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A PHASE IV RANDOMIZED TRIAL TO EVALUATE THE VIROLOGIC RESPONSE AND PHARMACOKINETICS OF TWO DIFFERENT POTENT REGIMENS IN HIV INFECTED WOMEN INITIATING TRIPLE ANTIRETROVIRAL REGIMENS BETWEEN 28 AND 36 WEEKS OF PREGNANCY FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION: NICHD P1081

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The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
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NICHD P1081 PROTOCOL TEAM ROSTER

- Protocol registration materials should be submitted via the Division of AIDS (DAIDS) Protocol Registration System (DPRS): https://daidses.niaid.nih.gov/protocolregistration or can be sent via email to epr@tech-res.com.

- General questions concerning this protocol should be sent via email to the full P1081 protocol team at NICHD.teamp1081@fstrf.org.

- Questions concerning clinical management of study participants and all communication regarding adverse experiences should be addressed to the P1081 Clinical Management Committee (CMC) at NICHD.p1081cmc@fstrf.org. Remember to include the participant's Patient Identification Number (PID) when applicable. Please do NOT disclose the study arm to which a participant is randomized unless specifically requested. The appropriate team member will respond to questions via email. A response should generally be received within 24 hours (Monday - Friday).

- For randomization or enrollment (Subject Enrollment System (SES)) screen questions, contact the Data Management Center (DMC) at 1-716-834-0900 x7301 or by email to rando.support@fstrf.org.

- For computer and data entry (eData) screen problems email user.support@fstrf.org or call the DMC at 1-716-834-0900 x7302.

- To order study agent, call the Clinical Research Products Management Center at (301) 294-0741. For questions or problems regarding study drug supplies, records, and returns, contact the DAIDS Protocol Pharmacist at lpurdue@niaid.nih.gov.

- For Expedited Adverse Event (EAE) questions, contact the DAIDS Regulatory Support Center (RSC) Safety Office via email at RSCSafetyOffice@tech-res.com; by telephone (1-800-537-9979 or 1-301-537-1709); or by fax (1-800-275-7619 or 1-301-897-1710).

- For questions about the DAIDS Adverse Experience Reporting System (DAERS), email DAIDS-ESSupport@niaid.nih.gov. Questions may also be sent within the DAERS application.

- Email the Computer Support Group (user.support@fstrf.org) at the DMC to have relevant site personnel added to the protocol email group NICHD.protp1081@fstrf.org. Inclusion in the protocol email group will ensure that sites receive important information about the study during its implementation and conduct.

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LIST OF COMMONLY USED ABBREVIATIONS

3TC	Lamivudine
ACTG	Adult AIDS Clinical Trials Group
AE	Adverse Event
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASQ	Ages and Stages Questionnaire
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BID	Twice daily
BRIEF	Behavior Rating Inventory of Executive Functioning
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
CRF	Case Report Form
CVL	Cervical-vaginal Lavage
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS, NIAID
DDST	Denver Developmental Screening Test
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
DPRS	DAIDS Protocol Registration System
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EFV	Efavirenz (Sustiva, Stocrin)
FDA	Food and Drug Administration
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
II	Integrase Inhibitor
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
INSTI	Integrase Strand Transfer Inhibitors
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LDMS	Laboratory Data Management System
MIRIAD	Mother-Infant Rapid Intervention at Delivery
MTCT	Mother-to-Child Transmission

NIAID	National Institute of Allergy and Infectious Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NONMEM	NONlinear Mixed-Effect Modeling
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OCTANE	Optimal Combination Therapy after Nevirapine Exposure
OHRP	Office for Human Research Protections
OR	Odds Ratio
PD	Pharmacodynamic
PCR	Polymerase Chain Reaction
PI	Protease inhibitor
PID	Patient Identification Number
PK	Pharmacokinetic(s)
PMTCT	Prevention of Mother-to-Child Transmission
PRO	Protocol Registration Office
QHS	Every night
RAL	Raltegravir, Isentress
RE	Regulatory Entity
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SES	Subject Enrollment System
TB	Tuberculosis
TNA	Total Nucleic Acid
TQQ	Ten Questions Questionnaire
UGT	UDP-glucuronosyltransferase
US	United States
VQA	Virology Quality Assurance
WHO	World Health Organization
WITS	Women and Infants Transmission Study
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, Third Edition
ZDV	Zidovudine, Retrovir

SCHEMA

A PHASE IV RANDOMIZED TRIAL TO EVALUATE THE VIROLOGIC RESPONSE AND PHARMACOKINETICS OF TWO DIFFERENT POTENT REGIMENS IN HIV INFECTED WOMEN INITIATING TRIPLE ANTIRETROVIRAL REGIMENS BETWEEN 28 AND 36 WEEKS OF PREGNANCY FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION: NICHD P1081

DESIGN: Multicenter two arm randomized open-label trial comparing the ability to achieve virologic suppression at delivery, tolerability, and safety.

SAMPLE SIZE: 334 evaluable mother-infant pairs (approximately 167 per arm), which is projected to require enrolling approximately 394 mother-infant pairs.

POPULATION: Human Immunodeficiency Virus (HIV)-1 infected pregnant women with a gestational age between 28 and 36 weeks who are antiretroviral (ARV) naïve or have received short-course zidovudine (maximum of 8 weeks) only for prevention of mother-to-child transmission (PMTCT) in previous pregnancies, and their infants.

STRATIFY BY: Gestational age at enrollment (28-30 weeks or 31-33 weeks or 34-36 weeks) and whether the women will use lamivudine/zidovudine or an alternative, locally supplied nucleoside reverse transcriptase inhibitor (NRTI) backbone.

REGIMEN: Antepartum – Participants will be randomized 1:1

Arm A: Lamivudine 150 mg/zidovudine 300 mg* twice daily (BID) + efavirenz 600 mg every night (QHS).

Arm B: Lamivudine 150 mg/zidovudine 300 mg* BID + raltegravir 400 mg BID.

*Alternative, locally supplied NRTI backbone may be used in place of lamivudine/zidovudine with permission of protocol team obtained prior to randomization.

Active labor:
All participants will continue to receive study drugs during labor. In addition, in place of the oral fixed dose combination of lamivudine 150 mg/zidovudine 300 mg (or alternative NRTI backbone), participants may receive intravenous zidovudine, other dosing regimens of oral zidovudine, oral lamivudine and/or additional drugs during labor, according to local standard of care/guidelines.

Infants:
Infants will receive ARV according to specific local guidelines.

TREATMENT DURATION: All women will receive their randomized study regimen from study entry through delivery. Women who meet local guidelines for receiving antiretroviral therapy (ART) will continue triple ART after delivery according to local guidelines. These women can receive study supplied drugs for up to 8 weeks after delivery to facilitate the transition to local standard of care for treatment for maternal health and/or prevention of breast milk transmission. Women who do not meet local guidelines for receiving triple ART will stop study supplied drugs immediately after delivery. Women randomized to Arm A (efavirenz) may continue lamivudine/ zidovudine for a period of time after stopping efavirenz at the discretion of the local investigator.

STUDY DURATION: Women will be followed for 6 months after delivery. Infants will be followed until 6 months of age and may participate in an extension phase: developmental assessment of infants, lasting up to 4 years of age.

OBJECTIVES:

Primary Objectives:

1. To compare the ability of two triple ARV regimens (one containing efavirenz and the other raltegravir) begun during the third trimester of pregnancy to achieve a viral load of < 200 copies/mL at the time of delivery.
2. To compare the safety and tolerability of two triple ARV regimens (one containing efavirenz and the other raltegravir) begun during the third trimester of pregnancy.

Secondary Objectives:

1. To compare the kinetics of viral decay between the treatment regimens:
   a. Compare decay of plasma and vaginal HIV-1 RNA and DNA between the treatment regimens.
   b. Compare decay of plasma HIV-1 infectivity between the treatment regimens.
2. To compare infant outcomes including stillbirth, premature birth, low birth weight, perinatal HIV transmission, neurodevelopmental outcomes and to compare (in HIV-infected infants) drug resistance between the two treatment regimens.
3. To assess the baseline prevalence and selection of HIV-1 drug-resistance to the study drugs, using standard genotyping and ultrasensitive genotyping methods.

Exploratory Objectives:

1. To describe the population pharmacokinetic (PK) parameters of efavirenz and raltegravir during the third trimester of pregnancy and postpartum using sparse sampling and to evaluate potential relationships between PK parameters, pharmacogenomics and viral load changes.

2. To describe the maternal vaginal and infant nasopharyngeal and oropharyngeal microbiome environment and the potential association with adverse outcome in HIV exposed uninfected children.

1.0 INTRODUCTION

1.1 Background

The current PMTCT strategies based on the use of triple ARV regimens after the first trimester through labor, appropriate management of delivery, and avoidance of breastfeeding have been successful in lowering the rates of HIV perinatal transmission to less than 2%.[1,2,3,4] Results of clinical trials for PMTCT suggest that women receiving triple ARV regimens that effectively reduce HIV-1 Ribonucleic Acid (RNA) to <1,000 copies/mL or undetectable levels are associated with significantly lower risk of perinatal HIV-1 transmission.[5,6,7,8] Townsend [9] published data from a study in a cohort of HIV-infected pregnant women from the United Kingdom and Ireland in which the transmission rate was only 0.1% in 2,117 pregnant women on triple ARV regimens who achieved viral suppression. Also, there was evidence that being on a triple ARV regimen at conception and starting a triple ARV regimen earlier in pregnancy were associated with a lower risk of transmission after adjusting for viral load. This strategy is strongly dependent on early access to prenatal care and availability of ARVs for PMTCT with viral suppression and appropriate approach of mode of delivery.

A considerable number of pregnant women enter into prenatal care after the 28th week of gestation even in developed countries. Approximately one quarter of HIV-infected persons in the United States (US) are unaware that they are infected.[10] The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study, which was a prospective, multicenter study funded by the Centers for Disease Control and Prevention, offered voluntary, rapid HIV testing to women with undocumented HIV status late in pregnancy. Among 7,753 women with available test results from 17 US hospitals, 52 (0.7%) were HIV-infected.[11] Brazilian data published in 2007 from a cohort of HIV-infected pregnant women at a public hospital showed that the mean gestational age of initiation of prenatal care was 24 ± 8 weeks of gestation.[3]

Also, some pregnant women seroconvert late during pregnancy.[12] A Brazilian study addressing primary HIV-1 infection during pregnancy showed an incidence of HIV-1 seroconversion of 0.8/1,000 (CI 95% 0.4-1.5/1,000).[13] These women are more likely to transmit infection to their newborn, as plasma viral loads directly correlate with the risk of mother-to-child transmission (MTCT) of HIV-1. Decay dynamics of HIV-1 depend on the inhibited stage of the viral life cycle and are used as a measure of the effectiveness of ARV drugs and drug regimens.[14,15,16] Rapid reduction in viral load may be critical in minimizing both transplacental and intrapartum transmission of HIV-1 to the infant if ARV treatment is initiated late in pregnancy.

1.2 Study Rationale

Much virologic, immunologic and tolerability data derived from prospective clinical trials have shown the efficacy of various combinations of ARVs to treat HIV-1 infection. Most of these studies were done in HIV-infected adults with the primary efficacy outcomes based on the decline of plasma viral load within the first 24-48 weeks of starting therapy and on the durability of the virologic response, as well as changes in Cluster of Differentiation 4 (CD4)+ T-cell counts after 48 weeks of therapy. [17,18,19,20,21] Suppressive ARV regimens containing the Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) efavirenz have been extensively studied in non-pregnant adults, demonstrating rapid reduction in plasma HIV viral load.[22,23] ARVs in the newest class to be approved, integrase inhibitors (IIs), have proven to be very potent in pre-clinical, and phase II and III clinical studies in adult participants, are generally well tolerated, and demonstrate strong efficacy with rapid reduction in plasma viral load in both treatment-naïve and treatment-experienced participants. [21,24,25,26,27] HIV-infected pregnant women presenting for care late in pregnancy need a rapid response and effective ART in order to minimize the risk of HIV transmission to their newborn. No data are available comparing the effects of NNRTIs and IIs in pregnant women. The goal of this protocol is to compare the safety, tolerance, virologic and pharmacologic responses of representatives of these two ARV classes in HIV-infected pregnant women presenting late for care.

1.3 Study Drugs

1.3.1 Efavirenz (Sustiva®, Stocrin®)

Efavirenz (Sustiva®, Stocrin®) is an NNRTI currently recommended as a first line agent for use in HIV-infected adults. *In vitro* studies show that efavirenz is an NNRTI that "tight-binds" in a nearly irreversible manner to the reverse transcriptase enzyme to make cell-free virions non-infectious. This property of efavirenz may rapidly reduce the infectivity of virions in maternal plasma, and thus reduce the risk of transmission to the infant during the decay phase of plasma viremia.

In a preclinical developmental toxicology study, severe fetal malformations (anencephaly, anophthalmia, microophthalmia, cleft palate) were observed in 3 of 20 cynomolgus monkeys exposed to efavirenz throughout pregnancy. This led to an initial recommendation that efavirenz use should be avoided during the first trimester of pregnancy.[28,29,30,31] However a recent review of human data on safety of efavirenz use in pregnancy found no increased risk of overall or central nervous system congenital anomalies with first-trimester exposure to efavirenz, and current World Health Organization (WHO) recommendations include use of efavirenz as first line therapy during pregnancy.[32] Furthermore, efavirenz is also recommended as an

important alternative for HIV/tuberculosis (TB) co-infected pregnant women.

Efavirenz PK data are available from P1026s for 25 women who received standard efavirenz doses of 600 mg once a day during the third trimester of pregnancy and again postpartum.[33] Median (range) efavirenz area under the curve (AUC) during the third trimester was not different from postpartum (55.4 (13.5-220.3) µg*hr/mL vs. 58.3 (22.7-214.4 µg*hr/mL)), while 24 hour trough concentration (C24h) was significantly lower (1.60 (0.23-8.13 µg/mL vs. 2.05 (0.31-8.43) µg/mL, $p<0.05$)). Efavirenz C24h exceeded the target of 1.0 µg/mL in 22 of 25 participants (88%) during the third trimester and 23 of 25 (92%) postpartum. These data suggest that standard efavirenz dosing of 600 mg once a day is appropriate for use in this protocol.[33]

1.3.2 Raltegravir (Isentress®)

Raltegravir (Isentress®) is an HIV-1 II with potent *in vitro* activity against HIV-1 strains including those resistant to currently available ARV drugs and has synergistic *in vitro* activity with currently available ARV drugs. Recent studies have highlighted differences in the first two phases of decay in plasma viremia with II-based therapy in which the first phase is slightly faster than that seen with standard NNRTI-based ART. Furthermore, II-based highly active antiretroviral therapy (HAART) also affects the dynamics of plasma viremia during the second phase of ART by reducing the viremia derived from chronically-infected cells. These unique properties of II-based ART may be highly desirable for pregnant women receiving ART aimed at decreasing MTCT.[34]

Raltegravir PK in non-pregnant adults is characterized by rapid oral absorption (T_{max} of around 3 hours) and a terminal half-life of around 9 hours. Geometric mean PK parameters with chronic dosing of 400 mg twice a day are $AUC_{0\text{-}12hr}$ of 14.2 uM*hr [90% confidence interval (CI) 8.3 25.8] and C_{12hr} of 142 nM [90% CI 88 229].[25] Raltegravir is eliminated primarily by hepatic metabolism, predominantly by UDP-glucuronosyltransferase (UGT) 1A1 with minor contributions from UGT1A9 and UGT1A3.[35] Raltegravir is not a substrate, inhibitor or inducer of cytochrome P450 enzymes.[46] Food has been shown to have an unpredictable effect on raltegravir PK, and raltegravir has been administered without regard to food in phase III studies.[36]

The standard raltegravir dose of 400 mg twice daily was chosen in order to maintain a C_{12h} several fold above the *in vitro* IC95 of 0.033 ± 0.025 uM (0.015 ± 0.011 ug/mL).[46] Although limited data suggested a possible association between the short-term ARV activity of raltegravir (change from baseline in HIV RNA at day 10 and slope of HIV RNA decrease

from day 2 to 8) and the corresponding C_{12hr} value on day 10 of treatment (but not $AUC_{0\text{-}12hr}$ or C_{max}), pharmacodynamic (PD) analyses utilizing intensive PK sampling obtained from the initial phase II and III raltegravir protocols did not identify clinically meaningful correlations between raltegravir exposure, as measured by AUC or C_{trough}, and longer term antiviral effects.[35] In a study of treatment naïve HIV-infected individuals, no differences were seen in antiviral response after 48 weeks of therapy among participants receiving 2 NRTIs plus raltegravir at doses of 100 mg, 200 mg, 400 mg or 600 mg twice daily.[24] In non-pregnant human adults, raltegravir at all doses studied had a safety profile much the same as placebo; no dose-related toxicities were observed.

Developmental toxicity studies of raltegravir were performed in rabbits (at oral doses up to 1,000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The highest doses in these studies produced systemic exposures in these species approximately 3 to 4 fold the exposure at the recommended human dose. In reproductive toxicity studies raltegravir did not affect fertility in either male or female rats at 600 mg/kg/day. In a toxicokinetic study in pregnant and lactating rats, raltegravir crossed the placental barrier with fetal exposure values up to 1.5 to 2.5 fold greater than in maternal plasma drug concentrations. It also concentrated in milk about 3 fold compared to plasma. In rabbits, mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours post dose at a maternal dose of 1,000 mg/kg/day. In developmental toxicity studies in rats, a slight increase in the incidence of supernumerary ribs relative to the control group was found at the highest dose of 600 mg/kg/day. No external or visceral abnormalities and no other fetal or postnatal developmental effects were noted at this dose. Raltegravir has not been shown to be genotoxic in a battery of *in vitro* assays in bacteria and mammalian cells designed to detect mutagenicity, direct Deoxyribonucleic Acid (DNA) damage or clastogenicity.[37]

Data published by Iwamoto and colleagues concerning safety, tolerability and PK of raltegravir in healthy participants showed that the drug was well tolerated and exhibits a PK profile supportive of twice-daily dosing with multiple doses of 100 mg and greater achieving trough levels >33 nM. After multiple-dose administration, steady state was achieved within 2 days.[27]

Markowitz and colleagues published a study where 35 ARV naïve participants were enrolled (6–8 participants per treatment group) and completed 10 days of therapy. The mean baseline $\log_{10}$ HIV RNA level ranged from 4.5 to 5.0 log10 copies/mL in each group. On day 10, the mean decrease from baseline in the $\log_{10}$ HIV RNA level was -0.2 copies/mL for the placebo group and -1.9, -2.0, -1.7 and -2.2 $\log_{10}$ copies/mL for the raltegravir 100-, 200-, 400-, and 600-mg treatment

groups, respectively.[38] In another study conducted by the same author, in which 198 participants were enrolled (160 on raltegravir and 38 on efavirenz), the mean HIV-1 RNA level ranged from 4.6 to 4.8 $\log_{10}$ copies/mL at baseline. At weeks 2, 4, and 8, the proportion of participants achieving an HIV-1 RNA level below 50 copies/mL was greater in each of the raltegravir treatment groups than in the efavirenz group. By week 24, all treatment groups appeared similar, with plasma HIV-1 RNA levels below 400 copies/mL in 85% to 98% of participants and below 50 copies/mL in 85% to 95% of participants. These reductions were maintained through week 48, at which time 85% to 98% of participants had plasma HIV-1 RNA <400 copies/mL and 83% to 88% were <50 copies/mL. Five (3%) participants on raltegravir and 1 (3%) on efavirenz experienced virologic failure before week 48.[24]

Grinsztejn and colleagues published the results of a phase II randomized controlled trial of the safety and efficacy of raltegravir in treatment-experienced participants with multidrug-resistant virus.[21] They showed that in all raltegravir groups there was a decrease of about 2 $\log_{10}$ copies per mL in HIV-1 RNA from baseline noted as early as 2 weeks after initiation of treatment which was sustained through 24 weeks. The difference in change in viral load from baseline between the raltegravir and placebo groups at week 24 was –1·45 (95% CI –1·84 to –1·06) $\log_{10}$ copies/mL with raltegravir 200 mg ($p<0·0001$), –1·52 (–1·90 to –1·14) $\log_{10}$ copies/mL with raltegravir 400 mg ($p<0·0001$), and –1·49 (–1·85 to –1·13) $\log_{10}$ copies/mL with raltegravir 600 mg ($p<0·0001$).

Lennox and colleagues published in 2009 data from a study in which they compared the safety and efficacy of raltegravir with efavirenz as part of combination ART for treatment-naïve participants.[39] The conclusion was that raltegravir-based combination treatment had rapid and potent ARV activity which was non-inferior to that of efavirenz at week 48. Furthermore, efavirenz is also recommended for HIV/TB co-infected pregnant women receiving anti-TB therapy.

Raltegravir PK data from P1026s are available for 42 pregnant women who received standard raltegravir doses of 400 mg BID during the third trimester and postpartum.[40] Third trimester median (range) raltegravir AUC was decreased (5.4 (1.4-36.5) µg*hr/mL vs. 11.6 (1.6-39.9) µg*hr/mL, $p<.001$) compared to postpartum, while there was no significant difference in median C12h (0.064 (0.0114-0.607) µg/mL vs. 0.0797 (0.0199-1.340), $p=0.3$). Raltegravir C12h exceeded the PK target of 0.035 µg/mL in 33 of 41 (80%) women during the third trimester compared to 30/38 (79%) postpartum. These women demonstrated a high rate of virologic response to raltegravir, with HIV RNA viral loads below 400 copies/mL in 92% of participants at delivery. Given this high rate of virologic response, the large variability in raltegravir plasma

concentrations seen in non-pregnant adults and the lack of a clear relationship between raltegravir concentrations and virologic effect, use of the standard non-pregnant adult 400 mg BID dose is recommended in pregnant women.[40,41]

1.4 Dynamics of Viral Decay With ART

Some studies in non-pregnant adults have compared viral decay with different ARV regimens. The Adult AIDS Clinical Trials Group (ACTG) A5095 study compared three treatment regimens: zidovudine/lamivudine/efavirenz, zidovudine/lamivudine/abacavir, and a four-drug regimen of zidovudine /lamivudine/abacavir/efavirenz. ACTG A5095 established the superiority of the efavirenz-containing regimen to the triple-nucleoside abacavir-containing regimen.[42,43] ACTG A5166s, a substudy of A5095, has shown that viral load declined more quickly in people treated with zidovudine, lamivudine and efavirenz than in those treated with zidovudine, lamivudine and abacavir. The faster viral load decline corresponded with the better virologic response in the efavirenz group, leading to suggestions that measurements of viral load decline might be an early predictor of longer-term response in clinical trials. Overall, the first phase of viral load decline was faster for those on the three-drug efavirenz regimen than for the triple-nucleoside combination. Viral load measurements were taken prior to and at study entry, and at days 2, 7, 10 and weeks 2, 4 and 8. Viral load fell at a faster rate in the efavirenz group than in the abacavir group during both the first phase and the second. The four-drug group was intermediate between the two. Viral load decay was modeled by a curve with two smooth exponential phases ("biexponential"); decay rates were estimated by fitting the observed data to the curve. In the model, the viral load decreases by a fixed percentage each day during each phase. This also yields a figure for the "half-life," or time it takes for half an existing population of cells to disappear.[44]

The findings from ACTG A5095 have been reinforced by a recent analysis of ACTG 5142, whose objectives were to compare phase-1 decay half-life of three regimens to evaluate gender differences and to relate phase-1 decay half-life to longer-term virologic responses: lopinavir/ritonavir + efavirenz vs. lopinavir/ritonavir + 2 NRTIs vs. efavirenz + 2 NRTIs. Phase-1 decay half-life was significantly shorter for efavirenz than for lopinavir (1.1 vs. 1.3 days, $p = 0.03$). They concluded that early viral clearance, as evaluated by phase-1 viral load decay and day 7 viral load change was greater for efavirenz than for lopinavir/ritonavir with efavirenz or lopinavir/ritonavir. Phase-1 decay was not different for participants by gender and race/ethnicity. Day 7 viral load change predicted week 48 virologic outcome.[45]

A phase II study (P004), evaluating ARV naïve participants enrolled for 48 weeks of combination therapy, with randomization to one of the four dosages of raltegravir or to efavirenz, in addition to tenofovir and lamivudine, showed that individuals in the raltegravir arm achieved an HIV RNA < 50 copies/mL earlier

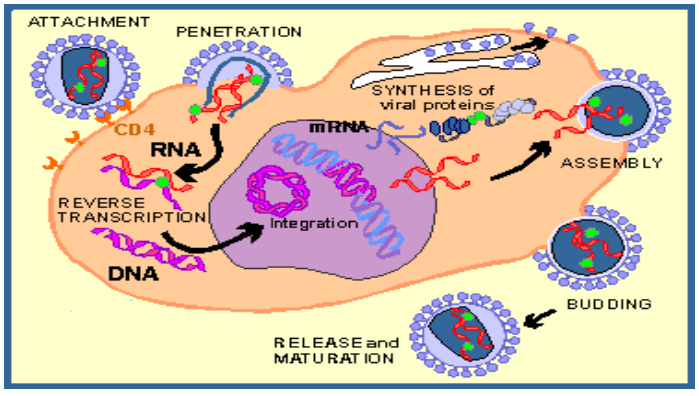
than participants receiving efavirenz ($p < .05$). Plasma viral loads were 70% lower at initiation of second-phase decay for individuals taking raltegravir than for those taking efavirenz ($P < 0.0001$). This challenges the current hypothesis that second-phase virus originates from infected long-lived cells, as an II should not impact viral production from this cell population.[34]

Since the rate of decline of HIV-1 RNA viral load in women who begin triple ART during the third trimester is critical to determine the most desirable ARV regimen and there are no previous clinical trials that have addressed this issue, we are proposing to compare virologic suppression, kinetics of viral decay, PK, efficacy and safety with NNRTI and II containing ARV regimens. Further research is also needed on whether the effects of intensive combination treatment on viral load differ in various body compartments, such as plasma and genital tract secretions, and how this may relate to risk of perinatal transmission, so vaginal compartment HIV viral load will be assessed at several time points.

1.5 Virion Infectivity Could Vary By HAART Regimen

While plasma viral load correlates directly with the risk of PMTCT, it does not completely determine the risk for *in utero* or peripartum HIV-1 transmission.[46] Factors such as the gestational age that ART is initiated, the transfer of ARV to the fetus/infant for chemoprophylaxis, maternal HIV-1 DNA load, and maternal CD4 count also influence the risk of MTCT.[47,48] One factor that has not yet been evaluated in clinical trials, and is especially pertinent to women beginning ART very late in gestation, is the effect of triple ARV regimens on the infectivity of cell-free and cell-associated virus, and its relation to the risk of MTCT.

Figure 1: Cellular sites of ARV activity. Nucleoside/tide and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI) block reverse transcription of viral RNA and integration of the cDNA, and interfere with HIV-1 infecting new cells. NRTI are added by the polymerase of reverse transcriptase to elongating cDNA, but by chain termination inhibit the formation of cDNA; NNRTI bind to a side pocket of the reverse transcriptase enzyme and through conformational changes impair its function; and integrase strand transfer inhibitors (INSTIs) block insertion of viral DNA into the human DNA.



Effective triple ART does not directly prevent HIV-1 infected cells from producing viruses. ART prevents infectious cycles. Rather, NRTI, NNRTI and INSTI inhibit the infection of new cells (Figure 1). During the first few months of ART the number of infected cells decreases and results in release of progressively fewer viral particles, which decreases plasma viral load. The plasma viral load declines in a predictable rate, in three phases; it falls below the limit of detection of clinical viral load assays when the infected cells that remain produce little virus. If protease inhibitors (PIs) are included in an ARV regimen, the inhibition of post-production processing of viral proteins by PI causes cells to produce defective, non-infectious virus.

Following initiation of triple ART, the infectivity of plasma decreases rapidly. During the time when the plasma HIV-1 RNA load remains detectable, the infectivity of virions to the fetus/infant should depend on pharmaco-dynamics and kinetics of the drugs used to treat HIV infection.

Specific NNRTI have virucidal activity against HIV-1, due to the tight-binding mode of inhibition of reverse transcriptase.[49] Efavirenz is one of several NNRTI that binds tightly, and *in vitro* rapidly inactivates the virus abolishing infectivity of virions that bud from the cells following removal of extracellular drug.[50] Thus, efavirenz-based ART has the theoretical advantage of immediately reducing the infectious risk of an individual to his/her sexual partner and an infected mother to her fetus/infant.

INSTI binding to HIV-1 integrase have been modeled, and relatively slow off-rates have been observed by this class of compounds, which suggests that the inhibitor may be stably bound to the preintegration complex.[51] However, compounds vary in their off-rates. Comparison of the effects of efavirenz to raltegravir on the infectivity of viral particles could not be found.

NICHD P1081 will include an evaluation of the differences in infectivity achieved with the use of efavirenz and raltegravir in late presenting pregnant women.

1.6 Transmission and Selection of Drug-Resistant HIV-1

Transmitted drug-resistant HIV-1 identified in plasma by consensus sequencing (concentration > 25-50%) can persist in the plasma for 2 to 5 years [1,2,3,4], and appears to compromise the efficacy of ART.[7,8,9] Low-level (< 25-50%) concentrations of drug-resistant mutants have been identified at the time of acute sero-conversion using assays with a greater sensitivity compared to consensus methods.[11,12] The prevalence and persistence of low-level mutants and their effects on ART have not been thoroughly described, although, recently, low concentration mutants were reported to diminish the efficacy of ART.[52]

Transmitted resistance has been detected by consensus sequencing in a small but significant proportion of pregnant women in Rio de Janeiro, and additional resistance was detected when pregnant women stopped ART postpartum. Among 197 HIV infected but ARV-naïve pregnant women receiving care in Rio de Janeiro, resistance mutations were detected in 10.7% (NRTI mutations in 5.6%, NNRTI mutations in 2.0%, and PI mutations in 3.0%). Among 80 HIV-infected postpartum women in Rio de Janeiro who had received HAART during pregnancy five (6.5%) had new resistant virus detected upon stopping ART (2.5% for NRTI, 3.75% for NNRTI).[53,54] In another study in Brazil, new nelfinavir resistance mutations were detected in 4 (23.5%) of 17 women postpartum, and 3 women developed new zidovudine resistance mutations. No NNRTI resistance mutations were observed.

The number of mutations required for a virus to become resistant to the ARV combination is often described as "the genetic barrier to resistance." PIs, except for nelfinavir, require multiple mutations in the virus for high-level resistance. The requirement for multiple mutations is a significant obstacle to the selection of drug-resistant virus, thus PIs have a high genetic barrier to resistance. In contrast, most NRTIs require one or two mutations and NNRTIs and INSTIs require any of several single-base mutations. However, efavirenz has a long half-life, which is thought to preclude low drug-levels despite missed doses which can reduce the risk of selecting drug-resistant variants when the accompanying NNRTI similarly have long half-lives, such as tenofovir and emtricitabine. Raltegravir has a relatively shorter half-live and a similarly low genetic barrier to resistance.

Very few studies have focused on the consequences of low-level drug-resistance in pregnant women starting ART. One large study, Optimal Combination Therapy after Nevirapine Exposure (OCTANE), compared the quantity of drug-resistance in women prior to starting nevirapine (NVP)-based ART, who either did or did not have a history of previous single-dose NVP. Among these women, the level of mutation was associated with virologic failure and death, in women previously treated with NVP, but similar levels were not predictive in women not treated with single-dose NVP (see Figure 2[55]).

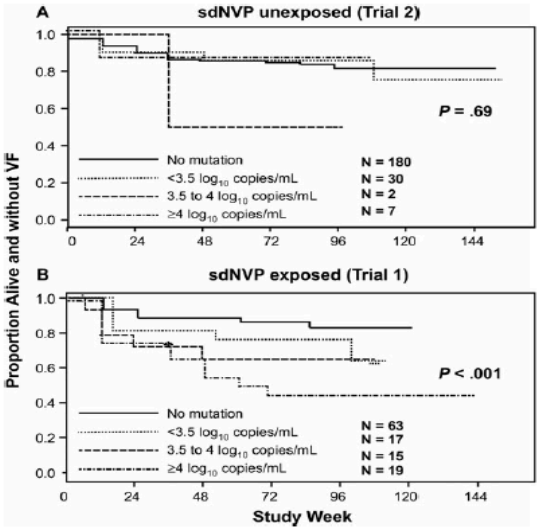


Figure 2. Kaplan-Meier plots showing the proportion of women in trial 2 (*A*, women without single-dose nevirapine [sdNVP] exposure) and trial 1 (*B*, women with sdNVP exposure) alive and without virologic failure (VF) in each of 3 categories of mutant copy number detected at entry compared to women with no mutations detected. *P* values from proportional hazards models.

Given uncertainties, an investigation of drug-resistant viruses present in pre-ART viral population at low-concentrations is warranted to further understand the role of pre-existing drug resistance on 1) viral suppression by the two different drug classes; and 2) selection of additional mutants when therapy is discontinued post-partum. In NICHD P1081, we will determine the prevalence of drug-resistance mutations at high and low concentrations in women presenting for care late in pregnancy and whether low-frequency mutations appear to compromise the rate that ART suppresses viral replication.

1.7 Genital Tract HIV RNA/DNA

Genital tract levels of HIV are independently associated with the risk of MTCT of HIV. In a sub-study of a randomized trial of breast versus formula feeding in Kenya, both cervical and vaginal HIV DNA levels were associated with the risk of infant HIV infection, after adjustment for CD4+ cell count, prematurity, genital ulcers, exposure to breast milk, and mastitis.[56] None of the women in this study received ART. In a study from Thailand, genital tract HIV RNA levels were significantly reduced among women receiving zidovudine compared to placebo.[57] In both treatment groups, the risk of transmission to the infant was significantly associated with detectable HIV RNA in the cervical-vaginal lavage (CVL), in both high (> 10,000 copies/mL) and low (< 10,000 copies/mL) plasma HIV RNA groups. These data clearly showed the ability of ARV drugs to reduce genital tract RNA levels and the association of genital tract HIV levels with transmission. In a case-control analysis of a subset of women enrolled to the Women and Infants Transmission Study (WITS), the level of HIV DNA detected in CVL, but not the level of HIV RNA, was associated with the risk of vertical transmission of HIV among women not delivering by cesarean section before the onset of labor, thus with potential exposure of the infant to HIV in the genital tract.[58] The adjusted risk of transmission increased by a factor of 2.28 (1.09-4.78) for each one log increase in CVL HIV DNA level. In this study, the majority of women were receiving ARVs, predominantly zidovudine monotherapy. Thus, data are consistent in showing an association between genital tract HIV levels and risk of vertical transmission, independent of plasma HIV RNA levels, but it is still not clear whether cell-free (RNA) or cell-associated (DNA) HIV is more important for transmission. In addition, the data available to date on genital HIV and transmission are from untreated women or women receiving zidovudine monotherapy. Triple ARV regimens may suppress genital tract viral load to a greater extent. This suppression may help to account for lower transmission rates among women on triple ARV regimens.

The majority of studies have shown a correlation between plasma HIV RNA levels and genital tract HIV RNA levels or DNA detection. However, many studies demonstrate some women with persistently detectable genital tract HIV despite undetectable plasma HIV RNA. In studies done before the triple ARV era, plasma HIV RNA levels and CD4+ cell count depletion were consistently associated with detection of HIV RNA or DNA in the female genital tract.[59] In one study of

women on various ARV regimens, HIV RNA was detectable in the genital tract from CVL among 25% of women with undetectable plasma HIV RNA. This finding was more frequent among women on less intensive ARV regimens.[60] However, even among women on triple ARV regimens, 8 (28.6%) of 28 had detectable HIV RNA, most with detectable plasma HIV RNA. In another study that evaluated plasma and genital tract RNA levels before and for 28 weeks after triple ARV initiation, 98% of women had undetectable plasma RNA and 95% had undetectable genital tract RNA after 18 weeks of therapy. With repeated sampling, 47% of women had at least one episode of genital tract HIV detection despite consistently undetectable plasma HIV RNA levels.[61] In a study of plasma and genital tract RNA levels among 38 pregnant women, 2 (22%) of the 9 women with undetectable plasma HIV RNA levels had detectable vaginal HIV RNA.[62] A study of 268 women from the WITS detected genital tract HIV shedding in 57% of women overall, including among 130 (80%) of 163 women with detectable plasma RNA and among 27 (33%) of 83 women with plasma HIV RNA under 500 copies/mL.[63] Seventy-four percent of these 27 women were on ART, including 14 (52%) on a PI. Other studies have confirmed the strong association between plasma HIV RNA levels and detection of HIV in the genital tract, and a small proportion of women with persistently detectable genital tract HIV even with undetectable plasma HIV RNA.[64,65] In a subsequent study from WITS of 290 women with undetectable plasma HIV RNA, 44 (15%) had detectable HIV RNA in cervical swab specimens.[66] In a multivariable analysis of factors associated with genital tract HIV detection, only NNRTI use (compared to PI use, odds ratio (OR) 2.24, 95% confidence interval 1.13-4.45) and illicit drug use (OR 2.41, 0.96-5.69) were found to be associated with genital tract detection of HIV RNA. Thus, plasma HIV RNA level is not an adequate predictor of genital tract HIV detection, and the risk of genital tract HIV shedding may vary by the ARV regimen used.

Several studies have evaluated the rate of decrease of genital tract HIV RNA after initiation of ART. A drop of 0.9 log in both cervical and vaginal RNA levels was seen after 1 week of zidovudine therapy.[67] A study of vaginal swab RNA levels among treatment-naïve women initiating stavudine, lamivudine, and NVP found an initial decay rate of 1.2 $\log_{10}$ virions/day.[68] In a study in Brazil, genital tract HIV RNA in CVL decreased by a mean of 1.44 $\log_{10}$ after 1 month on triple ARV therapy, primarily zidovudine and lamivudine with either efavirenz or nelfinavir.[69] Three women starting ARV therapy with detectable CVL RNA levels and studied intensively had a 0.7-2.1 $\log_{10}$ drop in genital tract RNA levels within 1-14 days of starting therapy.[70] A drop in genital tract RNA levels of 1-2 logs within 2-4 weeks of initiating ARV therapy would be expected with two nucleosides and either an NNRTI or unboosted PI based on current data. Data are needed on the change in genital tract HIV RNA levels on newer agents such as boosted PIs and IIs.

As discussed above, a variety of sampling methods has been used for assessing HIV in the female genital tract. Possible options include CVL with a sterile solution, cervical wicks, cervical and vaginal swabs, or cytobrush samples from

the cervix. For virology, the best site for sampling, cervical os or vagina, has not been determined. Given that we will be sampling pregnant women, with the intent being to assess HIV levels and possible associations with vertical transmission, sampling of the vaginal milieu, rather than the cervical os, is reasonable. Vaginal secretions sampling will allow assessment of HIV levels that would be encountered by the infant during labor and vaginal delivery. CVL, while allowing sampling of the entire vaginal area, has been found to be less sensitive and more variable than either cervical sampling with wicks or cytobrushes or swabs.[71,72] Vaginal swabs have been shown to have similar results to cervical wicks, vaginal wicks and CVL cell pellet.[73] Given that sampling of the vaginal milieu, rather than just the cervix, is desired and given the ease of obtaining specimens with vaginal swabs since no speculum placement is required, vaginal swab sampling has been chosen for determination of HIV RNA and DNA levels in this study. Use of the vaginal aspirator for the large number of vaginal specimens planned for virologic testing is cost prohibitive and its use for virologic testing has not been validated compared to other methods.

1.8 Microbiome

The microbiome and metagenomics are transforming research on health and disease. This is true when it comes to pregnancy and pregnancy outcomes. There is a linkage between microorganisms, detected by DNA-sequencing technology, and preterm delivery, premature rupture of membranes, intrauterine growth restriction, gestational diabetes, late abortions, and still birth.[74] Increased risk of HIV transmission to the partner and the newborn child has been associated with bacterial vaginosis and other disturbances of the microbiota caused by sexually transmitted infections.[75] In a retrospective analysis of cervicovaginal specimens, the presence of lactobacilli species and *Gardnerella vaginalis* was significantly higher in 10 women who transmitted HIV to their children compared to 54 nontransmitters.[76] The vaginal/uterine microbiota directly or through an immune modulation may affect HIV vertical transmission as well as the health of HIV exposed uninfected children.

HIV exposed uninfected children are an increasing population around the world. Morbidity and mortality among these infants are higher than in HIV unexposed children. It has been noted that these children have an increased incidence of lower respiratory tract infections and serious infections with encapsulated bacteria compared to HIV unexposed children.[77] The maternal vaginal or infant oral and respiratory microbiota may play a role in these adverse infant outcomes.

Maternal vaginal swabs and infant nasopharynx and oropharynx swabs will be collected for future evaluations of the microbiota. See Appendix V for more information.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To compare the ability of two triple ARV regimens (one containing efavirenz and the other raltegravir) begun during the third trimester of pregnancy to achieve a viral load of < 200 copies/mL at the time of delivery.

2.1.2 To compare the safety and tolerability of two triple ARV regimens (one containing efavirenz and the other raltegravir) begun during the third trimester of pregnancy.

2.2 Secondary Objectives

2.2.1 To compare the kinetics of viral decay between the treatment regimens:

a. Compare decay of plasma and vaginal HIV-1 RNA and DNA between the treatment regimens.

b. Compare decay of plasma HIV-1 infectivity between the treatment regimens.

2.2.2 To compare infant outcomes including stillbirth, premature birth, low birth weight, perinatal HIV transmission, neurodevelopmental outcomes and to compare (in HIV-infected infants) drug resistance between the two treatment regimens.

2.2.3 To assess the baseline prevalence and selection of HIV-1 drug-resistance to the study drugs, using standard genotyping and ultrasensitive genotyping methods.

2.3 Exploratory Objectives

2.3.1 To describe the population PK parameters of efavirenz and raltegravir during the third trimester of pregnancy and postpartum using sparse sampling and to evaluate potential relationships between PK parameters, pharmacogenomics and viral load changes.

2.3.2 To describe the maternal vaginal and infant nasopharyngeal and oropharyngeal microbiome environment and the potential association with adverse outcome in HIV exposed uninfected children.

3.0 STUDY DESIGN

Primary Hypothesis:

1) Efavirenz and raltegravir are effective, safe and tolerable as part of HAART regimens to be used in late pregnancy when rapid viral load suppression is for PMTCT of HIV.

Secondary Hypotheses:

1) Efavirenz-based triple ARV regimens will decrease the level and infectivity of plasma and cell-associated virus more rapidly (by 1 week of ART) compared to II-based triple ARV regimens.

2) Transmitted HIV drug-resistance among women will be prevalent at 10-15% of the population. Transmitted resistance will be associated with delayed decay of plasma HIV-1 RNA levels compared to women without primary resistance, and, when ART is stopped with further selection of resistance (especially selection of lamivudine and/or NNRTI resistance).

3.1 Overview

NICHD P1081 is a Phase IV multicenter, randomized, open-label trial to evaluate two different potent drug regimens in HIV-infected pregnant women initiating triple ARV regimens in the third trimester. The study population is HIV-1 infected pregnant women with gestational age 28-36 weeks who are ARV naïve or have received ART with short-course zidovudine (maximum of 8 weeks) for PMTCT in previous pregnancies, and their infants.

Women will be randomized 1:1 to Arm A (lamivudine/zidovudine + efavirenz), or Arm B (lamivudine/zidovudine + raltegravir) to compare the ability to achieve a viral load < 200 copies/mL at the time of delivery, tolerability, and safety of two different potent drug regimens. Alternative, locally supplied NRTI backbone may be used in place of lamivudine/zidovudine with permission of the protocol team obtained prior to randomization. The randomization will be stratified based on gestational age at enrollment (28-30 weeks versus 31-33 weeks versus 34-36 weeks) and the chosen NRTI backbone (lamivudine/zidovudine vs. alternative NRTI backbone).

Women in Arm A will receive standard non-pregnant adult doses of efavirenz once daily. Women in Arm B will receive the standard non-pregnant adult dose of raltegravir BID. The randomization will be stratified based on whether lamivudine/zidovudine or a locally supplied alternative NRTI backbone will be used to ensure balance of alternative NRTI backbone use between study arms.

All women will receive their randomized study regimen from study entry through delivery. Women who meet local guidelines for receiving ART will continue triple

ART after delivery and through breastfeeding according to local guidelines. These women can receive study drugs for up to 8 weeks after delivery to facilitate the transition to local standard of care. Women who do not meet local guidelines for receiving triple ART will stop study drugs immediately after delivery. Women randomized to Arm A (efavirenz) may continue lamivudine/zidovudine for a period of time after stopping efavirenz at the discretion of the local investigator.[78]

Infants will receive ARVs according to specific local guidelines.

Women will be followed for 6 months after delivery. Infants will be followed for 6 months after birth and may participate in an extension phase: developmental assessment of infants, lasting up to 4 years of age.

3.2 HIV Drug Resistance Testing

All women will have HIV drug-resistance testing done at a local Clinical Laboratory Improvement Amendments (CLIA) certified (for US sites) or DAIDS-Virology Quality Assurance (VQA) certified (for non-US sites) laboratory on a specimen drawn at screening. Since these are late presenting women and it is important to start ARVs as soon as possible to maximize prevention of perinatal HIV transmission, the results of this test will not be required before enrollment and initiation of study ART. A participant, in conjunction with her local provider, can use her resistance test results to determine whether they warrant a reconsideration of remaining on study medication. All women enrolled will remain in study follow up for safety monitoring and virologic evaluations regardless of regimen changes. Randomized participants who begin study therapy before resistance test results are available and are later discovered to have had detectable genotypic resistance to any of the study drugs in any of the study arms at screening (whether or not they decide to change study drugs) will be excluded from the primary analyses but included in secondary analyses (see Section 8.0 for details).

3.3 Sparse Sampling PK

All women will have blood collected that may be used for ARV drug assays at the week 1 and subsequent visits until delivery, and, for study participants who continue triple ARV regimens at the week 2-4 postpartum visit. ARV assay data will be used to perform a population analysis of ARV PK during the third trimester of pregnancy.

3.4 Genital Tract Viral Load

Vaginal swabs for maternal genital tract HIV RNA and DNA and microbiome polymerase chain reaction (PCR) will be collected on all women at entry, week 1, week 2, week 4, and every 2 weeks until delivery (36-38 weeks of gestation), and at 24 weeks postpartum.

3.5 Viral Decay and Viral Infectivity Dynamics

To study viral decay, serial determinations of plasma HIV RNA will be performed at local labs in all women to compare the rate at which plasma HIV-1 RNA decreases by study arm. Virion infectivity will be evaluated on plasma collected during visits week 1 until delivery and batch tested using an infectivity assay at the end of the study. The ratio of virion infectivity to HIV-1 RNA level will be compared between study arms.

Refer to Appendix I, Maternal Schedule of Evaluations and Appendix II, Infant Schedule of Evaluations, for a complete description of the clinical and laboratory evaluations to be performed.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Naïve to ART or have received ART with short course zidovudine (maximum of 8 weeks) for PMTCT in previous pregnancies.

4.1.2 Willingness and ability to sign informed consent. Participant must be of an age to provide legal informed consent as defined by the country in which the participant resides. If not, the informed consent must be signed by a legal guardian/parent, as per country guidelines.

4.1.3 Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. The same method may be used at both time points. All samples tested must be whole blood, serum or plasma. Documentation maybe abstracted from medical records to satisfy these criteria for infection.

The first test may be any of the following:

- HIV-1/2 Antigen and Antibodies test and confirmed HIV-1 from HIV-1/2 antibody differentiation test
- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One rapid antibody test AND one [enzyme immunoassay OR Western blot OR immunofluorescence OR chemiluminescence]
- One enzyme immunoassay AND one [Western blot OR immunofluorescence OR chemiluminescence]
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

If the first test(s) is positive, a second sample must be collected and tested using any of the tests listed above (except for qualitative RNA assays) at a laboratory participating in an appropriate external quality assurance program and either College of American Pathologists/CLIA approved (for US laboratories) or DAIDS-approved (for non-US laboratories).

It is strongly recommended that all kits/methods of analysis are Food and Drug Administration (FDA) approved.

4.1.4 Viable pregnancy with gestational age of ≥ 28 to ≤ 36 weeks based upon menstrual history and/or ultrasound.

Note: If menstrual history is unknown or if there is a discrepancy between menstrual history and ultrasound, determination of gestational age should be based upon best available methodology at each site.

4.1.5 Participant intends to continue pregnancy.

4.1.6 Willingness and intent to deliver at the participating clinical site and to be followed for the duration of the study at the site or associated outpatient facility.

4.1.7 Participant willing to comply with study regimen.

4.1.8 Participant agrees to use two reliable methods of contraception after delivery if randomized to the efavirenz arm and is sexually active. A barrier method of contraception (condoms, diaphragm, or cervical cap) together with another reliable form of contraception must be used for 4 weeks after stopping efavirenz.

4.2 Exclusion Criteria

4.2.1 Active labor defined as onset of regular contractions or cervical dilatation greater than 2cm.

4.2.2 Use of ART during current pregnancy.

4.2.3 Chemotherapy for active malignancy.

4.2.4 HIV genotypic resistance, as defined in Appendix IV, to efavirenz or raltegravir or to NRTIs that will be included in the ART regimen. Note: A lack of HIV drug-resistance test results at the time of enrollment is not exclusionary.

4.2.5 Serious active opportunistic infection and/or serious bacterial infection including active TB or unstable or severe medical condition within 14 days of study entry.

4.2.6 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.7 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would compromise the outcome of this study.

4.2.8 Vomiting or inability to swallow medications due to an active, pre-existing condition that prevents adequate swallowing and absorption of study medication.

4.2.9 Known allergy/sensitivity to any study drugs or their formulations or sulfonamide allergy.

4.2.10 The following laboratory values (within 30 days of enrollment):

- Hemoglobin ≥ Grade 3
- Absolute neutrophil count ≥ Grade 2
- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥ Grade 2
- Serum creatinine ≥ Grade 1
- Platelet count ≥ Grade 3

4.2.11 Evidence of pre-eclampsia (such as persistent diastolic blood pressure > 90 mmHg).

4.2.12 Receipt of disallowed medications described in Section 4.3.

4.3 Disallowed Medications

Participants will be randomized at time of enrollment and must be eligible to enroll in either study arm. Therefore participants receiving any disallowed medications listed below under any of the study medications are not eligible for enrollment.

4.3.1 Raltegravir

Raltegravir is eliminated mainly via a UGT1A1-mediated glucuronidation pathway and, therefore, the compound may be subject to drug-drug interactions when co-administered with drugs that are known to be UGT1A1 inducers or inhibitors. However, raltegravir is not anticipated to affect the metabolic clearance of drugs metabolized by UGT1A1 given its low UGT1A1 inhibitory (IC50 for the inhibition of UGT1A1 >50 μM) and induction potential. Since raltegravir is neither an inducer nor inhibitor of

cytochrome P-450 enzymes, raltegravir is not expected to result in metabolic drug interactions with substrates of cytochrome P-450.

The following medications/therapies are contraindicated in this study because they are potent broad inducers of drug metabolism, inducers of CYP3A (thus potential inducers of glucuronidation), and their co-administration with raltegravir will likely result in altered (lowered) drug levels of raltegravir:

- phenobarbital
- phenytoin
- rifampin

4.3.2 NRTIs

There are no disallowed medications due to drug interactions with NRTIs. Stavudine (d4T) and zidovudine should not be used together.

4.3.3 Efavirenz

The following medications are disallowed due to potential drug interactions with efavirenz:

- Rifampin, rifabutin, ergot derivatives, voriconazole, St. John's Wort
- Antihistamines: cisapride, loratadine, astemizole
- Sedative hypnotics: alprazolam, clorazapam, diazepam, estazolam, flurazepam, midazolam (except during labor), triazolam, zolpidem
- Anticonvulsants, except lamotrigine, gabapentin, and levetiracetam
- Calcium channel blocker: bepridil

4.4 Protocol Registration and Participant Enrollment Procedures

This protocol is open to all NICHD US and non-US sites that have been approved to participate by the NICHD network. Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) (ICFs) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Note that the "Extension Phase: Developmental Assessments in Infants" (Appendix VII) will not be activated for enrollment when Version 3.0 of the protocol opens. It is anticipated that site notification to activate this extension phase with guidance to begin enrolling infants to the extension phase will occur by a formal protocol action (likely a letter of Amendment).

A Site Implementation Plan is required from each site participating in the study. International sites are required to complete section I, site accrual and capacity, and section II, plans for providing antiretroviral medications during labor and delivery. Domestic sites are only required to complete section II, plans for providing antiretroviral medications during labor and delivery. The plan will be submitted to the protocol team for review and approval before protocol registration can occur.

Written informed consent for study participation must be obtained before any study related procedures are performed.

For participants from whom a signed ICF has been obtained, a Screening Checklist PS2001 must be entered through the DMC SES prior to study enrollment. Eligible participants are enrolled through the DMC SES using the P1081 enrollment screen. For all participants from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the initial protocol step for any reason, a Screening Failure Results form must be completed and keyed into the database.

4.5 Co-enrollment Procedures

Co-enrollment of study infants into P1097, P1110 and P1115 are allowed. Co-enrollment of study mothers to P1026s is permitted. Co-enrollment into other studies requires the approval of the NICHD P1081 protocol co-chairs and the co-enrollment protocol team.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

5.1.1 Drug Regimens

- Women will be randomized to:

  Arm A: Lamivudine 150 mg/zidovudine 300 mg* BID + efavirenz 600 mg QHS; or,

  Arm B: Lamivudine 150 mg/zidovudine 300 mg* BID + raltegravir 400 mg BID

*Alternative, locally supplied NRTI backbone may be used in place of lamivudine/zidovudine with permission of protocol team obtained prior to randomization.

Dosing during labor: All participants will continue to receive study drugs during labor. In addition, in place of the oral fixed dose combination of lamivudine 150 mg/zidovudine 300 mg (or alternative NRTI backbone), participants may receive intravenous zidovudine, other dosing regimens of oral zidovudine, oral lamivudine and/or additional drugs during labor, according to local standard of care/guidelines.

Infants:

Infants will receive ARVs according to specific local guidelines.

5.1.2 Drug Administration

- Lamivudine 150 mg/zidovudine 300 mg*
  Administered as one Lamivudine 150 mg/zidovudine 300 mg (Combivir) fixed-dose combination tablet by mouth BID

- Efavirenz 600 mg
  Administered as one 600 mg tablet by mouth QHS on an empty stomach

- Raltegravir 400 mg
  Administered as one 400 mg tablet by mouth BID

  See Appendix III for dietary recommendations for ARTs.

*Alternative, locally supplied NRTI backbone may be used in place of lamivudine/zidovudine with permission of protocol team obtained prior to randomization.

5.1.3 Treatment Duration

All women will receive their randomized study regimen from study entry through delivery. Women who meet local guidelines for receiving ART will continue triple ART after delivery according to local guidelines. These women can receive study drugs for up to 8 weeks after delivery to facilitate the transition to local standard of care. Women randomized to Arm A (efavirenz) may continue lamivudine/zidovudine for a period of time after stopping efavirenz at the discretion of the local investigator.

5.2 Drug Formulation

Lamivudine 150 mg/zidovudine 300 mg (Combivir) fixed-dose combination tablet. Store between 2° and 30°C (36° and 86°F).

Efavirenz (Sustiva, Stocrin, EFV) 600 mg tablets. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Raltegravir (Isentress, RAL) 400 mg tablets. Store at 20° to 25°C (68° to 77°F); excursions 15° to 30°C (59°to 86°F) and protect from moisture. Dispense in original container with desiccant.

5.3 Drug Supply, Distribution and Pharmacy

5.3.1 Study Product Supply/Distribution

Lamivudine 150 mg/zidovudine 300 mg (Combivir) fixed-dose combination tablet will be supplied by GlaxoSmithKline.
Note: locally provided supplies of the innovator lamivudine 150 mg/ zidovudine 300 mg (Combivir) may be used in the event that study-supplied lamivudine 150 mg/zidovudine 300 mg (Combivir) is not available at the site. Study supplies of lamivudine 150 mg/zidovudine 300 mg (Combivir) cannot be used to replace local supplies.

Efavirenz will be supplied by Merck for international sites and by Bristol-Myers Squibb for US sites. Note: locally-provided supplies of the innovator efavirenz (Sustiva, Storcin) may be used in the event that study-

supplied efavirenz is not available at the site. Study supplies of efavirenz cannot be used to replace local supplies.

Raltegravir will be supplied by Merck and Company.
Note: locally provided supplies of the innovator raltegravir may be used in the event that study-supplied raltegravir is not available at the site. Study supplies of raltegravir cannot be used to replace local supplies.

Alternative, NRTI backbone and ARV regimen during labor and delivery used according to the specific local guidelines in place of lamivudine/ zidovudine (Combivir) will not be supplied by the study.

5.3.2 Study Agent Acquisition/Distribution

Study products will be available through the NIAID Clinical Research Products Management Center. The site pharmacist can obtain the study products for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.3.3 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study products in US clinical research sites must be returned to the NIAID Clinical Research Products Management Center (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the section Study Product Management Responsibilities.

6.0 PARTICIPANT MANAGEMENT

Questions concerning clinical management of study participants and all communication regarding adverse experiences should be addressed to the P1081 CMC at NICHD.p1081 cmc@fstrf.org. Remember to include the participant's PID when applicable. Please do NOT disclose the study arm to which a participant is randomized unless specifically requested. The appropriate team member will respond to questions via email. A response should generally be received within 24 hours (Monday - Friday).

6.1 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (AEs) (DAIDS AE Grading Table), Version 2.0, dated November 2014, must be used for screening eligibility and for grading toxicities when

specifically noted below and is available at http://rsc.tech-res.com/safetyandpharmacovigilance/. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to the study agent must be explored.

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator with any treatment modifications as described in Section 6.2. Laboratory normals will be the institutional values of the lab performing the tests. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2 or baseline.

When a regimen or drug is stopped for toxicity, an alternative triple ARV regimen that does not predispose to the same toxicity (and which may contain drug(s) from the original regimen if not suspected to cause toxicity) should be immediately started. If this is not possible and the participant is receiving efavirenz, the participant may continue their NRTI combination for a period of time after stopping efavirenz at the discretion of the local investigator.

6.1.1 General Toxicity Reporting Guidelines

- Grade 1 or 2 Toxicity: No requirement to report to CMC.
- Grade 3 or Grade 4 Toxicity:
  - The investigator should attempt to confirm any unexpected laboratory test results as soon as possible but always within 72 hours to determine if the result was spurious.
  - The P1081 CMC must be notified of confirmed ≥Grade 3 Serious Adverse Events (SAEs) considered possibly, probably, or definitely related to study drugs within 72 hours at NICHD.p1081cmc@fstrf.org. (See Section 7.0 for EAE reporting guidance.)

6.2 Participant Management

6.2.1 General Guidelines

- The following general guidelines apply to all toxicities, unless superseded by directions in the following sections that give specific information on management of hypersensitivity reactions, liver toxicities, anemia, neutropenia, and elevated amylase.
- If the study regimen must be permanently discontinued, another triple ARV regimen (which may contain drug(s) from the original regimen if not suspected to cause toxicity) should be started according to local guidelines. Study follow-up should continue regardless of regimen changes.

6.2.2 Management of General Toxicities

- Grade 1 - Continue study drugs; routine monitoring.
- Grade 2 - Continue study drugs; monitor closely with more frequent visits when clinically indicated.
- Grade 3 - Continue study drugs while awaiting confirmatory results unless the clinician believes that remaining on study drugs would be unsafe. In this case, proceed as below.
- Confirmed Grade 3 events - Study drugs should be discontinued until resolution to ≤Grade 2 or the site investigator has compelling evidence that the toxicity is definitely NOT related to study drugs. This must be discussed with and approved by the P1081 CMC within 72 hours of site awareness. If the event resolves to ≤Grade 2, in less than 7 days, study drugs can be restarted. If the toxicity does not resolve within 7 days, the study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1. If the toxicity recurs or evolves to ≥Grade 3, the study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.
- Grade 4 (even before confirming) - All study drugs must be held or changed to another triple ARV regimen as described in Section 6.2.1 unless the site investigator has compelling evidence that the event is not due to study drug and it would be in the best interest of the woman to remain on study drug. The CMC must be notified of all Grade 4 events. This must be discussed with and approved by the P1081 CMC within 72 hours of site awareness. Participants experiencing AEs requiring permanent discontinuation of study drugs should be followed at least weekly until resolution of the AE to Grade ≤2 or baseline or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.

6.2.3 Cutaneous Toxicity and Suspected Hypersensitivity Reaction

The study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1 if confirmed Grade 3 or 4 skin toxicity occurs or if any grade cutaneous reaction occurs with any of the following: (a) systemic symptoms (fever, clinical hepatitis, muscle or joint aches); (b) allergic symptoms (urticaria, wheezing); (c) exfoliation; (d) mucosal involvement; or (e) elevated ALT ≥Grade 3, eosinophilia, granulocytopenia or renal dysfunction ≥Grade 3.

6.2.4 Liver Toxicity (clinical hepatitis and asymptomatic elevated transaminases)

Grade 1 or 2 ALT (and not present at baseline): The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, alcoholic stools, right upper quadrant pain or hepatomegaly. If asymptomatic, treatment may be continued. If symptoms or signs of clinical hepatitis are present, study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.

Participants with symptomatic or asymptomatic ≥Grade 3 elevations in ALT should have this finding confirmed with a second test within 72 hours. Participants with confirmed ≥Grade 3 ALT elevation will have study drugs permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.

6.2.5 Specific Toxicity Management for Other Laboratory Abnormalities:

Anemia
Evaluate for causes of anemia other than drug toxicity. Therapy with iron, folate and erythropoietin are allowed if indicated. If no other cause of anemia is identified and Grade 2 or 3 toxicity is present (and not present at baseline), consider switching zidovudine to investigator-selected locally available NRTIs. Continuation of the study drugs is allowed with substitution for zidovudine. For confirmed Grade 4 toxicity for which a relationship to study drugs cannot be ruled out, study treatment must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.

Neutropenia
Therapy with Granulocyte Colony-Stimulating Factor is allowed. If Grade 2, 3, or 4 toxicity is present (and not present at baseline), consider switching zidovudine to investigator-selected locally available NRTIs. Continuation of the study drugs is allowed with substitution with zidovudine. Discuss change with the CMC.

6.2.6 Management of Specific Toxicities During Pregnancy

Creatinine:
If >Grade 1, always evaluate for possible pre-eclampsia.

Proteinuria:
If >Grade 2, evaluate for possible pre-eclampsia. Grade 2-4 proteinuria by dipstick must be confirmed with a 24-hour urine collection. If Grade 2-3 proteinuria is confirmed and pre-eclampsia is present, the participant may

continue study drugs. However, if Grade 3 proteinuria occurs without pre-eclampsia or Grade 4 proteinuria is present, study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.

Nausea/vomiting:
If >Grade 3 nausea/vomiting persists >3 days and is thought to be drug-related and not pregnancy-related, study drugs must be permanently discontinued and changed to another triple ARV regimen as described in Section 6.2.1.

If fetal demise occurs after study entry:
The woman will continue to be followed on study/on treatment. In addition, the following must be documented:

- Ultrasound or fetal assessment(s) performed as clinically indicated to diagnose fetal demise.
- Assessment of antepartum complications which may have caused fetal demise (including but not limited to: placenta previa, abruptio placenta, unexplained vaginal bleeding, uterine/abdominal trauma, intrauterine growth retardation, oligohydramnios, polyhydramnios, maternal/fetal blood incompatibility, maternal alpha-feto protein abnormality, maternal infection, maternal substance use, cholestasis of pregnancy, maternal diabetes).
- Obstetrical exam (fundal height, gestational age assessment, cervical examination if indicated).
- Complete narrative of pregnancy course and assessment of relationship of fetal demise to study regimen sent to the P1081 CMC via email at NICHD.p1081cmc@fstrf.org. If available, copies of the placental pathology report and autopsy report are also requested.

6.2.7 General Approach to Infant Toxicity Management

Infants will be exposed to study drug *in utero*. Events related to study drugs will therefore be expected at birth or soon after.

All infant events will be reported and assessed as to study drug relationship.

6.2.8 Follow-up of Abnormal Events and Laboratory Values

All new abnormal clinical events and laboratory values occurring in enrolled participants will be followed closely until resolution. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of AEs according to their best medical judgment and local practice. For any persistent Grade 3 or 4 clinical or laboratory study drug Serious Adverse Drug Reactions, evaluations should be repeated approximately weekly (or more frequently if necessary) until toxicity falls below Grade 2 or returns to baseline, and as appropriate thereafter. Alternate explanations will be sought for all clinical and laboratory abnormalities.

6.2.9 Management of HIV Drug Resistance and Inadequate Virologic Response

Per Section 3.2, study drugs may be started before the HIV drug-resistance test results from the specimen drawn at screening are available. If the HIV drug-resistance test results from the screening specimen identify resistance mutations to one or more study drugs (see Section 3.2 and Appendix IV), but the participant began study treatment before the resistance test results were available, the results should be discussed with the clinical care provider and the CMC. If the participant decides to discontinue one or more study drugs, another triple ARV regimen (which may contain drug(s) from the original regimen) should be started. All women enrolled will remain in study follow up for safety monitoring and virologic evaluations regardless of regimen changes.

Inadequate virologic response will be managed according to local guidelines, in consultation with the CMC. In this study, inadequate virologic response is defined as follows:

- For women with entry HIV RNA ≥10,000 copies mL, a decrease in HIV RNA of < 1.0 $\log_{10}$ after 4 weeks on study drugs.
- For women with entry HIV RNA <10,000 copies/mL, HIV RNA > 1,000 copies/mL after 4 weeks on study drugs.

If local guidelines or the CMC's recommendation require changing one or more study drugs, another triple ARV regimen (which may contain drug(s) from the original regimen) should be started. All women enrolled will remain in study follow up for safety monitoring and virologic evaluations regardless of regimen changes.

6.3 Criteria for Treatment Discontinuation

Study drugs may be discontinued for any of the following reasons:

- The participant requires treatment with disallowed medications.
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.2.
- The participant experiences inadequate virologic response that requires changing one or more study drugs per local guidelines or CMC recommendation, as described in Section 6.2.9.
- Participant is repeatedly noncompliant with study treatment as prescribed, as determined by the site investigator.
- Clinical reasons believed life threatening by the site investigator, even if not addressed in the toxicity management of the protocol.
- Request of the primary care provider if s/he thinks the study treatment is no longer in the best interest of the participant.
- Request by the participant.

In the event of treatment discontinuation, the participant will be asked to continue scheduled evaluations until the end of the protocol.

6.4 Criteria for Study Discontinuation

The participant will be discontinued from the study for any of the following reasons:

- The participant or legal guardian refuses further treatment and/or follow-up evaluations and decides to discontinue participation in the study.
- The investigator determines that further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The study is cancelled at the discretion of the National Institutes of Health (NIH), the IRB or EC, FDA, Office for Human Research Protections (OHRP), or the pharmaceutical sponsor(s) or other governmental agencies.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0, January 2010, of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAERS, an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0, January 2010, of the DAIDS EAE Manual, will be used for this study.

The study agents for which relationship assessments are required are maternal raltegravir, efavirenz, lamivudine, zidovudine and other maternal ARV agents used during the study.

In addition to reporting all SAEs as defined above, other events that sites must report in an expedited fashion include fetal demises, malignancies, study drug overdoses, all immune reconstitution inflammatory syndrome events that qualify as SAEs, seizures and hepatotoxicities whether or not symptomatic or related to study drug, and all other Grade 3 or 4 related toxicities (except Grade 3 neutropenia and anemia) for which a relationship to study drug cannot be ruled out.

The death of any participant after enrollment or within 30 days of study completion, regardless of the cause, must be reported immediately and no later than 3 reporting days of first becoming aware of the death. After the 30-day period, deaths need to be reported only as part of long-term follow-up studies. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAE's submitted to the RSC, sites must file an updated SAE report to the RSC with the final or stable outcome (Status Code page 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

All reports submitted to the RSC must also be documented on the appropriate clinical case report forms (CRFs) and submitted to the study database through the eData system. Reconciliation of the two databases will be performed at regular intervals.

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), Version 2.0, dated November 2014, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

7.4 EAE Reporting Period

The EAE reporting period for this study for the mothers is until 30 days after stopping maternal study drug and for the infants it is 30 days after birth.

After the protocol-defined AE reporting period, unless otherwise noted, only Serious Unexpected Suspected Adverse Events as defined in Version 2.0, January 2010, of the EAE Manual will be reported to DAIDS for the duration of the participant's enrollment in the study, and after study completion if the study staff become aware of the events on a passive basis (from publicly available information).

7.5 CRF Recording Requirements for Laboratory Test Results, Signs, Symptoms, and Diagnoses

The results of all protocol-required laboratory tests performed at screening, entry, and post-entry must be recorded on CRFs, regardless of severity grade.

All abnormal (severity Grade 1 and higher) signs, symptoms, and diagnoses occurring within 30 days prior to study entry must be recorded on CRFs. All abnormal (severity Grade 1 and higher) signs, symptoms, and diagnoses occurring post-entry must also be recorded on CRFs at all visits.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a multicenter, international, two-arm, open-label randomized trial of two potent triple ARV regimens in HIV-infected pregnant women who are ARV naïve or have received short-course zidovudine (maximum of 8 weeks) only for PMTCT in previous pregnancies, and are initiating ARVs between 28 and 36 weeks gestation. The primary objectives are to compare the two regimens with respect to the ability to achieve a plasma viral load <200 copies/mL at delivery, tolerability and safety. The secondary objectives are to compare the kinetics of viral decay, compare infant outcomes, and assess baseline prevalence of HIV-1 drug resistance and selection of new drug-resistance mutations. The exploratory objectives focus on describing population PK parameters and their potential relationships with pharmacogenomics and viral load changes; and the maternal vaginal and infant nasopharyngeal and oropharyngeal microbiome environment and their potential association with adverse infant outcomes.

The target sample size is 334 evaluable women (approximately 167 per arm), which is anticipated to require enrolling approximately 394 women over a period of approximately 3 years (see Section 8.4 for details).

The choice of the primary efficacy endpoint is complex because women will enroll and deliver at various gestational ages, so that the duration of treatment prior to delivery will range from a few days to 12 weeks. Desirable characteristics for an ARV regimen being initiated in the third trimester of pregnancy for PMTCT include the ability to reduce viral load as quickly as possible, to achieve virologic suppression by the time of delivery, and to be well tolerated (to avoid treatment interruptions which could lead to loss of suppression).

The primary efficacy analysis will compare the proportions of women who achieve viral load <200 copies/mL at delivery (or if there is no viral load measurement at delivery, at the closest measurement prior to delivery) and the primary tolerability analysis will compare the proportions of women who discontinue efavirenz or raltegravir (whichever was assigned) prior to delivery. However, an important secondary analysis will use a composite outcome measure that combines efficacy and tolerability, specifically a composite binary outcome measure of (1) rapid viral load decrease which is sustained until delivery, defined as both achieving a specified minimum drop in plasma HIV-1 RNA from entry to week 2 (see Section 8.2.2 for details) and maintaining plasma HIV-1 RNA <1,000 copies/mL after 4 weeks on study drugs until delivery, and (2) tolerability defined as remaining on efavirenz or raltegravir (whichever was assigned) until delivery. One limitation of this composite outcome measure is that the relative importance of its components may differ according to anticipated treatment duration; for example, for a woman who presents late in the third trimester, it may be most important to maximize the viral load reduction within the first 2 weeks even if tolerability issues arise after

several weeks of treatment, while for a woman who presents at the beginning of the third trimester, the ability to sustain viral load suppression and be tolerated for up to 12 weeks becomes more important. Since the regimen that achieves the best response rate on the composite outcome measure may not necessarily dominate all of its components, additional analyses will compare the treatment arms with respect to each component of the composite endpoint (rapid viral load decrease from entry to week 2, viral load <1,000 copies/mL after 4 weeks on study drugs until delivery, and tolerability) to provide additional insight into the results of the composite outcome measure analysis.

HIV drug resistance testing for the study drugs will be done at screening. Depending on site capabilities for HIV drug resistance testing, results may only be available in 1-3 weeks. Since these are late presenting women and it is important to start ARVs as soon as possible to maximize prevention of perinatal HIV transmission, the women may be randomized and started on study ARV prior to receipt of the resistance test results. However, the women and their providers may decide to discontinue the study drugs once the HIV drug resistance test results are available, which greatly complicates the statistical analyses and interpretation of the study results. The frequency of resistance to specific study drugs may differ (e.g., efavirenz resistance may be more common than raltegravir resistance), which could lead to differential rates of study drug discontinuation in the randomized study arms. Also, the decision as to whether or not to change the study ARVs may be subjective and may depend on which study drug is involved (e.g., a regimen change may be more likely if an efavirenz resistance mutation is identified than if a lopinavir resistance mutation is identified, because high-level resistance can develop with just a single efavirenz resistance mutation but only with multiple lopinavir resistance mutations) and on factors that are also related to the likelihood of treatment success or failure (e.g., viral load), which could introduce confounding. Finally, the proportion of women who receive the results of the resistance test on the screening specimen before enrollment (and may therefore become ineligible for enrollment) may differ between sites. After extensive debate over various analysis approaches, the protocol team has decided that the best approach would be to exclude from the primary analysis all randomized participants who are later discovered to have had detectable genotypic resistance (as defined in Appendix IV) to any of the study ARVs in any of the study arms at screening (whether or not they decided to switch ARVs), and to increase the sample size accordingly to maintain the desired power. This post-randomization exclusion will be balanced across the randomized arms and avoid bias because it will be based on a pre-randomization characteristic (resistance to any of the study ARVs in any of the study arms), though the results of the primary analyses will generalize only to the population of women who do not have resistance to any of the study ARVs.

The women who are excluded from the primary analyses due to resistance at screening will be included in secondary analyses, which will attempt to compare the two real-world strategies of starting therapy with either Arm A or Arm B and

possibly switching ARVs when the resistance test results become available. Note that these secondary analyses may be hard to interpret if women with resistance at screening are more often excluded from enrollment at some sites than at others (e.g., due to more rapid turnaround for the resistance testing). Data will be collected on the reasons for non-enrollment of women who have consented, to inform the interpretation of the results and permit sensitivity analyses restricted to sites with high rates of enrollment of the women who turn out to have drug resistance mutations in the specimen drawn at screening.

An open-label trial is proposed because the number of pills per day and frequency of administration vary between treatment arms. Potential sources of bias with an open-label study include increased attribution and reporting of specific toxicities in a treatment arm. Also, physicians may be more likely to change ART if the treatment arm is perceived as suboptimal and this could introduce bias to the tolerability analyses. An attempt will be made to minimize these biases by setting up stringent criteria for toxicity management (Section 6.1), participant management including regimen modification (Section 6.2), treatment discontinuation (Section 6.3), and inadequate virologic response (Section 6.2.9).

8.2 Outcome Measures

8.2.1 Primary Outcome Measures

Efficacy:

- Plasma HIV-1 viral load <200 copies/mL at the delivery visit (or if there is no viral load measurement at the delivery visit, viral load <200 copies/mL within 3 weeks prior to delivery).

Evaluable women will be those who have a viral load measurement at the delivery visit or within 3 weeks prior to delivery. Non-evaluable women (missing viral load measurement due to missed visits, specimen or laboratory error) will be excluded from the primary analysis. Sensitivity analyses will be conducted to assess the potential impact of missing evaluations on the conclusions of the study (see Section 8.6 for details).

Tolerability until labor and delivery:

- Discontinuation of efavirenz or raltegravir (whichever was assigned) prior to labor and delivery for any reason (including loss to follow-up) will be considered a treatment failure in this analysis (note: switching any of the NRTIs with continuation of efavirenz or raltegravir will not be considered a treatment failure).

Women who received at least one dose of efavirenz or raltegravir will be evaluable for the tolerability analysis.

Safety through week 24 postpartum:

- Maternal and infant AEs of Grade ≥3 as defined in the DAIDS toxicity table.

Women who received at least one dose of a study drug, and their infants will be evaluable for the safety outcome measures.

8.2.2 Secondary Outcome Measures

Secondary Efficacy Outcome Measures

- Virologic suppression to below the lower limit of quantification of the assay at delivery.
- Composite outcome measure that combines efficacy and tolerance: binary outcome measure of (1) a successful viral load (plasma HIV-1 RNA) decrease from entry to study week 2 (day 11-17) and viral load <1,000 copies/ml at all time points after 4 weeks on study drugs, until delivery; and (2) tolerability (remaining on the assigned study regimen). The viral load decrease and tolerability components of the composite outcome measure will be defined as follows:
  - Rapid viral load decrease for women who deliver after 4 weeks on study drugs: A successful viral load decrease is defined as having both (i) a plasma HIV-1 RNA level ≥2.0 $\log_{10}$ below baseline or <200 copies/mL at study week 2 (day 11-17) and (ii) a plasma HIV-1 RNA level <1,000 copies/mL at all time points after 4 weeks on study drugs, until delivery. Evaluable women delivering after 4 weeks on study drugs are those with a viral load measurement at study week 2 (day 11-17) and at least one subsequent viral load measurement after 4 weeks on study drugs and before or during labor/delivery.
  - Rapid viral load decrease for women who deliver before or at 4 weeks on study drugs: A successful viral load decrease is defined as a plasma HIV-1 RNA level ≥2.0 $\log_{10}$ below baseline or <200 copies/mL at study week 2 (day 11-17). Evaluable women delivering before or at 4 weeks on study drugs are those with a viral load measurement at study week 2 (day 11-17).
  - Tolerability: Discontinuation of efavirenz or raltegravir prior to delivery for any reason (including loss to follow-up) will be considered a treatment failure in this analysis (note: switching any of the NRTIs with continuation of efavirenz or raltegravir will not be considered a treatment failure). All women who received at least one dose of efavirenz or raltegravir will be evaluable for the tolerability component of the composite outcome measure.

The baseline value will be the value obtained at the study entry visit. If this value is not available, then the baseline value will be the screening value.

Non-evaluable women (missing viral load measurement due to early delivery, missed visits, specimen or laboratory error) will be excluded from the analysis. Differential rates of non-evaluability or preterm delivery between study arms could lead to biased results; for example, an excess of preterm deliveries in one arm could lead to more women in that arm delivering before 4 weeks on study drugs and therefore not needing to maintain viral load <1,000 copies/ml after 4 weeks on study drugs, which could inflate the response rate in that arm. To address this concern, the rates of non-evaluability and preterm delivery will be compared between study arms, additional analyses will compare the study arms with respect to each individual component of the composite outcome measure, and sensitivity analyses will be conducted to assess the potential impact of missing evaluations on the conclusions of the study (see Section 8.6 for details).

Kinetics of viral decay

- Viral load in maternal blood and vaginal swabs at weeks 4 and 6 after starting treatment.
- Log_{10} change in viral load from entry (or screening, if there is no entry viral load) to each time point prior to delivery.
- Infectivity of plasma during the initial 2 weeks of ART.

Infant outcomes

- Stillbirth/fetal demise, premature birth (<34 or <37 weeks gestation), low birth weight (<1500 or <2500 grams), infant HIV infection status (per International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) definitions), neurodevelopmental outcomes (described in Appendix VII); resistance in HIV-infected infants.

HIV-1 drug resistance

- HIV-1 drug resistance mutations at screening, at 2-4 weeks postpartum in women who have stopped ART, and at the time of inadequate virologic response (defined in Section 6.2.9) using standard and ultrasensitive genotyping methods.

8.2.3 Exploratory Outcome Measures

- PK parameters as described in the Clinical Pharmacology Plan (Section 9.0).
- Maternal vaginal or infant oral and respiratory microbiota.
- Infant lower respiratory tract infections and serious infections with encapsulated bacteria.

8.3 Randomization and Stratification

A dynamic permuted block system will be used to randomize women in approximately equal numbers to either the efavirenz-based or raltegravir-based triple ARV regimen, with balancing by institution. To ensure balance in the treatment groups, the randomization will be stratified by gestational age at enrollment (28-30 weeks or 31-33 weeks or 34-36 weeks) and the chosen NRTI backbone (lamivudine/zidovudine vs. alternative locally supplied NRTI backbone). There will be no limit on the number of women in each stratum. The rationale for stratifying the randomization by gestational age is that women who enter the study later in gestation will be less likely to achieve the desired viral load decrease compared with women who enroll earlier in gestation. The rationale for stratifying the randomization by the chosen NRTI backbone is ensure balance in the two treatment arms, in case of unforeseen differential effects on viral load, tolerance, safety, or pregnancy outcomes.

8.4 Sample Size and Accrual

8.4.1 Sample Size

The sample size was chosen to provide 80% power to detect an important difference between treatment arms in the primary efficacy outcome measure (defined in Section 8.2.1), with a two-sided Type I error rate (α) of 0.05, and allowing for interim efficacy analyses and non-evaluable women. A difference of 15% or more between treatment arm response proportions was deemed important to detect.

In IMPAACT P1025, a cohort study of HIV-infected pregnant women at IMPAACT sites in the US, 67 (76%) of 88 women who initiated a triple ARV regimen (most commonly protease-inhibitor based) in the third trimester achieved a viral load <400 copies/mL at delivery, and the adjusted probability in a multivariable model was 79% (95% confidence interval 69% to 87%).[79] In a multicenter randomized placebo-controlled trial of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve adults (19% women) with no baseline resistance to efavirenz, tenofovir, or emtricitabine, the proportion of participants achieving viral load <50 copies/ml after 8 weeks of treatment (the

anticipated median duration of treatment in P1081) was approximately 75% in the raltegravir arm and approximately 39% in the efavirenz arm (102); note that this analysis counted those who did not complete the study treatment as failures (3.2% in the raltegravir arm and 6% in the efavirenz arm), which differs from the P1081 primary endpoint. Based on these studies, the P1081 team anticipates the response proportion in the raltegravir arm to be approximately 75% and selected the sample size to provide 80% power to detect a difference in response proportions of 75% versus 60%.

Table 1 shows the sample sizes required to provide 80% power to detect a 15% difference in response probabilities between treatment arms with two-sided α=0.05, allowing for two interim efficacy analyses and non-evaluable women (defined in Section 8.2.1). A sample size of 334 evaluable women (approximately 167 per arm) would be required for 80% power to detect a difference in response proportions of 75% vs. 60% between treatment arms. If 5% of enrolled women are non-evaluable for the primary outcome measure and 10% of enrolled women (based on the studies summarized in Section 1.6) are excluded from the primary analyses due to genotypic resistance to any of the study drugs at screening (as defined in Appendix IV), a total of 394 women (approximately 197 per arm) would need to be enrolled. The proportions of women who are non-evaluable or have genotypic resistance to any of the study drugs at screening will be monitored (see Section 8.5) and the target accrual will be modified accordingly if needed.

Table 1: Sample size required to provide 80% power to detect a 15% difference in response proportions between treatment arms with two-sided alpha=0.05*.

Response Proportions**	Number of evaluable women per treatment arm	Total accrual required per treatment arm#	Total accrual required (both arms combined)#
50% vs. 65%	184	217	434
60% vs. 75%	167	197	394
70% vs. 85%	135	159	318
80% vs. 95%	90	106	212

* Two-sided Chi-square test with continuity correction, allowing for two interim analyses and one final analysis with Haybittle-Peto spending function. Calculated using PASS 11 software.

**Each scenario also covers the symmetric scenario above 50% (obtained by subtracting each percentage from 100%); for example, the sample sizes for 60% vs. 75% would be the same as the sample sizes for 40% vs. 25%.

Allowing for 5% non-evaluable and 10% excluded due to ARV resistance at screening.

Table 2 shows the power to detect various 15% differences in response proportions between treatment arms with the selected sample size of 334 evaluable women. The power would be at least 76% in all scenarios and would be greater than 80% if the response proportions were both above 60%.

Table 2: Power to Detect Various 15% Differences in Response Proportions with N=334 Evaluable Women and alpha=0.05*.

Response Proportions**	Power with N=167 evaluable women per arm
50% vs. 65%	76%
60% vs. 75%	80%
70% vs. 85%	88%
80% vs. 95%	98%

*Two-sided Chi-square test with continuity correction, allowing for two interim analyses and one final analysis with Haybittle-Peto spending function. Calculated using PASS 11 software.

**Each scenario also covers the symmetric scenario above 50% (obtained by subtracting each percentage from 100%); for example, the sample sizes for 60% vs. 75% would be the same as the sample sizes for 40% vs. 25%.

In the event that the target number of evaluable participants is not reached, Table 3 gives the power to detect a 15% difference between arms (60% vs. 75% or 65% vs. 80%) with different numbers of evaluable participants per treatment arm. The power would remain $\geq$75% if at least 155 women per arm were evaluable, and this sample size would provide at least 80% power to detect a 15% difference if both response proportions were above 65%.

Table 3: Power to Detect a 15% Difference in Response Proportions with Different Numbers of Evaluable Women*.

Number of evaluable women per treatment arm	Power to Detect Difference in Response Proportions of 60% vs. 75%	Power to Detect Difference in Response Proportions of 65% vs. 80%
145	74%	78%
150	75%	79%
155	77%	81%
160	78%	82%
165	80%	83%

* Two-sided Chi-square test with continuity correction, allowing for two interim analyses and one final analysis with Haybittle-Peto spending function. Calculated using PASS 11 software.

8.4.2 Accrual

Enrollment to Version 2.0 of the P1081 protocol was paused on December 2, 2014, and a total of 19 women were enrolled by then. The Version 2.0 women who were enrolled to the efavirenz and raltegravir arms will be included in the Version 3.0 analyses and will count toward the target sample size.

Enrollment to P1081 will resume when Version 3.0 of the protocol is approved. Taking into account the varying time required for regulatory and bioethics approval at the anticipated study sites, the protocol team expects that the Brazil, Thailand, and US sites will resume enrollment during the first 12 months after the Version 3.0 amendment is released and will enroll 30-35 women during that period; after all these sites are enrolling, the protocol team expects that the accrual rate will reach 10-11 per month. The protocol team expects the African sites to be ready to begin enrollment about 12 months after the amendment is released and projects that the overall enrollment rate will reach about 18 enrollments per month (if all sites open as expected) in the second year after the amendment is released, so that enrollment can be completed during the third year after the amendment is released. The proportions of women who are non-evaluable (as defined in Section 8.2.1) or who are found to have had genotypic resistance to any of the study drugs at screening (as defined in Appendix IV) will be monitored and the target accrual will be modified accordingly if needed.

The study team does not expect any clinically important race/ethnicity differences in the intervention effect and is not aware of any studies that strongly support or negate the existence of such differences. While the P1081 sample size is not sufficient to provide high statistical power to detect such differences, analyses describing the intervention effect according to race/ethnicity will be performed per NIH policy. Since P1081 will not enroll men, it will not be possible to assess whether or not the intervention effect may vary according to gender.

8.5 Monitoring

8.5.1 Routine Monitoring

The core protocol team (which will have the same membership as the study CMC defined in Section 6.0) will have regular conference calls to ensure that its members are aware of ongoing issues concerning the conduct of the study and will review reports about the status of the study on a monthly basis (the frequency may be decreased if the study team deems this appropriate). These will include reports on accrual, baseline characteristics, AEs, specimen completeness, and the proportions of

women who are non-evaluable for the primary outcome measure or are found to have had genotypic resistance to any of the study drugs at screening (as defined in Appendix IV). These reports will present results that are pooled across the randomized treatment arms and not broken out according to arm.

The core protocol team will monitor safety closely. A summary of maternal and infant AEs will initially be generated monthly to help identify possible safety issues early on. The frequency of these reports may be decreased to bimonthly or quarterly if no significant safety concerns are identified.

Accrual to this study will be monitored by the NICHD and protocol co-chairs in accordance with standard operating procedures. Also, the team will monitor site protocol activation of the African sites to ensure that the number of sites participating is sufficient to complete the accrual in a timely fashion. If accrual is not adequate to meet the enrollment goals specified in Section 8.4.2, the team will identify the reasons for lack of accrual and possibly amend the protocol accordingly.

A full protocol monitoring plan with more specific details will be prepared before the study opens to accrual.

8.5.2 Interim Analyses

This study will also be monitored by a NIAID-sponsored Data and Safety Monitoring Board (DSMB). The DSMB will review information concerning accrual, characteristics of participants, quality and completeness of data and specimen collection, retention, AEs, and the proportions of women who are non-evaluable for the primary outcome measure or who are found to have had genotypic resistance to any of the study drugs at screening (as defined in Appendix IV) at least annually after the first woman is randomized.

Two interim efficacy analyses will be conducted when data on the primary outcome measure are available for approximately one third and two thirds of the planned enrollment. Under the accrual assumptions in the protocol, we anticipate that these interim analyses would be reviewed approximately one year and two years after the first enrollment to Version 3.0. The interim efficacy analysis schedule may be modified if accrual assumptions turn out to be inaccurate or if recommended by the DSMB.

The interim efficacy analyses will be based on comparison of the primary outcome measure between treatment arms, as described in Section 8.6. The Haybittle-Peto stopping boundary will be used as a guideline for considering a recommendation of early stopping. This guideline requires a p-value <0.001 at an interim analysis for early stopping to be considered.

To assist with decisions about recommending early stopping for lack of benefit (futility), conditional power and predicted interval analyses will be presented to the DSMB. The conditional power analysis will assess the power to detect the hypothesized treatment differences specified in Section 8.4 upon continuation, conditional on the data observed so far. The predicted interval analysis will provide information on effect size estimates and potential improvement in precision upon continuation, under various assumptions regarding the data yet to be collected (e.g., that hypothesized treatment differences are true, that the observed trend continues, that the null hypothesis is true, and under best-case and worst-case scenarios).[80] As a non-binding guideline for lack of benefit (futility), if the conditional power is low, say less than 20%, and the projected improvements in precision of effect estimates upon continuation are small, a recommendation of early termination may be considered. However, due to the lack of and need for efficacy and safety data for potent ARV regimens in the P1081 study population, the protocol team requests that the DSMB consider both the results of the above analyses and other factors that may argue for or against continuation (including whether there are safety or ethical concerns, the accrual rate, information to be gained from secondary objectives and sub-studies, new internal or external scientific information, and the existence/progress of other trials addressing the study questions), in deciding whether to recommend early stopping.

Although a recommendation for early termination would be based primarily on the primary efficacy analysis, consideration should be given to the consistency of effects seen on the primary and secondary efficacy outcome measures. Strong evidence of a difference in the primary outcome measure favoring one arm, but with evidence favoring the other arm with an important secondary efficacy outcome measure, might support the continuation of both arms. However, a significant difference between arms with respect to a secondary efficacy outcome measure, in the absence of strong evidence of a difference with respect to the primary outcome measure, would not be grounds for early stopping of an arm.

8.6 Analyses

A statistical analysis plan specifying full details of all proposed analyses will be developed prior to the commencement of analyses for the first review by the DSMB. Here we limit the description of the proposed analyses to those for the primary outcome measures. Unless otherwise indicated, all analyses will follow the intent-to-treat principle and will include all women randomized. As discussed in Section 8.1, women who are found to have had genotypic resistance at screening to any of the study drugs (as defined in Appendix IV) will be excluded from the primary analyses and included in secondary analyses.

The primary efficacy analysis will be based on a comparison of the primary outcome measure, namely the proportions of evaluable women (as defined in Section 8.2.1) in each arm who achieve viral load <200 copies/mL at delivery using the Cochran-Mantel-Haenszel test, stratified according to gestational age at enrollment (28-30 weeks versus 31-33 weeks versus 34-36 weeks). [Note that the analysis will not be stratified according to the chosen NRTI backbone.] Secondary efficacy analyses will compare the treatment arms with respect to the composite efficacy/tolerability outcome measure and each component of this composite outcome measure (rapid viral load decrease from entry to week 2, viral load <1,000 copies/mL after 4 weeks on study drugs until delivery, and tolerability). In light of the conservative spending function that will expend minimal Type I error in the interim efficacy analysis, unadjusted point estimates, p-values, and confidence intervals will be presented to summarize the results in the final analysis.

Sensitivity analyses will be conducted to assess the potential impact of missing data on the conclusions of the study. Of primary concern are missing viral load measurements at delivery for women who have achieved a successful viral load decrease at time points at which measurements are available. The sensitivity analyses will be done in two ways: (a) as an extreme, by assuming that a missing viral load measurement at delivery would have shown successful or unsuccessful viral load decrease in a way that would minimize the difference between randomized groups, and (b) more plausibly, by assuming that a missing viral load measurement at delivery would have shown an unsuccessful viral load decrease with probability equal to the estimated probability of an unsuccessful viral load decrease at delivery among women in the same group who had that evaluation and had a successful viral load decrease at other evaluations prior to delivery.

Secondary efficacy analyses will repeat the above analyses with all evaluable participants included, regardless of whether or not genotypic resistance to any of the study drugs was detected at screening. These analyses will compare the two real-world strategies of starting therapy with either Arm A or Arm B and possibly switching ARVs when the resistance test results become available, subject to the potential biases described in Section 8.1. These analyses will be conducted two ways: (1) with switching ARVs due to the screening resistance test results

considered to be a treatment failure; and (2) with switching ARVs due to the screening resistance test results not counted as a treatment failure.

The final tolerability and safety analyses will each be based on a comparison of the proportions of women and infants in each arm who meet the primary tolerability and primary safety outcome measures specified in Section 8.2.1, using the Cochran-Mantel-Haenszel test, stratified according to gestational age at enrollment (28-30 weeks or 31-33 weeks or 34-36 weeks).

The final analysis will be performed after all women and infants have completed the week 24 study visit.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

The clinical pharmacology objectives of this study are:

- To describe efavirenz and raltegravir PK parameters during the third trimester of pregnancy.
- To assess the potential relationships between ARV concentrations and viral load changes/viral decay.

Rationale – Few clinical trials describe the pharmacology of ARV drugs in pregnant women, limiting our ability to design appropriate dosing schedules for these agents in pregnant woman infected with HIV. The few ARV pregnancy pharmacology studies that exist have primarily involved non-randomized cohort studies with intensive PK sampling. The populations in these studies may represent only a subset of pregnant HIV-infected women and the studies include no PD assessments of the relationships between ARV concentrations and viral load response. As virologic response and MTCT may be related to drug exposure in plasma, data from this trial may greatly improve our understanding of both the PK and PD of ARVs during pregnancy.

9.2 Primary and Secondary Data

9.2.1 PK Sampling Data

9.2.1.1 Dosing history (date, time and amount of last two doses of study drug prior to study dose and of study dose)

9.2.1.2 Last two meals (dates and times, description) (See Appendix III)

9.2.1.3 Height and weight on day of sampling and pre-pregnancy weight

9.2.1.4 Date and time PK samples drawn

9.2.1.5 Efavirenz, 8-hydroxy-efavirenz and raltegravir concentrations in sparse PK samples

9.2.1.6 Ratio of unbound/total drug concentrations for efavirenz

9.2.1.7 Maternal plasma alpha-1 acid glycoprotein and albumin concentrations

9.2.2 Demographic and Historical Data

9.2.2.1 Maternal age and race/ethnicity

9.2.2.2 Infant gestational age, birth length and weight

9.2.2.3 Date, name, frequency and route of administration for non-ARV medications taken in last 7 days

9.2.2.4 Maternal laboratory studies: complete blood count (CBC) with differential and platelets, AST, ALT, total bilirubin, blood urea nitrogen (BUN), electrolytes, glucose, creatinine, total amylase and HIV RNA

9.2.3 Infant HIV Infection Status

9.2.4 PK Parameters

9.2.4.1 Population CL/F. V/F, and, t1/2; mean and population variances for all drugs

9.2.4.2 Individual predicted empiric Bayesian CL/F. V/F, t1/2, steady-state pre-dose concentrations and AUC

9.3 Laboratory Analysis and Reporting

Site: Plasma PK samples will be sent to the IMPAACT Specialized Clinical Pharmacology Laboratory at University of California, San Diego, where they will be assayed for plasma concentration of raltegravir, efavirenz and alpha-1 acid glycoprotein. Specimens may then be shipped to other IMPAACT or ACTG Specialized Clinical Pharmacology Laboratories depending on assay availability and work load. All samples will be destroyed after the primary assays have been completed for the PK/PD studies.

Methods to be used: All methods will be standardized with a filed Methods Report, under Good Clinical Laboratory Practice conditions such as those currently used in

the University of California, San Diego and University of Alabama at Birmingham labs, or will be derived from published methods.

Reporting of Assay Data: Assays will be batched in sufficient participant numbers to provide analysis by routine assays. All PK samples will be registered in the Laboratoy Data Management System (LDMS) database.

9.4 Study Design, Modeling, and Data Analysis

Women will be randomized 1:1 to receive lamivudine/zidovudine* + efavirenz or lamivudine/zidovudine* + raltegravir to compare the virologic response, tolerability, and safety of two different potent drug regimens.

*Or alternatively locally supplied NRTI backbone

All women will have single random plasma samples collected for drug assay at study visits starting with week 1 after entry and at all subsequent antenatal visits. Samples will also be collected from participants still receiving study ARVs at the 2-4 week postpartum visit.

Demographic data, recent dosing history including food intake, delivery information and sample collection times will be collected. Alpha-1 acid glycoprotein and albumin concentrations will be determined from one of the PK samples. Raltegravir, or efavirenz and 8-hydroxy-efavirenz concentrations will be measured in these specimens.

The sparse PK data from the single samples will be used in a population PK/PD analysis for each drug with the program NONlinear Mixed-Effect Modeling (NONMEM). An open one-compartment with first order absorption will be employed as the base model. Alternative and more complex models will be evaluated as indicated by the data. These data may be nested with intensive third trimester PK data from IMPAACT P1026s to assist in describing the drug absorption and distribution phases of the concentration time profile. The influence of covariates on ARV disposition will be assessed; specifically age, height, weight, sex, binding protein concentrations, ethnicity, 8-hydroxy-efavirenz concentrations and duration of therapy and laboratory measurements. 8-hydroxy-efavirenz/efavirenz ratios will be used to assess CYP 2B6 activity and help identify the poor metabolizer phenotype sub-population. Empiric Bayesian post-hoc estimates of individual participant's apparent clearance, apparent volume of distribution and drug exposure will be determined and will be generated for further exploratory analyses. Relationships between drug exposure parameters and virologic response parameters will be explored.

9.5 Anticipated Outcomes

The data from this study will allow unique PK/PD analyses for raltegravir and efavirenz during pregnancy. PK parameters during pregnancy will be compared to historical PK data from non-pregnant adults and will provide additional information regarding the variability of ARV drug exposure during pregnancy. Post-hoc estimates of ARV AUC, plasma concentration at end of dosing interval and intra-participant variability will serve as the basis for exploratory analyses of the relationship between viral load changes and viral decay with raltegravir and efavirenz exposure.

10.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, Good Clinical Practice Guidelines and 45 Code of Federal Regulations Part 46.

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent documents (Appendix VI) and any subsequent modifications must be reviewed and approved by the IRB or EC responsible for oversight of the study. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant (or parent or legal guardian). Each site which receives US Department of Health and Human Services funding and follows the US Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric participants and determines when a study participant must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent. The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant confidentiality. All records will be kept in a secured area with limited access. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as

necessary for monitoring by the FDA, Office for Human Research Protections (OHRP), the local IRB or EC, local or national regulatory agencies, NIH, study staff, and study monitors, and other sponsors, as applicable the Safety Monitoring Committee, and other sponsors, as applicable.

The protocol chairs and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from NIH must be obtained for the disclosure of any said confidential information to other parties.

10.3 Study Discontinuation

The study may be discontinued at any time by NIH, FDA, and OHRP, the IRB or EC, the pharmaceutical sponsors, or other governmental agencies as part of their duties to ensure that research participants are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by NICHD policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

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

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.

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APPENDIX I
MATERNAL SCHEDULE OF EVALUATIONS

	ANTEPARTUM							POSTPARTUM				Event Driven Evaluations	
	Screening[1]	Entry	Week 1[2] Day 7 (± 2days)	Week 2[2] Day 14 (± 3days)	Week 4 (± 4 days)	Every 2 weeks (± 4 days)	Labor/ Delivery collected during labor or < 48 hours postpartum	Week 2 (2-4 weeks)	Week 6 (± 7 days)	Week 16 (± 14 days)	Week 24 (± 14 days)	Inadequate virologic response	Premature Study Discontinuation
CLINICAL EVALUATIONS													
Informed Consent	X												
History/HIV assessment[3]	X	X	X	X	X	X	X	X	X	X	X		X
Targeted physical exam[4]	X	X	X	X	X	X	X	X	X	X	X		X
Hematology[5]	1mL	1mL		1mL	1mL		1mL			1mL	1mL	1mL	1mL
Chemistries[6]	2mL	2mL		2mL	2mL		2mL				2mL		2mL
Urine dipstick	X												
HIV confirmatory test[7]	1mL												
HIV RNA PCR[8]	6ml	6mL	6mL	6mL	6mL	6mL	6mL				6mL	6mL	6mL
Vaginal swabs[9]		X	X	X	X	X					X		
Genotyping for HIV-1[10]	5ml											5ml	
CD4[11]	1mL	1mL			1mL		1mL			1mL	1mL	1mL	1mL
Other Studies[12]	5mL	5mL	5mL	5mL	5mL	5mL	5ml	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL
TOTAL BLOOD VOLUMES	21mL	15mL	11mL	14mL	15mL	11mL	15mL	5mL	5mL	7mL	15mL	18mL	15mL

APPENDIX I – FOOTNOTES FOR MATERNAL SCHEDULE OF EVALUATIONS

1. Screening evaluations must be performed within 30 days prior to Entry. Laboratory results should be obtained. Entry and ART should be started as soon as possible.
2. Visit must occur at least 48 hours after the previous visit. Preferred target days are Day 7 and Day 14 after Entry.
3. A complete history is required at Screening and interim history (diagnoses and signs/symptoms) is required at subsequent visits. Screening only: Documentation of HIV infection for eligibility can be historical.
4. For physical exam, record height and weight at all visits. If fetal ultrasound is needed to confirm gestational age (must be completed before entry), results of ultrasound obtained through clinical care may be abstracted and used as confirmation of gestational age or fetal ultrasound can be performed during the screening process; fetal ultrasound is not required by the protocol if not needed to confirm gestational age. Presence of fetal heart tones should be documented at each visit until delivery.
5. Hematology includes CBC with differential and platelet count.
6. Chemistries include AST, ALT, total bilirubin, glucose and creatinine.
7. Obtain *only* if source documentation is not available. Documentation of HIV infection for eligibility can be historical.
8. 6 mL EDTA blood sample will be collected for local real-time plasma HIV RNA testing using a CLIA-certified assay (for US laboratories) or DAIDS-VQA certified assay (for non-US laboratories).
9. Two vaginal swabs to be collected and placed in sterile cryovial tubes for storage at <= -70 degrees Celsius freezer for batched testing of viral load and microbiome in the maternal reproductive tract. Refer to Appendix V for instructions on collection and processing.
10. At Screening and whenever inadequate virologic response (defined in section 6.2.9) occurs, HIV genotyping will be performed at a local/regional laboratory. The laboratory performing the testing must have a record of successful performance for HIV genotyping in the VQA External Quality Assurance program. Enrollment may occur and study drugs may be started before the HIV genotype test results from the screening specimen are available.
11. CD4 counts must be performed at a CLIA certified (for US sites) or DAIDS Immunology Quality Assurance -certified (for non-US sites) laboratory. Note: Only an absolute CD4 count is required for this protocol.

12. This plasma will be used for batched studies, including antiretroviral concentrations, low-level drug resistance, and viral infectivity. Plasma will be used to measure drug levels only through the 2-4 week postpartum visit.

APPENDIX II
INFANT SCHEDULE OF EVALUATIONS

	Birth (+48 hrs)	Week 2 (2-4 weeks)	Week 6 (± 7 days)	Week 16 (± 14 days)	Week 24 (± 14 days)	Documentation of HIV infection	Premature Study Discontinuation
History[1]	X	X	X	X	X		X
Physical exam[2]	X	X	X	X	X		X
Offer participation in extension phase: INFANT DEVELOPMENTAL ASSSSMENT (Appendix VII) STUDY NEURODEVELOPMENTAL / NEUROPSYCOLOGICAL EVALUATIONS[3]					X		
Hematology[4]	0.5mL	0.5mL					0.5mL[8]
Chemistries[5]	1mL						
HIV TNA or HIV DNA or HIV RNA[6]	2mL	2ml	2mL	2mL	2ml		2mL
HIV-1 RNA PCR[6]						2mL	
Genotyping[7]						2mL	
Oral and nasopharyngeal swab collection [9]		X			X		
TOTAL BLOOD VOLUME	3.5mL	2.5ml	2mL	2ml	2ml	4mL	2.0ml - 2.5ml

APPENDIX II – FOOTNOTES FOR INFANT SCHEDULE OF EVALUATIONS

1. A complete history is required at birth and at subsequent visits. Birth history includes labor and delivery record, Apgar score, birth weight and length, gestational age, and sex.
2. Physical exam includes length, weight, and head circumference.
3. Sites will not start offering participation in this extension phase until the protocol team notifies them that enrollment into the extension phase has been activated.
4. Hematology includes CBC with differential and platelet count.
5. Chemistries include AST, ALT, and creatinine.
6. HIV TNA (total nucleic acid), HIV DNA or HIV RNA: Obtain *only* if source documentation is not available. If the initial test is positive, confirm as soon as possible by HIV-1 RNA PCR. Tests must be performed at a CLIA certified (for US sites) or DAIDS VQA-certified (for non-US sites) laboratory.
7. Genotyping will be completed if HIV infection is confirmed by the HIV-1 RNA. Genotyping must be drawn at the time of the confirmation of HIV-1 RNA PCR and must be performed at a CLIA certified (for US sites) or DAIDS VQA-certified (for non-US sites) laboratory.
8. Obtain only if premature discontinuation occurs before week 6 visit.
9. Two swabs (one from nasopharynx and one from oropharynx) to be placed in a sterile cryovial tubes for storage at <= -70 degrees Celsius freezer.

APPENDIX III
DIETARY RECOMMENDATIONS FOR ANTIRETROVIRAL THERAPIES

Efavirenz: Take on an empty stomach (fasting at least 1 hour before or 2 hours after a meal).

Raltegravir: Take without regards to meals.

Lamivudine/zidovudine: No food requirement.

APPENDIX IV
RESISTANCE MUTATIONS FOR ANTIRETROVIRAL STUDY DRUGS

Mutations in reverse transcriptase:
Zidovudine (ZDV)
M41L
D67N
K70R
L210W
T215Y/F
K219K/Q
insertion at 69-XX
151-complex (A62V=V75I=F77L=116Y=Q151M

Lamivudine (3TC) or Emtricitabine (FTC)
K65R
M184V

Efavirenz (EFV)
L100I
K101P
K103N
V106M
V108I
Y181C/I
Y188L
G190S/A
P225H

Tenofovir disoproxil fumarate (TDF)[1]
K65R
insertion at 69-XX
K70E
M41L+L210W+ at least one of: D67N, K70R, T215F/Y or K219Q/E

Footnote:
1. Philip A Chan et al. Journal of the International AIDS Society 2012, 15:17701.
http://www.jiasociety.org/index.php/jias/article/view/17701

Mutations in integrase:
Raltegravir (RAL)
E92Q
G140S/A
Y143R/C
Q148H/R/K
N155H

APPENDIX V
VAGINAL SPECIMEN COLLECTION, PROCESSING AND SHIPPING

Vaginal Swabs for Virology Testing

Vaginal swabs to evaluate genital tract HIV RNA and DNA levels and to evaluate the microbiome will be obtained on all women at entry, week 1, week 2, week 4, and every 2 weeks until delivery (36-38 weeks of gestation), and at 24 weeks postpartum.

At each time point for vaginal collection, FLOQSwabs with nylon tips and plastic shafts will be inserted gently into the vagina to a depth of about 3 cm and rolled around the circumference of the vaginal wall. A single swab will be inserted at a time, but two swabs will be collected at each time point. After collection, each swab will be inserted into a cryovial, the end broken off and the tube capped. The tube will be labeled with the participant's PI, date and time of collection, and specimen type. Specimens will be labeled with LDMS labels. Tubes will be frozen at -70ºC or colder.

The cryovials containing swabs should be transported to the processing lab within 1 hour if possible. If that is not feasible, they should be refrigerated and then transported on cold packs or wet ice or they could be frozen and transported on dry ice. If wet ice is used, then the cryovials should be placed inside a plastic bag to keep them dry during that transport. Swabs should be frozen at -70ºC or colder within 4 hours of collection.

Specimens will be batch shipped at the end of the study for virology testing to:
Lisa M. Frenkel, M.D. – SPECIALTY LABORATORY (LDMS# 238)
Professor/Department of Pediatrics and Laboratory Medicine
Division of Infectious Diseases and Virology
University of Washington
Seattle Children's Hospital and Research Institute
1900 Ninth Avenue
UW Mail Stop 359300
Seattle, WA 98101-1304
Phone: (206) 987-5140
Email: lfrenkel@u.washington.edu

Specimens will be batch shipped at the end of the study for microbiome testing to:
Adriana Weinberg, M.D.
University of Colorado Denver
Mail Stop 8604
12700 E. 19th Avenue, Room 11126
Aurora, CO 80045
Phone: 303-724-4480
Email: adriana.weinberg@ucdenver.edu

Vaginal swabs can be ordered from Quidel/Diagnostic Hybrids Inc., item #502CS01. Information is available at http://www.quidel.com/cultures-fluorescent-tests/floqswabs/floqswabs

APPENDIX VI
SAMPLE INFORMED CONSENT

A Phase IV Randomized Trial to Evaluate the Virologic Response and Pharmacokinetics of Two Different Potent Regimens in HIV-infected Women Initiating Triple Antiretroviral Regimens Between 28 and 36 Weeks of Pregnancy for the Prevention of Mother-to-Child Transmission: NICHD P1081

INTRODUCTION

You and your baby are being asked to take part in this research study because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS and you have not taken any anti-HIV medication or have only taken a short course of zidovudine in past pregnancies. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to/allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

In this study, one of two different anti-HIV medications will be given along with zidovudine and lamivudine to HIV-infected pregnant women to compare how safe the medications are, how tolerable they are and how well they can lower the amount of HIV in the blood. **We will see if one of these two drugs, efavirenz, or raltegravir, lowers the amount of HIV in the blood faster than the other.**

WHAT DO I/DOES MY BABY HAVE TO DO IF I AM/MY BABY IS IN THIS STUDY?

Screening visit to see if you can be in the study

If you decide you want you and your baby to be in this study, we will do some tests to see if you are able to enter the study.

- The screening visit will happen when you are about 24-36 weeks pregnant.
- We will get a medical history and we will ask you questions about how you are feeling, what medications you are taking and information about alcohol and drug use.
- You will have a physical exam that includes height, weight, and fetal heart rate.
- A urine sample will be taken.
- An exam will be done to see how long you have been pregnant.
- We will take a blood sample to see if the HIV in your blood is resistant to any of the drugs that are being evaluated in this study. The results of this test are not required before

you enter the study. If, however, the results show that the HIV in your blood is resistant to any of the drugs being evaluated in this study, you and your doctor will decide if you should stay on the study drugs.

- We will take blood samples to test you for HIV, to see how much HIV is in your blood, and to see how many CD4 cells (white blood cells that fight infection) are in your blood.
- About 21 mL or 4 teaspoons (*sites - add locally relevant description of blood volume)* of blood in total will be taken from you for screening and other tests.
- You will be told the results of these tests taken now and at other times during the study as soon as they are available.

<u>If you do not enroll into the study</u>

- If the tests show that you are not eligible to participate, you will continue to receive care from your usual provider who will help you decide if you should continue to take your HIV drugs or not after your baby is born.

- If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of the screening visits, some demographic (e.g., age, gender, race), clinical (e.g., disease condition, diagnosis), and laboratory (e.g., CD4+ cell count, viral load, HIV resistance testing) data are being collected from you so that the researchers may determine whether there are patterns or common reasons why people do not join the study.

<u>Study visits while you are pregnant if you enroll into the study</u>

- The first study visit will be done as soon as possible but within 30 days of the screening visit.
- You will be randomized (like the flip of a coin) to have an equal chance of receiving one of two anti-HIV drug medications *[sites insert locally relevant description]* in one of the following study groups:
  - If you are in Arm A, you will take one lamivudine/zidovudine tablet two times a day plus one efavirenz tablet once each night on an empty stomach fasting at least 1 hour before or 2 hours after a meal. At any time during the study, if you stop taking efavirenz, your primary care physician may recommend that you continue to take lamivudine/zidovudine for a period of time.
  - If you are in Arm B, you will take one lamivudine/zidovudine tablet two times a day plus one raltegravir tablet twice a day.
- If your doctor believes that you should not receive lamivudine/zidovudine, he may replace lamivudine/zidovudine with a different medication combination. Your doctor will make this decision before you are randomized to Arm A or Arm B.
- If your doctor thinks you should continue to take anti-HIV medications for your own health you may continue to take study-supplied medications for up to 8 weeks after delivery while your doctor arranges your treatment.
- You will come to the clinic up to 10 times while you are still pregnant and each visit will last about *(sites – add local information about time for study visits).*

- The total amount of blood to be drawn at each visit will be between 11-15 mL (less than 3 to 4 teaspoons), [*sites - add locally relevant description of blood volume]* depending on the tests to be done.
- You will have medical check-ups to include a history, physical exam and blood tests to see how much HIV is in your blood and to see how your body is fighting infection. Other information from your routine obstetrical care will be collected by the study.
- We will ask you about when you took your most recent doses of medicines.
- You will have vaginal swabs taken at each visit which can be obtained without the use of a vaginal speculum. Two swabs will be collected, one at a time. The swab will be gently inserted into the vagina for about 1 inch and rolled around the wall of the vagina. These swabs will be tested at the end of the study for amount of HIV and other microbes. You will not receive the results of these tests.

Special blood studies

During each study visit while you are pregnant, 5 mL or less than 1 teaspoon (*sites – add locally relevant description of blood volume*) of the blood will be used for special studies. These will include a measurement of the amount of medication in the blood, additional testing to see how fast HIV goes down in your blood, and additional testing for HIV resistance to medications. You will not receive the results of these special tests.

Study visits while you are in labor

While you are in labor, you may get intravenous (through a tube that is placed in a vein) zidovudine, which is given to HIV-infected pregnant women, along with the other drugs you have been taking. Your doctors may give you different or additional drugs during labor as part of your care, if they think you need them.

- You will have a medical check-up to include a history, physical exam and blood tests to see how much HIV is in your blood and to see how your body is fighting infection.
- We will ask you about when you took your most recent doses of medicines.
- About 15 mL or 3 teaspoons (*sites - add locally relevant description of blood volume)* of blood in total will be drawn at this visit.
- 5 mL or less than 1 teaspoon (sites – add locally relevant description of blood volume) of the blood will be used for special studies.

Study visits after you have your baby

- You will be seen in the clinic four times after you have your baby.
- Each visit will last about *(sites – add local information about time for study visits)* and the total amount of blood to be drawn will be between 5-15 mL or 1-3 teaspoons (*sites - add locally relevant description of blood volume)* of blood depending on the tests to be done.
- You will have a medical check-up to include a history, physical exam and blood tests to see how much HIV is in your blood and to see how your body is fighting infection.
- You will have a vaginal swab taken one time which can be obtained without the use of a vaginal speculum. Two swabs will be collected, one at a time. The swab will be gently inserted into the vagina for about 1 inch and rolled around the wall of the vagina.
- 5 mL or less than 1 teaspoon (*sites – add locally relevant description of blood volume*) of blood will be used for special studies. These will include measurement of the amount of medication in the blood and additional testing for HIV resistance to medications. You will not receive the results of these special tests.
- If you are taking efavirenz (Arm A), you should use two methods of contraception (a barrier method such as condom, diaphragm or cervical cap) together with another form of contraception for 4 weeks after you stopped taking efavirenz.

Study visit if the amount of HIV in your blood is high

- If your doctor finds that the study drugs are not working and the amount of HIV in your blood is higher than expected, you will have blood tests to measure the amount of HIV in your blood and to see how your body is fighting infection. You will receive the results of these tests as soon as they are available.
- About 18 mL or 3-4 teaspoons (*sites - add locally relevant description of blood volume)* of blood in total will be taken at this visit.
- 5 mL or less than 1 teaspoon (*sites – add locally relevant description of blood volume*) of the blood will be used for special studies.

Study visit if you have to leave the study early

- You will have a medical check-up to include a history, physical exam and blood tests to see how much HIV is in your blood and to see how your body is fighting infection.
- About 15 mL or 3 teaspoons (*sites - add locally relevant description of blood volume)* of blood in total will be taken at this visit.
- 5 mL or less than 1 teaspoon (*sites – add locally relevant description of blood volume*) of the blood will be used for special studies.

Study treatment after your participation in this study ends

- If your doctor thinks you should continue to take anti-HIV medications for your own health, you may receive study-supplied anti-HIV medications for up to 8 weeks after delivery while your primary care physician arranges your treatment.

Study visits for your baby

- After you deliver your baby, your baby will start taking anti-HIV medication prescribed by your baby's doctor.
- Your baby will take anti-HIV medication for as long as your doctor prescribes it.
- Your baby will be in this study until he/she is 6 months old. At the 6 month visit, you may be asked to have your baby continue in a study of child development that will last until 4 years of age.
- At birth and four other times while your baby is in this study, your baby will have a medical check-up and a physical examination that includes length, weight, and head measurement.
- Your baby's blood will be taken at birth and four times during the study for routine tests and to test for HIV.
- Each of your baby's study visits will last about *(sites – add local information about time for study visits)* and the total amount of blood to be drawn will be between 2 and 4 mL or less than 1 teaspoon (*sites - add locally relevant description of blood volume)* of blood, depending on the tests to be done.
- If your baby has a positive test for HIV infection, you will be asked to return for an additional blood draw of 4 mL, or less than 1 teaspoon, to confirm HIV infection. If your baby has HIV infection, your doctor will make sure you have a place to take your baby for HIV treatment and care.
- Your baby will have a nose and mouth swab taken at two visits. A swab will be gently inserted into the nose and another into the mouth for about 1 inch and rolled around. Two swabs will be collected, one at a time.

Storage of Blood Samples

Your samples will be stored at a special laboratory facility [*sites can amend according to local regulations*]. The samples may be sent to the US.for storage and testing [*sites can amend according to local regulations*]. Only approved researchers will have access to them. People who work at the facility will also have access to your samples to keep track of them. These people won't have information that directly identifies you. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the NIH. There is no time limit on how long your samples will be stored.

The researchers do not plan to contact your regular doctor with the results of studies done using your stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your medical care. If the researchers decide that the result of a certain study provides important information for your medical care, your study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your samples stored for future research studies. You can still participate in this study even if you make this decision. You may withdraw your consent for

the storage and use of your samples at any time. If you withdraw your consent, these stored samples will be destroyed. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my blood samples to be stored for use in future NIH-approved, HIV-related research studies.

_____ Yes _____ No _____ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 394 HIV-infected women and their infants will take part in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You and your baby will be in this study until 6 months after you have your baby. You may be asked for permission for your baby to continue in this study until he/she is 4 years of age.

After the study

If you/your baby can no longer come to the clinic for study visits before the end of the study, you and your baby will be asked to come to the clinic for a final study visit. This visit will include a medical history, physical exam, and blood tests to see how much HIV is in your blood and to see how well your body is fighting infection. If your baby is found to be infected with HIV *[sites: add local referral information as appropriate]*.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

The study doctor may need to take you/your baby off the study early without your permission if:

- The study is cancelled by the National Institute of Child Health and Human Development (NICHD), US Food and Drug Administration (FDA), NIH, the drug companies supporting this study, the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research participants.
- You are/your baby is not able to attend the study visits as required by the study.
- Continuing in the study may be harmful to you/your baby.

If you/your baby have/has to stop taking the study medications before your participation in the study is over, the study staff will discuss other options that may be of benefit to you/your baby. The study doctor will ask you/your baby to continue to be part of the study and return for some study visits and procedures.

The study doctor may also need to take you/your baby off the study drug without your permission if:

- Continuing the study drug may be harmful to you/your baby
- You/your baby need(s) a treatment that you/your baby may not take while on the study
- You are/your baby is not able to take the study drug as required by the study

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. The study treatments may involve risks to the fetus that are currently unforeseeable. If you have questions concerning additional study drug side effects please ask the medical staff at your site.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, signs and symptoms of inflammation from other infections may occur soon after anti-HIV treatment is started.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Integrase Inhibitor

Raltegravir, (RAL, Isentress™)
Merck & Co., Inc.

The following side effects have been associated with the use of raltegravir:

- Upset stomach
- Headache
- Tiredness
- Weakness
- Trouble sleeping
- Rash, which can be severe
- Feeling anxious
- Depression, suicidal thoughts and actions
- Paranoia (an abnormal sense of fear)

- Low blood platelet count
- Muscle tenderness, weakness or injury which can be serious and lead to kidney damage

Cancers have been seen in people who took raltegravir with other HIV drugs. The types of cancers seen are typical for people with very sick immune systems. It is unknown if the cancers were related to raltegravir use.

If you develop a rash with any of the following symptoms stop using raltegravir and contact your Health Care Provider right away:

- Fever
- Generally ill feeling
- Extreme tiredness
- Muscle or joint aches
- Blisters or sores in mouth
- Blisters or peeling of the skin
- Redness or swelling of the eyes
- Swelling of the mouth or face
- Problems breathing

Sometimes allergic reactions can affect body organs, like the liver and cause liver problems which can lead to liver failure. Contact your Health Care Provider right away if you have any of the following signs or symptoms of liver problem:

- Yellowing of the skin or whites of the eyes
- Dark or tea colored urine
- Pale colored stools/bowel movements
- Nausea/vomiting
- Loss of appetite
- Pain, aching or tenderness on the right side below the ribs

In some patients receiving raltegravir blood tests showed abnormally elevated levels of a muscle enzyme—creatine kinase which may cause muscle pain, tenderness or weakness this type of muscle break down can be serious and lead to kidney damage including kidney failure. Contact your HCP right away if you have any unexplained muscle pain, tenderness, or weakness…

- Dizziness
- Clumsiness and lack of coordination.

<u>Nucleoside Analogue</u>

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Lamivudine (3TC, EPIVIR®)
GlaxoSmithKline

The following side effects have also been associated with use of lamivudine:
If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting
- Abnormal pancreatic and liver function blood tests

Zidovudine (RETROVIR®)
GlaxoSmithKline

The following side effects have been associated with use of zidovudine:

- Decrease in the number of white blood cells that help fight infection
- Decrease in the number of red blood cells that may cause weakness, dizziness, and fatigue
- Muscle aches, weakness, and wasting
- Headache
- Upset stomach
- Vomiting
- Decrease in appetite
- Vague overall feeling of discomfort
- Lack of energy
- Feeling tired
- Sleeplessness
- Heartburn

Non-Nucleoside Reverse Transcriptase Inhibitor

Efavirenz (EFV, SUSTIVA®, STOCRIN®)
Bristol-Myers Squibb or Merck & Co., Inc.

The following side effects have been associated with the use of efavirenz:

A small number of people may experience the following serious psychiatric problems:

- Depression, which may be severe
- Suicidal thoughts or attempts (rarely)
- Aggressive behavior
- Psychosis-like symptoms, such as abnormal thinking, paranoia, and delusions

People with a history of psychiatric problems may be at greater risk for these serious psychiatric problems.

Side effects associated with the central nervous system may include the following:

- Dizziness
- Trouble sleeping
- Abnormal dreams
- Drowsiness
- Confusion
- Difficulty concentrating
- Hallucinations
- A feeling of strangeness and losing touch with reality
- An exaggerated feeling of well-being
- Agitation or anxiety

If alcohol or mind- or mood-altering drugs are used with efavirenz, it is possible that the central nervous system side effects could become worse.

Serious liver problems and worsening liver disease can occur. These problems can be life-threatening. People with these conditions may have abnormal liver function blood tests. If you are developing liver problems, you may have one or more of the following: yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale-colored stools, itchy skin.

Additional side effects include:

- Rash, which in rare cases may be severe
- Upset stomach
- Loose or watery stools
- Headache
- Abnormal increases in the amount of triglycerides and cholesterol in the blood
- Abnormal increases in pancreatic enzyme levels in the blood and/or inflammation of the pancreas (pancreatitis) which may result in stomach pain, nausea and/or vomiting.

Efavirenz and Pregnancy

The use of this drug during pregnancy and especially early pregnancy should be avoided. Efavirenz may cause fetal harm when taken during the first 3 months of pregnancy. **Serious birth defects, including open spine, water on the brain, and cleft palate, have been seen in the offspring of animals and women on efavirenz in early pregnancy. The risks of taking efavirenz later in pregnancy are not known. However, efavirenz taken after the first 3 months of pregnancy are not expected to cause birth defects. The World Health Organization and some country guidelines recommend that it is safe for women to take efavirenz throughout pregnancy.**

A false-positive urine-screening test for marijuana has been seen with one particular test brand and has not been seen when using other screening tests or with tests used to confirm results for marijuana.

There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if protease inhibitors were the cause of these bleeding episodes.

Other Risks

There is the risk of serious and/or life threatening side effects when non-study medications are taken with study drugs. For your/your baby's safety, you must tell your/your baby's HIV care provider and the study doctor or nurse about all medications you take/your baby takes before the start of this study and also before starting any new medications while you are/your baby is in the study. You must tell the study doctor or nurse before you or your baby join in any other research studies while on this study.

The use of potent antiretroviral drug combinations may also be associated with altered fat metabolism including elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your baby's doctor immediately. It is also important that while participating in the study, you do not/your baby does not take any other prescription drugs or over-the-counter medications without first talking to your/your baby's doctor or study nurse.

If you are in Arm A (you take efavirenz) and you are sexually active, after delivery, you should use two methods of contraception (a barrier method such as condom, diaphragm or cervical cap) together with another form of contraception for 4 weeks after you stopped taking efavirenz.

Social Risks

If you join this study, some hospital staff and all study staff will know that you have HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be

sure that others do not learn your HIV status. However, sometimes if you receive special treatment or attend a special clinic, it may make others wonder if you have HIV.

Risks of Drawing Blood

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

Risks of Collecting Vaginal/Nasal/Oral Swabs

Collection of swabs may cause minor discomfort during collection, but no other risks are expected.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You/your baby may receive no benefit from being in this study. **You and your baby may benefit from the more frequent monitoring of HIV levels and for side effects. Information learned from this study may help other pregnant women who have HIV if one of the drug combinations works better than the standard regimen of lamivudine/zidovudine usually given to pregnant women to decrease the chance of HIV passing to the baby.** We do not know if taking raltegravir or efavirenz in addition to the other anti-HIV drugs will decrease the chance of your baby getting HIV.

WHAT OTHER CHOICES DO I/DOES MY BABY HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you/your baby
- treatment with experimental drugs, if you/your baby qualify(ies)
- no treatment (not recommended for pregnant women)

If you choose not to be in this study, you will be offered the local standard treatment with anti-HIV drugs. Please talk to your doctor about these and other choices available to you/your baby. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

United States sites

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands

for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal FDA.

People who may review your records include the US FDA, the site IRB or Ethics Committee, other national regulatory agencies, the NIH, the OHRP, study staff, study monitors, and drug companies supporting the study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Sites outside the United States

Efforts will be made to keep your/your baby's personal information confidential. We cannot guarantee absolute confidentiality. Your/your baby's personal information may be disclosed if required by law. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

Your/your baby's records may be reviewed by the US FDA, the site IRB or Ethics Committee, other national regulatory agencies, the NIH, the OHRP, study staff, study monitors, and drug companies supporting the study, and their designees.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the study-related visits and procedures and the anti-HIV medications given to you or your baby in this study. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your baby is taking part in a research study.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your

insurance company. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time. Your decision will not have any impact on your participation or your baby's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you or your baby are otherwise entitled.

We will tell you about new information from this or other studies that may affect your/your baby's health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *name of the investigator or other study staff*
- *telephone number of above*

For questions about your/your baby's rights as a research participant, contact:

- *name or title of person on the IRB or other organization appropriate for the site*
- *telephone number of above*

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in and allow your baby to take part in this study, please sign your name below.

Participant's Name (print)	Participant's Signature and Date
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
Study Staff Conducting	Study Staff Signature and Date
Witness' Name (print)	Witness's Signature and Date

APPENDIX VII
EXTENSION PHASE: NEURODEVELOPMENTAL ASSESSMENT OF INFANTS: NICHD P1081S

1. INTRODUCTION

1.1 Background

Efavirenz has been associated with severe fetal neurological malformations (anencephaly, anophthalmia, microophthalmia) in cynomolgus monkeys exposed to efavirenz from the beginning of pregnancy. Cases of neural tube defects have been reported in human infants following first trimester efavirenz exposure, but a meta-analysis of 23 studies including 2026 live births after first trimester efavirenz exposure demonstrated a very low rate of neural tube defects (1 case; 0.05%) that was similar to the rate in the general population and no increase in overall rate of birth defects.[1] Based on these and other data, the 2013 WHO guidelines recommended that efavirenz can be used safely as first-line therapy throughout pregnancy.[2]

The present study includes administration of efavirenz to pregnant women in the third trimester, well after the formation of neural tube derivatives, and thus completely avoids contributing to the risk of congenital defects.

Studies describing the effects of prenatal efavirenz exposure on infant neurodevelopmental outcomes are limited. Schneider, et al published an uncontrolled study documenting normal intellectual, psychomotor and growth outcomes in 13 infants born to HIV-1 infected pregnant women from Rwanda treated with triple ARV regimens including efavirenz at 8 weeks of pregnancy and continued for 6 months after delivery.[3] Westreich conducted a Denver Developmental Screening Test (DDST) on 41 infants out of 136 (30%) whose mothers identified as having taken efavirenz from before conception; 11 of the 41 infants (27%) scored as suspect for developmental delay.[4] However, this uncontrolled study had no efavirenz-unexposed comparison group administered the DDST, the DDST norms are based on a US reference group and may not be applicable to other sociocultural settings, and the DDST is a screening rather than diagnostic test which has low to moderate specificity (0.43-0.80 in population for which test has been validated).[5] In addition, only 30% of the efavirenz exposed infants underwent DDST, raising concern for bias in who was approached or willing to have DDST. These infants had efavirenz exposure from the very beginning of their in utero life, so there is no information about exposures that begin in the third trimester; in fact, the published manuscript [6] that includes the DDST data presented as a poster in 2010,[4] states that 75% of women who became pregnant while receiving efavirenz stopped their efavirenz during that pregnancy, so this study's results may have very low applicability to late-pregnancy exposure.

Current WHO Guidelines [2] include triple ARV regimens with efavirenz as a recommended regimen for prophylaxis for PMTCT and for treatment of women throughout gestation. Furthermore, efavirenz is also recommended as an important alternative for HIV/TB co-infected pregnant women.

Given the lack of data describing infant developmental outcomes following third trimester efavirenz use, this protocol includes an optional substudy that would perform screening and comprehensive neurodevelopmental assessments beginning at 1 year of age in both study arms to evaluate potential specific areas of deficit and broad developmental outcomes and to compare them between study arms.

1.2 Comprehensive Neurodevelopmental Assessments

Comprehensive neurodevelopmental assessments will be done in the infants at 1 and 4 years of age to monitor potential specific areas of deficit and broad developmental outcomes for each arm of the study.

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III),[7] which covers cognitive, language and motor functioning will be administered at 1 year of age. All five scales will be administered: Cognitive, Language (Receptive and Expressive), Motor (Fine and Gross), Social-Emotional, and Adaptive Behavior (Conceptual, Social, and Practical). The Bayley scales are the most commonly used test instrument internationally to assess development in very young children, and has been used extensively in Africa and Brazil.[8] The Bayley will require approximately 30-60 minutes to administer, depending on the time required to adapt the child to the test setting.

The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III),[9] which covers multiple domains including cognitive, language, visual processing, and processing speed, which has a motor component, will be administered at 4 years of age. The preschool version of the Behavior Rating Inventory of Executive Functioning (BRIEF),[10] a parent questionnaire, will be administered to assess executive functioning skills. The evaluation at age 4 will be able to cover neurodevelopmental domains in a more comprehensive fashion. These will take 1½ to 2 hours to administer.

1.3 Screening Neurodevelopmental Assessments

Screening assessments will be completed at 1, 2, 3 and 4 years of age along with a physical examination in order to monitor for any developmental problems, to obtain additional information from parent report, and to support retention of participants.

The Ages and Stages Questionnaire (ASQ) is a caregiver report screening questionnaire for children ages 4 months to 5 years, which will be completed with the caregiver by a trained assessor.[11] The questions cover a broad range of

developmental milestones that can be observed by caregivers in the home setting. This measure has subscales including Communication, Gross Motor, Fine Motor, Personal-Social, and Problem-Solving, which covers the same domains as the Bayley subscales. The ASQ will provide some data on development for 1 year olds who cannot be tested for any reason, as well as providing a check on the validity of the adapted Bayley scores. The ASQ will provide monitoring data for years 2, 3 and 4, and will again provide a validity check on the 4 year old neuropsychological assessment. The ASQ can be administered in 10-15 minutes.

The Ten Questions Questionnaire (TQQ) is a brief screening for significant neurological impairment that has been frequently used internationally with no need for significant adaptation (other than translation). It will be administered at the same time as the ASQ. The TQQ can be completed in a few minutes.

Feedback will be provided to parents/caregivers on whether the child's performance in each developmental domain is broadly within age expectation. Specific scores will not be given as tests are not normed for each site. Referrals will be made for further intervention to available resources if problems are found.

2. OBJECTIVE

To compare infant neurodevelopmental outcomes in HIV-exposed infants between the two treatment regimens.

3. STUDY DESIGN

Infant Neurodevelopmental Assessments

At 1 year of age, infants will have a comprehensive neurodevelopmental assessment using the BSID-III, which covers cognitive, language and motor functioning. At 4 years of age, infants will be tested using the WPPSI-III, which covers cognitive, language, visual processing, and processing speed. In addition, parent questionnaires measuring development and basic motor and sensory processing will be administered at 1, 2, 3 and 4 years of age.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Infant who participated in NICHD P1081.

4.2 Enrollment Procedures

Eligible participants may enroll into the "Extension Phase: Developmental Assessment of Infants" once notified by the protocol team that this extension phase has been activated for enrollment.

Participant enrollment is done through the Data Management Center (DMC) Subject Enrollment System (SES). When a signed informed consent form has been obtained, a Screening Checklist must be entered through the DMC SES. For all participants from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the initial protocol step for any reason, a Screening Failure Results form must be completed and keyed into the database.

5. PARTICIPANT MANAGEMENT

Questions concerning clinical management of study participants and all communication regarding adverse experiences should be addressed to the P1081 CMC at NICHD.p1081cmc@fstrf.org. Remember to include the participant's Patient Identification Number (PID) when applicable. Please do NOT disclose the study arm to which a participant is randomized unless specifically requested. The appropriate team member will respond to questions via email with a "cc" to NICHD.teamp1081@fstrf.org. A response should generally be received within 24 hours (Monday - Friday).

5.1 Criteria for Study Discontinuation

The participant will be discontinued from the study for any of the following reasons:

- The legal guardian refuses further follow-up evaluations and decides to discontinue participation in the study.
- The investigator determines that further participation would be detrimental to the participant's health or well-being.
- The legal guardian fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The study is cancelled at the discretion of the NIH, the IRB or EC, FDA, OHRP, or the pharmaceutical sponsor(s) or other governmental agencies.

6. EXPEDITED ADVERSE EVENT REPORTING

6.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0, January 2010, of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The DAERS, an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit EAEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

6.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0, January 2010, of the DAIDS EAE Manual, will be used for this study.

The study agents for which relationship assessments are required are maternal raltegravir, efavirenz, lamivudine, zidovudine and other maternal ARV agents used during the study.

In addition to reporting all SAE's as defined above, other events that sites must report in an expedited fashion include malignancies, **study drug overdoses, all immune reconstitution inflammatory syndrome events that qualify as SAEs,** seizures and hepatotoxicities whether or not symptomatic or related to study drug, and all other Grade 3 or 4 related toxicities (except Grade 3 neutropenia and anemia) for which a relationship to study drug cannot be ruled out.

The death of any participant after enrollment or within 30 days of study completion, regardless of the cause, must be reported immediately and no later than 3 reporting days of first becoming aware of the death. After the 30-day period, deaths need to be reported only as part of long-term follow-up studies. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAEs submitted to the RSC, sites must file an updated SAE report to the RSC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

All reports submitted to the RSC must also be documented on the appropriate clinical CRFs and submitted to the study database through the eData system. Reconciliation of the two databases will be performed at regular intervals.

6.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), Version 2.0, dated November 2014, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.4 EAE Reporting Period

Only **Serious Unexpected Suspected Adverse Events** as defined in Version 2.0, January 2010, of the EAE Manual will be reported to DAIDS **for the duration of the participant's enrollment in the study, and after study completion** if the study staff become aware of the events on a passive basis (from publicly available information).

6.5 CRF Recording Requirements for Laboratory Test Results, Signs, Symptoms, and Diagnoses

The results of all protocol-required laboratory tests performed at screening, entry, and post-entry must be recorded on CRFs, regardless of severity grade.

All abnormal (severity grade 1 and higher) signs, symptoms, and diagnoses occurring within 30 days prior to study entry must be recorded on CRFs. All abnormal (severity grade 1 and higher) signs, symptoms, and diagnoses occurring post-entry must also be recorded on CRFs at all visits.

7. STATISTICAL CONSIDERATIONS

7.1 Outcome Measures

IQ scores (from the Bayley and Wechsler scales), executive functioning skills (from the BRIEF questionnaire), and neurodevelopmental deficits (from the TQQ and the ASQ).

7.2 Data Analyses

Neurodevelopmental assessments will be given annually at ages 1 to 4 years. The infant neurodevelopmental data analyses will be performed after all infants have completed their year 1 evaluations and then again after all infants have completed the entire study.

Neurodevelopmental data analyses will be based on comparisons of the two study arms. Two sample t-tests will be used to compare IQ scores between treatment arms at ages 1 and 4 years. For the TQQ and ASQ, which have binary (yes/no) outcomes, chi-square tests will be used to compare the frequencies of identified deficits between the two study arms.

7.3 Sample Size

The sample sizes available for the neurodevelopmental analyses are expected to be smaller than for the primary outcomes both because of attrition and because not all participants will choose to participate. Loss to follow-up is expected to be relatively small at the 1 year assessment, but may increase significantly by the 4

year assessment. For this reason, sample sizes ranging from 50% to 90% of the original have been used for the following calculations.

Table 1 shows the effect size detectable between the two study arms with 80% power and 0.05 two-sided α, and the precision (1/2 width of the 95% confidence interval) for estimating the within-arm mean, with sample sizes ranging from 50% to 90% of the initial sample. The effect sizes were calculated using PASS 11 under the model of two sample t-tests. The differences detectable with 80% power range from 0.32 to 0.43 standard deviations and the precision ranges from 0.16 to 0.22 standard deviations. To obtain the minimum detectable effect size and precision for a specific test, the numbers in Table 1 need to be multiplied by the standard deviation of the test. For example, using an IQ test (i.e., Bayley or WPPSI) with a standard deviation of 15, this translates into 80% power to detect differences between arms of 4.8 to 6.5 IQ points, and precision (1/2 width of 95% confidence intervals) of 2.4 to 3.2 IQ points (see Table 1).

Table 1: Detectable differences between two study arms with 80% power and alpha=0.05, and, precision for estimating the within-arm mean

% of initial sample size	Number of evaluable children per treatment arm	Total number of children	Minimum detectable effect size		Precision of estimate of within-arm mean (1/2-width of 95% confidence interval)	
			Number of standard deviations	IQ points (s.d. of 15)	Number of standard deviations	IQ points (s.d. of 15)
50%	85	170	0.43	6.5	+/-0.22	+/- 3.2
60%	101	202	0.40	6.0	+/-0.20	+/- 2.9
70%	118	236	037	5.6	+/-0.18	+/- 2.7
80%	135	270	0.34	5.1	+/-0.17	+/- 2.5
90%	152	304	0.32	4.8	+/-0.16	+/- 2.4

The ASQ and TQQ both provide binary outcomes for various potential problem areas. Table 2 shows the detectible difference in proportion of participants experiencing neurodevelopmental deficits with 80% power and overall 2-sided α =0.05. The detectable difference in proportions between the study arms ranges from 0.12 to 0.22, corresponding to odds ratios from 0.22 to 0.51, depending on the available N and proportion in Arm 1.

Table 2: Detectable difference in proportion of participants experiencing neurodevelopmental deficits with 80% power and overall 2-sided $\alpha = 0.05$

Proportion in Arm 1	N/arm	Detectible proportion in Arm 2	Detectible difference in proportions	Odds ratio
0.20	85	0.05	0.15	0.22
	101	0.06	0.14	0.26
	118	0.07	0.13	0.30
	135	0.08	0.12	0.33
	152	0.08	0.12	0.36
0.30	85	0.12	0.18	0.32
	101	0.13	0.17	0.35
	118	0.14	0.16	0.39
	135	0.15	0.15	0.42
	152	0.16	0.14	0.45
0.40	85	0.20	0.20	0.37
	101	0.21	0.19	0.40
	118	0.23	0.17	0.44
	135	0.24	0.16	0.46
	152	0.25	0.15	0.49
0.50	85	0.28	0.22	0.39
	101	0.30	0.20	0.43
	118	0.32	0.18	0.46
	135	0.33	0.17	0.49
	152	0.34	0.16	0.51

8.0 EXTENSION PHASE: INFANT SCHEDULE OF EVALUATIONS

	Week 52[1] (Age 1 year)	Week 104[1] (Age 2 years)	Week 156[1] (Age 3 years)	Week 208[1] (Age 4 years)
NEURODEVELOPMENTAL / NEUROPSYCOLOGICAL EVALUATIONS				
Bayley Scales of Infant and Toddler Development-Third Edition (BSID III)[2]	X			
Ages and Stages Questionnaire (ASQ)[2]	X	X	X	X
Ten Questions Questionnaire (TQQ)[2]	X	X	X	X
Wechsler Preschool and Primary Scale of Intelligence (WPPSI III) and Behavior Rating Inventory of Executive Function-Preschool Version [2]				X[3]

FOOTNOTES FOR EXTENSION PHASE: INFANT SCHEDULE OF EVALUATIONS

1. Visit window is ± 30 days.
2. Neurodevelopmental and neuropsychological evaluations may be performed outside the visit window with permission from the protocol psychologist.
3. The WPPSI III cannot be administered until the child is at least 4 years old.

9.0 REFERENCES

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SAMPLE INFORMED CONSENT

A Phase IV Randomized Trial to Evaluate the Virologic Response and Pharmacokinetics of Two Different Potent Regimens in HIV-infected Women Initiating Triple Antiretroviral Regimens Between 28 and 36 Weeks of Pregnancy for the Prevention of Mother-to-Child Transmission, Infant Development Substudy: NICHD P1081S

INTRODUCTION

You are being asked for your baby to take part in this research study because your baby participated in the first part of this P1081 study. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (*insert name of Principal Investigator*). Before you decide if you want your baby to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to/allow your baby to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

In this study, we want to measure how infants learn and develop over the first 4 years of life. We would like to understand if the development is different for infants whose mothers took efavirenz during pregnancy and infants whose mothers took raltegravir during pregnancy.

WHAT DO I/DOES MY BABY HAVE TO DO IF MY BABY IS IN THIS STUDY?

- **At 1, 2, 3 and 4 years of age,** your baby will have a physical examination that includes length, weight, and head measurement. You will be asked about your baby's health at each of these visits.
- **When your baby is one year old,** your baby will have a test to check his/her motor skills and behavior and learning abilities. This test is a series of developmental play tasks and takes between 30-60 minutes to administer.
- **At 1, 2, 3 and 4 years of age,** you will be asked to complete two questionnaires about your baby's development which will take about 10-20 minutes to answer.
- **When your baby is 4 years old,** your baby will have a neuropsychological test to check his/her language and motor skills. This test will take about 1-1½ hours to complete.
- You will be told whether your baby is developing according to his/her age expectation and a referral for further testing will be made if problems are found.
- Each of your baby's study visits will last about *(sites – add local information about time for study visits)*.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 334 infants may take part in this study.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You and your baby will be in this study until your baby is 4 years of age.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

The study doctor may need to take you/your baby off the study early without your permission if:

- The study is cancelled by the NICHD network, US Food and Drug Administration (FDA), NIH, the drug companies supporting this study, the Office for Human Research Protections (OHRP), other national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research participants.
- You are/your baby is not able to attend the study visits as required by the study.
- Continuing in the study may be harmful to you/your baby.

WHAT ARE THE RISKS OF THE STUDY?

There are no risks in taking the neurodevelopmental or neuropsychological tests other than your baby might find some parts of the tests difficult to do.

Social Risks

If you join this study, some hospital staff and all study staff will know that you have HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatment or attend a special clinic, it may make others wonder if you have HIV.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You/your baby may receive no benefit from being in this study. **You and your baby may benefit from the information you will receive about your baby's development. Information learned from this study may help with advice to other pregnant women about which HIV drugs to take during pregnancy.**

WHAT OTHER CHOICES DO I/DOES MY BABY HAVE BESIDES THIS STUDY?

Instead of being in this study, your baby's regular doctor can monitor your baby's development at your baby's regular check-ups.

WHAT ABOUT CONFIDENTIALITY?

United States Sites:
To help us protect your privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify

you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal FDA.

People who may review your records include the US Food and Drug Administration, the site IRB or Ethics Committee, other national regulatory agencies, the NIH, the OHRP, study staff, study monitors, and drug companies supporting the study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Sites outside the United States:
Efforts will be made to keep your/your baby's personal information confidential. We cannot guarantee absolute confidentiality. Your/your baby's personal information may be disclosed if required by law. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

Your/your baby's records may be reviewed by the US FDA, the site IRB or Ethics Committee, other national regulatory agencies, the NIH, the OHRP, study staff, study monitors, and drug companies supporting the study, and their designees.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

There is no cost to you for the study-related visits and procedures given to you or your baby in this study. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your baby is taking part in a research study.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or leave this study/take your baby out of the study at any time. Your decision will not have any impact on your participation or your baby's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you or your baby are otherwise entitled.

We will tell you about new information from this or other studies that may affect your/your baby's health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *name of the investigator or other study staff*
- *telephone number of above*

For questions about your/your baby's rights as a research participant, contact:

- *name or title of person on the IRB or other organization appropriate for the site*
- *telephone number of above*

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in or allow your baby to take part in this study, please sign your name below.

_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Study Staff Conducting	Study Staff Signature and Date
_____	_____
Witness' Name (print)	Witness's Signature and Date