mothers' health during the initial hospitalization and following discharge will also be collected. Length of hospital stay and readmissions will be noted as will the use of any antibiotics for treatment of infections. Maternal diagnoses including chorioamnionitis, post-partum endometritis, wound infections, urinary tract infections, pneumonias, etc., will be recorded. Any adverse reactions to the medications as well as the adherence to the medications provided will also be tracked.

7.3 Randomization and Blinding Procedures

Participants will be randomized at 20-24 weeks gestation in a double-blinded fashion to receive either the active agent (metronidazole/erythromycin/ampicillin) or matched placebo. The randomization will be designed by the HIVNET Statistical Center and employ permuted block algorithms with varying block size, blocked within study site to ensure that balance between assignments is maintained within each study site. Study drug will be packaged according to the randomization and sent to the study site. Randomization will be performed on site by assigning study drug to participants in sequential order. These procedures will be coordinated with the HIVNET Statistical Center and detailed in the study specific Manual of Operations. HIV-positive and HIV-negative subjects will be randomized in separate strata.

7.4 Sample Size and Accrual

The rate of HIV-1 transmission at 4-6 weeks is the primary endpoint for this study. The control arm 4-6 weeks transmission probability is estimated to be 11%. This estimate is based on the recent HIVNET 012 results using the nevirapine regimen involving a single dose to the mother at onset of labor and the single dose to the infant soon after delivery.²³ For a one-sided 0.025-level chi-square statistic to provide 90% power to detect a reduction in vertical transmission from 11% to 7.5%, 2870 mother/infant pairs would be needed in the trial. However, allowing for up to 3% loss-to-follow-up rates during pregnancy, and 5% missing information post-delivery, the majority of this due to early mortality,³⁴ the trial will require 3120 mother/infant pairs. The investigators will work very hard to achieve the proposed 3% loss to follow-up. However, if that rate is not achieved, sample sizes will be recalculated so that they reflect the actual lost-to-follow-up rates. A 3% lost-to-follow-up rate was achieved in Malawi in the chlorhexidine study.³⁵

7.5 Monitoring and Analysis

An intent-to-treat analysis will be conducted using the entire sample from both sites. The incidence of HIV-1 transmission and mortality rates will be determined among infants in each study arm. Binary endpoints will be compared between treatment arms using contingency tables or, if time dependent (death/drop-out), Kaplan Meier curves. Adjustment for potential confounders will be done through logistic regression or proportional hazards models. Single continuous outcomes (viral load, CD4 counts, etc.) will be compared with t-tests or non-parametric analysis. If needed, variable transformations such as logarithms will be used. Adjustment for confounders will be made with linear models. Repeated measures such as symptoms and anthropometric indices will be evaluated using generalized estimation equations.

An initial safety analysis will be performed after the first three months of accrual. Additional analyses of safety and formal interim analyses of efficacy will then be performed at approximately six month intervals during the remainder of the projected 18-24 month 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

employment of the standard single stage one-sided 0.025-level test 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 NIAID Vaccine and Prevention DSMB.

Recommendations regarding trial continuation and modification of study conduct will be based on safety as well as efficacy considerations. In the assessment of safety measures, particular attention will be given to monitoring the incidence of preterm birth, motivated in part by recent data showing a relationship between asymptomatic trichomonas, treatment with metronidazole, and increased risk for preterm birth.¹¹

Timing of transmission will be estimated by assuming that if the infant HIV PCR test was positive within 24 to 48 hours of birth, that transmission likely occurred prenatally, while if it was negative within 24 to 48 hours of birth but positive at 4-6 weeks, that MCT occurred in the intrapartum period. The investigators are aware that some of the infants who turn HIV-positive between discharge and 4-6 weeks will do so because of breast feeding, but at this time have no way to determine the proportion of the converters due to breast feeding vs. perinatal transmission.

In addition to viral load and CD4 counts, several variables will be evaluated for their relationship to MCT (and child health) in each group including BV and FFN status, plasma serum zinc and vitamin levels, the presence of STDs, histologic chorioamnionitis, length of PROM and labor, obstetric interventions, and gestational age and/or preterm birth.

7.5.1 Definition of HIV Infected/Uninfected Infant for HIVNET Perinatal Protocols

Following is the standard HIVNET definition adopted by the HIVNET Perinatal Working Group; if this definition changes before implementation of this protocol, adoption of these alterations will be considered so that a standard definition is used for all HIVNET perinatal transmission protocols:

An infant less than 15 months of age will be considered to be infected with HIV if two separate peripheral blood specimens from different days are drawn and each specimen is positive by at least one of the following assays: HIV-1 culture, HIV-1 DNA PCR, HIV RNA RT-PCR. At least one of these tests will be done in a laboratory which is approved to perform the assay for protocol testing. A positive result will be confirmed no later than the next scheduled visit and sooner if possible.

For PCR on dried blood spots, the Organon-Teknika NucliSens assay will be used.

Infants greater than 15 months of age who are reactive for HIV-1 antibody by two different EIAs or HIV-1 Western Blot will be considered to be HIV-1 infected.

A non-breastfed infant born to an HIV-infected mother will be considered to be uninfected with HIV when two separate peripheral blood specimens are drawn on different days and both are negative either for HIV DNA, HIV RNA, and/or HIV culture. All of these tests will be performed in a laboratory which is approved to perform the assay for protocol testing. Specimens will be drawn at least 4 weeks apart and will be drawn when the infant is four weeks of age or older and has been off antiretrovirals for at least two weeks. At least one specimen will be drawn when the infant is greater than 8 weeks of age. Infants who are >9 months of age will be considered to be uninfected if they are nonreactive by EIA for HIV-1 antibody.

A breastfed infant born to an HIV-infected mother will be considered to be HIV uninfected if after 8 weeks from the time of weaning two separate peripheral blood specimens are drawn on different days and both are negative either for HIV DNA, HIV RNA and/or HIV culture. All of these tests will be performed in a laboratory which is approved to perform the assay for protocol testing. Specimens will be drawn at least 4 weeks apart and after the infant has been off antiretrovirals for at least two weeks.

In cases where there is one positive specimen for HIV DNA, HIV RNA, or HIV culture, the infant will be considered uninfected only if the last two subsequent specimens are negative by the same initially positive marker and one other marker.

8.0 HUMAN SUBJECTS

8.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (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. The mother must give written informed consent for herself and her baby's participation in the study. According to Federal regulations, for studies in fetuses *in utero* when the purpose of the study is to meet the health needs of the fetus, and the fetus will be placed at minimum risk necessary to meet these needs, or the risk to the fetus is minimal and the purpose of the study is to gain important biomedical knowledge that cannot be obtained by other means, the father's written informed consent is also required, unless his identity or whereabouts cannot reasonably be

determined, or he is not reasonably available, or the pregnancy resulted from rape. The informed consents 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 mother (and father, if applicable).

8.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done only with coded numbers. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the HIVNET or the NIAID.

8.3 Study Discontinuation

With proper justification, the study may be discontinued at any time by the HIVNET Scientific Steering Group or the NIAID.

9.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by DAIDS and HIVNET policies. Any presentation, abstract, or manuscript will be made available for review by the HIVNET Manuscript and Presentation Review Committee prior to submission.

10.0 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 and Prevention.

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APPENDICES

- I. SCHEDULE OF EVALUATIONS**
- II. SAMPLE INFORMED CONSENT**
- III. ADVERSE EVENT REPORTING REQUIREMENTS**
- IV. DIVISION OF AIDS TOXICITY TABLES FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES**
- V. DIVISION OF AIDS TOXICITY TABLES FOR GRADING SEVERITY OF PEDIATRIC ADVERSE EXPERIENCES**

APPENDIX I SCHEDULE OF EVALUATIONS

Maternal Evaluations	Pre-entry/ Screening	Enrollment (20- 24 weeks)	26-30 weeks	36 weeks	Labor and Delivery	Infant Follow-up visits (4-6 weeks; 3, 6, 9 12 months)
Laboratory:						
HIV test (using two different EIA tests, with confirmation by WB)	X					
Syphilis test (RPR for screening TPHA for confirmation)	X					
BV status (Gram Stain, clue cells, whiff test, and pH)		X	X			
Presence of Candida, Trichomonas (2 wet mounts)		X	X			
FFN status (ELISA) ¹		X	X			
Blood for CBC, CD4; Plasma for: Zinc/Folate/Vitamins ¹ , Viral Load ^{1,2}		X		X		
Cervical swab for: HIV load ^{1,2} , Gonorrhea Culture		X	X			
Cervical swab for Chlamydia EIA and STD DNA (LCR) ¹		X				
Placenta, membranes and cord for histology					X	
Colostrum for Viral Load ^{1,3}					X	
Breast Milk for Viral Load ^{1,3}						X
Non-Laboratory						
Informed consent	X	X				
Randomization		X				
Demographics		X				
Obstetric/Medical History		X	X	X	X	
Sexual History		X	(X)			
Gestational Age		X			X	
Antibiotic/other medication usage		X	X	X	X	
Pill counts/adherence			X		X	X (4-6 weeks only)
Adverse events			X		X	X (4-6 weeks only)
Length of labor/ROM					X	
Clinical chorioamnionitis					X	
Obstetric interventions					X	
General Health						X
Breastfeeding practices						X

¹ Specimens to be stored for later analysis

² In HIV-positive women only

³ Specimens will be collected from all participants; however, only the specimens from HIV-positive women will be tested.

Neonate Evaluations

Neonate Evaluations	Birth (24-48 hours)	4-6 weeks	3 months	6 months	9 months	12 months
Laboratory:						
CBC	X (heelstick)	X (heelstick)	X (heelstick)			X (venous draw)
HIV RNA PCR ¹	X ⁵ (heelstick)	X ² (heelstick)				X ³ (venous draw)
ALT		X ³				
Non-Laboratory:						
Weight	X	X	X	X	X	X
Height, Head Circumference		X	X	X	X	X
Gestational Age	X					
General Health	X	X	X	X	X	X
Non-serious Adverse Events	X	X				
Serious Adverse Events	X	X	X			

¹ Only specimens from infants born to HIV positive women will be tested.

² A positive test will be confirmed by a RNA PCR on a separate specimen no later than the next scheduled visit and sooner if possible.

³ In infants receiving nevirapine. If the ALT result is a grade 1 or 2 abnormality, the test will be repeated at the 3 month visit. If the result is a grade 3 or 4 abnormality, the test will be repeated within one week of the test result.

APPENDIX II. SAMPLE INFORMED CONSENTS

1.0 SCREENING INFORMED CONSENT

2.0 ENROLLMENT INFORMED CONSENT

1.0 SCREENING INFORMED CONSENT

Sample Informed Consent for trials sponsored by the Division of AIDS, NIAID, NIH

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

NOTE FROM OPRR (OFFICE FOR PROTECTION FROM 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 OR INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENTS 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 FORWARDED TO FHI FOR ANY IMC-SPONSORED TRIAL. SPONSOR-APPROVED CHANGES IN AN IMC-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.

PHASE III TRIAL OF ANTIBIOTICS TO REDUCE CHORIOAMNIONITIS-RELATED PERINATAL HIV TRANSMISSION, HIVNET 024, version 2.0

SCREENING INFORMED CONSENT FORM

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(add in-country co-investigator)

INTRODUCTION:

You are being asked to take part in the screening for the research study named above, because you are pregnant. This study will use three drugs approved to fight infection. Before you decide whether or not to take part in the screening for this study, we would like to explain to you the purpose of the study, any risks to you, and what is expected of you.

This informed consent document gives you information about the screening visit part of the study that will be discussed with you. Once you understand the study, and if you agree to take part in the screening, you will be asked to sign this consent or make your mark in front of someone. You will be given a copy to keep.

Please note that:

- a. Your participation in this research is entirely voluntary;
- b. You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care.

PURPOSE OF THE STUDY:

The purpose of this research study is to see if antibiotic drugs given to treat an infection of the uterus during pregnancy can reduce the chances of HIV, the virus that causes AIDS, being passed from an HIV-positive mother to her baby. Antibiotic drugs are drugs used to fight infections in the body. The study will also see if these drugs improve the birthweight of the baby or prevent delivering the baby too early in an HIV positive or an HIV negative woman. Three drugs will be used in this study. These drugs have been approved for the treatment of infection of the uterus. Many women have used these drugs. Some studies have shown that an infection of the uterus during pregnancy is associated with a mother with HIV passing the virus to her baby. None of these drugs is being given to treat HIV infection.

This research study will enroll about 1850 women at this site and about 1850 women at a site in (Blantyre/Lilongwe). Your participation in the study will last about 16 months.

If you are interested in volunteering for this research study, you will need to meet the requirements for enrollment. You are being asked to give your permission to be tested for HIV and to see if you can be in the study.

If you meet the study requirements, you will be given more information about the study in another consent form. If you agree to participate in the study you will be asked to sign or make your mark on that consent form.

PROCEDURES:

After you sign this consent form, you will be asked to give a blood sample. About two teaspoons of blood will be needed. Your blood sample will be tested to see if you are infected with HIV or syphilis. Your test results will be available in one week. You will be asked to return to the clinic in one to two weeks to get your test results. Your test results will be explained to you. If you want to be in this research study, you must receive your HIV test results.

If your syphilis test shows that you have syphilis, you will be offered treatment at this clinic. You will not have to pay for this treatment.

You will be asked questions about any previous pregnancies and your medical history. Based on the results of your HIV test and your pregnancy and medical history, you may be asked to be in the study.

If your HIV test result is not positive but it is also not negative, you will not be able to be in this study. This type of test result means that doctors can not tell whether you are or are not infected with HIV.

RISKS and/or DISCOMFORTS:

Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm.

If you have HIV, knowing your HIV status may cause you anxiety. If others find out your HIV status, you may have trouble finding or keeping a job and have problems being accepted in your family and community.

POTENTIAL BENEFITS:

You may receive no direct benefit from these tests. However, you will receive information about your HIV status.

COSTS TO YOU:

There is no cost to you for these tests.

CONFIDENTIALITY:

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study.

Your records may be reviewed by the National Institutes of Health, the U.S. agency that sponsors this research; the U.S. Food and Drug administration, the agency that reviews research; the pharmaceutical sponsors of this research and the study monitors.

RESEARCH-RELATED INJURY:

If you are injured as a result of participation in this screening, the study clinic will give you immediate necessary treatment for your injuries. The cost of this treatment will not be charged to you. You will then be told where you may receive additional treatment for injuries. There is no compensation provided for research-related injuries.

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

If you ever have questions about this screening or in case you are injured as a result of participation in this screening, you should contact (name of local investigator or study clinician) at (telephone number or address). If you ever have questions about your rights as a research subject you may call (name and title of IRB member) at (telephone number or address).

SIGNATURE PAGE:

If you have read the informed consent, or had it read and explained to you, and you understand the information and voluntarily agree to be screened to join this study, please sign your name or make your mark below.

Volunteer's name Volunteer's signature Date

Witness' name Witness' signature Date

2.0 ENROLLMENT INFORMED CONSENT

Sample Informed Consent for trials sponsored by the Division of AIDS, NIAID, NIH

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

NOTE FROM OPRR (OFFICE FOR PROTECTION FROM 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 OR INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENTS 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 FORWARDED TO FHI FOR ANY IMC-SPONSORED TRIAL. SPONSOR-APPROVED CHANGES IN AN IMC-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.

PHASE III TRIAL OF ANTIBIOTICS TO REDUCE CHORIOAMNIONITIS-RELATED PERINATAL HIV TRANSMISSION, HIVNET 024, version 2.0

ENROLLMENT INFORMED CONSENT FORM

Taha Taha, MD, PhD (add in-country co-investigator)
Co-Principal Investigator
Johns Hopkins University
School of Hygiene and Public Health
615 North Wolfe Street, Room E-6007
Baltimore, MD 21205
(410)614-5255

INTRODUCTION:

You are being asked to take part in the research study named above, because you are pregnant. This study will use three drugs approved to fight infection. Before you decide whether or not to take part in this study, we would like to explain to you the purpose of the study, any risks to you, and what is expected of you.

This informed consent document gives you information about the study which will be discussed with you. Once you understand the study, and if you agree to take part, you and your baby's father, if

available, will be asked to sign this consent or make your mark in front of someone. You will be given a copy to keep.

Please note that:

- a. Your participation in this research is entirely voluntary;
- b. You may decide not to take part or to withdraw from the study at any time without losing the benefits of your standard medical care.

PURPOSE OF THE STUDY:

The purpose of this research study is to see if antibiotic drugs given to treat an infection of the uterus during pregnancy can reduce the chances of HIV, the virus that causes AIDS, being passed from an HIV-positive mother to her baby. Antibiotic drugs are drugs used to fight infections in the body. The study will also see if these drugs improve the birthweight of the baby or prevent delivering the baby too early in an HIV positive or an HIV negative woman. The three drugs used in this study to treat infection of the uterus are metronidazole, erythromycin and ampicillin. These drugs have been approved for this use. Many women have used these drugs. Some studies have shown that an infection of the uterus during pregnancy is associated with passing HIV from an HIV positive mother to her baby. None of the antibiotic drugs is being given to treat HIV infection.

Some drugs called antiretrovirals have been shown to reduce the chances of HIV being passed from an HIV-infected mother to her baby when given to mothers for several weeks during pregnancy. AZT is one of these drugs, and is approved for this use in the United States. More recently, a study in Uganda has shown that a drug called nevirapine can help reduce the chance (by about half) of a mother with HIV from passing the HIV virus to her baby, when given as a one-time dose to the mother during labor/delivery and to the baby soon after birth. Nevirapine has been approved as a treatment for HIV in adults and children in the US. However, the use of nevirapine to prevent passing of HIV from an infected mother to her child is still considered experimental. Experimental means that it may only be used in a research study in a limited number of people. None of these antiretroviral drugs are widely available in Malawi. If you have HIV, you and your baby will be offered nevirapine. You do not have to accept nevirapine to participate in this study.

This research study will enroll about 1850 women at this site and about 1850 women at a site in (Blantyre/Lilongwe). Participation in the study will last about 16 months.

PROCEDURES:

After you sign the informed consent and have had a chance to ask questions, you will have three study visits before you go into labor. At this first visit you will be asked about your health and any medications you have taken recently. You will be asked questions about your sexual history. Some people may be embarrassed by these questions. You may choose not to answer any of the questions if you wish. You will have a pelvic exam (an examination of your vagina) and will be tested for sexually transmitted diseases. You will have about 2 teaspoons of blood drawn for tests. If you do not have HIV, some of your blood will be stored for future approved studies. You will be given vitamins to take by mouth every day until delivery.

At this visit you will be assigned by chance (like the tossing of a coin) to take the antibiotic study drugs or placebo. A placebo is a pill that looks just like the study drug but has no medicine in it. One

woman of every two will receive antibiotic study drugs. One woman of every two will receive placebo. The study doctors and you will not know if you are taking the antibiotic study drug or placebo. Both groups of women, those assigned the antibiotic study drugs (metronidazole and erythromycin) and those assigned the placebo will take their pills by mouth three times a day for 7 days. You will be asked to bring your pill packs, even if they are empty, to your next study visit.

At your second visit, you will be asked questions about your health and any medications you have taken since the last visit. You will have a pelvic exam and will be tested for sexually transmitted diseases. Your pill packs given to you at the first visit will be collected from you. You will be given pill packs to take home with you for when you go into labor. If you decide to join this study, you must agree to deliver your baby at the study hospital/clinic.

At your third visit you will be asked about your health and any medications that you have taken since the last visit. You will have about 2 teaspoons of blood drawn for tests.

When you go into labor, you will again begin taking either antibiotic study drugs or placebo as assigned. Women assigned antibiotic study drugs (metronidazole and ampicillin) and those assigned placebo will take pills by mouth every four hours until the baby is delivered. You will return to the hospital to deliver your baby. Your pill packs will be collected from you and you will be asked about medications you have taken since your last visit. After delivery, your placenta and cord will be tested to see if you had an infection during delivery. A sample of your breast milk will be collected. If you have HIV, your breast milk will be stored for future tests for this study. If you do not have HIV, your milk will be discarded. Your baby will be weighed and examined. A few drops of blood will be collected from your baby's heel for tests. If you have HIV, your baby's blood will be tested for HIV. The results of your baby's HIV test will be given to you.

If you have HIV, you and your baby will be offered nevirapine. If you choose to accept the nevirapine for you and your baby, at the second visit you will be given one pill to take by mouth at the beginning of labor, in addition to the antibiotic study drugs. If you do not give birth to your baby within 48 hours of taking your nevirapine pill, you will be given another nevirapine pill to take. Your baby will receive one dose of nevirapine by mouth in a syrup after birth. If you do not want you or your baby to take nevirapine, you do not have to accept it. You and your baby can still be in the study even if you do not take nevirapine. At the end of this form you and your baby's father, if available, will sign or make your mark to indicate whether you want nevirapine for you and your baby.

If you do not want nevirapine for you and your baby, or if you do not have HIV, you will be given a placebo pill at the second visit to take when you go into labor, in addition to the antibiotic study drugs. This pill has no medicine in it. You do not have to accept this pill. You and your baby can still be in the study even if you do not take this pill.

After delivery, you will continue taking the antibiotic study drugs or placebo 3 times a day until you do not have any more drugs. You will bring your pill packs to your next clinic visit, even if they are empty.

You and your baby will return for about 5 study visits during the year after your baby is born. At each visit you will be asked questions about your health, your baby's health, and your breastfeeding

practices. At each visit some of your breast milk will be collected. If you have HIV, your milk will be stored for future tests in this study. If you do not have HIV, your milk will be discarded. During at least two of the visits your baby will have a heelstick to get a few drops of blood for tests. At the last study visit, your baby will have a small spoonful (1 ml) of blood drawn with a needle. If you have HIV, your baby's blood will be tested for HIV. The results of your baby's HIV test will be given to you. You may return to this clinic at any time during the study to see a study nurse or doctor if you or your baby is sick.

If something unexpected causes you to deliver somewhere besides this hospital, you will still be asked to continue study visits so that the research staff can gather more information which may be useful and important for future subjects. You will be asked to come to the hospital within 7 days after the birth of your baby so your baby can get the nevirapine, if you choose to accept it for your baby.

Some of your blood and placenta will be stored for later tests for this study. If you have HIV, some of your breast milk will be stored for later tests for this study. If you do not have HIV, some of your blood and your baby's blood will be stored for future approved studies. These future studies may be related to HIV, preterm birth, or causes of infant death. Your and your baby's name will not be linked to any of these samples. They will be identified by a code to protect your privacy.

You and your baby will receive all of your standard medical care as part of this study. You should tell your study nurse or doctor when taking any non-study medications or enrolling in other research studies.

All pills given to you should be kept at room temperature away from heat and light. If you miss a dose, take it as soon as possible unless it is almost time for the next dose. If it is almost time for the next dose, then skip the missed dose and go back to your regular dosing schedule. Do not take two doses at once.

RISKS and/or DISCOMFORTS:

All three antibiotics have been studied and used extensively in pregnant women. However, we want to let you know of possible but rare problems. Some women are allergic to the antibiotics. Allergic means you have a certain kind of reaction after taking the drug. A very small number of people who take each of these drugs have serious reactions. If you experience any of the following, you should stop taking the pills and contact the study clinic immediately: skin rash; vomiting; severe stomach cramping; tightness of chest; swelling of eyelids, face or lips; wheezing or difficulty breathing.

Rarely, people taking these antibiotics have numbness or tingling in their arms and legs, seizures, and other nervous disorders. If you experience any of these side effects, you should stop taking the pills and contact the study clinic immediately.

Some studies have shown that women who take metronidazole during pregnancy are more likely to deliver their baby too early. Some studies have shown that taking metronidazole has no effect on when a woman delivers her baby. Some studies have shown that women who take metronidazole during pregnancy are less likely to deliver their baby too early.

If the medicine upsets your stomach, take your erythromycin pill two times a day for 2-3 days. If the

medicine still upsets your stomach, take your erythromycin pill one time a day for 2-3 days. Continue taking your medicine until it is gone.

Do not drink alcohol while taking the pills. This may make you feel very sick. Wait for at least 3 days after you have stopped taking the pills to drink any alcohol.

Taking nevirapine may cause some side effects, which are listed below. This list includes the more serious or common side effects that may be related to taking nevirapine. If you have questions about these or other side effects, ask your study doctor or nurse. Possible side effects of nevirapine are:

- Rash, which has rarely been severe enough to require hospitalization and has been fatal
- Fever
- Headache
- Upset stomach (nausea)
- Swelling of the liver, which may rarely lead to severe and life-threatening liver damage, and very rarely fatal liver failure.

Since you and your baby will take only one dose of nevirapine, the risk of having these effects is much less likely. In a study conducted with about 600 babies who received one dose of nevirapine within 2-3 days after birth, no rashes related to nevirapine were seen. At the time you and your baby are discharged from the hospital, you will receive instructions on what to do if you see any rash on you or your baby. It is very important that you tell the study doctor or nurse right away about any rash.

Nevirapine has not been given with the antibiotics used in this study. We do not know if there will be an interaction between the nevirapine and study antibiotics.

There may be some more risks from taking non-study drugs with the study drugs. There may be risks to your baby from taking these drugs, but no risks are known at the moment.

Some women experience mild discomfort during a pelvic exam. Some people experience discomfort when blood is drawn and may feel dizzy or even faint. You may have a bruise or swelling where the needle goes into your arm.

POTENTIAL BENEFITS:

By taking part in this research study, you will receive vitamins to take during pregnancy that may help you and your baby. Being in this study may reduce the chance of having your baby too soon and may help the overall health of your baby, but no guarantee can be made. If you have HIV, taking part in this study may reduce the chance of your baby being infected with HIV, but no guarantee can be made. If you have HIV, you and your baby will be offered nevirapine. Taking nevirapine may reduce the chances of your baby being infected with HIV, but no guarantee can be made. You may receive no benefit from this study. However, knowledge gained from this study may help others in the future.

NEW FINDINGS:

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- a. the study doctor decides that continuing in the study would be harmful to you;
- b. the study is cancelled by the United States National Institutes of Health (NIH);
- c. the study is cancelled by the United States Food and Drug Administration;
- d. other administrative reasons;
- e. your baby's father objects to your baby being in the research study.

If you need a treatment not allowed on this study or you have a bad reaction to the study drugs, you will stop taking the study drugs, but you and your baby will be requested to continue to have follow-up study visits.

ALTERNATIVES TO PARTICIPATION:

There are no drugs widely available to women in Malawi to help prevent an HIV-positive mother from passing HIV to her baby.

If you do not participate in this study or withdraw from this study, you and your baby will receive standard medical care at this clinic/hospital.

Before you decide to take part in this study, your study clinician will give you information about the risks and any potential benefits of participating in this research study.

COSTS TO YOU:

There is no cost to you for participating in the study. All of your drugs and study visits are free.

CONFIDENTIALITY:

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study.

Your records may be reviewed by the National Institutes of Health, the U.S. agency that sponsors this research; the U.S. Food and Drug administration, the agency that reviews research; the pharmaceutical sponsors of this research and the study monitors.

RESEARCH-RELATED INJURY:

If you are injured as a result of participation in this study, the study clinic will give you immediate necessary treatment for your injuries. The cost of this treatment will not be charged to you. You will then be told where you may receive additional treatment for injuries. There is no compensation provided for research-related injuries.

NOTE: You are not giving up any of your legal rights by signing this informed consent document.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS:

If you ever have questions about this study or in case you are injured as a result of participation in this research study, you should contact (*name of local investigator or study clinician*) at (*telephone number or address*). If you ever have questions about your rights as a research subject you may call (*name and title of IRB member*) at (*telephone number or address*).

SIGNATURE PAGE

CONSENT TO JOIN THE STUDY

If you have read the informed consent or had it read and explained to you and understand the information, and you voluntarily agree to join this study, please sign your name or make your mark below.

Volunteer's name Volunteer's signature Date

Witness' name Witness' signature Date

If reasonably available:

Father's name Father's signature Date

CONSENT TO TAKE NEVIRAPINE (HIV POSITIVE PARTICIPANTS ONLY)

If you have read the informed consent or had it read and explained to you and understand the information, and you want to receive nevirapine for you and your baby, please sign or make your mark below.

Volunteer's name Volunteer's signature Date

Witness' name Witness' signature Date

If reasonably available:

Father's name Father's signature Date

APPENDIX III. ADVERSE EXPERIENCE REPORTING REQUIREMENTS

Adverse Experience Reporting Guidelines

These guidelines were compiled using the Code of Federal Regulations, the International Conference on Harmonization Guidelines, and from experience gained through previous reporting of adverse experiences and dialogue with the Regulatory Affairs Branch of the Division of AIDS. Procedures for reporting of SAEs are adapted from the DAIDS SAE Reporting Manual dated February 15, 1999.

1.0 Adverse Experience Definitions

The following definitions are compiled from 21 CFR 312.32(a) (*final rule effective April 6, 1998*) and the ICH (International Conference on Harmonisation) Technical Requirements for Registration of Pharmaceuticals for Human Use.

Adverse Experience (AE): Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

Serious Adverse Experience (SAE): A *serious* adverse experience is an adverse experience occurring at any dose that results in the any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, 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. Examples of such medical events include allergic brochospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization. *Note that the DAIDS SAE reporting procedures described here are based on a different, more inclusive definition of “serious adverse event”.*

Patient/Subject Identification: If an infant of an enrolled mother is not born alive, the patient is considered the mother and the adverse experience (e.g. stillbirth) should be reported as her experience. If the infant is born alive (even if s/he lives only very briefly), the infant is considered the patient and the adverse experience should be reported as the infant’s experience.

1.1 Adverse Experience Grading

Toxicity grades are assigned by the site to indicate the severity of Adverse Experiences. The DAIDS “Table for Grading Severity of Adverse Experiences” (Toxicity Table) can be found in Appendices IV and V. The Toxicity Table should be used by site clinicians to assign toxicity grades to all Adverse Experiences. For clinical events or laboratory abnormalities NOT identified in the Toxicity Table, refer to the specific “Guide for Estimating Severity Grade” within the Toxicity Table. There are five toxicity grades that can be assigned to an SAE, which are defined as follows:

- 1 = Mild

- 2 = Moderate
- 3 = Severe
- 4 = Life -threatening
- 5 = Death

2.0 Non-Serious Adverse Experiences

Non-serious Adverse Experiences in the mother between labor and the 4-6 week visit, regardless of relatedness or expectedness to the study product, must be documented on the Illness/Adverse Experience case report form.

All Adverse Experiences in infants, regardless of relatedness or expectedness to the study product, that occur between delivery and the 4-6 week visit must be documented on the Illness/Adverse Experience case report form.

Abnormalities at Baseline/Enrollment

For participants who enter a study with documented pre-existing abnormalities, an AE should be reported if:

- the severity increases a full grade level or more over baseline;
- the severity increases to a reportable level using the Guide for Estimating Severity from the DAIDS Toxicity Table;
- the participant's condition becomes serious, in the opinion of the clinician, due to the increasing severity of the abnormality.

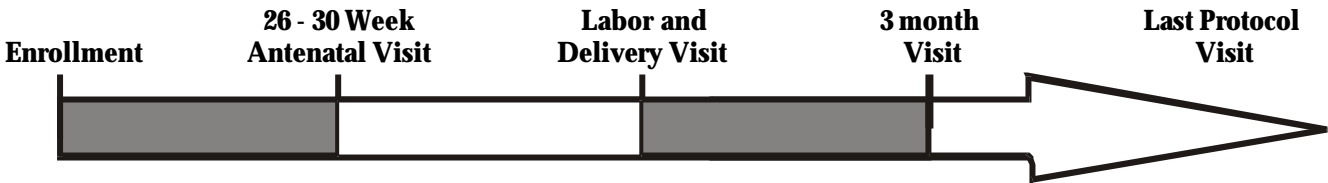
All pre-existing abnormalities should be recorded in the patient's medical chart.

Follow-up Information

A new Illness/Adverse Experience case report form is **not** required when submitting follow-up information for a previously reported AE. The existing case report form should be updated and resubmitted. Abnormal lab results for tests done to verify or further diagnose an AE that was previously reported should not be reported as a new AE. This information should be added to the comments section of the original case report form.

3.0 Serious Adverse Experiences

3.1 Occurring between enrollment and the 26-30 week visit or between labor and delivery and the 3 month visit



Reportable regardless of Relationship to Investigational Product

- Death, includes: neonatal deaths, regardless of whether the neonate was being followed as part of the protocol
- Cancer, includes: new onset and recurrent malignancies
- Congenital Anomaly/Birth Defect or Spontaneous Abortion, includes:
 - Congenital anomaly/birth defect occurring in a neonate/infant born to a mother who has received Investigational Product or
 - Spontaneous abortion occurring in a mother who has received Investigational Product
- Permanent Disability/Incapacity. A permanent disability/incapacity is defined as a substantial disruption of a person’s ability to conduct normal life functions.
- Immune Dysfunction, includes: autoimmune and immune deficiency diseases

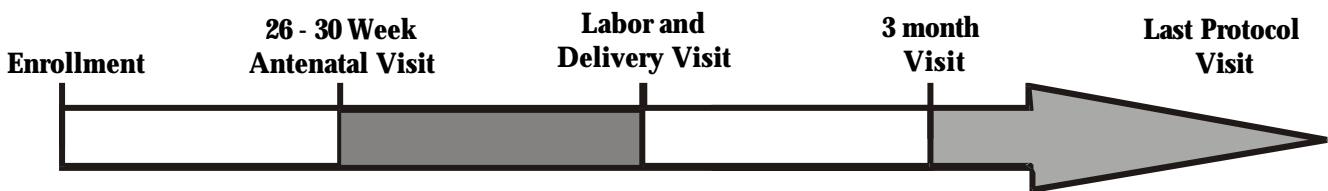
Submit SAE Form to FHI within 3 working days of site awareness. DEATHS assessed as definitely, probably, or possibly related: Notify FHI within 24 hours of site awareness and submit SAE Form within 3 working days of site awareness.

Reportable if relationship to Investigational Product is assessed as: definitely, probably or possibly related

- Recurrent event with new etiology or higher toxicity grade
- Grade 3 or 4 event not previously reported for this volunteer on this protocol.
- Grade 1 or 2 event considered unusual by the site investigator not previously reported for this volunteer on this protocol AND considered unusual by the site investigator.

Submit SAE Form to FHI within 3 working days of site awareness

3.2 Occurring between the 26-30 week antenatal visit and labor and delivery or after the 3 month visit



Reportable regardless of relationship to Investigational Product

- Immune Dysfunction, includes: autoimmune and immune deficiency diseases

Submit SAE Form to FHI within 3 working days of site awareness

Reportable if relationship to Investigational Product is assessed as:

definitely, probably, or possibly related

- Death, includes: neonatal deaths, regardless of whether the neonate was being followed as part of the protocol
- Cancer, includes: new onset and recurrent malignancies
- Congenital Anomaly/Birth Defect or Spontaneous Abortion, includes:
 - Congenital anomaly/birth defect occurring in a neonate/infant born to a mother who has received Investigational Product or
 - Spontaneous abortion occurring in a mother who has received Investigational Product
- Permanent Disability/Incapacity. A permanent disability/incapacity is defined as a substantial disruption of a person’s ability to conduct normal life functions.

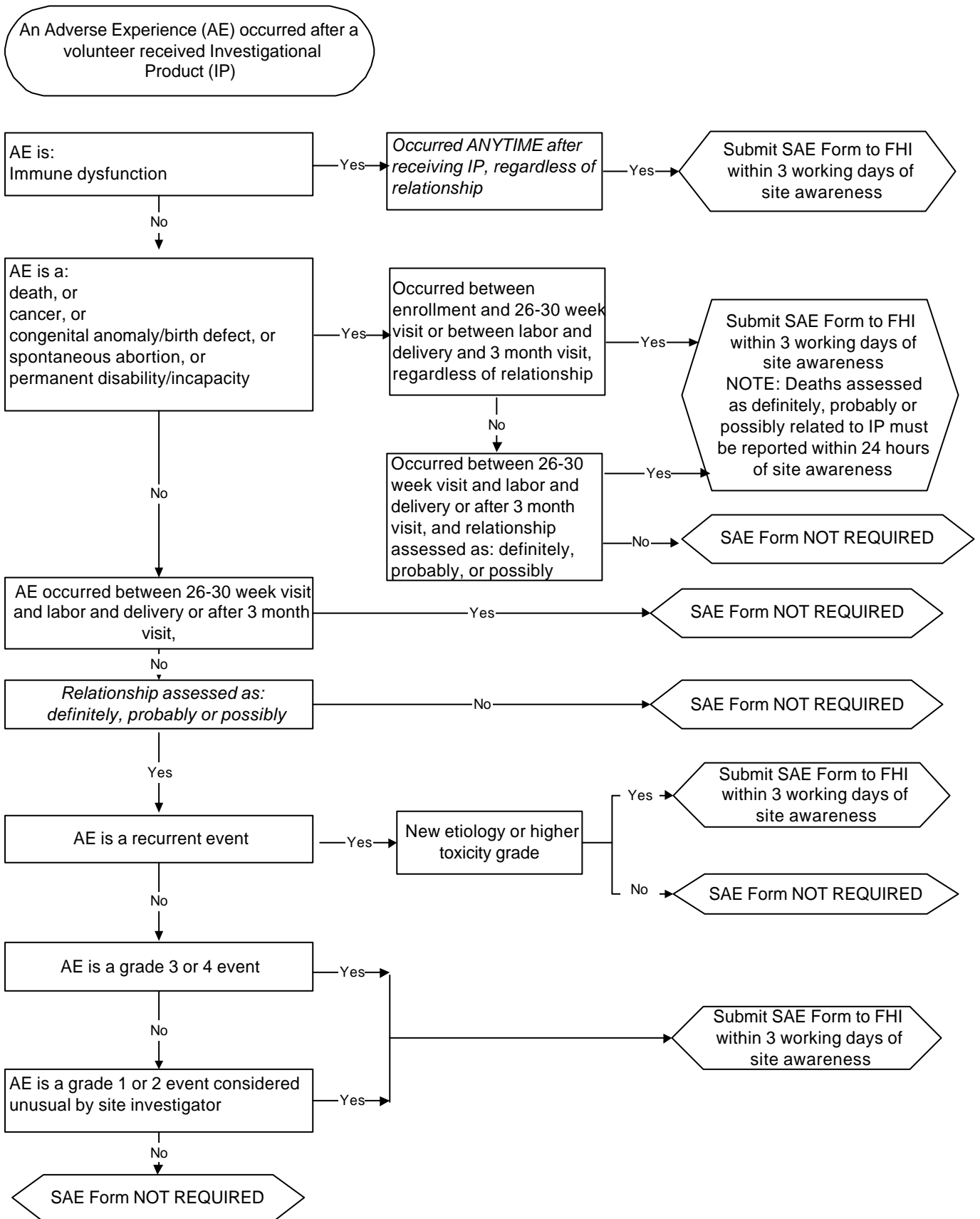
Submit SAE Form to FHI within 3 working days of site awareness

Table 8-1 summarizes reportable SAEs.

TABLE 8-1. REPORTABLE SAEs

EVENT	REPORT IF EVENT OCCURS	REPORT IF RELATIONSHIP TO INVESTIGATIONAL PRODUCT	REPORTING TIME FRAME
Death* (includes neonatal deaths) Cancer Congenital anomaly/Birth defect Spontaneous abortion Permanent disability/Incapacity	From Enrollment through the 26-30 week visit and from labor and delivery through the 3 month visit.	Definitely Probably Possibly Not related	Submit completed SAE Form to FHI Office within 3 working days of site awareness *Deaths assessed as definitely, probably or possibly related to Investigational Product must be reported to FHI within 24 hours of site awareness
	Between 26-30 week visit and labor and delivery or after 3 month visit	Definitely Probably Possibly	Submit completed SAE Form to FHI within 3 working days of site awareness
Immune dysfunction	ANYTIME after receiving Investigational Product during study follow-up	Definitely Probably Possibly Not related	Submit completed SAE Form to FHI within 3 working days of site awareness
Recurrent event with new etiology or higher toxicity grade Grade 3 or 4 event Grade 1 or 2 event considered unusual	From Enrollment through the 26-30 week visit and from labor and delivery through the 3 month visit.	Definitely Probably Possibly	Submit completed SAE Form to FHI within 3 working days of site awareness

IDENTIFYING REPORTABLE SAEs: NON-VACCINE PROTOCOLS



Adapted from DAIDS SAE Reporting Manual for Vaccine and Prevention Research Programs

3.3 Relationship Assessment

Relationship between a Serious Adverse Experience and an Investigational Product is determined by the site investigator or subinvestigator. In general, relationship is one of the main criteria used to determine the reportability of a Serious Adverse Experience to FHI. There are four relationship assessment categories:

- Definitely related
- Probably related
- Possibly related
- Not related

In some cases, events assessed by the site investigator as *Not related* to the Investigational Product are not reported on an SAE Form. However, such events must have an alternative, definitive etiology documented in the volunteer's medical record.

3.4 Follow-Up Information

In most cases, resolution or follow-up information pertaining to previously reported SAEs does not need to be reported to FHI as an Updated SAE Report.

For the circumstances listed below, or as requested by FHI, clinical sites are required to submit follow-up information as soon as it becomes available. Additional information may include copies of diagnostic test results, laboratory reports, or medical record progress notes. All additional information should be clearly marked as Update information and should include the Protocol Number and Volunteer ID Number.

SAEs that warrant MEDWATCH Forms

This form is used to report to the FDA and product manufacturers serious adverse experiences that are *unexpected and possibly, probably or definitely related* to FDA-approved drugs. For events that warrant a MEDWATCH Form, FHI may request additional and/or more detailed information from the site. It is important that sites obtain the requested follow-up information in a timely manner because FHI must submit MEDWATCH Forms to FDA within 15 calendar days of receiving an SAE Form. If the requested information will not be available within this 15-day time period, notify FHI as soon as possible.

SAEs that warrant FDA Safety Reports Forms

Safety Reports used to report to the FDA and product manufacturers serious adverse experiences that are *unexpected and possibly, probably or definitely related* for investigational drugs. For events that warrant a Safety Report, FHI may request additional and/or more detailed information from the site. It is important that sites obtain the requested follow-up information in a timely manner because FHI must submit a Safety Report to FDA within 15 calendar days of receiving an SAE Form. If the requested information will not be available within this 15-day time period, notify FHI as soon as possible.

Changes to Relationship Assessment

The clinical site obtains new information which *changes* the site investigator's assessment of the relationship between the event and Investigational Product.

Updated Death Information

The clinical site obtains new information from the Death Certificate or autopsy results after

an SAE Form is submitted. This pertains to deaths initially reported with limited or preliminary information

3.5 Recurrent Events

Serious Adverse Experiences (SAEs) recurring in the same volunteer on a particular protocol are only reportable to FHI under the following circumstances:

1. Recurrent episode is attributed to a NEW ETIOLOGY, or
2. Recurrent episode has progressed to a higher reportable toxicity grade level

3.6 Means Of Reporting Serious Adverse Experiences (SAEs)

Serious Adverse Experiences (SAEs) that meet reporting requirements must be reported on a Division of AIDS SERIOUS ADVERSE EXPERIENCE FORM. Completed forms should be submitted to FHI via FAX.

FHI Office Phone: 919-544-7040

FHI Office FAX: 919-544-0207

FHI Office Hours: Monday through Friday 8:00 am –5:00 pm (ET)

After Hours: Answering machine available

Mailing address: International Master Contractor
Family Health International
2224 E NC Highway 54
Durham, NC 27713

4.0 Documentation

The following documentation is described in the study specific Manual of Operations:

- Illness/Adverse Experience Form: this form is used to report AEs to the SC;
- SAE Form: this form is used to report SAEs to FHI;
- MEDWATCH FDA form 3500: this form is used to report to the FDA and product manufacturers serious adverse experiences that are unexpected and possibly, probably or definitely related to FDA-approved drugs;
- Safety Report: a safety Report is used to report to the FDA and product manufacturers serious adverse experiences that are unexpected and possibly, probably or definitely related to an investigational drug;
- Serious Adverse Experience Database: Family Health International will keep a database documenting all notifications of SAEs (AE number, date of occurrence, date identified, date notification was received by the Protocol Chair, and date the SAE was reported to FHI, DAIDS, RAB, the manufacturer and FDA). The data will be reconciled with study CRFs at a study monitoring visit.

APPENDIX IV. DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

Guidelines

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal
R_x = Therapy
Mod = Moderate
ADL = Activities of Daily Living

LLN = Lower Limit of Normal
Req = Required
IV = Intravenous
Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Table use the scale below to estimate grade of severity:

GRADE 1	Mild	Transient or mild discomfort (< 48 hours); no medical intervention/therapy required
GRADE 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 AE. Clinical events considered to be serious or life-threatening include, but are not limited to: **seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.**

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
HEMATOLOGY				
Hemoglobin	9.5 g/dL – 10.5 g/dL	8.0 g/dL – 9.4 g/dL	7.9 g/dL – 6.5 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1000 – 1500/mm ³	750 – 999/mm ³	500 – 749/mm ³	<500/mm ³
WBC	>13,000	>15,000	>20,000	>30,000 or <1,000
Percent Polys + Bands	>80%	90%	≥95%	-----
Platelets	100,000 – 120,000/mm ³	75,000 – 99,999/mm ³	50,000 – 74,999/mm ³	20,000 – 49,999/mm ³
CD4 Counts				
Uninfected	300 - 400/mm ³ <300 or <20%	<300/mm ³ <200 or <18%	<200/mm ³ <100 or <15%	<100/mm ³ <50 or <12%
Infected				
Fibrinogen	100-200 mg/dl OR 400-600 mg/dl	<100 mg/dl OR >600mg/dl	<50 mg/dl OR associated with gross bleeding OR associated with disseminated coagulation	-----
Prothrombin Time (PT)	>1.0 – 1.24 x ULN	>1.25 – 1.49 x ULN	>1.5 – 3.0 x ULN	>3.0 x ULN
PTT	>1.0 – 1.66 x ULN	>1.66 – 2.33 x ULN	>2.33 – 3.0 x ULN	>3.0 x ULN
CHEMISTRIES				
CPK	≥4 ULN	≥6 ULN	≥10 ULN	≥20 ULN
Creatinine	>1.0 – 1.5 x ULN	>1.5 – 1.9 x ULN	>2.0 – 6.0 x ULN	>6. x ULN
SODIUM				
Hyponatremia	130 – 135 meq/L 146 – 150 meq/L	123 – 129 meq/L 151 – 157 meq/L	116 – 122 meq/L 158 – 165 meq/L	<116 meq/L >165 meq/L
Hypernatremia				

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
POTASSIUM				
Hyperkalemia	5.0 – 5.5 meq/L	5.6 – 6.0 meq/L	6.1 – 6.5 meq/L	>6.6 meq/L
Hypokalemia	3.2 – 3.4 meq/L	3.0 – 3.1 meq/L	2.5 – 2.9 meq/L	<2.5 meq/L
PHOSPHATE				
Hypophosphalemia	2.0 – 2.4 mg/dL	1.5 – 1.9 mg/dL	1.0 – 1.4 mg/dL	<1.0 mg/dL
CALCIUM				
Hypocalcemia	7.8 – 8.4 mg/dL	7.0 – 7.7 mg/dL	6.1 – 6.9 mg/dL	<6.1 mg/dL
Hypercalcemia	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	>13.5 mg/dL
MAGNESIUM				
Hypomagnesemia	1.2 – 1.4 meq/L	0.9 – 1.1 meq/L	0.6 – 0.8 meq/L	<0.6 meq/L
BILIRUBIN				
Hyperbilirubinemia	>1.0 – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 – 5 x ULN	>5 x ULN
GLUCOSE				
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL
Hyperglycemia (nonfasting and no prior diabetes)	116 – 180 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL
Triglycerides	-----	400 – 750 mg/dL	751 – 1200 mg/dL	>1200 mg/dL
URIC ACID				
Hyperuricemia	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
LIVER TRANSAMINASE (LFTs)				
AST (SGOT)	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
GGT	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
Alk Phos	1.25 – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 10.0 x ULN	>10.0 x ULN
PANCREATIC ENZYMES				
Amylase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	5.0 x ULN
Pancreatic amylase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	5.0 x ULN
Lipase	>1.0 – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	5.0 x ULN
CARDIOVASCULAR				
Cardiac Arrhythmia	-----	Asymptomatic; dysrhythmia, no R _x req	transient Recurrent/persistent symptomatic R _x req	dysrhythmia; Unstable dysrhythmia; hospitalization and R _x req
Hypertension	Transient, increase >20 mm Hg diastolic BP, no R _x req.	Recurrent; chronic increase >20 mm Hg diastolic BP; R _x req.	Acute R _x req; outpatient hospitalization possible	OR Hospitalization req OR end organ damage
Hypotension	Transient orthostatic hypotension with heart rate increased by >20 beats/min OR decreased by <10 mm Hg systolic BP, no R _x req.	Symptoms OR BP decreased by <20 mm Hg systolic, correctable with oral fluid R _x .	IV fluid req. OR hospitalization	Mean arterial pressure <60 mm Hg. OR end organ damage, OR shock, vasopressor R _x req.
Pericarditis	Minimal effusion	Mild/mod asymptomatic effusion, no R _x .	Symptomatic effusion, pain, EKG changes.	Tamponade OR pericardiocentesis OR surgery req.
Hemorrhage, blood loss	-----	Mildly symptomatic no R _x req.	Gross blood loss OR 1-2 units transfused	Massive blood loss OR >2 units transfused.

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	<i>GRADE 1</i> MILD	<i>GRADE 2</i> MODERATE	<i>GRADE 3</i> SEVERE	<i>GRADE 4</i> POTENTIALLY <i>LIFE THREATENING</i>
GASTROINTESTINAL				
Nausea	Mild OR transient, reasonable intake maintained	Mod discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization req
Vomiting	Mild OR transient; 23 episodes per day OR mild vomiting lasting < 1 week	Mod OR persistent 45 episodes per day; OR vomiting lasting ≥ 1 week	Severe vomiting of all food/fluids in 24 hrs OR orthostatic hypotension OR IV Rx req.	Hypotensive shock OR hospitalization req. for IV Rx. req.
Diarrhea	Mild OR transient; 3-4 loose stools per day OR mild diarrhea lasting < 1 week	Mod OR persistent; 5-10 loose stools per day OR diarrhea lasting ≥ 1 week	> 10 loose stools/day, bloody diarrhea; OR orthostatic hypotension OR electrolyte imbalance, >2 L IV fluid required	Hypotensive shock OR severe electrolyte imbalance
Oral Discomfort/Dysphagia	Mild discomfort, no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids	Unable to drink fluids; IV fluids req.
Constipation		Moderate abdominal pain 78 hours with impaction require output prescription	Requiring disimpaction or hospital treatment	Distention with vomiting OR obstipation
RESPIRATORY				
Cough (for aerosol studies)	Transient, no Rx	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic Rx req.	-----
Bronchospasm Acute	Transient; no Rx ; FEV1 or peak flow reduced to 70%-80%	Rx req; normalizes with bronchodilator; FEV1 or peak flow 50%-60%	No normalization with bronchodilator; FEV1 or peak flow 25% - 49%, retractions	Cyanosis; FEV1 or peak flow <25% OR intubated
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O ₂ therapy

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
NEUROLOGIC				
Neuro-cerebellar	Slight incoordination dysdiadochokinesia	OR Intention tremor OR dysmetria OR slurred speech OR nystagmus	Ataxia requiring assistance to walk or arm incoordination interfering with ADLs	Unable to stand
Neuro-psych/mood	-----	-----	Severe mood changes requiring medical intervention; Suicidal ideation	Acute psychosis req hospitalization; Suicidal gesture/attempt
Paresthesia (burning, tingling, etc.)	Mild discomfort; no Rx req.	Mod discomfort; non-narcotic analgesia required	Severe discomfort; OR narcotic analgesia req with symptomatic improvement	Incapacitating; OR not responsive to narcotic analgesia
Neuro-motor	Mild weakness in muscle of feet but able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (unable to dorsiflex toes or foot drop, and mod proximal weakness e.g., in hands interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted	Confined to bed or wheel chair because of muscle weakness
Neuro-sensory	Mild impairment (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE THREATENING
MUSCULOSKELETAL				
Arthralgia/Arthritis	Arthralgia	Arthralgia with joint effusion or moderate impairment of activity	Frank arthritis with or without effusion OR resulting in severe impairment of activity	-----
Myalgia	Myalgia without limitation of activity	Muscle tenderness at other than injection site or with moderate impairment of activity	Frank myonecrosis OR with severe impairment of activity	-----
CUTANEOUS				
Rash/Dermatitis	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req surgery, exfoliative dermatitis
Local Reaction	Erythema OR induration <15 x 15 cm (225 cm ²)	Erythema, induration, or Edema >15 x 15 cm (225 cm ²)	Ulceration OR super infection OR phlebitis	Necrosis of the skin
URINALYSIS				
Proteinuria				
Random urine	1+	2 – 3+	4+	Nephrotic syndorme
24 hour urine	200 mg-1 g loss/day OR <0.3% OR <3 g/l	1 – 2 g loss/day OR 0.3 – 1.0% OR 3 – 10 g/l	2 – 3.5 g loss/day OR >1.0% OR >10 g/l	Nephrotic syndrome OR >3.5 g loss/day
Hematuria	Microscopic only ≤ 10 rbc/hpf	> 10 rbc/hpf	Gross, with or without clots OR RBC casts	Obstructive OR transfusion req

TABLE FOR GRADING SEVERITY OF ADULT ADVERSE EXPERIENCES

-continued-

PARAMETER	<i>GRADE 1 MILD</i>	<i>GRADE 2 MODERATE</i>	<i>GRADE 3 SEVERE</i>	<i>GRADE 4 POTENTIALLY LIFE THREATENING</i>
MISCELLANEOUS				
Fever Oral >12 hours	37.7 – 38.9C (100.0 – 101.5F)	39.0 –39.5C (101.6 – 102.9F) or max temp of 103F	39.6 – 40.5C (103 – 105F) or max temp of 103.5F	>40.5C (205F) or max temp >105F
Headache	Mild; no R _x req, OR non-narcotic analgesia R _x	Mod; OR responds to initial narcotic R _x	Severe; intractable; OR requiring repeated narcotic R _x	Requiring hospitalization, associated with neurologic, respiratory or cardiovascular abnormalities
Allergic Reaction	Pruritus without rash at injection site	Localized urticaria at injection site	Generalized urticaria angioedema	Anaphylaxis
ADL*	Normal activity reduced <48 hours	Normal activity reduced 25-50% >48 hours	Normal activity reduced >50%; cannot work > 48 hours	Unable to care for self
EYE		Mild pain, visual changes, conjunctival erythema, abnormal slit lamp	Loss of vision, clinically diagnosed uveitis, mod-severe pain, glaucoma	-----

* ADL = Activities of Daily Living

APPENDIX V. DIVISION OF AIDS TOXICITY TABLE FOR GRADING SEVERITY OF PEDIATRIC ADVERSE EXPERIENCES

**DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (≤ 3 MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs**

For other findings, the Toxicity Table for children >3 months of age (September 1993) is applicable.
Values are for term newborns

Preterm infants should be judged by a comparison of local normal ranges and the newborn ranges identified here.

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMATOLOGY				
Hemoglobin				
1-7 days old	13.0-14.0	12.0-12.9	<12	Cardiac Failure Secondary to Anemia
8-21 days old	12.0-13.0	10.0-11.9	<10.0	Cardiac Failure Secondary to Anemia
22-35 days old	9.5-10.5	8.0-9.4	<8.0	Cardiac Failure Secondary to Anemia
36-56 days old	8.5-9.4	7.0-8.4	<7.0	Cardiac Failure Secondary to Anemia
57-90 days old	9.0-9.9	7.0-8.9	<7.0	Cardiac Failure Secondary to Anemia
Abs Neutrophil Ct				
1 day old	5000-7000	3000-4999	1500-2999	<1500
2-7 days old	1750-2500	1250-1749	750-1249	<750
8-56 days old	1200-1800	900-1199	500-899	<500
57-90 days old	750-1200	400-749	250-399	<250
Bilirubin				
<7 days old		20-25	26-30	>30
7-60 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
61-90 days old	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
Creatinine				
<7 days old	1.0-1.7	1.8-2.4	2.5-3.0	>3.0
7-60 days old	0.5-0.9	1.0-1.4	1.5-2.0	>2.0
61-90 days old	0.6-0.8	0.9-1.1	1.2-1.5	>1.5
Cr Clearance				
<7 days old	35-40	30-34	25-29	<25
7-60 days old	45-50	40-44	35-39	<35
61-90 days old	60-75	50-59	35-49	<35
Low Calcium				
<7 days old	6.5-6.9	6.0-6.4	5.5-5.9	<5.5
7-60 days old	7.6-8.0	7.0-7.5	6.0-6.9	<6.0
61-90 days old	7.8-8.4	7.0-7.7	6.0-6.9	<6.0
High Calcium				
<7 days old	12.0-12.4	12.5-12.9	13.0-13.5	>13.5
7-60 days old	10.5-11.2	11.3-11.9	12.0-13.0	>13.0
61-90 days old	10.5-11.2	11.3-11.9	12.0-12.9	≥ 13.0

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (>3 MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
HEMATOLOGY				
Hemoglobin >3 mo to <2 y.o.	9.0-9.9	7.0-8.9	<7.0	Cardiac Failure Secondary to anemia
Hemoglobin ≥2 y.o.	10-10.9	7.0-9.9	<7.0	Cardiac Failure Secondary to anemia
Abs Neutrophil Ct	750-1200	400-749	250-399	<250
Platelets		50,000-75,000	25,000-49,999	<25,000 or bleeding
PT	1.1-1.25xN	1.26-1.5xN	1.51-3.0xN	>3xN
PTT	1.1-1.66xN	1.67-2.33xN	2.34-3.0xN	>3xN
GASTROINTESTINAL				
Bilirubin	1.1-1.9xN	2.0-2.9xN	3.0-7.5xN	>7.5xN
AST (SGOT)	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
ALT (SGPT)	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
GGT	1.1-4.9xN	5.0-9.9xN	10.0-15.0xN	>15.0xN
Pancreatic Amylase	1.1-1.4xN	1.5-1.9xN	2.0-3.0xN	>3.0xN
Total Amylase + Lipase*	1.1-1.4xN	1.5-2.4xN	2.5-5.0xN	>5.0xN
Uric Acid	7.5-9.9	10-12.4	12.5-15.0	>15.0 or Gout
CPK	See Neuromuscular Toxicity			
Abdominal Pain	Mild	Moderate- No Rx Needed	Moderate Rx Needed	Severe- Hospital and Rx
Diarrhea	Soft stools	Liquid stools	Liquid Stools and Mild Dehydration Bloody stools	Dehydration requiring IV therapy or Hypotensive Shock
Constipation	Mild	Moderate	Severe	Distention and Vomiting
Nausea	Mild	Moderate- Decreased po intake	Severe- Little po intake	Unable to ingest food or fluid for >24 hours
Vomiting	<1 episode/day	1-3 episodes/day or duration>3d	>3 episodes/day or duration>7d	Intractable Vomiting

*Both amylase and lipase must be elevated to the same grade or higher (i.e. if total amylase is Grade 4, but lipase is only Grade 1, the Toxicity Grade is 1.) In pediatric HIV patients, the most common source of serum amylase is the salivary glands. Salivary amylase elevations are generally not clinically significant. When amylase is released from damaged pancreatic cells, it can be a marker of pancreatitis. In most cases of clinical pancreatitis, lipase will also be elevated. However, lipase is also a non-specific marker. Combined elevation of amylase and lipase (each >5 x normal) often indicates pancreatic disease and requires evaluation. However, in the absence of pancreatic disease, drug can be resumed even at Grade 3 and 4 toxicities.

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (>3 MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs
-continued-

PARAMETER	GRADE 1	GRADE 2	GRADE 3	GRADE 4
RENAL AND ELECTROLYTES				
CREATININE				
2 Months-2 Years	0.6-0.8	0.9-1.1	1.2-1.5	>1.5
2 Years-Adolescent	0.7-1.0	1.1-1.6	1.7-2.0	>2.0
Adolescents	1.0-1.7	1.8-2.4	2.5-3.5	>3.5
Creatinine Clearance	60-75cc/min/1.73 m ²	50-59 cc/min/1.73 m ²	35-49 cc/min/1.73 m ²	<35 cc/min/1.73 m ²
ELECTROLYTES				
High Sodium	145-149		150-155	>155 or mental status changes
Low Sodium	130-135		129-124	<124 or mental status changes
High Potassium	5.0-5.9	6.0-6.4	6.5-7.0	>7.0 or Cardiac arrythmias
Low Potassium	3.0-3.5	25-2.9	2.0-2.4	<2.0
High Calcium	10.5-11.2	11.3-11.9	12.0-12.9	≥ 13.0
Low Calcium	7.8-8.4	7.0-7.7	6.0-6.9	<6.0
Low Magnesium	1.2-1.4	0.9-1.1	0.6-0.8	<0.6 or Cardiac arrhythmias
Hypoglycemia	55-65	40-54	30-39	<30 or Mental status changes
Hyperglycemia	116-159	160-249	250-400	>400 or Ketoacidosis
Proteinuria	Tr-1 + <150 mg/day	2+ 150-499 mg/day	3+ 500-1000 mg/day	4+ or nephrotic syndrome >1000 mg/day
Hematuria	Microscopic <25 cells/hpf	Microscopic ≥ 25 cells/hpf	Gross	Obstruction or Transfusion requirement
Comments Calcium values are corrected for albumin concentration. CrCl values do not apply to infants <2 months old.				
OTHER				
Allergy	Pruritis without Rash	Pruritic Rash	Mild Urticaria	Severe urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal)		38.5-40	>40	Sustained Fever: >40, >5 days
Cutaneous		Diffuse maculopapular rash, dry desquamation	Vesiculation, ulcers	Exfoliative dermatitis, Stevens-Johnson or Erythema multiforme, Moist desquamation
Stomatitis	Mild discomfort	Painful; difficulty swallowing, but able to eat and drink	Painful; unable to swallow solids	Painful; requires IV

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (> 3MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs
-continued-

SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
CENTRAL NERVOUS SYSTEM				
Seizures	None	1 Uncomplicated Sz +/- Temp Elevation	1 Sz/Month for ≥2 consecutive Months Or 3 Sz over 6 Months; No Temp Elevation	>1 Sz/ Month; No Temp elevation; No Decrease in Sz Frequency Despite dose reduction
Seizures are an ubiquitous symptom of numerous systemic or CNS disturbances; alternative explanations should be vigorously sought and eliminated. Status epilepticus represents a severe end of the seizure spectrum, but should be considered as a single seizure event. The need for chronic or acute anticonvulsant medication should be made on a clinical basis. Seizures as a manifestation of drug toxicity are usually primarily generalized. Focal (partial onset) seizures are suggestive of focal central nervous system pathology and should be appropriately investigated, although they may be a manifestation of drug toxicity. Beware of focal seizures which secondarily generalize; these should be approached diagnostically as partial onset seizures. Children with underlying epileptic conditions who experience persistent breakthrough seizures despite maximal anticonvulsant therapy coincident with beginning the trial medication should be considered Grade 4.				
Headache	≤1/Month <2hrs duration	>1/Month >2 hrs duration Moderate to Severe Responds to non-narcotic analgesia or prophylaxis	>2/Month >2hrs duration Moderate to Severe Responds to narcotic analgesia, or does not respond to prophylaxis	>4/Month; >2hrs Duration; Moderate to Severe; Non-Responsive to narcotic Analgesia; or persistently Recurrent despite prophylaxis No decrease in frequency or Severity despite dose reduction
Headache is a non-specific symptom, but may be a symptom of CNS/intracranial pathology. Appropriate diagnostic measures should be pursued. Duration refers to the waxing and peak phases, not to the resolution/waning phases of the headache. Mild refers to a grade of headache pain which does not affect function or activity. Moderate to severe refers to a grade of headache which affects function or activity.				
Mental Status and Behavior	Changes which do not Affect Function	Changes requiring pharmacologic or other therapy; or mild lethargy, sedation or somnolence which resolves with rest	Changes not improved by drugs or other therapies; or onset of convulsion, memory impairment, lethargy, sedation, or somnolence which does not respond to rest	Onset of delirium, obtundation, coma, or psychosis, or Grade 3 toxicity which does not respond to dose reduction
Behavior refers to the development of attention deficits with or without hyperactivity, depression, mania, agitation, sleep disorders, phobias, obsessive-compulsive behaviors, or anxiety. Mental status refers to the level of consciousness, memory function, language and analytical operation, and non-dominant hemisphere functioning. Alternative explanations should be sought.				
Balance and Posture	None	None	Ataxia, dizziness, vertigo, tremor, impaired postural balance	Onset of movement disorder; or Grade 3 toxicity which does not respond to dosage adjustment
"Ataxia" can be mistakenly diagnosed in the face of central weakness or peripheral neuropathy, which should not be considered a drug toxicity of this category. Movement disorders refer to tardive or other dyskinesias, dystonias, chorea, or ballismus. Alternative explanations should be sought.				

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (> 3MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs
-continued-

SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Visual	None	Blurriness, diplopia, or horizontal nystagmus of <1 hour duration, with spontaneous resolution	≥1 episode of Grade 2 symptoms per week, or an episode of Grade 2 Sx lasting 1hour with spontaneous resolution by 4 hours or vertical nystagmus	Decrease in visual acuity, visual field deficit, or oculogyric crisis, or Grade 3 Sx which persist after dose reduction
Many of the symptoms in this category can be the result of CNS pathology, or alternatively can be an external (i.e., non-CNS) neuro-ophthalmologic disorder. Appropriate diagnostic investigations should be pursued.				
Myelopathy	None	None	None	Myelopathic/spinal cord symptoms, such as : Pyramidal tract weakness and disinhibition sensory level, loss of proprioception, bladder/bowel dysfunction
HIV can cause spinal cord syndromes rarely in children. Other infectious agents can cause myelopathies as well. Alternative explanations should be sought				
PERIPHERAL NERVOUS SYSTEM				
Neuropathy/Lower Motor Neuropathy	None	Mild transient Paresthesia only	Persistent or progressive paresthesias, burning sensation in feet, or mild dysesthesia; no weakness; mild to moderate deep tendon reflex changes; no sensory loss	Onset of significant weakness, decrease or loss of DTRs, sensory loss in “stocking glove” distribution, radicular sensory loss, multiple cranial nerve involvement; bladder or bowel dysfunction, fasciculations, respiratory embarrassment from chest wall weakness. Grade 3 symptoms which do not resolve with dose reduction
Infectious agents other than HIV can precipitate a neuropathy and should be considered, especially CMV. Neuropathies which do not resolve after dose reduction or discontinuation should be pursued for alternative infectious or non-infectious etiologies, since drug-related neuropathies will usually resolve after dose reduction or drug discontinuation. It should be borne in mind that many subjects will worsen for up to one month after drug discontinuation prior to improvement (“coasting”). Abnormalities should be confirmed by nerve conduction studies (NCS) +/- electromyographic studies (EMG).				
Myopathy or Neuromuscular Junction Impairment	Normal or mild (<2xN) CPK elevation	Mild proximal weakness and/or atrophy not affecting gross motor function. Mild myalgias, +/- mild CPK elevation(<2xN)	Proximal muscle weakness and/or atrophy affecting motor function +/-CPK elevation; or severe myalgias with CPK elevation; or severe myalgias with CPK >2 x N; Consider confirmatory EMG and/or muscle bx	Onset of myasthenia-like symptoms (fatigable weakness with external, variable ophthalmoplegia and/or ptosis), or neuromuscular junction blockade (acute paralysis) symptoms(confirm with EMG); or Grade 3 symptoms which do not resolve on dose adjustment; confirm with muscle bx
HIV can produce a myopathy, and should be differentiated. Drug-induced myopathy can be accompanied by normal CPK levels. On occasion neuropathic or central weakness can mimic myopathic weakness.				

DIVISION OF AIDS (DAIDS)
TABLE FOR GRADING SEVERITY OF
PEDIATRIC (> 3MONTHS OF AGE) ADVERSE EXPERIENCES
For
Vaccine & Prevention Research Programs
-continued-

SYMPTOM	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Clinical symptoms <i>not otherwise specified</i> in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values <i>not otherwise specified</i> in this table	Abnormal, but requiring no immediate intervention; follow	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity. Requires immediate evaluation, treatment, and usually hospitalization. Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug.

NEVIRAPINE TOXICITY: SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EXPERIENCES

USE THIS APPENDIX FOR GRADING CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EXPERIENCES

GRADE 1	GRADE 2	GRADE 3*	GRADE 4*
CUTANEOUS/SKIN RASH/DERMATITIS			
Erythema, with or without pruritis	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritis; OR typical target lesions without blistering, vesicles, or ulcerations in the lesions.</p> <p>B. Urticaria</p>	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to study drug:</p> <ol style="list-style-type: none"> 1. 5 x ULN AST, ALT or 2 x baseline if baseline > ULN. 2. fever, >39°C 3. blistering and/or vesiculation of cutaneous eruptions 4. any site of mucosal lesions; OR <p>B. angioedema; OR</p> <p>C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR</p> <p>D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, new lymphadenopathy, edema, myalgia, and/or arthralgia; OR</p> <p>E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following:</p> <ol style="list-style-type: none"> 1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (<10% body surface area), (Nikolski's sign)(Stevens Johnson Syndrome, SJS) 2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause. 	Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (>10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)
*When a Grade 3 or 4 cutaneous/skin rash/dermatitis adverse experience is suspected, a Dermatology consult for photographs and biopsies is required.			