IMPAACT 2007

Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Sponsored by:
National Institute of Allergy and Infectious Diseases
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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Transaminase
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CNS	Central nervous system
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
D4T	Stavudine
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DAERS	DAIDS Adverse Event Reporting System
DBS	Dried Blood Spot
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
EAE	Expedited Adverse Event
EC	Ethics Committee
EFV	Efavirenz
EIA	Enzyme Immunoassay
FDA	(US) Food and Drug Administration
FSTRF	Frontier Science and Technology Research Foundation
FTC	Emtricitabine
GCLP	Good Clinical Laboratory Practice
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional Review Board
IND	Investigational New Drug
IoR	Investigator of Record
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
LPV/r	Lopinavir/ritonavir
MVC	Maraviroc
MOP	Manual of Procedures
NFV	Nelfinavir
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Development

NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PIBA	Press-in-bottle Adaptor
PID	Participant Identification Number
PK	Pharmacokinetics
PMTCT	Prevention of Mother To Child Transmission
PoR	Pharmacist of Record
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center
SES	Subject Enrollment System
SID	Study Identification Number
SMC	Study Monitoring Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
US	United States
WBC	White Blood Cell
WHO	World Health Organization
X4/DM	X4/dual-mixed tropic
ZDV	Zidovudine

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SCHEMA

Purpose: To determine an appropriate dose of maraviroc solution during the first six weeks of life for infants born to HIV-1 infected mothers.

Design: Phase I safety and pharmacokinetics (PK) study with two sequential dosing cohorts stratified by maternal use of efavirenz (EFV).

Study Population: Infants born to HIV-1 infected mothers and are receiving a single or combination antiretroviral (ARV) regimen for prevention of perinatal HIV transmission that does not include a potent cytochrome P450 CYP3A4 inhibitor or inducer (mothers will also be enrolled in the study but will not receive study drug).

Sample Size: Up to 72 mother-infant pairs to achieve a target of 36 evaluable infants receiving the final recommended dose of maraviroc.

Cohort 1: Stratified by infant *in utero* exposure to maternal EFV, with concurrent enrollment of both strata. Breastfeeding and formula feeding infants are eligible for this cohort; infant exposure to maternal EFV after birth is not relevant to eligibility or stratum assignment.

Up to 36 mother-infant pairs to achieve a target of 12 evaluable infants (6 in each stratum) receiving the dose of maraviroc that passes safety and PK guidelines for the relevant stratum and is recommended for Cohort 2.

Stratum 1A: n = 6-18 infants without *in utero* exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery).

Stratum 1B: n = 6-18 infants with *in utero* exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery).

Cohort 2: Stratified by infant exposure to maternal EFV after birth, with enrollment of each stratum opening upon dose selection from the corresponding stratum in Cohort 1. Breastfeeding and formula feeding infants are eligible for Stratum 2A; only breastfeeding infants are eligible for Stratum 2B.

Up to 36 mother-infant pairs to achieve a target of 24 evaluable infants (12 in each stratum) receiving the final recommended dose of maraviroc that passes safety and PK guidelines for the relevant stratum.

Stratum 2A: n = 12-18 infants without any exposure to maternal EFV either *in utero* (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding.

Stratum 2B: n = 12-18 breastfeeding infants with exposure to maternal EFV both *in utero* and after birth while breastfeeding (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding).

Study Drug: Cohort 1: Single doses of maraviroc solution at two time points: within 3 days of life and at one week (7-14 days) of life. The initial starting dose for this cohort will be 8 mg/kg; dose adjustment may occur as needed based on experience within the cohort.

Cohort 2: Daily dosing of maraviroc solution starting within 3 days of life and continuing up to 42 days of life. The initial starting dose for this cohort will be determined based on experience in Cohort 1. Dose adjustments for the cohort may occur as needed based on experience within the cohort.

Study Duration: Approximately 28 months total. Accrual is expected to require approximately 24 months and enrolled infants will be followed for four months.

Primary Objectives

- To evaluate the safety and tolerability of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
- To evaluate the pharmacokinetics of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.
- To determine an appropriate dose of maraviroc solution during the first six weeks of life.

Secondary Objectives

- To assess safety through 16 weeks of life following administration of maraviroc solution during the first six weeks of life.
- To determine age-related changes in maraviroc pharmacokinetic parameters during the first six weeks of life.
- To explore the impact of maraviroc treatment on viral tropism in the event of perinatal transmission of an X4/dual-mixed tropic strain of HIV.

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Figure 1A: IMPAACT 2007 Overview of Study Design – Cohort 1

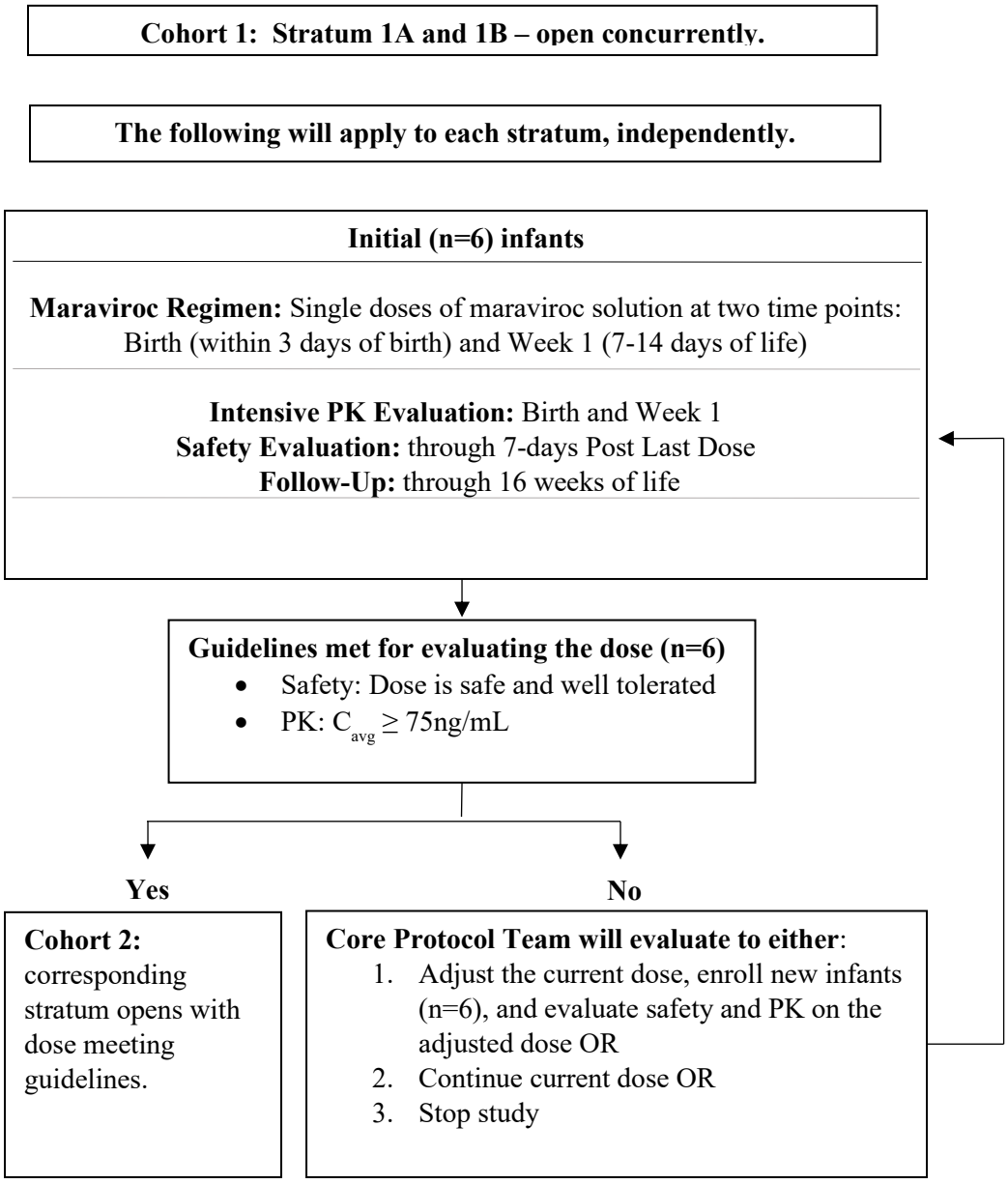
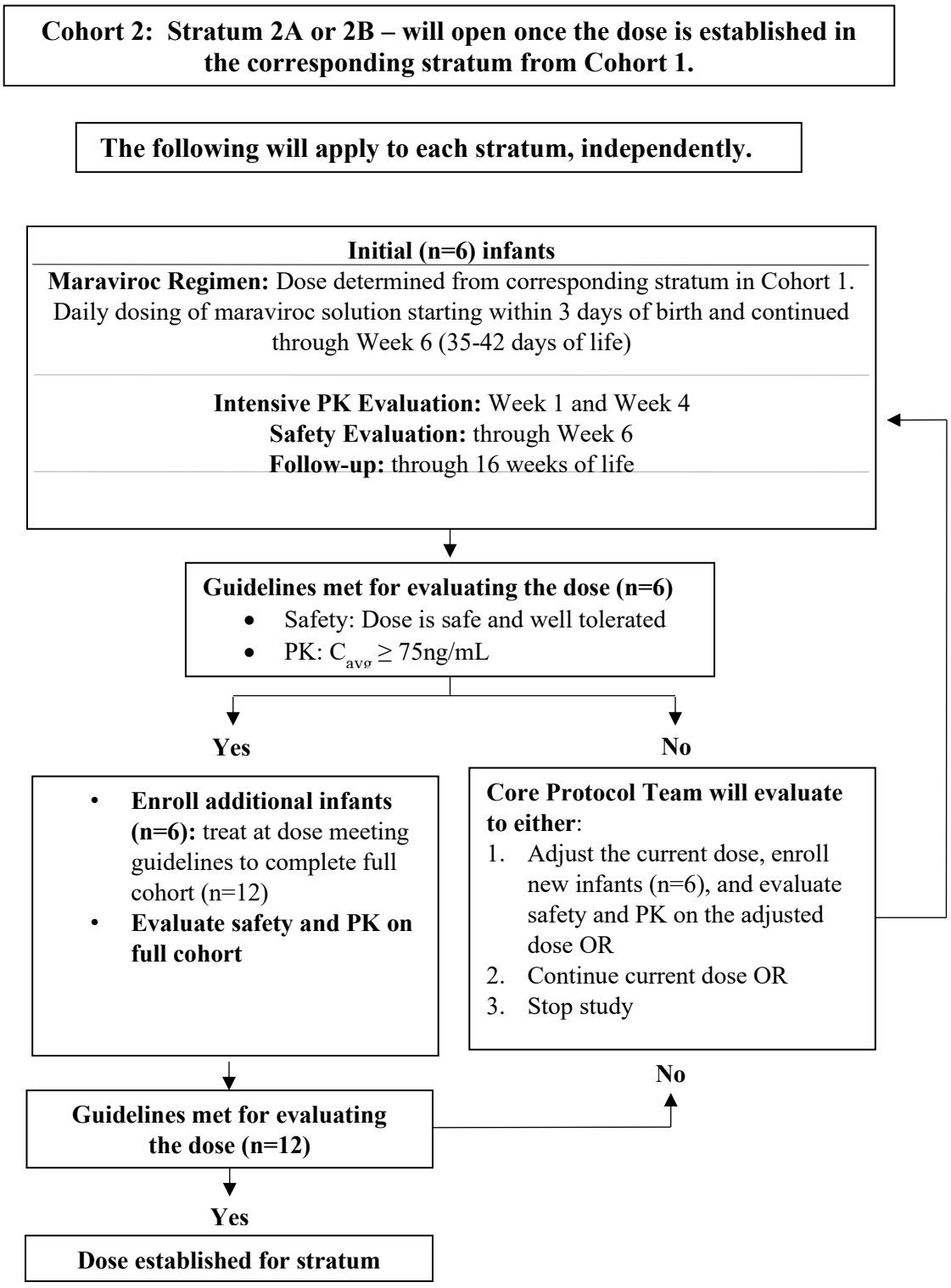


Figure 1B: IMPAACT 2007 Overview of Study Design - Cohort 2



1 INTRODUCTION

1.1 Background

While there is a critical need for ARVs for use as prophylaxis and treatment of neonates, neonatal safety and dosing information are not available for most ARVs. Of the nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitor (NNRTIs), only zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), stavudine (d4T), and nevirapine (NVP) are approved for use in neonates less than 14 days of age. Of the protease inhibitors, only nelfinavir (NFV) has pharmacokinetic (PK) data available for neonates, but these data demonstrate highly variable plasma concentrations and the optimal dosing regimen remains uncertain.[1, 2] The powder formulation of NFV that was studied in neonates is no longer commercially available and NFV is not approved in children less than two years old. Lopinavir/ritonavir (LPV/r), is available as a pediatric solution, but its dosing is uncertain in the first weeks of life and its use is not recommended in neonates less than two weeks old and 42 weeks post-menstrual age after several cases of life-threatening toxicities, including bradyarrhythmias, cardiac dysfunction, metabolic acidosis and CNS disturbances, were reported in neonates.[3, 4] No neonatal safety or PK data following neonatal dosing are available for any of the integrase inhibitors, so these drugs are not approved for use in neonates. The three-drug ARV regimen with the greatest experience in neonates is ZDV/3TC/NVP, and alternative agents for use in this population are urgently needed.

Maraviroc is a CCR5 receptor antagonist used in the treatment of HIV-1 infection. The safety and efficacy of maraviroc have been confirmed in Phase II-IV clinical trials. Maraviroc works as an entry inhibitor, blocking entry of HIV into vulnerable host lymphocytes. It was approved to treat CCR5 tropic HIV-1 infected adults in 2007. Current United States (US) guidelines recommend maraviroc for use in HIV-1 infected adults as second line therapy, due to lack of virologic benefit when compared with other recommended regimens and the need for twice daily dosing. [5]

Postnatal prophylaxis with multiple antiretroviral agents is currently recommended for HIV-exposed neonates at high risk for acquiring HIV infection. Due to the lack of adequate neonatal safety and PK data, the ARV options are limited to several NRTI's and the NNRTI nevirapine, as indicated above, that can be safely used in neonates. Maraviroc, as an HIV entry inhibitor, has a different mechanism of action from the NRTIs and NNRTIs, making it attractive as a potential component of neonatal prophylaxis regimens. Maraviroc's novel mechanism of action might be especially valuable for infants born to mothers with HIV strains resistant to the more commonly used ARV classes.

Turn-around time for diagnostic tests of HIV-1 infection has improved in recent years, and HIV-1 infected neonates are now routinely identified in the first days and weeks of life. Strategies for early treatment of HIV-1 infected newborns with intensive four drug regimens have been proposed, with a goal of either improving outcome or limiting the size of the latent reservoir to achieve long-term remission, but the drugs available for use in neonates are limited. Maraviroc may also prove to be of value for early treatment of those infants who fail prophylaxis and are diagnosed with HIV-1 infection, although this protocol will be limited to the study of maraviroc as prophylaxis in the first six weeks of life.

Because over 90% of HIV-1 infected neonates are infected with CCR5 tropic virus alone, maraviroc, as a CCR5 receptor antagonist, has the potential to play an important role in infant

prophylaxis.[6] Before maraviroc can be studied as part of a prophylaxis regimen to prevent perinatal HIV transmission, a Phase I study to investigate safety and PK in neonates is needed.

1.2 Maraviroc Pharmacokinetics and Safety in Adults

Based on data from healthy adult volunteers, maraviroc is well absorbed following oral dosing with C_{max} typically occurring 0.5-4 hours after dosing. The *in vitro* protein-adjusted IC_{90} for maraviroc against wild-type virus is 2.1 ng/mL. The oral PK of maraviroc are not dose proportional, although the non-proportionality is most marked at doses below 100 mg. This dose non-proportionality is thought to result from absorption (P-glycoprotein and other transporters) rather than elimination. Maraviroc was dosed in initial clinical pharmacology studies as an oral solution and in later clinical studies as research and commercial tablet formulations. A comparison of the PK of the oral solution to the research tablet demonstrated that maraviroc exposure following the solution dose was moderately higher (12%) than that following the tablet in the fasting state. The overall PK profile of the solution doses was similar to that of the research tablet (75 mg).[7]

Maraviroc is primarily metabolized by CYP3A4 with renal clearance contributing approximately 23% of total clearance (in the absence of metabolic inhibitors). Maraviroc does not inhibit any of the major cytochrome P450 enzymes (CYP 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4) *in vitro* at clinically relevant concentrations. Therefore, maraviroc is unlikely to inhibit the metabolism of co-administered drugs that are metabolized by cytochrome P450 enzymes. Since maraviroc is a CYP3A4 substrate, the concentration of maraviroc is increased by CYP3A4 inhibitors (including HIV protease inhibitors [PI]; except tipranavir/ritonavir) and decreased by CYP3A4 inducers (such as rifampin, etravirine, and efavirenz). In adults, maraviroc dose adjustments are recommended if it is to be co-administered with such agents, including efavirenz.[8]

The safety and efficacy of oral maraviroc for treatment of HIV-1 infection have been confirmed in Phase II, Phase III, and Phase IV clinical trials. Cumulatively, the safety and tolerability of maraviroc has been evaluated in >4,600 participants (patients and healthy volunteers) in over 50 clinical studies during the clinical development program. Cumulative post-marketing exposure to maraviroc up to 31st March 2014 is estimated to be 56,769 patient-years.[7]

Based upon the pooled data from the Phase III treatment-experienced studies, A4001027 and A4001028, the most common (>10% incidence in any treatment group) treatment-related treatment emergent adverse events (TEAEs) in the maraviroc treatment group were diarrhea, nausea, and headache. Similarly, data from the Phase III treatment naïve study A4001026 reported the most frequently reported treatment-related TEAEs (>10% incidence in any treatment group) in the maraviroc treatment group were nausea and headache.[8]

Safety concerns raised by pre-clinical models and the Phase I/IIa studies of maraviroc include postural hypotension. Theoretical concerns based on the drug's mechanism of action include an increased risk for infection and the development of malignancy. However, the Phase IIb/III studies that administered maraviroc in adults at a dose equivalent of 300mg (QD or BID) did not show any increased frequency relative to placebo of symptomatic postural hypotension, QTc interval prolongation, infections or malignancy. Postural hypotension is recognized to be the dose-limiting toxicity of maraviroc but at recommended doses, the effect is not clinically significant. When maraviroc was administered to healthy volunteers at doses higher than the recommended dose, symptomatic postural hypotension was seen at a greater frequency than in placebo. However, when maraviroc was given at the recommended dose in HIV-1 infected

participants in Phase III trials, symptomatic postural hypotension was seen at a rate similar to placebo (approximately 0.5%).[8]

Review of post-marketing and clinical trial data has identified the occurrence of very rare reports of hepatotoxicity and hepatic failure with allergic features in patients taking maraviroc. In these cases, hepatotoxicity has occurred in association with rash and/or other features of hypersensitivity, such as fever and eosinophilia, shortly after starting maraviroc (typically within 1 month). These cases are confounded by co-suspect medications which make it difficult to determine causality, however, it is possible that maraviroc may play a role in the development of drug-induced hypersensitivity.[8]

1.3 Maraviroc in Infants and Children

To begin to assess the potential for use of maraviroc in pediatric populations, PHIVCO conducted a pediatric study (Study A4001031) to determine maraviroc PK, safety and efficacy in combination with optimized background therapy in antiretroviral-experienced children 2 to <18 years of age. The maraviroc dose in this study was based on the participant's body surface area and adjusted for concomitant medication if participants were receiving potent CYP3A4 inhibitors and/or inducers. Participants demonstrated good virologic response if they achieved the target concentration of $C_{avg} \geq 100$ ng/mL, the exposure associated with near-maximal efficacy in treatment-experienced adults, and no new toxicities in children were observed. In addition, preliminary analyses suggest that maraviroc dosing in children two to less than 18 years of age could also be determined by weight bands, which may be preferable in resource sparse areas.

Safety results from Study A4001031 suggest that, in HIV-1-infected, treatment-experienced children aged two to <18 years maraviroc (administered twice-daily, in addition to OBT) was generally well-tolerated. Overall, 285 all causality TEAEs were reported for 74 (71.8%) participants up to Week 48. The proportion of participants with TEAEs in the four cohorts ranged from 64.5% to 79.1%. The TEAEs reported were predominantly Grade 1 in severity followed by Grade 2. The most commonly (>10% of participants) reported TEAEs, were diarrhea (17 [16.5%] participants), vomiting (17 [16.5%] participants), and upper respiratory tract infection (14 [13.6%] subjects). Six participants had Grade 3 or 4 TEAEs, none of which were considered to be related to maraviroc by the investigator.

A total of 12 (11.7%) participants experienced 15 SAEs up to Week 48: two participants each in Cohorts 1, 2, and 3; and six participants in Cohort 4. The majority of SAEs reported were infections. No SAEs were attributed to maraviroc by the investigator. No deaths occurred in the 48 Week reporting period.

No new safety concerns were identified regarding the occurrence of serious hypersensitivity reactions, hepatotoxicity, malignancies, infections, autoimmune diseases, rhabdomyolysis /muscle toxicity or other AE of special interest in subjects receiving maraviroc. Treatment - emergent Category C events (Grade 1 pulmonary tuberculosis and Grade 1 recurrent pneumonia) were reported in two participants in Cohort 4 and considered not related to study drug. Grade 3 and 4 laboratory abnormalities were reported in 14% of participants up to the 48-week study period. The most common laboratory abnormality was Grade 3 decreases in absolute neutrophil count experienced by 8 participants (1 each in Cohort 1 and 3, and 3 each in Cohort 2 and 4). There was no Grade 4 neutropenia.

To date, maraviroc plus other background therapy appears to be well-tolerated and effective, with a manageable safety profile in children.

Since childhood growth and maturation are most prominent during infancy, from a clinical pharmacology perspective, maraviroc absorption, distribution, metabolism and elimination are constantly changing during childhood. Due to these developmental changes in immature body organs, a PK and safety study from birth to 2 years of age has been requested by regulatory authorities. However, maraviroc's recommended use in only second line regimens limits its relevance to older infants and toddlers on initial HIV treatment regimens, who have other effective options for combination antiretroviral regimens, making a PK and safety study in HIV-1 infected older infants up to age 2 years impractical at this time. However, as discussed above, maraviroc may have a role as a component of neonatal prophylactic regimens.

An important safety consideration is whether the use of maraviroc in newborns could lead to selective transmission of X4/dual-mixed tropic (DM) strains or lead to inferior outcomes among neonates who are born having been infected *in utero* with X4/DM virus. While some data suggest that infants born to mothers with DM virus may be at elevated risk of becoming infected with X4/DM strains, most infants are born with R5 virus, and even viral populations that are initially X4/DM generally shift to CCR5 as the infant ages.[9-12] It is not expected that use of maraviroc by neonates would significantly alter the risk of transmission of X4/DM virus because maraviroc will only be given in addition to the standard of care prophylaxis regimen, and should thus only add to prophylactic efficacy. For infants already HIV-1 infected at birth, the brief exposure to maraviroc that would occur while the infant was receiving other antiretrovirals as prophylaxis would likewise not be expected to alter outcomes. In fact, while maraviroc is recommended for patients with R5 virus, two recent studies demonstrated that adults with non-R5 virus treated with maraviroc did not have a decline in CD4 count despite the absence of viral suppression.[8, 13]

Maraviroc is metabolized by CYP3A4 and its clearance is induced when administered with efavirenz, an agonist of CYP3A4 activity. As a result, the recommended maraviroc dose is doubled in adults receiving both maraviroc and efavirenz.[8] In many areas of the world with high prevalence of HIV, efavirenz is part of the ARV combination regimen most commonly used during pregnancy. Efavirenz is readily transferred during pregnancy from mother to fetus infant across the placenta and after birth from mother to infant via breast milk.[14, 15] Transplacental and breast milk transfer of efavirenz may result in accumulation of biologically active plasma efavirenz concentrations in neonates with the potential to induce neonatal CYP3A4 maraviroc clearance. This study will separate neonates into two strata, with and without exposure to maternal efavirenz, so that the impact of maternal efavirenz use during pregnancy and breastfeeding can be evaluated and the need for different maraviroc dosing in efavirenz exposed neonates can be determined.

1.4 Rationale

While maraviroc has promise for use as part of regimens to prevent or treat neonatal HIV infection, its efficacy cannot be studied until its safety and PK have been established in this population. Addition of maraviroc to a standard of care prophylaxis regimen might benefit infants by reducing the risk of perinatal transmission. This Phase I study will evaluate the safety and PK of maraviroc in infants whose mothers are HIV-1 infected and are at risk for perinatal HIV transmission. Due to the significant drug-drug PK interaction between maraviroc and efavirenz in adults, study infants will be stratified by exposure to maternal efavirenz. The maraviroc exposure target will be a C_{avg} of $\geq$ 75 ng/mL, which is the exposure associated with near-maximal efficacy in the treatment-naïve adult study (MERIT) of maraviroc given with ZDV/3TC. [16]

Although it is expected that the majority of infants enrolling in the study will not be born with HIV infection, it will be important to assess for potential switch of virus tropism after exposure to maraviroc among the few, if any infected infants. Maternal HIV RNA levels will be collected to correlate with perinatal transmission risk, and a sample for maternal viral tropism will be stored to be run in the event that the infant is found to be HIV-1 infected. In addition, since understanding of the pathogenesis of HIV transmission continues to evolve, with the consent of the mother, any blood sample that is not used will be stored for future testing if new methodologies are developed to better elucidate mechanisms of perinatal HIV transmission from mother to child.

The protocol team has been working in cooperation with ViiV Healthcare to create this study with the intention of producing data for fulfillment of a pediatric written request pursuant to the Best Pharmaceutical's for Children's Act and for labelling changes for the Company's product.

1.5 Hypotheses

Maraviroc will be well tolerated in full-term infants and can be safely administered to achieve usual drug exposure targets ($C_{avg} \geq 75$ ng/mL) as in adults treated with maraviroc.

Note: The maraviroc exposure target of $C_{avg} \geq 75$ ng/mL was selected because this is the exposure associated with near-maximal efficacy in the treatment-naïve adult study (MERIT) of maraviroc given with ZDV/3TC. [16]

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

2.1.1 To evaluate the safety and tolerability of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.

2.1.2 To evaluate the pharmacokinetics of maraviroc solution, during the first six weeks of life, when administered with ARV prophylaxis to HIV-1 exposed infants at risk of acquiring HIV-1 infection with and without exposure to maternal EFV.

2.1.3 To determine an appropriate dose of maraviroc solution during the first six weeks of life.

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 To assess safety through 16 weeks of life following administration of maraviroc solution during the first six weeks of life.

2.2.2 To determine age-related changes in maraviroc pharmacokinetic parameters during the first six weeks of life.

2.2.3 To explore the impact of maraviroc treatment on viral tropism in the event of perinatal transmission of an X4/dual-mixed tropic strain of HIV.

3 STUDY DESIGN

This is a Phase I, multi-center, open label, intensive PK study to evaluate the safety and PK of maraviroc solution when administered with a single or combination ARV regimen for prevention of perinatal HIV transmission to HIV-1 exposed infants at risk of infection. Refer to Figures 1A and 1B for an overview of the study design, to Sections 4.1-4.2 for the study eligibility criteria, and to Section 4.4 for a description of the study recruitment, screening, and enrollment process. Study sites will be located in Kenya, South Africa, Thailand, Uganda, and the United States.

The protocol will enroll two sequential dosing cohorts. Cohort 1 will be stratified by *in utero* exposure to maternal EFV and Cohort 2 will be stratified by exposure to maternal EFV during breastfeeding, as follows:

Cohort 1: HIV-exposed infants stratified by infant *in utero* exposure to maternal EFV, with concurrent enrollment of both strata. Breastfeeding and formula feeding infants are eligible; infant exposure to EFV after birth is not relevant to eligibility or stratum assignment.

Up to 36 mother-infant pairs will be enrolled in this cohort to achieve a target of 12 evaluable infants (6 in each stratum) receiving the dose of maraviroc that passes safety and PK guidelines for each stratum and is recommended for Cohort 2.

Stratum 1A: n = 6-18 infants without *in utero* exposure to maternal EFV (no EFV exposure during the eight weeks immediately prior to delivery).

Stratum 1B: n = 6-18 infants with *in utero* exposure to maternal EFV (EFV exposure for a minimum of two weeks immediately prior to delivery).

Cohort 2: HIV-exposed infants stratified by infant exposure to maternal EFV after birth, with enrollment of each stratum opening upon dose selection from the corresponding stratum in Cohort 1. Breastfeeding and formula feeding infants are eligible for Stratum 2A; only breastfeeding infants are eligible for Stratum 2B.

Up to 36 mother-infant pairs to achieve a target of 24 evaluable infants (12 in each stratum) receiving the final recommended dose of maraviroc that passes safety and PK criteria for each stratum.

Stratum 2A: n = 12-18 infants without any exposure to maternal EFV either *in utero* (no EFV exposure during the eight weeks immediately prior to delivery) and if breastfeeding while breastfeeding.

Stratum 2B: n = 12-18 breastfeeding infants with exposure to maternal EFV both *in utero* and after birth while breastfeeding. (EFV exposure for a minimum of two weeks immediately prior to delivery and while breastfeeding).

The study will implement a dose-finding algorithm based on real time safety and PK data as described in Section 9.2.

Mothers-infant pairs will be enrolled within three days of infant birth and infants will receive their first dose of maraviroc solution at entry. Infants enrolled in Cohort 1 will receive a second dose of maraviroc solution one week (7-14 days) after birth. Infants enrolled in Cohort 2 will

receive daily dosing of maraviroc solution through six weeks (35-42 days) of life. Intensive PK sampling will be performed in both cohorts per the schedule described in Section 6.0.

Infants will be followed for 16 weeks (112-140 days) of life, with clinical and laboratory evaluations as shown in the Schedules of Evaluations in Appendix IB (Cohort 1) or IC (Cohort 2). Mothers will have evaluations performed at screening and entry only as shown in Appendix IA.

4 STUDY POPULATION

This study will be conducted in full-term infants up to 3 days old, born to HIV-1 infected mothers. Infants will be enrolled in pairs with their mothers, although only infants will receive study drug. Mother-infant pairs will be selected for the study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.5 and 4.6, respectively.

4.1 Inclusion Criteria

All of the following criteria must be met in order for mother-infant pairs to be included in this study:

4.1.1 Mother is of legal age to provide independent informed consent for research participation and is willing and able to provide written informed consent for her and her infant's participation in this study.

4.1.2 Mother has confirmed HIV-1 infection based on testing of two samples collected at different time points:

- Sample #1 may be tested using any of the following:
  - Two rapid antibody tests from different manufacturers or based on different principles and epitopes
  - One enzyme immunoassay (EIA) OR Western Blot OR immunofluorescence OR chemiluminescence
  - One HIV DNA PCR
  - One quantitative HIV RNA PCR (above the limit of detection of the assay)
  - One qualitative HIV RNA PCR
  - One HIV total nucleic acid test

- Sample #2 may be tested using any of the following:
  - Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
  - One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
  - One HIV DNA PCR
  - One quantitative HIV RNA PCR (above the limit of detection of the assay)
  - One qualitative HIV RNA PCR
  - One HIV total nucleic acid test

All samples tested must be whole blood, serum, or plasma. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to Good Clinical Laboratory Practice (GCLP) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in a CLIA-certified (US sites) or VQA-certified (non-US certified) laboratory. For tests performed in other (non-GCLP-compliant or non-VQA-certified) settings, adequate source documentation including the date of specimen collection, date of testing, test performed, and test result must be available.

4.1.3 At entry, infant meets EFV exposure requirements, based on mother's report and confirmed by medical records if available, as follows:

For Cohort 1, Stratum 1A

4.1.3.1 Infant born to a mother who did not receive EFV during the eight weeks immediately prior to delivery.

Note: Breastfeeding and formula feeding infants are eligible for this stratum.

For Cohort 1, Stratum 1B

4.1.3.2 Infant born to a mother who received EFV for a minimum of two weeks immediately prior to delivery.

Note: Breastfeeding and formula feeding infants are eligible for this stratum.

For Cohort 2, Stratum 2A

4.1.3.3 Infants born to a mother who did not receive EFV during the eight weeks immediately prior to delivery and if breastfeeding, mother is not receiving maternal EFV.

Note: Breastfeeding and formula feeding infants are eligible for this stratum.

For Cohort 2, Stratum 2B

4.1.3.4 Breastfeeding infants born to a mother who received EFV for a minimum of two weeks immediately prior to delivery, intends to breastfeed for a minimum of six weeks and will continue to receive maternal EFV while breastfeeding.

Note: Only breastfeeding infants are eligible for this stratum.

4.1.4 At birth, infant's estimated gestational age was at least 37 weeks.

Note: If gestational age at birth is not documented in the infant's available birth records, study staff may assess gestational age at the earliest possible opportunity during the screening period and use this assessment for purposes of eligibility determination.

4.1.5 At birth, infant's weight was at least 2 kg.

Note: If weight at birth is not documented in the infant's available birth records, study staff may assess infant weight at the earliest possible opportunity during the screening period and use this assessment for purposes of eligibility determination.

4.1.6 At entry, infant is less than or equal to 3 days old.

4.1.7 At entry, infant has ≤ Grade 2 AST, ALT, total bilirubin, hemoglobin, white blood cell counts, and platelet counts.

4.1.8 At entry, infant has initiated antiretroviral prophylaxis that does not include a potent CYP3A4 inhibitor or inducer. (See Section 5.11).

4.1.9 At entry, infant is assessed by the site investigator or designee as generally healthy based on review of available medical records, other available medical history information, and physical examination findings.

4.1.10 Born after singleton delivery (not after multiple birth).

4.2 Exclusion Criteria

Mother-infant pairs must be excluded from the study if any of the following are identified at any time during screening:

4.2.1 Infant has any other condition that, in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives; for example, severe congenital malformation, other medical condition, or clinically significant finding from physical examination.

4.2.2 At entry, any positive infant HIV nucleic acid test result (results are not required to be available prior to entry but any positive results obtained prior to entry are exclusionary).

4.2.3 At entry, infant or breastfeeding mother is receiving any disallowed medication listed in Section 5.11.

4.2.4 Mother received maraviroc during pregnancy.

4.3 Co-Enrollment Considerations

Co-enrollment in A Phase IV Randomized Trial to Evaluate the Virologic Response and Pharmacokinetics of Two Different Potent Regiments in HIV Infected Women Initiating Triple Antiretroviral Regiments between 28 and 36 Weeks of Pregnancy for the Prevention of Mother-to-Child Transmission: NICHD P1081 is allowed. Co-enrollment in other studies is not precluded but requires approval from the protocol teams of both studies.

4.4 Recruitment, Screening, and Enrollment Process

Although mother-infant pairs will not be enrolled in this study until after delivery, recruitment will typically begin with provision of information about the study to HIV-1 infected pregnant women attending antenatal and/or Prevention of Mother to Child Transmission (PMTCT) clinics. The study-specific informed consent process will typically be conducted during the second or third trimester of pregnancy; however, the process may be conducted, in whole or in part, after infant birth.

It is generally expected that the informed consent process will take place over the course of more than one session, and women will be invited to bring their partners or other persons of their choosing to these sessions, if they wish. The informed consent process will include detailed review of the study informed consent form (ICF), time to address any questions or concerns each woman may have, and an assessment of each woman's understanding before proceeding to her informed consent decision. The process will be fully documented and only women who are able to demonstrate understanding will be asked to provide written informed consent for themselves and their infants to take part in the study.

Eligibility screening will be initiated after written informed consent is provided. Maternal screening will include confirmatory HIV-1 testing (if needed) and assessment of other maternal eligibility requirements. If at any time it is determined that a woman is not eligible for the study, or that study participation may not be feasible or in the best interest of a given woman or infant, the eligibility screening process will be discontinued.

Study staff will remain in contact with potentially eligible women as they approach their expected dates of delivery, with instructions provided to inform study staff upon onset of labor. Study staff will arrange to see each woman as soon as possible after delivery to discuss the study again and confirm continued consent for study participation. Infant screening — including review of medical records and other available medical history information, physical examination, and specimen collection for laboratory testing — may occur prior to confirmation of continued consent but final eligibility determination and next steps toward enrollment will only proceed after confirmation of continued consent.

Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment and the cohorts open for enrollment. Mother-infant pairs who are found to meet the study eligibility criteria will be enrolled and infants will receive their first dose of maraviroc solution within 3 days of life. Screening procedures may be performed on the day of enrollment; however, the mother's HIV test results and the infant's hematology and chemistry test results must be available for eligibility determination prior to enrollment.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, participant identification numbers (PIDs) will be assigned to the mother and infant. For pairs found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and prescribing information for the cohort in which the infant has been enrolled. For pairs who are found to be ineligible for the study, or who do not enroll in the study for any reason, a case report form (CRF) will be completed to record the screening outcome. Refer to Section 9.6 for more information on monitoring participant accrual in this study.

4.5 Participant Retention

Once a mother-infant pair is enrolled in this study, study staff will make every effort to assist them with full adherence and to retain them for the protocol-specified duration of follow-up and thereby minimize potential biases associated with loss-to-follow-up. Refer to Sections 9.6.1 and 9.6.3 for more information on monitoring participant accrual in this study.

4.6 Participant Withdrawal or Termination from the Study

Regardless of the participant, retention procedures referenced above, mothers may voluntarily withdraw from the study at any time. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Infant is not administered initial dose of study drug within 3 days of birth.
- Infant re-locates away from the study site or is otherwise determined to be lost-to-follow-up.
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the infant participant, after consultation with the Core Protocol Team.
- The study is stopped or canceled by the sponsors, government or regulatory authorities, site IRBs/ECs, the US Food and Drug Administration (FDA), NIAID or the Office for Human Research Protections (OHRP).

Should the mother of an enrolled infant die, no longer have custody, or no longer be available for any reason, no further study drug should be administered and no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from an authorized guardian, as defined locally. Study sites may continue to provide care for the infant as needed and appropriate (outside of the study) consistent with the local standard of care but no study-specific procedures may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued infant study participation, the infant must be terminated from the study. Refer to Section 13.3 for further guidance on guardian consent for study participation.

For any infant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations as described in Section 6.12. In the event that the circumstances that led to an infant's withdrawal or termination change (e.g., the family returns to the study site area after having re-located previously), the site investigator or designee should contact the Core Protocol Team to discuss options for resumption of follow-up.

5 STUDY DRUG CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. Refer to Figures 1A and 1B for an overview of the study design and to the Investigator's Brochure (IB) for further information about the study drug.

5.1 Study Drug

Study drug is defined as maraviroc 20 mg/mL oral solution.

5.2 Study Drug Formulation

Maraviroc will be supplied as 20 mg/mL oral solution. The solution will be supplied, ready to use, in a 250 mL white high-density polyethylene (HDPE) bottle, with a polypropylene (PP) closure. Each bottle contains 235 mL of solution. Each bottle requires insertion of a press-in-bottle adaptor (PIBA) prior to the first dose administration; this PIBA will be provided separately from the bottle.

5.3 Study Drug Regimens

5.3.1 Study Drug Regimen for Cohort 1

Infants in Stratum 1A and Stratum 1B will receive two single doses of maraviroc solution as follows:

First single dose:
Maraviroc 8mg/kg* oral solution as a single dose within 3 days of birth.

Second single dose:
Maraviroc 8mg/kg* oral solution as a single dose at Week 1 (Day 7-14) of life.

For each dose, refer to Table D in Appendix II, Maraviroc Weight Based Dosing Table for Oral Solution, and use the infant's current weight at the visit to determine the dose. A new study drug prescription will be required in order for the site pharmacist to dispense the new dose.

*If a dose adjustment is required for Cohort 1 (Stratum 1A or Stratum 1B), the selected table in Appendix II will be communicated to study sites via a protocol Clarification Memorandum.

Note: If the Core Protocol Team determines that a stratum dose or dosing schedule adjustment is required and the appropriate dose is not included in Appendix II, an updated dosing table will be provided through an appropriate mechanism.

Any infants in Cohort 1 with an indication of HIV-1 infection prior to the second single dose will have study drug permanently discontinued (i.e., the second dose will not be administered), see Section 6.11.

5.3.2 Study Drug Regimen for Cohort 2

Infants in Stratum 2A will receive daily doses of maraviroc solution as follows:

- Maraviroc oral solution once or twice daily at the dose and frequency determined from Stratum 1A* will be administered within 3 days of birth and continued for up to 42 (35 to 42 days) of life. Refer to the selected Table in Appendix II, Maraviroc Weight Based Dosing Table for Oral Solution, and use the infant's current weight at the visit to determine the dose.

Infants in Stratum 2B will receive daily doses of maraviroc solution as follows:

- Maraviroc oral solution once or twice daily at the dose and frequency determined from Stratum 1B* will be administered within 3 days of birth and continued for up to 42 (35 to 42) days of life. Refer to the selected Table in Appendix II, Maraviroc Weight Based Dosing Table for Oral Solution and use the infant's current weight at the visit to determine the dose.

*The initial dose size and frequency selected in Appendix II for Cohort 2 (Stratum 2A or Stratum 2B) and any dose adjustments required will be communicated to study sites via a protocol Clarification Memorandum. A new study drug prescription will be required in order for the site pharmacist to dispense the new dose.

Note: If the Core Protocol Team determines that a stratum dose or dosing schedule adjustment is required and the appropriate dose is not included in Appendix II, Maraviroc Weight Based Dosing Table for Oral Solution, an updated dosing table will be provided through an appropriate mechanism.

Any infants with confirmed HIV-1 infection identified within the six-week dosing period will have study drug permanently discontinued (study drug should be held upon first indication of infection and pending confirmation of initial positive test, see Section 6.11).

5.4 Study Drug Preparation

Bottle preparation:
The PIBA must be inserted to the maraviroc oral solution bottle and the bottle must be labelled with the date and time of opening and the 60 days expiration date. Ensure that the work area is clean and only the materials necessary are present.

Dose preparation:
An oral dosing syringe consisting of a polypropylene barrel & HDPE Plunger will be required for dose preparation. Syringe gradations should be appropriate for the dose required. The syringes must be suitable for use with the PIBA system.

The required volume of the maraviroc oral solution must be withdrawn from the prepared bottle using the appropriate size syringe. Syringes may be re-used during take home dosing. All syringes should be cleaned and dried after use. Cleaning is performed by rinsing the plunger and barrel with water, and allowing to air dry. Inspect the dosing syringe prior to each dose withdrawal and administration to ensure the syringe is clean and dry.

Polypropylene syringe cap may be used to transport the study drug containing syringe from the pharmacy to the clinic.

Each dose should be prepared and administered following detailed instructions that will be provide in the study-specific Manual of Procedures.

5.5 Study Drug Administration

Cohort 1

The first single dose administered within 3 days of birth and the second single dose administered at one week (day 7-14) of life, will be prepared by the site pharmacist and administered orally by study staff. Administration will occur in the context of PK specimen collection as described in Sections 6 and 10. If the participant vomits most or all of the dose within the first 30 minutes after administration, the dose should not be repeated. The PK sampling should not be completed, and the infant should be followed for toxicity. An additional infant should be enrolled for PK evaluation.

Cohort 2

The first dose administered within 3 days of birth, will be prepared by the site pharmacist and administered orally by the study staff. The Week 1 and Week 4 doses will be administered orally by the parent or caregiver or study staff and directly observed in the clinic as described in Section 6 and 10 (the parent or caregiver will be instructed not to administer the dose in the home on the days of the PK visits). The parent or caregiver will administer all other doses orally.

Site staff will instruct the parent or caregiver how to properly prepare and administer each dose following instructions that will be provided in the study-specific Manual of Procedures.
If the infant vomits most or all of the dose within the first 30 minutes after administration, the dose should be repeated. If the infant vomits within 30 minutes after administration on a PK sampling day, the PK sampling should be rescheduled within 1-2 days when the infant can receive another study drug dose.

Infants' parents or caregivers will be counseled as needed throughout the study to help ensure adherence. Site staff will confirm full adherence with dosing three days prior to scheduling the PK visit for Cohort 2.

5.6 Study Drug Acquisition

Maraviroc 20 mg/mL oral solution will be supplied by PHIVCO (Pfizer/ViiV). Maraviroc oral solution will be available through the Clinical Research Products Management Center (CRPMC). Comar 1 mL oral syringes, Comar 5 mL oral syringes and Polypropylene (PP) syringe caps will be available through the CPRMC for study drug preparation and administration.

The other components of the antiretroviral (ARV) regimen will not be supplied by the study. Upon successful completion of protocol registration procedures, the site pharmacist can obtain the study drug and oral syringes for this study by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.7 Study Drug Storage

Unopened bottles of maraviroc oral solution should be stored at 15 to 30°C (59 to 86°F). Bottles should be maintained in an upright orientation.

Once the bottle of maraviroc oral solution is opened, it should be stored at 15 to 30°C (59 to 86°F), and maintained in an upright orientation. Once opened, the shelf life of maraviroc oral solution stored at 15 to 30°C (59 to 86°F) is 60 days. Once the maraviroc oral solution bottle is opened, label the drug with date opened and the expiration date.

Maraviroc oral solution held within a dosing syringe for administration is stable for 24 hours at 15°C to 30°C.

5.8 Study Drug Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study product must be returned to the NIAID CRPMC (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.

5.9 Final Disposition of Study Drug

Any unused study drug remaining at US sites after the study is completed or terminated must be returned to the CRPMC. At non-US sites, any remaining study drug will be destroyed. Site pharmacists will follow the relevant instructions for return or destruction of unused study drug provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.10 Concomitant Medications

5.10.1 Antiretroviral Concomitant Medications

ARVs taken by each infant's mother to which the infant may have been exposed in-utero and all ARVs taken by enrolled infants will be source documented and recorded on CRFs as part of the ARV exposure history obtained at each visit. In addition, for breastfeeding infants while receiving maraviroc all ARVs taken by the infant's mother, to which the infant may have been exposed through breastmilk will be source documented and recorded on CRFs. As needed, mothers will be counseled on the importance of adherence to antiretroviral regimens both for their own health and for prevention of HIV transmission to their infants.

5.10.2 Other Concomitant Medications

In addition to the ARV medications described above, while the infant is receiving maraviroc all other concomitant medications received by infants and medications taken by breastfeeding mothers to which a breastfeeding infant may have been exposed through breastmilk, must be source documented and recorded on CRFs.

5.11 Disallowed Medications for Infants and Breastfeeding Mothers

Any infant exposed to any of the following medications (either directly or through breastfeeding) considered prohibited while on study drug must have the study drug permanently discontinued but will remain in follow-up for safety.

Potent CYP3A inhibitors such as:
- atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, saquinavir, cobicistat
- boceprevir, telaprevir
- elvitegravir
- ketoconazole, itraconazole, clarithromycin

Potent CYP3A inducers such as:
- efavirenz (Strata 1A and 2A only), etravirine
- rifampin
- St. John's Wort
- carbamazepine, phenobarbital, and phenytoin

Other:
- isoniazid

In the event that a need for one or more of the above-listed medications is identified, the site investigator or designee should notify the Core Protocol Team.

6 STUDY VISITS AND PROCEDURES

Refer to Section 4.4 for a description of the study recruitment, screening, and enrollment process. An overview of the study visits and evaluation schedules including blood draw volumes are provided in Appendix I as follows: Appendix IA-Mothers; Appendix-IB Cohort 1 Infants; and Appendix-IC Cohort 2 Infants. Presented in this section is additional information on visit-specific study procedures. As indicated in Appendix IA, maternal evaluations are required only at Screening and Entry.

All visits and procedures must be performed at the clinical research site or associated facilities identified in the site's approved Study Implementation Plan and must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 11 for more information on documentation requirements and completion of CRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up. All procedures specified to be performed at scheduled visits should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the allowable visit window.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform mothers (or other authorized guardians if applicable) of clinically meaningful physical exam findings and laboratory test results when available.

6.1 Mother Screening Visit

The Screening Visit may be performed during pregnancy or within 3 days after delivery. Multiple visits may be conducted within this timeframe to complete all required procedures, if necessary.

Written informed consent must be obtained before any study-specific screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined. Ineligible women may rescreen for study participation at a later time.

Mother Screening Visit Procedures *(During pregnancy or within 3 days of delivery)*	
Administrative and Regulatory	• Obtain written informed consent • Obtain screening number from SES • Assign PIDs to mother and infant • Assess eligibility
Clinical	• Obtain available medical record documentation of mother's HIV infection status • Obtain available medical records and medical and medications history
Laboratory	*Collect blood for:* • HIV-1 test (confirmatory tests as needed)

6.2 Mother Entry Visit

The mother and her infant are enrolled as a pair, therefore final eligibility determination for both the mother and infant must be completed prior to enrollment. In the event that a woman is found to be ineligible on the day of enrollment, enrollment should not occur.

Note: No further maternal evaluations are performed following completion of the Entry Visit; for administrative and data collection purposes, mothers are therefore considered "off study" upon completion of the Entry Visit.

Maternal Entry Visit Procedures *(within 0 - 3 days of delivery)*	
Administrative and Regulatory	Immediately prior to Entry: • Review elements of informed consent and confirm mother's continued consent for study participation*
Clinical	• Obtain available medical records and update medical and medications history since screening.
Laboratory	*Collect blood for:* • HIV-1 RNA • Storage (tropism testing)

**Perform prior to enrollment*

6.3 Infant Screening Visit

Infant screening procedures are to be done within 3 days after birth. Multiple visits may be conducted within this timeframe to complete all required procedures, if necessary. Written informed consent must be obtained before any study-specific screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

Refer to Section 4.4 for a description of the study recruitment, screening, and enrollment process.

Infant Screening Visit Procedures *(within 3 days of birth)*	
Administrative and Regulatory	• Assess eligibility
Clinical	• Obtain infant history information (since birth) – Medical/medications – ARV exposure – Infant feeding status • Perform complete infant physical exam (also assess gestational age if not documented in available medical records)
Laboratory	*Collect blood for*: • HIV NAT • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine • Plasma storage • DBS storage

The result of the HIV NAT performed at this visit is not required prior to entry; however, infants with any positive HIV NAT result available prior to entry are not eligible for enrollment for this study and should not be enrolled. In the event that the result of the HIV NAT performed at this visit is positive, the infant should return to the clinic as soon as possible for confirmatory testing.

6.4 Infant Entry Visit (Cohorts 1 and 2)/PK Sampling (Cohort 1)

In the event that a mother-infant pair is found to be ineligible on the day of enrollment, enrollment should not occur.

For Cohort 1, the Entry Visit may be conducted over multiple days as a split visit. The administrative and regulatory procedures should be conducted on the first day of the split visit; procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination.

Infant Entry Visit Procedures *(within 3 days of birth)*	
Administrative and Regulatory	• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file
Study Drug	• Prescribe study drug • Administer initial dose within 3 days of birth (for Cohort 1, administer dose within 1 hour after collection of pre-dose PK sample) • Dispense study drug for home administration (Cohort 2 only) • Provide instructions and adherence counseling for home administration of study drug (Cohort 2 only)
Laboratory	• EFV level (Cohort 1, Stratum 1B only), see Section 6.4.1 • PK sample collection (Cohort 1 only), see Section 6.4.1

**Perform prior to enrollment*

6.4.1 Cohort 1 Intensive PK

PK sampling for maraviroc must be initiated on the same day as the first dose of maraviroc (within 3 days of birth), and conducted over the course of up to 72 hours according to the following time points: pre-dose (< 1 hour before dosing), then post dose 1 – 2 hours, 4 - 8 hours, 11 – 13 hours, 20 – 24 hours, and 48 – 72 hours after the observed dose. Depending on site capacity, mothers and their infants may stay at the clinical research facility overnight for PK sampling. The same procedure can be followed for obtaining the PK samples 48 − 72 hours after dosing.

For infants in Stratum 1B only, an additional sample for analysis of EFV levels should also be drawn at any time on the same day the first maraviroc dose is given.

6.5 Week 1 Visit/PK Sampling (Cohorts 1 and 2)

The Week 1 Visit is targeted to take place on Day 7, counted from the date of birth as Day 0, with an allowable visit window of +7 days.

Week 1 Visit Procedures (Day 7 to Day 14)	
Administrative and Regulatory	• None
Clinical	• Update infant history information – Medical/medications – Feeding Status – ARV exposure • Review screening HIV NAT result, if available (if positive; see Section 6.11) • Perform targeted physical exam • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8 and/or if clinically indicated (consult Core Protocol Team if indicated)
Study Drug	• Administer study drug within 1 hour after collection of pre-dose PK sample • Prescribe and dispense study drug for home administration as needed (Cohort 2 only) • Provide instructions and adherence counseling as needed for home administration of study drug (Cohort 2 only)
Laboratory	*Collect blood for:* • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine • EFV level (Stratum 1B and 2B only) • PK sample collection, see Section 6.5.1 – 6.5.3

6.5.1 Cohort 1 Limited PK

PK sampling for maraviroc must be initiated on the same day as the dose of maraviroc and conducted over the course of up to 26 hours according to the following time points: pre-dose (<1 hour before dosing), then post dose 1- 2 hours and 22 – 26 hours after the observed dose.

For infants in Stratum 1B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

6.5.2 Cohort 2 Intensive PK with Once Daily dosing

Maraviroc samples should be drawn according to the following time points: pre-dose (< 1 hour before dosing), post dose 1 – 2 hours, 4 - 8 hours, 11 – 13 hours, 20 – 24 hours after the observed dose. Further operational details are found in Section 10.2.2.

For infants in Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

6.5.3 Cohort 2 Intensive PK with Twice Daily dosing

Maraviroc samples should be drawn according to the following time points: pre-dose (< 1 hour before dosing), post dose 1 – 2 hours, 3 - 5 hours, 6 – 8 hours, and 11 – 13 hours after the observed dose. Further operational details are found in Section 10.2.3.

For infants in Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

6.6 7-Day Post Dose Safety Visit (Cohort 1 only)

This visit is targeted to take place seven days after the Week 1 visit (7 days after receiving the last dose of study drug), with an allowable window of ± 3 days.

7 Day Post Dose Safety Visit (7 days after Week 1 visit ± 3 days) (Cohort 1 only)	
Administrative and Regulatory	• None
Clinical	• Update infant history information – Medical/medications – Feeding status – ARV exposure • Perform targeted physical exam • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8 and/or if clinically indicated (consult Core Protocol Team if indicated)
Laboratory	*Collect blood for:* • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine

6.7 Week 4/PK Sampling (Cohort 2 only)

The Week 4 Visit is targeted to take place on Day 28, counted from the date of birth as Day 0, with an allowable window of -7 to +3 days.

Week 4 Visit Procedures (Day 21 to Day 31) (Cohort 2 only)	
Administrative and Regulatory	• None
Clinical	• Update infant history information – Medical/medications – Feeding status – ARV exposure • Perform targeted physical exam • Review/update adverse events (perform evaluations as needed per Section 8.0)
Study Drug	• Administer study drug (< 1 hour prior to PK sampling) • Prescribe and dispense study drug for home administration as needed. Provide instructions and adherence counseling as needed for home administration of study drug.
Laboratory	*Collect blood for:* • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine • EFV level (Stratum 2B only) • PK sample collection, see Section 6.7.1 – 6.7.2

6.7.1 Cohort 2 Intensive PK with Once Daily dosing

Maraviroc samples should be drawn pre-dose (< 1 hour before dosing), post dose 1 – 2 hours, 4 - 8 hours, 11 – 13 hours, and 20 – 24 hours after the observed dose. Further operational details are found in Section 10.2.2.

For Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during this study visit.

6.7.2 Cohort 2 Intensive PK with Twice Daily dosing

Maraviroc samples should be drawn pre-dose (< 1 hour before dosing), post dose 1 – 2 hours, 4 - 8 hours, and 11 – 13 hours after the observed dose. Further operational details are found in Section 10.2.3.

For Stratum 2B only, a single EFV sample should be drawn at any time during this study visit.

6.8 Week 6 Visit (Cohorts 1 and 2)

The Week 6 Visit is targeted to take place on Day 35, counted from the date of birth as Day 0, with an allowable window of +7 days.

Week 6 Visit Procedures (Day 35 to Day 42)	
Administrative and Regulatory	• None
Clinical	• Update infant history information – Medical/medications – Feeding status – ARV exposure (if breastfeeding) • Perform targeted physical exam • Review prior HIV NAT results, if available • Review/update adverse events (perform evaluations as needed per Section 8.0)
Study Product	• Collect any remaining study drug (Cohort 2 only)
Laboratory	*Collect blood for:* • HIV NAT • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine • DBS storage • EFV level (Stratum 2B only) • Population PK sample collection (Cohort 2 only, see Section 6.8.1)

In the event that the result of the HIV NAT performed at this visit is positive, the infant should return to the clinic as soon as possible for confirmatory testing per Section 6.11.

6.8.1 Cohort 2 Population PK with Once or Twice Daily Dosing

A single random maraviroc sample should be drawn at any time during this study visit.

6.9 Week 12 Visit (Cohort 2 only)

The Week 12 Visit is targeted to take place on Day 84, counted from the date of birth as Day 0, with an allowable window of ±7 days.

Week 12 Visit Procedures (Day 77 to Day 91) (Cohort 2 only)	
Administrative and Regulatory	• None
Clinical	• Update infant history information (since last visit) – Medical/medications – Feeding status – ARV exposure • Perform targeted physical exam • Review/update adverse events (perform evaluations as needed per Section 8.0)
Laboratory	*Collect blood for:* • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine

6.10 Week 16 Visit (Cohorts 1 and 2)

The Week 16 Visit is targeted to take place on Day 112, counted from the date of birth as Day 0, with an allowable window of +28 days.

Week 16 (Day 112 to Day 140) and Early Study Discontinuation Visit Procedures	
Administrative and Regulatory	• None
Clinical	• Update infant history information – Medical/medications – Feeding status – ARV exposure (if breastfeeding) • Perform targeted physical exam • Identify/review/update adverse events (abnormal lab values, signs, symptoms, diagnoses) • Perform additional evaluations per Section 8 and/or if clinically indicated (consult Protocol Team if indicated)
Laboratory	*Collect blood for:* • HIV NAT • CBC with differential and platelets • AST, ALT, total bilirubin, creatinine • DBS storage

At this visit, mothers will be informed of how to contact study staff with any post-study questions and arrangements should be made to provide the infant's mother with clinically meaningful test results from the final evaluations. In the event that the result of the HIV NAT performed at this visit is positive, the infant will be recalled to the clinic as soon as possible for confirmatory testing and referrals per Section 6.11. For all infants, referrals will be provided as needed to ensure transition to non-study sources of routine child health care.

6.11 Procedures for Infants with Positive HIV NAT Results

After enrollment, any infant with a positive HIV NAT test result should be recalled to the clinic as soon as possible for confirmatory testing; administration of maraviroc must be held pending receipt of the result of the confirmatory test. At the time of specimen collection for the confirmatory test, a sample for tropism testing and resistance testing should also be collected per Appendix IB or IC and the Laboratory Processing Chart (LPC). If HIV infection is confirmed, maraviroc will be permanently discontinued. However, the infant will remain in follow-up with visits and procedures performed per the relevant Schedule of Evaluations through Week 16, except that no further HIV testing and no further PK sampling will be performed.

All infants identified with HIV infection will be actively referred to non-study sources of HIV care and treatment.

6.12 Procedures for Infants who Prematurely Discontinue Study Participation

Refer to Section 4.6 for criteria for infant withdrawal or termination from the study. For any infant who discontinues study participation prior to completion of follow-up at Week 16, every effort should be made to complete a final series of study evaluations if possible. In general, the Week 16 Visit procedures should be performed, and arrangements should be made to provide the infant's mother with clinically meaningful test results from the final evaluations. The parent or guardian should also be provided information and referrals, as applicable, to non-study sources of care and treatment for the infant.

6.13 Maternal Medical and Medications History

At Screening and Entry visits, the following should be recorded on CRFs:

- All ARVs taken during the current pregnancy and any other medications within 30 days prior to study entry
- Any diagnoses that were new or ongoing during the current pregnancy
- Any signs or symptoms within 30 days prior to study Entry

6.14 Infant Physical Examinations

A physical examination is required at scheduled visits as indicated in Appendix IB and IC. Complete exams are required at the Screening Visits; targeted exams are required at all other scheduled visits.

Complete exams should include the following:

- Length measurement
- Weight measurement
- Auscultation of chest
- Examination of skin, head, mouth, neck, abdomen, extremities

Note: Inclusion criteria 4.1.4 and 4.1.5 permit study staff to assess infant gestational age and weight if these outcomes were not documented in medical records at birth. When applicable, these assessments should be performed at the earliest possible opportunity as part of the screening physical exam.

Targeted exams should include the following:

- Length measurement
- Weight measurement
- Auscultation of chest
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining site investigator. Also at all visits, the measurements listed above should be charted on standard infant growth charts and weight-for-age assessed in relation to WHO Growth Standards.

6.15 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at:

http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx

HIV NAT performed following the entry visit for diagnosis of infant infection must be performed in a laboratory that is CLIA-certified (for US sites) or DAIDS-VQA certified (for non-US sites) (refer to Section 4.1.2 for maternal HIV testing requirements). All samples tested must be whole blood, serum, or plasma.

6.15.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the LPC, which will be available on the IMPAACT website.

NIH recommendations for maximum pediatric and adult blood draw volumes will be followed in this study. For women, the volume of blood drawn shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. For infants, the volume of blood drawn at any study visit should not exceed 5 mL/kg in a single day or 9.5 mL/kg over any eight-week period. In the event that infant blood collection must be limited, available specimens will be prioritized for use in the following order: (1) safety (chemistries, CBC), (2) HIV Nucleic Acid Test, (3) PK, and (4) stored DBS.

6.15.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.15, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC.

Specimens collected, processed, and stored at site laboratories for PK evaluations are expected to be shipped to the designated testing laboratory as follows. For each infant in Strata 1A and 1B, PK samples from the Entry and Week 1 visits may be shipped together immediately after completion of the Week 1 visit. For each infant in Strata 2A and 2B, Week 1 and Week 4 samples should be shipped immediately after completion of each visit; Week 6 PK samples may be stored and shipped in batches monthly.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Infants' mothers (or other authorized guardians if applicable) will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Mothers may choose to provide or to decline informed consent for future research use of residual specimens with no impact on other aspects of infant participation in the study.

6.15.3 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 US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY MONITORING, ASSESSMENT AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Core Protocol Team and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Section 9.6.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the Core Protocol Team if unexpected concerns arise. Site investigators will record safety-related events on CRFs as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

Site investigators should notify the Core Protocol Team by e-mail within three business days of site awareness of any Grade 3 or higher adverse event regardless of relationship to maraviroc occurring throughout follow-up. This notification should include the diagnoses or symptom, grade, and relationship assessment.

7.1.2 Core Protocol Team

The Core Protocol Team is comprised of the Protocol Chair and Vice Chairs, Medical Officers, Statistician, Data Manager, Pharmacologist, Clinical Trials Specialist, and representatives from ViiV. The Core Protocol Team will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, study drug administration, and management of adverse events. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the Core Protocol Team will monitor participant safety through routine review of study data reports as described in Section 9.6.

7.1.3 Study Monitoring Committee

An independent IMPAACT SMC may contribute to monitoring participant safety in this study if needed. Refer to Section 9.6.3 for more information on the composition and role of the SMC in monitoring this study.

7.2 Safety-Related Recording on Case Report Forms

***Note**: This section refers to recording requirements on Case Report Forms for infant adverse events and pre-existing conditions. For information on severity grading and criteria for EAE reporting, refer to sections 7.3.3 and 7.3.2, respectively.*

Consistent with international good clinical practice guidelines, the term adverse event is used in this protocol to refer to any untoward medical occurrence identified in an enrolled infant who is administered study drug, which does not necessarily have a causal relationship with study drug. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis temporally associated with administration of study drug, whether or not related to study drug. This definition of adverse event will be applied to all infants in this study, beginning at the time of first dose of maraviroc. Any untoward medical occurrences identified between the time of infant birth and the time of the first dose of maraviroc solution will be considered pre-existing conditions.

All pre-existing conditions and adverse events identified in this study will be source documented in infant research records, consistent with the policies and procedures referenced in Section 11. Among other details, source documentation will include the date of onset and severity of each pre-existing condition and adverse event, with severity graded as described in Section 7.3.3. Source documentation for each adverse event will also include relationship to study drug, assessed according to the categories and definitions specified in Section 8.1.

All pre-existing conditions and adverse events will be recorded on the relevant adverse event case report form, regardless of severity grade and relationship to study drug. All laboratory test results will also be recorded on the relevant laboratory case report form.

CRFs used to record the above listed safety outcomes must be keyed into the study database within 48 hours of availability of the relevant clinical findings and laboratory test results at the site.

7.3 Expedited Adverse Event (EAE) Reporting

EAEs will be reported only for infants in this study.

7.3.1 Adverse Event Reporting to DAIDS

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

The DAIDS Adverse Experience Reporting System (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 NIAID Clinical Research Management System at CRMSsupport@niaid.nih.gov. Questions 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 expedited reporting, please contact DAIDS RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

The serious adverse event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agent for which expedited reporting is required is maraviroc solution. With respect to the relationship categories specified for purposes of participant and toxicity management in Section 8.1, the categories of definitely related, probably related, and possibly related will correspond to an assessment of "related" for EAE reporting; the categories of probably not related and not related will correspond to an assessment of "not related" for EAE reporting.

7.3.3 Grading Severity of Events

Adverse events identified in this study will graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, dated November 2014, which is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/

In addition, grading of infant malnutrition will follow the table below:

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Infant malnutrition	WHO weight-for-length Z score <-1 to >-2	WHO weight-for-length Z score <-2 to ≥-3	WHO weight-for-length Z score <-3	WHO weight-for-length Z score <-3 with life-threatening consequences

7.3.4 Expedited AE Reporting Period

- EAEs will be reported only for infants in this study. For each enrolled infant, the EAE reporting period begins at the time of administering the first dose of study drug and continues through the protocol-specified end of follow-up.

- After the protocol-defined AE reporting period, only suspected, unexpected, serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

Relationship categories for Adverse Events are as follows:

Definitely related	The event and administration of study drug are related in time, and a direct association can be demonstrated.
Probably related	The event and administration of study drug are reasonably related in time and the event is more likely explained by study drug than other causes.
Possibly related	The event and administration of study drug are reasonably related in time and the event can be explained equally well by causes other than study drug.
Probably not related	A potential relationship between the event and study drug could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than study drug.
Not related	The event is clearly explained by another cause not related to study drug.

As described in greater detail below, adverse events identified in enrolled infants will be managed based on their severity and assessed relationship to study drug. For grade 3 and higher events that may affect administration of study drug (as described in Sections 8.2), relationship to study drug will be assessed by site investigators as well as the Core Protocol Team.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Grade 3 or higher laboratory tests should be repeated as soon as possible (within one business day) and all grade 3 or higher adverse events should be re-evaluated in consultation with Core Protocol Team until improvement to grade 2 or lower. Additional evaluations beyond those listed in Appendix I may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study drug. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

8.2 General Management

The following general guidelines (by grade) apply to management of maraviroc in response to adverse events. Any infants who discontinue administration of maraviroc will remain in follow-up and per the relevant Schedule of Evaluations in Appendix I with the exception that no further PK sampling will be done.

8.2.1 Cohort 1

Grade 1 - The second maraviroc dose can be administered; routine monitoring.

Grade 2 - The second maraviroc dose can be administered; monitor closely; as per site investigator and work-up to exclude other causes.

Grade 3 – If the adverse event is a grade 3 laboratory value, the second maraviroc dose should be withheld while awaiting confirmatory results. For confirmed grade 3 laboratory values, and grade 3 clinical events, contact the Core Protocol Team and hold the second maraviroc dose until improvement to grade 2 or lower. If repeat assessment is Grade 2 or lower, manage per the grade of the repeat assessment. Alternatively, if the site investigator assesses the event as not related or probably not related to maraviroc, with approval from the Core Protocol Team, the second maraviroc dose may be administered.

Grade 4 - If the adverse event is a grade 4 laboratory value, the second maraviroc dose should be withheld while awaiting confirmatory results. For confirmed grade 4 laboratory values and grade 4 clinical events assessed as not related to maraviroc, the site investigator should contact the Core Protocol Team to determine if and when the second maraviroc dose should be administered. Otherwise, the second maraviroc dose should not be administered and the site investigator should contact the Core Protocol Team for further instructions.

8.2.2 Cohort 2

Grade 1 - Continue maraviroc; routine monitoring.

Grade 2 - Continue maraviroc; monitor closely; as per the site investigator, work-up to exclude other causes.

Grade 3 – The maraviroc dose should be withheld awaiting results of the confirmatory test. If Grade 3 abnormalities are confirmed, contact the Core Protocol Team, and the maraviroc should continue to be withheld until the abnormalities are Grade 2 or below unless the site investigator, with the approval of the Core Protocol Team, assesses the event as not related or probably not related to maraviroc administration and maraviroc should be continued. If the event is Grade 2 or lower, manage per the grade of the repeat assessment.

Grade 4 – The maraviroc dose should be withheld awaiting results of the confirmatory test. For Grade 4 adverse events determined to be at least possibly related to study drug, maraviroc should be permanently discontinued. For Grade 4 adverse events that are determined to be probably not related or not related to study drug, the investigator should contact the Core Protocol Team for further instructions.

Note: In the event of discontinuation of study drug, participants will be asked to continue to be followed until the 16 week visit.

8.2.3 Non- Maraviroc Antiretroviral Drug-related Toxicity

Toxicities resulting from components of a PMTCT regimen will be managed by the site investigator, according to best clinical practice; consultation with the Core Protocol Team is available but not required.

8.3 Criteria for Premature Discontinuation of Study Drug

Administration of maraviroc will be permanently discontinued in the event that:

8.3.1 The infant is determined to be HIV-1 infected (confirmed with two diagnostic tests), or

8.3.2 The infant experiences an adverse event that requires discontinuation as defined in Section 8.2, or

8.3.3 The infant requires isoniazid, rifampin, or any other disallowed medication listed in Section 5.11, or

8.3.4 The site investigator determines that further administration of maraviroc would be detrimental to the infant's health or well-being.

8.3.5 New data become available that indicate maraviroc should be discontinued as determined by the Core Protocol Team.

8.3.6 A Cohort 2B infant whose mother stops breastfeeding.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I study whose primary objectives are to evaluate the safety, tolerability and PK of maraviroc in infants. The ultimate objective is to determine an appropriate dose of maraviroc solution when administered to HIV-1 exposed infants at risk of HIV infection, along with standard PMTCT ARV prophylaxis, during the first 6 weeks of life. Both mother and infant will be enrolled, with the mother only having study visits at screening and entry and the infant followed through 16 weeks of life.

Infants will be stratified by maternal EFV-exposure, see Section 3.0, and will be enrolled into 2 sequential dosing cohorts defined as follows:

Cohort 1: divided into 2 strata, 1A and 1B, which will accrue concurrently.

Stratum 1A (Infants NOT exposed to maternal EFV *in utero*): n=6-18

Stratum 1B (Infants exposed to maternal EFV *in utero*): n=6-18

Cohort 2: divided into 2 strata, 2A and 2B, which will begin accrual pending dose determination from the corresponding stratum from Cohort 1

Stratum 2A (Infants NOT exposed to maternal EFV *in utero* or while breastfeeding) n=12-18

Stratum 2B (Breastfeeding infants exposed to maternal EFV *in utero* and while breastfeeding) n=12-18

A minimum of 12 and 24 infants (and their mothers) in Cohorts 1 and 2, respectively, will be accrued to the study. If an infant has unevaluable PK data, which reflects uncertainty about appropriate exposure to the study drug, then the infant will be replaced and will be excluded from both the PK and safety analyses during the dose-evaluation. However, the infant may be allowed to continue on-study drug and will be followed through week 16. It may be necessary to perform

sensitivity analyses on the final data to test whether the results of the final safety analysis are consistent with and without this infant's data.

The final enrollment target is 6 evaluable infants each from Stratum 1A and Stratum 1B, and 12 evaluable infants each from Stratum 2A and Stratum 2B, treated at the final dose recommended for each stratum.

9.2 Dose-Finding Algorithm

Cohort 1

Each strata (Stratum 1A and Stratum 1B) will enroll an initial group of 6 evaluable infants and their safety and PK data will be evaluated independently as follows.

The study will implement a dose-finding algorithm applied to each stratum based on real time PK data and safety through the 7 Day Post Dose Safety Visit from an initial group of 6 infants from Stratum 1A and Stratum 1B. If these 6 infants meet both safety and PK guidelines (specified in Section10.3), then the starting dose for the corresponding Cohort 2 stratum will be established, and that stratum will begin to accrue. If the infants receiving the initial Cohort 1 dose for the stratum do not meet either the safety or the PK guidelines, then the Core Protocol Team will evaluate whether to adjust the dose upwards or downwards. Individual dose adjustments will not be made. If the dose is changed, six new infants will be enrolled at the adjusted dose, and the evaluation of real time safety and PK will be repeated on these infants. If this second group of infants were to not meet the safety and/or PK guidelines, the Core Protocol Team would evaluate whether to adjust the dose. If the dose is adjusted, a third group receiving a second dose modification would be enrolled. The goal is to enroll six infants at a dose in each stratum in Cohort 1 who meet both safety and PK guidelines, providing adequate data to establish a starting dose for the corresponding Cohort 2 stratum.

Cohort 2

Each stratum (2A and 2B) will begin to enroll as soon as the starting dose is established from the corresponding Cohort 1 stratum, and will be evaluated independently as follows:

The same algorithm will apply to each stratum in Cohort 2 (2A and 2B) starting with six infants per stratum, except that the dose-finding algorithm applied to each stratum will be based on PK and safety data through the Week 6 Visit. If each stratum meets both safety and PK guidelines at a given dose (guidelines specified in Sections 9.6.2 and 10.3.2), then an additional six infants will be accrued and administered this dose to complete a full stratum of n=12 infants. Safety and PK will then be assessed on the full stratum. If safety and PK guidelines are met, then the dose is established for the stratum. Otherwise, the dose may be adjusted, a new group of six infants will be enrolled at the adjusted dose, and the evaluation procedures described above will be repeated. This will proceed until a full stratum of 12 infants administered a given dose has met both safety and PK guidelines.

Note: No more than 2 additional mother-infant pairs will be allowed to enroll to each stratum before the preliminary evaluation of PK and safety data on 6 initial participants has been completed. Please see detailed note in Section 9.6.2.1.

9.3 Endpoints and Outcome Measures

In the following sections, the words "Endpoint" and "Outcome" refer to dependent variables on which objectives will be evaluated. "Endpoint" refers to whether a specific criterion has been met, while "Outcome" refers to a continuous or categorical variable which is relevant to protocol objectives, but does not reflect a specific criterion.

9.3.1 Primary Endpoints (from the initial maraviroc dose through week 6 of life)

Safety

- For dose finding purposes: Adverse events of Grade 3 or higher or that result in discontinuation of study drug, judged by the Core Protocol Team to be at least possibly related to study drug. (Cohort 1: through 7 Day Post Dose Visit; Cohort 2: through Week 6 Visit).

- For analysis purposes: All adverse events of grade 3 or higher or that result in discontinuation of study drug.

PK

- Failure to meet PK target of $C_{avg} \geq 75$ ng/mL. C_{avg} represents the area under the curve (AUC) divided by the duration of the dosing interval used to determine AUC.

9.3.2 Primary Outcome Variables (from the initial maraviroc dose through week 6 of life)

Safety

- All adverse events (all severity grades).

PK

- PK parameters: C_{max}, T_{max}, AUC, C_{avg}, and for Cohort 2, also C_{trough}

9.3.3 Secondary Endpoints (from the initial maraviroc dose through week 16 of life)

Safety

- For dose finding purposes: Adverse events of Grade 3 or higher or that result in discontinuation of study drug, judged by the Core Protocol Team to be at least possibly related to the study drug.

- For analysis purposes: All adverse events of Grade 3 or higher or that result in discontinuation of study drug due to toxicity.

9.3.4 Secondary Outcome Variables (from the initial maraviroc dose through week 16 of life)

Safety

- All adverse events (all severity grades).

PK

- Changes in maraviroc PK parameters over first 6 weeks of life (Cohort 2 only)

Tropism

- Infant's viral tropism after exposure to maraviroc (infants who are HIV-1 infected only)
- Viral tropism at entry (mothers of infants who are HIV-1 infected only)

9.4 Randomization and Stratification

There will be no randomization. For each cohort, infants will be stratified, based on EFV-maternal exposure as follows:

Cohort 1: Infants to receive single doses of maraviroc solution between 0 and 3 days and day 7-14 of life.

- Stratum 1A: Infants NOT exposed to maternal EFV *in utero*
- Stratum 1B: Infants exposed to maternal EFV *in utero*

Cohort 2: Infants to receive daily dosing, starting within 3 days from birth and continuing through 6 weeks of life, with maraviroc solution at a dose determined on the basis of corresponding Stratum 1A or Stratum 1B data.

- Stratum 2A: Infants NOT exposed to maternal EFV *in utero* or through breastfeeding.
- Stratum 2B: Breastfeeding Infants exposed to maternal EFV *in utero* and while breastfeeding.

9.5 Sample Size and Accrual

Total accrual will depend upon the number of participants who must be enrolled to yield:

- 12 infants in Cohort 1 (6 for each stratum 1A, 1B) treated at the dose which has met safety and PK guidelines and is recommended for Cohort 2, and

- 24 infants in Cohort 2 (12 for each stratum 2A, 2B) treated at the final recommended dose for each stratum.

Note: No more than 2 additional mother-infant pairs will be allowed to enroll to each stratum before the preliminary evaluation of PK and safety data on 6 initial participants has been completed. Please see detailed note in Section 9.6.2.1

9.6 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.6.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, and the quality of study conduct. The team will closely monitor participant accrual and retention based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and accrual performance following activation. Accrual performance will be reported by the SDMC, by site and across sites, and the team will review and discuss performance at least monthly. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will similarly review participant retention and other key indicators of the quality of study conduct (e.g. adherence to study drug regimen, data quality, and data and specimen completeness) based on reports generated by the SDMC and take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

The IMPAACT Management Oversight Group will be provided monthly updates on participant accrual and retention.

Infant Safety

On behalf of the full Protocol Team, the Core Protocol Team will closely monitor infant safety through routine review of safety reports generated by the SDMC. These reports will provide tabulations of adverse events (defined in Section 7.2) identified in enrolled infants, including abnormal laboratory test results, signs, symptoms, and diagnoses. The Core Protocol Team will review these reports via conference call or other meeting at least monthly until the last participant enrolled has completed follow-up. At the time of each call, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports.

The Core Protocol Team will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. The Core Protocol Team will also monitor safety and take action as needed according to the following guidelines:

(1) In the event of **any adverse event that is life-threatening or results in death,** the Core Protocol Team will review the event as soon as possible (ideally within three working days) and assess its relationship to study drug.

Note: The term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- If either the site investigator or the Core Protocol Team assesses the event as possibly, probably or definitely related to study drug, participant accrual and administration of

study drug will immediately be paused to the stratum in which the triggering event had occurred and the Core Protocol Team will discuss how the study should proceed.

- If the site investigator and the Core Protocol Team assess the event as probably not or not related to study drug, participant accrual and administration of study drug will continue.

(2) In the event of any unresolvable disagreement within the Core Protocol Team on an issue which would impact decision making; or if the Core Protocol Team encounters **any other event or trend of concern** an SMC review of the relevant data will be requested. The Core Protocol Team may choose to pause participant accrual and/or administration of study drug, pending the outcome of the SMC review.

Dose Finding

During the dose finding stages of this study, the Core Protocol Team will also review the pharmacokinetic data, with the aim of determining the recommended dose for each cohort while protecting infant safety. The Core Protocol Team will review PK data reports at least monthly and take action as needed according to the guidelines in Section 9.6.2.

Following any pause, participant accrual and/or administration of study drug may be resumed if resumption is recommended by the Core Protocol Team or SMC.

9.6.2 Safety Guidelines for Evaluating the Dose

9.6.2.1 Safety Guidelines for groups of n=6 participants from each stratum in a given Cohort: Cohort 1 (1A, 1B) and 2 (2A, 2B) Started at a Given Dose Level

For each stratum in a given Cohort (Cohort 1 (1A and 1B) and Cohort 2 (2A and 2B), the frequency of adverse events at the starting dose of the study drug will be evaluated on the first 6 participants. The data will extend through the Day 7 Post Last Dose Safety Visit for Cohort 1and through the Week 6 Visit for Cohort 2.

If any of the following conditions occur, then the group of n=6 infants would not meet the safety guidelines:

- A life threatening adverse event or death assessed as at least possibly related to the study drug, or

  Note: The term life-threatening refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- A Grade 4 event that is assessed as probably or definitely related to the study drug.

- Three or more infants experienced a Grade 3 or higher adverse event assessed as at least possibly related to study drug or are discontinued from study drug due to an adverse event assessed as at least possibly related study drug.

If none of these conditions has been met, then the safety guidelines have been met.

Given the small sample sizes in each stratum within a cohort, the information available for safety decisions will be imperfect. Two types of sampling errors are possible: 1) in a stratum within a cohort where the true rate of toxicity is too high to warrant exposure to the current dose of study drug, the sample data may pass the safety guidelines; and 2) in a stratum within a cohort where the true rate of toxicity is low enough that further exposure to the current dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study drug were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Table (1) range from conditions under which a given dose level would cause a high incidence of severe and life threatening adverse events to conditions under which severe adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations, we assume that a sample of 6 infants is drawn from the participant population and that the safety guidelines, summarized above, are followed.

Table (1) uses a multinomial response model to assess the probability of failing the safety guidelines under each of these hypothetical situations. The calculations are performed as follows: Each of the 6 participants represents a trial, which may have 1 of 3 mutually exclusive outcomes: (1) a death or life threatening adverse event judged to be at least possibly related to study drug or a grade 4 event judged to be probably or definitely related to study drug; (2) a Grade 3+ event or treatment termination, not satisfying the guidelines set forth in #1, immediately above, but judged to be at least possibly related to study drug; and (3) a relatively benign outcome, satisfying neither the criteria in #1 nor #2, immediately above.

There are 3 sets of results under which this set of 6 trials would meet the safety guidelines:

- First set: all participants would fall under outcome #3, immediately above, or
- Second set: 5 participants would fall under outcome #3 and 1 participant would fall under outcome #2, with none falling under outcome #1, or
- Third set: 4 participants would fall under outcome #3 and 2 would fall under outcome #2, with none falling under outcome #1,

Thus, the probability of passing the safety criteria represents the sum of the probabilities of these sets of results, and “1 minus the probability of passing the safety guidelines” represents the probability of failing them. The “True Toxicity Rates” presented in Table (1) below, along with the true rate of having neither of the types of toxicity represented by the true toxicity rates (which is 1 - the sum of the true toxicity rates), provide the probabilities for the outcomes which are used in the multinomial calculations for each of the hypothetical situations evaluated below.

As examples of how to read Table (1): this table shows that there is a 78% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening Grade 3+ adverse event is 50%. Assuming that it would be undesirable to open a new group (stratum within a cohort) or accrue additional infants at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 0.2 % chance of failing, when the true rate of non-life threatening Grade 3+ adverse event is only 5% and the true rate of life threatening adverse event is zero. Assuming that the potential benefits associated with exposing additional infants to this dose of the drug would outweigh the risks associated with this

relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

Note: Once 6 mother-infant pairs have been accrued for the preliminary evaluation of the dose for each cohort-EFV stratum, the study will allow no more than 2 additional mother-infant pairs to enroll to that stratum before the preliminary evaluation of PK and safety data on these 6 initial participants has been completed. The PK and safety guidelines will determine decisions based on the first n=6 infants. If extra (up to 2) infants have been accrued and have evaluable data, then this additional information will be taken into account in decision making, such that: (1) if at least one infant experiences a life-threatening toxicity (including death) that is at least possibly related to the study drug, or a grade 4 toxicity that is probably or definitely related to the study drug or (2) the extra participants exhibit toxicities (grade 3+ or treatment termination that are at least possibly study drug related) that cause the percentage of toxicity in the total accrual for that cohort-stratum to exceed 33%, then the team will re-evaluate the dose and determine whether it is safe proceed. Note that, due to uncertainty as to whether any extra participants will actually have been accrued and evaluated prior to decision making based on the first 6 participants, Table 1 does not take account of the possibility that data from the extra participants may change decisions based on evaluation of date from the first 6. Since the extra participants provide additional potential for safety failure, the probability of failing safety guidelines, based on data from the first 6 participants plus up to 2 additional participants, is somewhat greater than that presented in Table 1.

Table 1: Probability that the First 6 Participants will Fail Safety Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Grade 3+ events or study treatment termination deemed at least possibly due to study drug, excluding Grade 4 events probably or definitely attributable to study drug	Life threatening adverse events (including death) deemed to be at least possibly attributable to study drug, or Grade 4 events probably or definitely attributable to study drug	
.50	.00	.66
.50	.05	.78
.50	.25	.98
.25	.00	.17
.25	.05	.41
.25	.25	.88
.05	.00	.002
.05	.05	.27
.05	.25	.82
.00	.05	.26
.00	.25	.82

9.6.2.2 Safety Guidelines for the n=12 participants of each stratum in a given Cohort: Cohort 2 (2A, 2B) Started at a Given Dose Level

For each stratum in Cohort 2, if the group of n= 6 infants meets both the safety and PK guidelines (see Section 10.3), then an additional 6 more infants will be accrued to complete the full cohort. The safety and PK results of the full-cohort of 12 infants will be evaluated. The final safety guidelines applied to a given starting dose of the study drug for the full cohort will make use of data from all infants started at that dose. The data will extend to the Week 6 visit.

If any of the following conditions occur, then a full cohort of 12 infants would not meet the safety guidelines:

- A life threatening adverse event assessed as at least possibly related to the study drug, or
- A Grade 4 event assessed as probably or definitely related to study drug, or
- More than 25% of the infants experience a Grade 3+ adverse event assessed as at least possibly related to study drug or are discontinued from study drug due to an adverse event assessed as at least possibly related.

If none of these conditions has occurred, then the safety guidelines have been met.

9.6.3 Monitoring by the SMC

An independent IMPAACT SMC will review this study regularly, following policies described in the IMPAACT Network Manual of Procedures.

SMC reviews will occur annually and focus on participant accrual, retention, study conduct, and safety (i.e., listing of Grade 3 and 4 events with corresponding treatment attributions). Additional SMC reviews focused on safety may also occur if requested by the Core Protocol Team as indicated in Section 9.6.1. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges identified during their reviews.

9.7 Analyses

The safety analysis will consist of descriptive statistics summarizing outcomes by strata within cohorts. See pharmacology Section 10 for description of PK analyses.

Summary of Dose Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety data from the dose-finding phase of the study. The data will be presented by stratum within each cohort and will include the results of the safety evaluations applied to each starting dose tested, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each stratum, every grade 3 or higher adverse event will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the protocol team's assessment of the probability that this event was due to the study drug.

Analysis of Data Representing Exposure to the Doses Selected for Each Stratum within a Cohort

The primary analyses will be conducted for each stratum based on infants who were exposed to the final selected dose and will be restricted to data through week 6 of life. Secondary analyses will include all infants, in subgroups for each dose received, and will include data through Week 16.

Each participant's safety data will be summarized as: the worst grade of adverse event experienced at these time points and the worst grade of adverse event assessed as at least possibly related to study drug. Frequency distributions of these safety outcomes will be presented. Listings of all Grade 3 or higher events will be provided.

The proportions of participants experiencing grade 3 or higher adverse events, bounded by exact 95% confidence intervals, will be presented. Similar analyses will present the proportions of participants with Grade 3 or higher events assessed as at least possibly related to study drug, again bounded by exact 95% confidence intervals. Table 2 presents the upper and lower limits of confidence intervals around potential results observed in the groups of n=6 and full cohorts of n=12 of the strata with and without maternal EFV.

Table 2: Percent of Participants Experiencing ≥ Grade 3 Adverse Events (or ≥ Grade 3 Adverse Events Attributed to the Study Medication) with Exact 95% Confidence Intervals

N*	n (%) With ≥ Grade 3 Adverse Events	95% C.I.
6	0 (0%)	0% -- 46%
12	0 (0%)	0% -- 27%
6	1 (17%)	.4% -- 64%
12	2 (17%)	2% -- 49%
6	2 (33%)	4% -- 78%
12	4 (33%)	10% -- 65%

The proportions of infants who have become HIV-1 infected will be presented, bounded by 95% confidence intervals. The upper and lower limits of the confidence intervals around selected, potential proportions occurring in the groups of n=6 and full cohorts will be similar to those presented in Table 2. The results will be presented separately for the EFV vs. non-EFV strata.

Additional Secondary Analysis on Tropism

Note that the study team expects only few infants (if any) to become HIV-1 infected during the study. Exploratory analysis will be performed in infants who become HIV-1 infected: (1) to determine the infant's viral tropism after exposure to maraviroc; and (2) to assess if the infant's viral tropism matches the mother's.

10 PHARMACOLOGY PLAN

The design and analysis plans for objectives 2.1.2, 2.1.3, and 2.2.2 are described in this section.

10.1 Pharmacology Overview and Objectives

This study is designed to assess the PK and safety of maraviroc solution in infants during the first six weeks of life. Cohort 1 infants will receive a single dose of maraviroc after enrollment and within 3 days of life and again at Week 1. PK samples will be drawn around each of these doses. Cohort 2 infants will receive daily dosing of maraviroc after enrollment and within 3 days of life through 6 weeks of life at a dose determined in Cohort 1. Cohort 2 infants will have intensive PK evaluations at Weeks 1 and 4, and an additional sparse PK sample at Week 6. Both cohorts will be stratified by maternal use of efavirenz, see Section 3.0 for stratification.

PK evaluable infants are those whose PK results provide data on the primary PK parameters of interest. Unevaluable infants will be replaced. See Section 9.1. Unevaluable infants would include infants taken off maraviroc due to HIV-1 infection, infants of breastfeeding mothers who stop taking EFV (Stratum 2B), infants who vomit within 30 minutes of maraviroc administration (Cohort 1), and any other reasons for which the protocol team may determine that the infant would be unevaluable.

10.2 Methods and Timing for Collections, Processing, Handling, and Storage

PK sample collection methods, processing, storage and shipping instructions are detailed in the LPC.

10.2.1 PK collections: Cohort 1

Entry (birth to 3 days)
The PK sampling for maraviroc must be initiated on the same day as the first dose of maraviroc (within 3 days of life) per Section 6.4. As mentioned in Section 6.4, the Entry Visit may be conducted as a split visit.

For infants in Stratum 1B only, an additional sample for analysis of EFV levels should also be drawn at any time on the same day the first maraviroc dose is given.

Week 1 (7 to 14 days)
Intensive PK sampling for maraviroc must be initiated on the same day as the dose of maraviroc and conducted as per Section 6.5.1

For infants in Stratum 1B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

10.2.2 Intensive PK collections: Cohort 2 with Once Daily Dosing

Intensive PK sampling should be scheduled so that the observed dosing of maraviroc is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Infants should take study drug for 3 days prior to the intensive PK visit; otherwise, the intensive PK visit should be re-scheduled.

Week 1 (7 to 14 days)
The Intensive PK sampling for maraviroc should be conducted as per Section 6.5.2

For infants in Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

Week 4 (21 to 31 days)
The Intensive PK sampling for maraviroc should be conducted as per Section 6.7.1

For infants in Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 4 visit.

10.2.3 Intensive PK collections: Cohort 2 with Twice Daily Dosing

Intensive PK sampling should be scheduled so that the observed dosing of maraviroc is as close as possible to 12 hours (generally 11-13 hours) after the previous dosing. Infants should have taken study drug for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled.

Week 1 (7 to 14 days)

The Intensive PK sampling for maraviroc should be conducted as per Section 6.5.3. For Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 1 visit.

Week 4 (21 to 31 days)
The Intensive PK sampling for maraviroc should be conducted as per Section 6.7.2. For Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during this study visit.

10.2.4 Population PK collection: Cohort 2 with Once or Twice Daily Dosing

Week 6 (35 to 42 days)
A single random sample for maraviroc population PK should be drawn at any time during the Week 6 visit.

For Stratum 2B only, an additional sample for analysis of EFV levels should also be drawn at any time during the Week 6 visit.

10.3 Starting Dose, PK Guidelines for Dose Adjustment and Interim Analyses

10.3.1 Starting Dose

The initial single doses for the first six infants enrolled into Strata 1A and 1B will be 8 mg/kg, based on extrapolation from adult and adolescent data, and expected differences in ontogeny of drug disposition in infants.

For Stratum 1B, in which infants may be exposed to efavirenz *in utero* or through breastfeeding, higher doses of maraviroc might be needed, IF efavirenz causes a clinically significant interaction with infant use of maraviroc. Whether such an interaction will occur is unknown for the following reasons. The efavirenz "dose", or the systemic exposure which each infant will receive from maternal transfer, is unknown and expected to be low at birth and lower during breastfeeding, and may be highly variable between infants. Further, the activity of CYP 3A4 is lower at birth than in

older infants and children, and the ability of efavirenz to induce the activity of this immature enzyme system (and the extent to which this immature enzyme system may be induced) in infants is unknown. Because of the uncertainties surrounding whether low passive exposure to efavirenz in infants will cause a clinically significant decrease in maraviroc exposure, and our lack of safety data for maraviroc use in infants at the outset of this study, infants in Stratum 1B will begin with the same 8 mg/kg single doses as infants in Stratum 1A.

10.3.2 PK Guidelines for Dose Adjustment

The study will implement a dose-finding algorithm (see Section 9.2) based on the review of real-time PK and safety data from Strata 1A and 1B separately, with an initial group of 6 infants in each of these strata with evaluable PK data. The maraviroc exposure target will be a C_{avg} of $\geq$ 75 ng/mL, which is the exposure associated with near-maximal efficacy in the treatment naïve adult study (MERIT) of maraviroc when dosed in combination with ZDV/3TC. [15] If the maraviroc exposure target (C_{avg} $\geq$75 ng/mL) is not met in 2 or more of the 6 infants at the Entry visit and the Week 1 visits, the Core Protocol Team will evaluate the PK and safety data and decide whether to adjust the dose, continue with the current dose, or stop the study. Enrollment of additional groups of six infants receiving adjusted doses (increased or decreased doses) will be allowed. If the safety and PK guidelines are met in Stratum 1A or 1B, then the corresponding Stratum 2A or 2B will open with n=6 infants in each stratum receiving daily dosing, with a dose size and frequency (once or twice daily) to be determined based on the Stratum 1A or 1B data. Strata 2A and 2B PK data from n=6 will be checked prior to the full accrual of n=12 for each stratum. Strata 2A and 2B will allow further dose adjustment for PK or safety as needed (see Section 9.2 for the Dose Adjustment algorithm based on both safety and PK guidelines). Final enrollment target is 12 infants in Stratum 2A and 12 infants in Stratum 2B with evaluable PK data on the final dose. If 3 or more of the 12 infants in Stratum 2A or 2B do not meet the maraviroc exposure target at both PK assessments (Weeks 1 and 4), the Core Protocol Team will evaluate the PK and safety data, and decide whether to change the dose, continue with the same dose, or stop the study. Enrollment of additional groups of 6 infants receiving adjusted doses (increased or decreased doses) will be allowed, and the process above will be repeated.

10.3.3 Timing of Interim Analyses

The PK data will be analyzed for each individual infant enrolled in this study in real-time. The individual PK analyses will be reviewed by the Core Team as soon as the results are available for each infant. A summary of the PK data will be prepared at the following times:

1. After the real-time PK analyses have been completed for the first 6 infants enrolled in any stratum at a given dose level.
2. In Stratum 1A or 1B at a given dose level: After two infants do not meet the PK guidelines.
3. In Stratum 2A or 2B at a given dose level: After two infants (at n=6) and three infants (at n=12) do not meet the PK guidelines.
4. The Core Protocol Team deems it important to assess the current dose.

10.4 Laboratory Performing the Assays

The laboratories performing the maraviroc and EFV assays will be detailed in the LPC.

10.5 Primary and Secondary Data Analysis Plan

The primary PK endpoint for all participants is whether or not maraviroc $C_{avg} \geq 75$ ng/mL at all PK assessments. The primary PK outcome variables are C_{avg}, AUC, and C_{max} for Strata 1A and 1B. C_{trough} is an additional primary PK outcome variable for Strata 2A and 2B. Other standard PK parameter estimates will also be calculated (half-life, elimination rate constant, oral clearance).

C_{max} and C_{trough} will be observed from the concentration versus time curve for each participant. Noncompartmental analyses of the intensive PK data will initially provide rough estimates of the AUC and C_{avg} in each participant in real-time. Compartmental modeling methods (using one or two compartment models in the software program, WinNonlin) may be explored and utilized if necessary for the real-time PK assessments to calculate the C_{avg}.

For interim analyses, population PK models will be constructed in NONMEM and simulations will be used to estimate appropriate doses. Both intensive and sparse PK data from the studies in both adults and children may be utilized, along with all of the data generated in each of the strata in this study, to maximize the available information and provide a rich and diverse dataset.

To determine maraviroc PK over the first six weeks of life, all available information regarding the evolution of maraviroc clearance, possibly interacting drugs and CYP 3A4 ontogeny with age will be included in the population modeling. Covariates of interest will be explored. The model can be used to simulate an optimal dosing scheme (with dose and/or frequency adjustments at appropriate times) to meet the PK targets throughout the course of dosing.

10.6 Anticipated Outcomes

The goal of this study is to gain an understanding of maraviroc PK in young infants, the ontogeny of maraviroc metabolism, the potential effect of maternal efavirenz use on infant maraviroc PK, and to have defined the dose(s) and dosing interval that achieve the desired systemic exposure in this population.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.4, data on screening and enrollment in this study will be collected using the DMC SES.

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled mother-infant pairs, including CRFs and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 11.2).

CRFs are completed by study site staff and, following quality control and quality assurance reviews, are keyed using a remote data entry system designated by the DMC and transferred

electronically to the DMC. Selected laboratory data are transferred electronically to the DMC through the LDMS.

At the DMC, computerized checks are applied to the transferred data and, when required, data queries are issued for resolution by study site staff. All data must be transferred to the DMC within timeframes specified in the forms instructions; queries must also be resolved in a timely manner.

Further information on the study CRFs and IMPAACT data management procedures, including a Forms Manual: Policies and Procedures for Forms Completion for DAIDS-Sponsored Clinical Trials, a comprehensive Computing Manual, and a User Manual for the SES, are available on the DMC portal at www.fstrf.org.

11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at: www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

Study sites must comply with DAIDS policies on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. In its policy on Requirements for Manual of Operational Procedures, DAIDS requires sites to establish SOPs for maintaining essential and source documents in compliance with these policies. Site SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study, and site SOPs should be followed throughout the study.

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for one or more of the study drugs for the indication for which it is evaluated in this study; or, if no application is filed, or if the application is not approved for this indication, records must be retained two years after the study is discontinued and the FDA is notified.

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, the US Food and Drug Administration, site drug regulatory authorities, site IRBs/ECs, the US Office for Human Research Protections, and other applicable regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Expectations for Data Usage

DAIDS acknowledges ViiV's intention to use the data from this Clinical Trial for the fulfillment of a pediatric written request pursuant to the Best Pharmaceuticals for Children's Act and for labeling changes for the Company's products.

11.4 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at:

www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

12 CLINICAL SITE MONITORING

Site monitors under contract to NIAID or NICHD will visit study sites to inspect study facilities and review participant study records including consent forms, CRFs, medical records, laboratory records, and pharmacy records, to ensure protection of study participants, compliance with the IRB/EC approved protocol, and accuracy and completeness of records. The monitors also will review essential document files to ensure compliance with all applicable regulatory requirements. Site investigators will make study facilities and documents available for inspection by the monitors.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific ICFs in accordance with 45 CRF 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must also promptly report to the IRB/EC any changes in the study and any unanticipated problems involving risks to participants or others.

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 14.2).

13.2 Vulnerable Participants

The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate. [17, 18] This study responds to that mandate and will provide clinical research data to inform maraviroc safety and dosing in full-term infants. The infants who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to infant participants as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart B, the specifications of 45 CFR 46.204 (d) are considered to apply; therefore, maternal participants will be asked to provide written informed consent for their own and their infant's study participation.

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children in Clinical Research, which is available at:

www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx

13.3 Informed Consent

Written informed consent for maternal and infant study participation will be obtained before any study-specific procedures are performed. The informed consent process may be conducted during pregnancy or, in whole or in part, after infant birth. If informed consent is obtained during pregnancy, the study will be discussed again with the mother after delivery and her prior consent decision will be confirmed at that time. If the mother changes her mind and withdraws her consent at that time, the mother-infant pair will not be enrolled in the study and no further study-specific procedures will be performed.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the unproven efficacy of the study drug for prevention of mother to child transmission and mothers will be extensively counseled on the importance of adherence to their standard of care ARV regimen for perinatal transmission and adherence to the infants ARV regimen.

As indicated above, it is generally expected that mothers will provide informed consent for their own and their infant's participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 13.2; all IRB/EC requirements will be followed.

As part of the informed consent process, mothers will be asked whether they agree to storage and future research testing of biological specimens, remaining after all protocol-specified testing has been completed. Future research testing of residual specimens may be declined with no impact on other aspects of infant study participation.

Should the mother of an enrolled infant die or no longer be available for any reason, no further study drug may be administered and no study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 12.2), all study sites must establish and maintain written procedures describing the standards that will be followed to

identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

There may be no direct benefit to mothers or infants who take part in this study. The infants in Cohort 1 only receive two single doses of maraviroc (in addition to standard of care ARVs) and should therefore not expect any benefit. The infants in Cohort 2 will receive daily doses of maraviroc for up to 42 days and while there is no established benefit, this may provide some prophylactic benefit (in addition to standard of care ARVs). Information learned in this study may be of benefit to infants born to HIV-1 infected mothers in the future, and mothers may appreciate the opportunity for themselves and their infants to contribute to HIV-related research.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of maraviroc. Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, and (rarely) infection at the site where the needle is inserted.

Maraviroc has been used widely in adults as second line treatment, see Section 1.2. A pediatric study was completed, to determine the safety and efficacy in combination with optimized background therapy in HIV-1 infected children 2 to <18 years of age, see Section 1.3. To date, maraviroc plus other background therapy appears to be well tolerated and effective, with a manageable safety profile in adult and pediatric populations. The most common treatment related adverse events seen in adults receiving maraviroc were diarrhea, nausea and headache. The most common treatment related adverse events seen in the pediatric study of children ages 2 to <18 years were gastrointestinal disorders. Two subjects in the 12-18 year old cohort met initial biochemical criteria of Hy's law but in final analysis, these liver toxicities were considered unlikely to be related to maraviroc. These subjects are described in detail in Section 1.3. For subjects in the 2-6 year old cohort, there were a few cases of grade 1 ALT/AST elevation but no higher grade liver toxicity was observed.

There may be other risks to study participants that are not currently known.

13.6 Potential Social Impacts

Participation in clinical research includes the risk of loss of confidentiality. Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as having HIV). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities.

13.7 Reimbursement/Compensation

Pending IRB/EC approval, participants will be reimbursed for costs associated with completing study visits (e.g., transport costs). Reimbursement amounts will be specified in site-specific ICFs or other materials if applicable per IRC/EC policies and procedures.

13.8 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 11.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms) will be identified by PID only. Likewise, communications between study staff and protocol team members regarding individual participants will identify participants by PID only.

Study sites are encouraged but not required by DAIDS policies to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

In addition to the above, a Certificate of Confidentiality has been obtained for this study from the US Department of Health and Human Services. This certificate protects study staff from being compelled to disclose study-related information by any US Federal, state, or local civil, criminal, administrative, legislative, or other proceedings. It thus serves to protect the identity and privacy of study participants. Because the certificate cannot be enforced outside of the US, however, it applies only to US sites and participants.

13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV infection identified among study participants to health authorities. Participants will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.10 Management of Incidental Findings

Site investigators will inform mothers (or other authorized guardians if applicable) of all clinically meaningful physical exam findings and laboratory test results, including results of HIV tests and hematology and chemistry tests. Mothers will not routinely receive infant PK test results in this study. When applicable, site investigators will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.11 Management of New Information Pertinent to Study Participation

Infants' mothers (or other authorized guardians if applicable) will be provided any new information learned over the course of the study that may affect their willingness to allow their infants to continue receiving study drug and/or remain in follow-up in the study.

13.12 Post-Trial Access to Study Drug

Participants will complete the study drug regimen prior to exiting the study. Therefore, post-study access to study drug is not applicable.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). The study drug maraviroc is provided by PHIVCO; however, these organizations are not involved in sponsorship or regulatory oversight of this study.

The Division of AIDS (DAIDS) within the NIAID is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study drugs prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 12. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

14.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS 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.

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, 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 ICFs 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, which is available on the RSC website:

http://rsc.tech-res.com/protocolregistration/

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the IMPAACT website: www.impaactnetwork.org.

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operations specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

Deviations should be reported to site IRBs/ECs and other applicable review bodies in accordance with the policies and procedures of these review bodies. Serious deviations that are associated with increased risk to one or more study participants and/or significant impacts on the integrity of study data must also be reported within IMPAACT, following procedures specified in the IMPAACT Manual of Procedures.

14.5 Critical Event Reporting

Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, which is available at:

www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/Safety.aspx

14.6 ClinicalTrials.gov

This protocol is not subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA). However, it will be registered in ClinicalTrials.gov to meet International Committee of Medical Journal Editors requirements.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Manual of Procedures.

16 REFERENCES

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17. National Institutes of Health, *Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research. Federal Register.* 1994.
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APPENDICES

Appendix IA: Maternal Schedule of Evaluations

Study Visit	Screen	Entry
Visit Window	During pregnancy through 0 – 3 days	0 – 3 days
Informed Consent	X	
HIV-1 Testing (if needed)	[3- 10 mL]	
Medical/Medication History	X	X
HIV-1 RNA		6 mL
Blood Storage (tropism testing)		8 mL
Total Maximum Blood Volume	10 mL	14 mL

Day 0 is defined as the date of delivery (infant date of birth). Screening and enrollment (all evaluations shown above) must occur within 3 days of delivery.

Appendix IB: Cohort 1 (Stratum 1A and 1B) – Infant Schedule of Evaluations

Study Visit	Screen	Entry	Week 1	7 Days Post Dose Safety	Week 6	Week 16 or Early Study Discontinuation
Visit Window	0 – 3 days	0 – 3 days	7 – 14 days	+/- 3days	35 – 42 days	112 – 140 days
Clinical						
History	X		X	X	X	X
Physical Exam	X		X	X	X	X
Laboratory						
HIV Nucleic Acid Test (NAT)	2 mL				2 mL	2 mL
CBC with differential and platelets	0.5 mL		0.5 mL	0.5 mL	0.5 mL	0.5 mL
AST, ALT, total bilirubin, creatinine	1 mL		1 mL	1 mL	1 mL	1 mL
Plasma Storage	1 mL					
Dried blood spot storage	From NAT				From NAT	From NAT
HIV Confirmatory Testing		*If the initial HIV NAT is positive, confirm as soon as possible with a repeat HIV NAT on a second sample drawn on a different day and collect an additional 6 mL for tropism and resistance testing, per the LPC. See Section 6.11 for further instructions. Note: 6 mL does not appear in totals below since this will be a sample drawn on an unscheduled visit.*				
Pharmacokinetics						
Intensive PK Sampling		3 mL (0.5 mL per sample)	1.5 mL (0.5 mL per sample)			
EFV level (Stratum 1B only)		0.5 mL	0.5 mL			
Total Maximum Blood Volume	4.5 mL	3.5 mL	3.5 mL	1.5 mL	3.5 mL	3.5 mL

Day 0 is defined as the infant's date of birth and all follow-up visits are scheduled from this date with the exception of the 7 Days Post Dose Safety Visit which is scheduled for 7 days (+/- 3 days) from the day of administration of the Week 1 dose of study drug. Screening and enrollment must occur within three days of birth.

Appendix IC: Cohort 2 (Stratum 2A and 2B) – Infant Schedule of Evaluations

Study Visit	Screen/Entry	Week 1	Week 4	Week 6	Week 12	Week 16 or Early Study Discontinuation
Visit Window	0 – 3 days	7 – 14 days	21 – 31 days	35 – 42 days	77 – 91 days	112 – 140 days
Clinical						
Medical History	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X
Laboratory						
HIV Nucleic Acid Test	2 mL			2 mL		2 mL
CBC with differential and platelet	0.5mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
AST, ALT, total bilirubin, creatinine	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
Plasma Storage	1 mL					
Dried blood spot storage	From NAT			From NAT		From NAT
HIV Confirmatory Testing		*If the initial HIV NAT is positive, confirm as soon as possible with a repeat HIV NAT on a second sample drawn on a different day and collect an additional 6 mL for tropism and resistance testing, per the LPC. See Section 6.11 for further instructions. Note: 6 mL does not appear in totals below since this will be a sample drawn on an unscheduled visit.*				
Pharmacokinetics						
Intensive PK Sampling		2.5 mL (0.5 mL per sample)	2.0 - 2.5 mL (0.5 mL per sample)			
Population PK Sampling				0.5 mL		
EFV level (Stratum 2B only)		0.5 mL	0.5 mL	0.5 mL		
Total Maximum Blood Volume	4.5 mL	4.5 mL	4.5 mL	4.5 mL	1.5 mL	3.5 mL

Day 0 is defined as the infant's date of birth and all follow-up visits are scheduled from this date.

Appendix II: Maraviroc Weight Band Dosing Tables For Solution
(Solution Concentration is 20 mg/mL)

Note: The tables listed below show unit doses of each maraviroc dose, which may or may not equal the total daily dose, depending on the dose frequency. Sections 5.3.1 and 5.3.2 include the dosing regimen for Cohort 1 (Stratum 2A or Stratum 2B) and Cohort 2 (Stratum 2A or Stratum 2B), respectively. The selected table for any stratum dose adjustments for Cohort 1 and the dose and frequency for Cohort 2 (Stratum 1A and Stratum 2B) will be communicated to study sites via a protocol Clarification Memorandum. If the Core Protocol Team determines that a stratum dose or dosing schedule adjustment is required and the appropriate dose is not included in the tables below, an updated dosing table will be provided through an appropriate mechanism.

Table A – Dose of 2 mg/kg

Weight Band (kg)	2 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	5 mg	0.25 mL
2.5-3.4	6 mg	0.3 mL
3.5-4.4	8 mg	0.4 mL
4.5-5.4	10 mg	0.5 mL
5.5-6.4	12 mg	0.6 mL

Table B – Dose of 4 mg/kg

Weight Band (kg)	4 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	8 mg	0.4 mL
2.5-2.7	10 mg	0.5 mL
2.8-3.1	12 mg	0.6 mL
3.2-3.6	14 mg	0.7 mL
3.7-4.1	16 mg	0.8 mL
4.2-5.4	20 mg	1 mL
5.5-6.0	25 mg	1.25 mL (1/4 tsp)

Table C – Dose of 6 mg/kg

Weight Band (kg)	6 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	14 mg	0.7 mL
2.5-2.9	16 mg	0.8 mL
3.0-3.4	20 mg	1 mL
3.5-3.9	25 mg	1.25 mL (1/4 tsp)
4.0-4.9	30 mg	1.5 mL
5.0-6.0	40 mg	2 mL

Table D – Dose of 8 mg/kg

Weight Band (kg)	8 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.5	20 mg	1 mL
2.6-3.1	25 mg	1.25 mL (1/4 tsp)
3.2-3.8	30 mg	1.5 mL
3.9-5.0	40 mg	2 mL
5.1-6.0	50 mg	2.5 mL (1/2 tsp)

Table E – Dose of 10 mg/kg

Weight Band (kg)	10 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	25 mg	1.25 mL (1/4 tsp)
2.5-2.9	30 mg	1.5 mL
3.0-3.9	40 mg	2 mL
4.0-4.9	50 mg	2.5 mL (1/2 tsp)
5.0-6.0	60 mg	3 mL

Table F – Dose of 12 mg/kg

Weight Band (kg)	12 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	30 mg	1.5 mL
2.5-3.3	40 mg	2 mL
3.4-4.1	50 mg	2.5 mL (1/2 tsp)
4.2-4.9	60 mg	3 mL
5.0-6.0	80 mg	4 mL

Table G – Dose of 14 mg/kg

Weight Band (kg)	14 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.8	40 mg	2 mL
2.9-3.5	50 mg	2.5 mL (1/2 tsp)
3.6-4.2	60 mg	3 mL
4.3-5.7	80 mg	4 mL
5.8-6.0	100 mg	5 mL (1 tsp)

Table H – Dose of 16 mg/kg

Weight Band (kg)	16 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	40 mg	2 mL
2.5-3.1	50 mg	2.5 mL (1/2 tsp)
3.2-3.7	60 mg	3 mL
3.8-4.9	80 mg	4 mL
5.0-6.0	100 mg	5 mL (1 tsp)

Table I – Dose of 18 mg/kg

Weight Band (kg)	18 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.7	50 mg	2.5 mL (1/2 tsp)
2.8-3.3	60 mg	3 mL
3.4-4.4	80 mg	4 mL
4.5-5.5	100 mg	5 mL (1 tsp)
5.6-6.0	120 mg	6 mL

Table J – Dose of 20 mg/kg

Weight Band (kg)	16 mg/kg	Volume (mL)
	Dose in (mg)	Volume to Administer
2.0-2.4	50 mg	2.5 mL (1/2 tsp)
2.5-2.9	60 mg	3 mL
3.0-3.9	80 mg	4 mL
4.0-4.9	100 mg	5 mL (1 tsp)
5.0-6.0	120 mg	6 mL

Appendix III-A: Cohort 1 Sample Informed Consent Form for Study Participation

IMPAACT 2007
Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

VERSION 1.0, 13 April 2016

You and your baby are being asked to participate in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that you and your baby will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[sites: insert site name]* are doing this study to test an anti-HIV medicine (ARV) given to babies. The medicine is called maraviroc. HIV is the virus that causes AIDS.

You and your baby are being asked to participate in this study because you are infected with HIV and there is a risk that the infection may be passed onto your baby. The transfer of HIV to newborn babies from HIV-infected mothers can occur at the time of birth.

The study will include about 70 mothers who have HIV and their babies. Mothers will be in the study for up to 3 days and babies will be in the study for 4 months.

The person in charge of the study at this clinic is *[sites: insert name of Investigator of Record]*. The United States National Institutes of Health is paying for the study.

1. The study is being done to test the safety and blood levels of maraviroc in newborn babies.

Babies born to mothers who have HIV usually take ARVs to prevent infection of HIV after birth. There are not many ARVs available for babies because many ARVs have not yet been tested in babies.

Maraviroc is an ARV that is used in adults in the United States and other countries. This study will look at whether maraviroc causes any bad side effects when given to newborn babies. It will also look at different doses of maraviroc to find what amount of maraviroc should be given to protect newborns.

2. It is your decision whether or not to join the study.

Deciding to join the study with your baby is voluntary. You are free to join or not join. If you join, you can change your mind and leave the study at any time. Your decision will have no effect on the medical care that you and your baby receive at this clinic. Your access to services and the benefits and rights you normally have will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about allowing your baby to join the study. You can bring other people here to learn about the study with you.

No matter what you decide about the study, you must continue to take your anti-HIV medicines. Your baby should also take anti-HIV medicine for 4-6 weeks after birth. Taking these medicines is the best known way to maintain your health and avoid passing HIV to your baby while breastfeeding.

3. Only mothers and their babies who qualify can participate in the study.

If you decide to join the study with your baby, we will first do some tests to see if you and your baby qualify. Some tests can be done while you are pregnant. Other tests will be done after your baby is born. More information about the tests is given in #4 and #5.

Finding out if you and your baby qualify

4. We will ask questions and discuss the study requirements with you.

To find out if you qualify for the study, we will:

- Review your medical records.
- Ask about your plans for feeding your baby and taking anti-HIV medicines after your baby is born.
- Talk with you about the study requirements and if you are able to meet these requirements.
- If needed, draw your blood (up to 10 mL or less than 2 teaspoons) for HIV testing. There are certain HIV tests that are required for mothers in this study. If the required tests are not in your medical records, we will do the tests that are needed.

These procedures may be done while you are pregnant or within 3 days after your baby is born. They will take 30-60 minutes *[sites: modify how much time this visit will take as needed]*.

If these procedures show that you may qualify for the study, you will be given contact information for the study staff. We will stay in contact as you get closer to your delivery date and ask you to contact us when your labor begins. We will not be involved in the delivery of your baby but will arrange to see you soon after your baby is born. You are welcome to contact us or return to the clinic at any time to talk about the study.

5. After delivery, we will collect more information and examine your baby.

To find out if your baby qualifies for the study, as soon as possible after your baby is born, we will:

- Review your and your baby's medical records.
- Ask about your and your baby's anti-HIV medicines.
- Ask about your baby's health and other medicines.
- Ask about how you are feeding your baby.
- Give your baby a physical examination
- Draw your baby's blood (about 4.5 mL or 1 teaspoon). These tests include:
  - A test to look at your baby's blood cells.
  - A test to check how well your baby's liver is working
  - An HIV test.
  - A portion of the blood will be stored for future HIV-related tests. The samples that will be tested will be chosen after the study is completed. You or the site investigator will not be told of the results because the test is for investigation only and will be done after the study is completed. We will ask you about saving these samples in a separate form.

These procedures will take about an hour. *[sites: modify how much time this visit will take as needed]*. The results of some of your baby's blood tests will be available within a couple of days. We will review the results and all other information to determine if you and your baby qualify for the study.

- If you and your baby do not qualify, we will tell you this and give you information on where you and your baby can receive medical care and other services you may need. We will destroy any of your blood remaining after testing.

- If you and your baby do qualify, we will ask you to confirm your decision for you and your baby to join the study. With your confirmation, you and your baby will be entered into the study.

Entering the study

6. If you and your baby qualify, you and your baby will enter the study within 3 days after the baby's birth.

On the day when you and your baby enter the study, we will:

- Draw your blood (14 mL or about 3 teaspoons) to test the amount of HIV in your blood and for future HIV-related testing.
- Ask about your health, anti-HIV medicines, and other medicines.
- If you took the ARV called efavirenz within 2 weeks before your delivery, we will draw your baby's blood (about 0.5 mL or a few drops) to test the amount of efavirenz in your baby's blood.

These procedures may take up to 3 days *[sites: modify how much time this visit will take as needed].*

Your baby will receive his or her first dose of maraviroc and then have blood drawn to test the amount of maraviroc in the blood over the next 3 days. More information is given in #8 below.

Being in the study

7. After entering the study, your baby will have 4 scheduled visits over 4 months.

Visits will be more frequent in the first 6 weeks. During this time, your baby will have 3 visits, at 1, between 2 and 3, and 6 weeks. After that your baby will have 1 more visit, at 4 months of age.

Each visit will take about 1 to 2 hours *[sites: modify how much time this visit will take as needed]*. At these visits, we will:

- Review your baby's medical records and ask you about how your baby is doing and any side effects
- Give your baby a physical examination
- Draw your baby's blood (2- 4 mL or less than 1 teaspoon) for tests. These tests will check
  - Your baby's blood cells
  - How well your baby's liver is working.
  - If your baby has HIV
  - At one visit, if you took efavirenz within 2 weeks before delivery, we will draw your baby's blood (about 0.5 mL or a few drops) to test the amount of efavirenz in your baby's blood.

These procedures will take about 1 to 2 hours *[sites: modify how much time this visit will take as needed]*. Babies may have more visits if they are sick or if we need to do more tests to check on their health.

8. Your baby will get 2 doses of maraviroc and participate in another study procedure. This procedure will very closely measure the amount of maraviroc in their blood.

Your baby will also have blood drawn to very closely measure the amount of maraviroc in his or her blood. This is called a pharmacokinetic (PK) test. Your baby will only get two doses of maraviroc, one with each PK test.

This PK test will happen within 3 days of your baby's birth and at the Week 1 visit. At these visits, you will bring your baby to the clinic and the study staff will give your baby maraviroc so that we know what time maraviroc was given. This is called directly observed therapy.

The first PK test (within 3 days of your baby's birth) will require a clinic visit for 3 days. Your baby will stay at the clinic for up to 13 hours after your baby takes maraviroc. Then your baby will need to return to the clinic 2 more times at 20 - 24 and 48-72 hours after they took maraviroc. *[sites: modify* If the study clinic is able, you may be allowed to stay at the clinic the night before and during your first PK visit.*]*

The second PK test will happen at the Week 1 visit and take 2 separate days in a row. Your baby will get a dose of maraviroc on the first day and a PK test will be started and the next day the PK test will be finished. Your baby will need to return to the clinic 22 to 26 hours after they took maraviroc.

[Sites: modify language as appropriate to indicate procedures for the intensive PK collection. A small plastic tube (like a "drip") will be placed in your baby's arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick your baby with a needle each time. The plastic tube will stay in place until all of the blood samples are drawn.*]*

We will draw a few drops or about 0.5 mL of blood at 6 different time points during the first day for the PK test (a total of 3.0 mL or ½ teaspoon) and at 3 time points during the second part of the PK test (a total of about 1.5 mL or less than ½ teaspoon). We will look at the amount of maraviroc in your baby's blood at each of these times.

9. Tests for how much maraviroc is in your baby's blood will be done at different laboratories.

We will do most of the HIV tests and tests to check your baby's blood here at our laboratory, but some of the blood tests will be done elsewhere. We will give you the results of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

The test to check the amount of maraviroc in your baby's blood will be done at laboratories in the United States or in other countries. Some tests may be done while the study is ongoing; others after the study is done.

10. We may stop your baby's maraviroc doses, one or both.

We may stop giving your baby maraviroc if:

- Your baby is not able to come to the study visits.
- Your baby is not able to take maraviroc.
- Your baby becomes infected with HIV.
- Continuing maraviroc may be harmful to your baby.
- You request to stop the maraviroc for your baby.

Even if your baby stops taking maraviroc, your baby will stay in the study, with the same schedule of visits.

If an HIV test that we do for the study shows that your baby has HIV infection, we will ask you to bring your baby to the clinic for another test. Your baby will not receive maraviroc and your baby will have additional blood drawn (6 mL or a little more than 1 teaspoon) for another HIV test to see if your baby truly is infected and to test for resistance to the study medicine. If the second test confirms HIV infection, your baby will stay in the study, with the same schedule of visits, but will be taken off maraviroc. At these visits your baby will have all procedures done except HIV testing and testing for how much maraviroc is in his/her blood. The study cannot provide care and treatment for babies with HIV infection, but we will give information, counseling, and referrals to where your baby can get the care and treatment they need.

11. We may take you and your baby off the study if:

- The study is stopped for any reason.
- We determine that you and your baby cannot meet the study requirements (for example, if you move away and cannot come to the clinic).
- We determine that staying in the study might harm you and your baby.

12. Please tell us if you wish you and your baby to leave the study.

You and your baby are free to leave the study at any time for any reason. The care that you and your baby receive at this clinic will not be affected, but it is important for us to know about your decision. We will ask you to bring your baby to the clinic for one last visit. At this visit, we will ask questions about your baby's health and medicines, give your baby a physical examination, and draw your baby's blood (less than 1 teaspoon) for tests. We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

Risks of the study

13. There is little risk from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to you and your baby. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

14. There are some risks from maraviroc.

Maraviroc (MVC, Selzentry®) is like any other medication or drug and may have side effects. Some of the most common or most serious effects are listed below. The list does not include all of the possible side effects. These lists include the more serious or common side effects with a known or possible relationship. If you have questions about side effects not included in these lists, you can ask us.

If your baby joins the study, we will tell you about the side effects of maraviroc that your baby will take. We will also check for any side effects during the visits and tell you what to do if your baby has any side effects.

15. We will tell you about the most severe side effects first.

First, you should know about the possible severe side effects. These effects are rare, but they can cause serious health problems and can result in death:

- Liver problems. The liver is an organ near the stomach. If your baby gets liver problems, he or she might have a rash on your baby's body; yellowing of the skin or whites of the eyes; dark or tea

colored urine; upset stomach or vomiting; or loss of appetite. If your baby develops any of these symptoms, stop maraviroc and contact your baby's doctor immediately.

- Heart problems, including a heart attack.

- Low blood pressure problems. Low blood pressure may cause your baby to be dizzy or faint. If your baby has kidney problems, he or she may be at an increased risk for low blood pressure. The kidneys are organs near the middle of the back and there is one kidney on each site of the body. Doctors usually find out about kidney problems from blood tests.

- Stroke

16. There are also more common and not severe side effects from maraviroc.

You should also know about the more common side effects. These side effects are not severe. There are many possible mild and moderate side effects. The most common ones are listed below:

<table>
<tr>
<td rowspan="4">Overall Body Effects
• Swelling of parts of the body
• Some infections, including herpes, colds, sore throat, flu and flu-like symptoms
• Muscle aches, spasms and pain
• Fever
• Rash
• Colds
• Cough
• Runny, congested nose</td>
<td>Effects on Your Child's Activity
• Sleeping problems
• Dizziness</td>
</tr>
<tr>
<td>Effects on Your Child's Belly
• Stomach pain or bloating
• Diarrhea</td>
</tr>
<tr>
<td>Effects on Your Child's Bladder
• Problems with urination</td>
</tr>
<tr>
<td>Effects on Your Child's Blood
• Low amounts of white blood cell counts (neutropenia), which could lead to risk of infection</td>
</tr>
</table>

The list above is not a complete list of all side effects for maraviroc. As a reminder, if your baby joins the study, we will tell you about the side effects of maraviroc your baby will take.

Note: Because of how maraviroc works in your baby's body, there is a possible increased risk your baby may get other infections or cancer. However, there is no evidence from clinical studies of an increase in serious infections or cancer.

Maraviroc contains soy lecithin. If your baby has or develops an allergy to soy (soya or soybeans) or peanuts, your baby may develop an allergic reaction to maraviroc. If your baby is allergic to soy or peanuts, please tell your baby's doctor immediately.

17. There may be other possible risks from maraviroc.

Immune reconstitution syndrome

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these symptoms may be life threatening. If your baby starts having new symptoms, or if you notice that your baby's existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

The use of some strong ARV combinations may be related to unusual position of body fat and weight loss. Some of the body changes may include body fat increasing around the abdomen, stomach area, chest or neck or body fat decreasing in the face, legs, or arms.

Risk of resistance

All ARVs can cause some resistance. Resistance means that the ARVs may not work against HIV if it is taken again in the future. To stop resistance, it is important that you give your baby the study medicine and ARVs as instructed, and do not miss any doses.

18. There could be risks of disclosure of you and your baby's information.

We will make every effort to keep your baby's information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, you and your baby's names will be written on some records. Despite our best efforts to keep you and your baby's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you and your baby could be treated badly or unfairly. You could feel stress or embarrassment.

[*US sites, insert:* To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.]

Benefits of the study

19. There may or may not be a benefit to your baby from being in the study.

By joining the study, you and your baby will be part of the search for anti-HIV medicines that may be better for your baby. There may or may not be a direct benefit to you or your baby by participating in this study. Your baby will have regular visits here and frequent checks on his or her health, including tests for HIV in your baby's blood. Information learned from this study may help other babies born to HIV-infected mothers at risk of HIV infection.

Other information about the study

20. There are no costs to you or your baby for being in the study.

There are no costs to you or your baby for study visits, maraviroc, or procedures. *[Sites: insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]*

21. You and your baby's study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of other site drug entities that may review records]*

- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- The US Food and Drug Administration
- The IMPAACT Network that is coordinating the study
- The companies that make maraviroc (PHIVCO)

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally. A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You and your baby's study information may be disclosed to other authorities if required by law.

22. If you or your baby gets sick or injured, contact us immediately.

You and your baby's health is important to us. We will make every effort to protect you and your baby's well-being and minimize risks to you and your baby. It is possible, however, that your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

If a study-related illness or injury occurs, we will treat your baby or tell you where you can get the treatment your baby needs. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health.

Who to contact

23. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study, contact:
  [sites: insert name and telephone number of investigator or other study staff]

- If you have questions about you and your baby's rights as a research participant, or problems or concerns about how you and your baby are being treated in the study, contact:
  [sites: insert name and telephone number of IRB contact person or other appropriate person/organization]

- If you or your baby has any health or other problems that may be related to his or her study participation, contact:
  [sites: insert name and telephone number of investigator or other study staff]

- If you or your baby want to leave the study, contact:
  [sites: insert name and telephone number of investigator or other study staff]

Signatures

24. If you agree to participate in this study, and your baby, please sign or make your mark below.

Before deciding whether to join this study with your baby, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your baby if you decide to join.

If you decide to allow your baby to join, we will tell you any new information from this study or other studies that may affect your willingness for your baby to stay in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

Participant's Name (print)		
Parent's Name (print) (Or Legal Guardian)	Parent's Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name (As appropriate)	Witness Signature	Date

Appendix III-B: Cohort 2 Sample Informed Consent Form for Study Participation

IMPAACT 2007
Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

VERSION 1.0, 13 April 2016

You and your baby are being asked to participate in the research study named above.

This form gives information about the study. Please read it, or have it read to you, and ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

After you understand the study, if you decide that you and your baby will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the Study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[sites: insert site name]* are doing this study to test an anti-HIV medicine (ARV) given to babies. The medicine is called maraviroc. HIV is the virus that causes AIDS.

You and your baby are being asked to participate in this study because you are infected with HIV and there is a risk that the infection may be passed onto your baby. The transfer of HIV to newborn babies from HIV-infected mothers can occur at the time of birth.

The study will include about 70 mothers who have HIV and their babies.. Your baby will receive the anti-HIV medicine being tested. Mothers will be in the study for up to 3 days and babies will be in the study for 4 months.

The person in charge of the study at this clinic is *[sites: insert name of Investigator of Record]*. The United States National Institutes of Health is paying for this study.

1. The study is being done to test the safety and blood levels of maraviroc in newborn babies

Babies born to mothers who have HIV usually take ARVs to prevent infection of HIV after birth. There are not many ARVs available for babies because many ARVs have not yet been tested in babies.

Maraviroc is an ARV that is used in adults in the United States and other countries. This study will look at whether maraviroc causes any bad side effects when given to newborn babies. It will also look at different doses of maraviroc to find what amount of maraviroc should be given to protect newborns.

2. It is your decision whether or not to join the study.

Deciding to join the study with your baby is voluntary. You are free to join or not join. If you join, you can change your mind and leave the study at any time. Your decision will have no effect on the medical care that you and your baby receive at this clinic. Your access to services and the benefits and rights you normally have will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about allowing your baby to join the study. You can bring other people here to learn about the study with you.

No matter what you decide about the study, you must continue to take your anti-HIV medicines. Your baby should also take anti-HIV medicine for 4-6 weeks after birth. Taking these medicines is the best known way to maintain your health and avoid passing HIV to your baby while breastfeeding.

3. Only mothers and their babies who qualify can participate in the study.

If you decide to join the study with your baby, we will first do some tests to see if you and your baby qualify. Some tests can be done while you are pregnant. Other tests will be done after your baby is born. More information about the tests is given in #4 and #5.

Finding out if you and your baby qualify

4. We will ask questions and discuss the study requirements with you.

To find out if you qualify for the study, we will:

- Review your medical records.
- Ask about your plans for feeding your baby and taking anti-HIV medicines after your baby is born.
- Talk with you about the study requirements and if you are able to meet these requirements.
- If needed, draw your blood (up to 10 mL or 2 teaspoons) for HIV testing. There are certain HIV tests that are required for mothers in this study. If the required tests are not in your medical records, we will do the tests that are needed.

These procedures may be done while you are pregnant or within 3 days after your baby is born. They will take 30-60 minutes. *[sites: modify how much time this visit will take as needed]*.

If these procedures show that you may qualify for the study, you will be given contact information for the study staff. We will stay in contact as you get closer to your delivery date and ask you to contact us when your labor begins. We will not be involved in the delivery of your baby but will arrange to see you soon after your baby is born. You are welcome to contact us or return to the clinic at any time to talk about the study.

5. After delivery, we will collect more information and examine your baby.

To find out if your baby qualifies for the study, as soon as possible after your baby is born, we will:

- Review your and your baby's medical records.
- Ask about your and your baby's anti-HIV medicines.
- Ask about your baby's health and other medicines.
- Ask about how you are feeding your baby.
- Give your baby a physical examination
- Draw your baby's blood (about 4.5 mL or 1 teaspoon) for tests. These tests include:
  - A test to look at your baby's blood cells
  - A test to check how well your baby's liver is working
  - An HIV test
  - A portion of the blood will be stored for future HIV-related tests. The samples that will be tested will be chosen after the study is completed. You or the site investigator will not be told of the

results because the test is for investigation only and will be done after the study is completed. We will ask you about saving these samples in a separate form.

These procedures will take about an hour *[sites: modify how much time this visit will take as needed]*. The results of some of your baby's blood tests will be available within a couple of days. We will review the results and all other information to determine if you and your baby qualify for the study.

- If you and your baby do not qualify, we will tell you this and give you information on where you and your baby can receive medical care and other services you may need. We will destroy any of your blood remaining after testing.

- If you and your baby do qualify, we will ask you to confirm your decision for you and your baby to join the study. With your confirmation, you and your baby will be entered into the study.

Entering the study

6. If you and your baby qualify, you and your baby will enter the study within 3 days after the baby's birth.

On the day when you and your baby enter the study, we will:

- Draw your blood (14 mL or about 3 teaspoons) to test the amount of HIV in your blood and for future testing.
- Ask about your health, anti-HIV medicines, and other medicines.

These procedures may take up to 3 days *[sites: modify how much time this visit will take as needed]*.

Your baby will also receive his or her first dose of maraviroc during this visit. We will show you how to give maraviroc to your baby. It is very important that you give your baby maraviroc as instructed. We will take as much time as needed for you to understand the instructions and identify strategies that will help you to give the study medicine to your baby as instructed.

Being in the study

7. After entering the study, your baby will have 5 scheduled visits over 4 months.

Visits will be more frequent in the first 12 weeks. During this time, your baby will have 4 visits, at 1, 4, 6, and 12 weeks. After that your baby will have 1 more visit at 4 months of age.

Each visit will take about 1 to 2 hours *[sites: modify how much time this visit will take as needed]*. At these visits, we will:

- Review your baby's medical records and ask you about how your baby is doing and any side effects
- Give your baby a physical examination
- Draw your baby's blood (1.5 mL - 4.5 mL or less than 1 teaspoon) for tests. These tests will check:
    - Your baby's blood cells
    - How well your baby's liver is working.
    - If your baby has HIV
    - If you took efavirenz within 2 weeks before delivery, we will draw your baby's blood (about 0.5 mL or a few drops) to test the amount of efavirenz in your baby's blood.

These procedures will take about 1 to 2 hours *[sites: modify how much time this visit will take as needed]*. Babies may have more visits if they are sick or if we need to do more tests to check on their health.

8. Your baby will also participate in another study procedure. This procedure will very closely measure the amount of maraviroc in their blood.

Your baby will also have blood drawn to very closely measure the amount of maraviroc in his or her blood. This is called a pharmacokinetic (PK) test. There will be two of these tests.

This collection will happen at the Week 1 and 4 visits. You must give your baby the medicine exactly as instructed and not miss but on the day of these visits, we will ask that you not give your baby maraviroc at home before coming to the clinic. Your baby will be given maraviroc at the clinic, so that we know what time and the exact amount of maraviroc he or she took. This is called directly observed therapy.

For the PK test, your baby will stay at the clinic for up to 13 hours after your baby takes maraviroc. If your baby is taking maraviroc two times a day, your baby will need to return to the clinic 20 - 24 hours after they took the medicine. If your baby is taking maraviroc only once a day, your baby will not need to return to the clinic. The study doctor will tell you how often your baby will take the medicine before the visit.

[Sites: modify language as appropriate to indicate procedures for the intensive PK collection. A small plastic tube (like a "drip") will be placed in your baby's arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick your baby with a needle each time. The plastic tube will stay in place until all of the blood samples are drawn.*]*

We will draw a few drops, about 0.5 mL of blood at 5 different time points at each PK test (a total of 2.5 mL or ½ teaspoon). We will look at the amount of study medicine in your baby's blood at each of these times.

At 6 weeks after birth your baby will also have one sample of blood drawn to measure the amount of maraviroc in his or her blood. At this visit, it is important that you can tell study staff the exact time you gave the study medicine to your child. We will draw about 0.5 mL (a few drops of blood) for this test.

9. Tests for how much of the study medicine is in your baby's blood will be done at different laboratories.

We will do most of the HIV tests and tests to check your baby's blood here at our laboratory, but some of the blood tests will be done elsewhere. We will give you the results of these tests at the next scheduled visit, or sooner, if necessary. We will explain the results and give you counseling and referrals as needed.

We will also draw blood for resistance and to check the amount of maraviroc in your baby's blood here in the clinic. These tests will be done at different laboratories in the United States. Some tests may be done while the study is ongoing; others after the study is done. We will try to give you the results of these tests when they have been tested during the study or after the study is over.

10. We may stop your baby's maraviroc.

We may stop your baby's study medicine if:

- Your baby is not able to come to the study visits.
- Your baby is not able to take the study medicine.
- Your baby becomes infected with HIV.
- Continuing maraviroc may be harmful to your baby.
- You request to stop the maraviroc for your baby.

Even if your baby stops the study medicine, your baby will stay in the study, with the same schedule of visits.
If an HIV test that we do for the study shows that your baby has HIV infection, we will ask you to bring your baby to the clinic for another test. Your baby will not receive maraviroc and your baby will have additional blood drawn (6 mL or a little more than 1 teaspoon) for another HIV test to see if your baby truly is infected and to test for resistance to maraviroc. If the second test confirms HIV infection, your baby will stay in the study, with the same schedule of visits, but will be taken off the study medicine. At these visits your baby will have all procedures done except HIV testing and testing for how much maraviroc is in his or her blood. The study cannot provide care and treatment for babies with HIV infection, but we will give information, counseling, and referrals to where your baby can get the care and treatment they need.

11. We may take you and your baby off the study if:

- The study is stopped for any reason.
- We determine that you and your baby cannot meet the study requirements (for example, if you move away and cannot come to the clinic).
- We determine that staying in the study might harm you and your baby.

12. Please tell us if you wish you and your baby to leave the study.

You and your baby are free to leave the study at any time for any reason. The care that you and your baby receive at this clinic will not be affected, but it is important for us to know about your decision. We will ask you to bring your baby to the clinic for one last visit. At this visit we will ask questions about your baby's health and medicines, give your baby a physical examination, and draw your baby's blood (less than 1 teaspoon) for tests. We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

Risks of the study

13. There is little risk from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to you and your baby. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

14. There are some risks from maraviroc.

Maraviroc (MVC, Selzentry®) is like any other medication or drug and may have side effects. Some of the most common or most serious effects are listed below. The list does not include all of the possible side effects. These lists include the more serious or common side effects with a known or possible relationship. If you have questions about side effects not included in these lists, you can ask us.

If your baby joins the study, we will tell you about the side effects of maraviroc that your baby will take. We will also check for any side effects during the visits and tell you what to do if your baby has any side effects.

15. We will tell you about the most severe side effects first.

First, you should know about the possible severe side effects. These effects are rare, but they can cause serious health problems and can result in death:

- Liver problems. The liver is an organ near the stomach. If your baby gets liver problems, he or she might have a rash on your baby's body; yellowing of the skin or whites of the eyes; dark or tea colored urine; upset stomach or vomiting; or loss of appetite. If your baby develops any of these symptoms, stop maraviroc and contact your baby's doctor immediately.

- Heart problems, including a heart attack.

- Low blood pressure problems. Low blood pressure may cause your baby to be dizzy or faint. If your baby has kidney problems, he or she may be at an increased risk for low blood pressure. The kidneys are organs near the middle of the back and there is one kidney on each site of the body. Doctors usually find out about kidney problems from blood tests.

- Stroke

16. There are also more common and not severe side effects from maraviroc.

You should also know about the more common side effects. These side effects are not severe. There are many possible mild and moderate side effects. The most common ones are listed below:

<table>
<tr>
<td rowspan="4">Overall Body Effects
• Swelling of parts of the body
• Some infections, including herpes, colds, sore throat, flu and flu-like symptoms
• Muscle aches, spasms and pain
• Fever
• Rash
• Colds
• Cough
• Runny, congested nose</td>
<td>Effects on Your Child's Activity
• Sleeping problems
• Dizziness</td>
</tr>
<tr>
<td>Effects on Your Child's Belly
• Stomach pain or bloating
• Diarrhea</td>
</tr>
<tr>
<td>Effects on Your Child's Bladder
• Problems with urination</td>
</tr>
<tr>
<td>Effects on Your Child's Blood
• Low amounts of white blood cell counts (neutropenia), which could lead to risk of infection</td>
</tr>
</table>

The list above is not a complete list of all side effects for maraviroc. As a reminder, if your baby joins the study, we will tell you about the side effects of maraviroc your baby will take.

Note: Because of how maraviroc works in your baby's body, there is a possible increased risk your baby may get other infections or cancer. However, there is no evidence from clinical studies of an increase in serious infections or cancer.

Maraviroc contains soy lecithin. If your baby has or develops an allergy to soy (soya or soybeans) or peanuts, your baby may develop an allergic reaction to maraviroc. If your baby is allergic to soy or peanuts, please tell your baby's doctor immediately.

17. There may be other possible risks of maraviroc.

Immune reconstitution syndrome

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases may occur soon after starting combination ARVs but can also occur later. Some of these

symptoms may be life threatening. If your baby starts having new symptoms, or if you notice that your baby's existing symptoms are getting worse after starting the ARVs, tell your doctor immediately.

The use of some strong ARV combinations may be related to unusual position of body fat and weight loss. Some of the body changes may include body fat increasing around the abdomen, stomach area, chest or neck or body fat decreasing in the face, legs, or arms.

Risk of resistance

All ARVs can cause some resistance. Resistance means that the ARVs may not work against HIV if it is taken again in the future. To stop resistance, it is important that you give your baby the study medicine and ARVs as instructed, and do not miss any doses.

18. There could be risks of disclosure of you and your baby's information.

We will make every effort to keep your baby's information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, you and your baby's names will be written on some records. Despite our best efforts to keep you and your baby's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you and your baby could be treated badly or unfairly. You could feel stress or embarrassment.

[*US sites, insert:* To help us protect your privacy, we have obtained a Certificate of Confidentiality that protects us from being forced to release information that may identify you, such as by the courts or police. The certificate cannot be used in all situations, but it can be used to resist demands for information that would identify you. The certificate does not protect against requests for information from the US federal government or from the US Food and Drug Administration. Regardless of the certificate, you can release information about your participation in the study to others, if you wish.]

Benefits of the study

19. There may or may not be a benefit to your baby from being in the study.

By joining the study, you and your baby will be part of the search for anti-HIV medicines that may be better for your baby. There may or may not be a direct benefit to you or your baby by participating in this study. Your baby will have regular visits here and frequent checks on his or her health, including tests for HIV in your baby's blood. Information learned from this study may help other babies born to HIV-infected mothers at risk of HIV infection.

Other information about the study

20. There are no costs to you or your baby for being in the study.

There are no costs to you or your baby for study visits, maraviroc, or procedures. *[Sites: insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]*

21. You and your baby's study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:
- *[insert name of site IRB/EC]*
- *[insert name of other site drug entities that may review records]*
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- The US Food and Drug Administration
- The IMPAACT Network that is coordinating the study
- The companies that make the study medicine (PHIVCO)

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your baby's name or identify your baby personally. A description of this study will be available on ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You and your baby's study information may be disclosed to other authorities if required by law.

22. If you or your baby gets sick or injured, contact us immediately.

You and your baby's health is important to us. We will make every effort to protect you and your baby's well-being and minimize risks to you and your baby. It is possible, however, that your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.

If a study-related illness or injury occurs, we will treat your baby or tell you where you can get the treatment your baby needs. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health.

Who to contact

23. If you have questions, concerns, or problems at any time, use these contacts.

- If you have questions about the study, contact:
  [sites: insert name and telephone number of investigator or other study staff]

- If you have questions about you and your baby's rights as a research participant, or problems or concerns about how you and your baby are being treated in the study, contact:
  [sites: insert name and telephone number of IRB contact person or other appropriate person/organization]

- If you or your baby has any health or other problems that may be related to his or her study participation, contact:
  [sites: insert name and telephone number of investigator or other study staff]

- If you or your baby want to leave the study, contact:
  [sites: insert name and telephone number of investigator or other study staff]

Signatures

24. If you agree to participate in this study, and your baby, please sign or make your mark below.

Before deciding whether to join this study with your baby, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your baby if you decide to join.

If you decide to allow your baby to join, we will tell you any new information from this study or other studies that may affect your willingness for your baby to stay in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

Participant's Name (print)		
Parent's Name (print) (Or Legal Guardian)	Parent's Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
Witness Name (As appropriate)	Witness Signature	Date

Appendix IV: Sample Informed Consent Form for Specimen Storage and Future Use

IMPAACT 2007
Phase I Safety and Pharmacokinetic Study of Maraviroc in HIV-1-Exposed Infants at Risk of Acquiring HIV-1 Infection

VERSION 1.0, 13 April 2016

You have decided to allow you and your baby to join the study named above. As part of the study, you and your baby will have blood drawn. After these samples are tested for the study, there may be some samples that are left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about the use of extra samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra samples at the end of the form.

1. It is your decision whether or not to allow the extra samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your or your baby's participation in the study. If you say no, all extra samples will be destroyed.

2. If you agree, you and your baby's extra samples will be kept in a repository.

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, the immune system, and other diseases. The research may be done in the United States or in other locations.

If you agree, the extra samples could also be used for research that looks at you or your baby's genes.

Any research done with the extra samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the persons whose samples will be used.

4. There is little risk to you and your baby.

When extra samples are used for research, they are labeled with a code number only. To protect you and your baby's privacy, no names are used. However, information such as age, gender, HIV status, and other health information may be linked to the samples. Information on which study medicines your baby received and your baby's immune system responses to the study medicines may also be linked to the samples.

There may be some risks from tests of you and your baby's genes. If others found out the results of these tests, they could treat you or your baby badly or unfairly. However, this is almost impossible because the

results of these tests will not be in you and your baby's study records and they will not be given to you or your baby.

5. There will be no benefit to you and your baby.

The research done with extra samples is not expected to give any information relevant to you and your baby's health. The results will not be given to you and your baby and will not be part of your or your baby's study records.

6. You and your baby will not be paid for use of you and your baby's samples.

There is no cost to you and your baby for use of you and your baby's extra samples. The samples will not be sold and you and your baby will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with you or your baby.

7. Information from research using extra samples may be reviewed by groups that oversee the research.

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research

The people who do research with the extra samples and the groups listed above are required to make efforts to information private and confidential.

The results of research done with extra samples may be presented publicly or published. However, no presentation or publication will use you and your baby's name or identify you and your baby personally.

8. If you have any questions, concerns, or problems related to you and your baby's extra samples, use these contacts.

- If you have questions about use of you and your baby's extra samples, contact:
  [sites insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of you and your baby's extra samples, contact:
  [sites insert name and telephone number of investigator or other study staff].

- If you have questions about your and your baby's rights as a research participant, or problems or concerns about how your baby is being treated in the study, contact:
  [sites insert name and telephone number of IRB contact person or other appropriate person/organization].

Signatures

9. If you agree to let you and your baby's extra samples be used, please sign or make your mark below.

_____ I agree to the storage and use of my extra samples and my baby's extra samples to be used for research on HIV, the immune system, and other diseases. I also allow my samples and my baby's samples to be used for tests of my genes and his or her genes.

_____ I agree to the storage and use of my extra samples and my baby's extra samples to be used for research on HIV, the immune system, and other diseases. I do not allow my samples and my baby's samples to be used for tests of my genes or his or her genes.

_____ I do not allow my extra samples or my baby's extra samples to be used for any research.

_____
Participant's Name (print)

_____	_____	_____
Parent's Name (print) (Or Legal Guardian)	Parent's Signature	Date
_____	_____	_____
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (As appropriate)	Witness Signature	Date