Assessment of Safety and Toxicity among Infants Born To HIV-1-Infected Women Enrolled in Antiretroviral Treatment Protocols in Diverse Areas of the World

A Limited Center Trial of the Adult AIDS Clinical Trials Group (AACTG) and the Pediatric AIDS Clinical Trials Group (PACTG), Conducted in Collaboration with the HIV Prevention Trials Network (HPTN)

Sponsored by:

The National Institute of Allergy and Infectious Diseases

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FINAL Version 1.0
January 6, 2005
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APPENDIX I: AACTG/PACTG SAMPLE INFORMED CONSENT

APPENDIX II: NICHD REPOSITORY SPECIMEN STORAGE FACT SHEET AND TEMPLATE CONSENT FORM
PARTICIPATING SITES

A5190-P1054 is a limited-center trial that will be implemented at registered sites outside the United States of America.

The list of participating international sites can be found in the A5190-P1054 Manual of Operations (MOOPS) on the Protocol-Specific Web Page (PSWP):

Additional sites may apply to the AACTG/PACTG Executive Committees for permission to register to A5190-P1054.
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Site Representatives
The site representatives are listed in the
A5190-P1054 Manual of Operations on the
Protocol-Specific Web Page:
STUDY MANAGEMENT

All questions concerning this protocol should be sent via e-mail to actg.teamA5190-P1054@fstrf.org. The appropriate team member will respond via e-mail with a "cc" to actg.teamA5190-P1054@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol e-mail group: International sites registering to this study should contact the Computer Support Group at the Data Management Center via e-mail (aactg.support@fstrf.org) to have the relevant personnel at the site added to the actg.protA5190-P1054 e-mail group as soon as possible. Inclusion in the protocol e-mail group will ensure that sites receive important information about the study during its implementation and conduct.

For questions concerning clinical medical management, including entry criteria, toxicity management, and co-enrollment, the protocol chairs/protocol vice chair will respond:
- Send an e-mail message to actg.teamA5190-P1054@fstrf.org (ATTN: Karin Nielsen, M.D., M.P.H., Judith Currier, M.D., M.Sc., and Susan Cu-Uvin, M.D.).
- Include the protocol number, patient identification number (PID), and a brief relevant history.

For nonclinical questions about inclusion/exclusion criteria, the CRF schedule of events, case report forms, registration, transfers, delinquencies, and other data management issues, the data managers will respond:
- Send an e-mail message to actg.teamA5190-P1054@fstrf.org (ATTN: Ann Walawander, M.A., Apsara Nair, M.S., and Laura M. Stevens, B.S.).
- Include the protocol number, PID, and a detailed question.

For pharmacologic questions, the protocol pharmacologist will respond:
- Send an e-mail message to actg.teamA5190-P1054@fstrf.org (ATTN: Edward Acosta, Pharm.D.)

For computer and screen problems, the SDAC/DMC programmers will respond:
- Send an e-mail message to actg.support@fstrf.org.

For protocol questions, the clinical trials specialists will respond:
- Send an e-mail message to actg.teamA5190-P1054@fstrf.org (ATTN: Barbara Brizz, B.S.N., M.H.S.Ed. and Kimberly Hudgens, B.S.).
STUDY MANAGEMENT (Cont'd)

For requests for copies of the protocol:
- Hard copies: Send an e-mail message to ADULT.OPS@fstrf.org (ATTN: Diane Delgado).
- Electronic copies can be downloaded from the Members area of the AACTG Web site (http://aactg.s-3.com).

Protocol registration: preliminary review:
- A preliminary review of the registration packet for completeness will be performed at the ACTG Operations Center.
- Sites must send their registration packet via e-mail to ICTUprotocol@s-3.com or call the International Program Coordinator, (301) 628-3474, with any questions about this preliminary review.
- The ACTG Operations Center will submit the completed protocol registration packet to the DAIDS Regulatory Compliance Center (RCC) for approval.

For Adult International AIDS Clinical Trial Units (AIACTUs) questions about protocol registration approval:
- Send an e-mail message to ICTUprotocol@s-3.com
- Call the International Protocol Registration Coordinator, 301-628-3474

For Computer and Screen Problems, The SDAC/DMC programmers will respond:
- Send an e-mail message to aactg.support@fstrf.org.

Any phone calls must be documented by e-mail to actg.teamA5190-P1054@fstrf.org. This will be the site’s responsibility.

Additional information concerning study management of AACTG studies can be found on the A5190-P1054 protocol-specific Web Page (http://aactg.s-3.com/members/pswp.htm).
# GLOSSARY

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<th>Description</th>
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<tr>
<td>AACTG</td>
<td>Adult AIDS Clinical Trials Group</td>
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<tr>
<td>AE</td>
<td>Adverse events</td>
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<tr>
<td>IACTU</td>
<td>International AIDS Clinical Trials Unit</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<tr>
<td>ATV</td>
<td>Atazanavir</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CSRC</td>
<td>Clinical Safety Research Committee (DAIDS)</td>
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<tr>
<td>CTS</td>
<td>Clinical Trials Specialist</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>D4T</td>
<td>Stavudine</td>
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<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
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<tr>
<td>DEXA</td>
<td>Dual-energy x-ray absorptiometry</td>
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<tr>
<td>DDI EC</td>
<td>Enteric-coated didanosine</td>
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<tr>
<td>DMC</td>
<td>Data Management Center</td>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<td>EAE</td>
<td>Expedited adverse event</td>
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<tr>
<td>EFV</td>
<td>Efavirenz</td>
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<td>EIA</td>
<td>Enzyme immunoabsorbant assay</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FTC</td>
<td>Emtricitabine</td>
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<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
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<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
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<td>IRB</td>
<td>Institutional review board</td>
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<td>3TC</td>
<td>Lamivudine</td>
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<td>LDL</td>
<td>Low-density lipoprotein</td>
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<td>Laboratory Processing Chart</td>
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<td>Lopinavir</td>
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<td>MOOPS</td>
<td>Manual of Operations</td>
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<td>MTCT</td>
<td>Mother to child transmission</td>
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<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
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<tr>
<td>NNRTI</td>
<td>Nonnucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
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<td>Nevirapine</td>
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<td>OHRP</td>
<td>Office for Human Research Protections</td>
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<td>PACTG</td>
<td>Pediatric AIDS Clinical Trials Group</td>
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GLOSSARY (Cont’d)

PCP  Pneumococcal Pneumonia Prophylaxis
PI  Protease inhibitor
PIP  Protocol Implementation Plan
PK  Pharmacokinetics
PSWP  Protocol-Specific Web Page
PTH  Parathyroid hormone
QD  Once every day
RCC  Regulatory Compliance Center
RPR  Rapid plasma reagin test
RT  Reverse transcriptase
RTV  Ritonavir
SASC  Scientific Agenda Steering Committee
SD  Single dose
SDAC  Statistical Data Analysis Center
TDF  Tenofovir disoproxil fumarate
VDRL  Venereal Disease Research Laboratory
ZDV  Zidovudine
Assessment of Safety and Toxicity among Infants Born to HIV-1-infected Women Enrolled in Antiretroviral Treatment Protocols in Diverse Areas of the World

**DESIGN:** A5190-P1054 is a prospective, observational, cohort study of infants born to HIV-1-infected women while enrolled in NIH-sponsored, international, antiretroviral (ARV) treatment protocols (for example, A5175, HPTN 052, P1032, A5207, A5208, and other future studies). These infants will be enrolled into A5190-P1054 and followed prospectively to describe the safety, toxicity, and potential side effects of in utero and breast milk exposure to the ARV drugs used in international treatment protocols. Ideally, infants will be enrolled into A5190-P1054 within 48 hours of birth. Subsequent to study entry, visits will occur at approximately 3, 6, 9, 12, and 18 months of age.

**DURATION:** Each participant will be followed on study until approximately 18 months of age.

**SAMPLE SIZE:** The sample size for this study will depend on the number of women who become pregnant while enrolled in the NIH-sponsored, international, ARV treatment trials. The estimate is that approximately 270-410 infants will be enrolled into A5190-P1054 initially (see section 9.3 for further details).

**POPULATION:** Infants born to HIV-1-infected women who are, or become, pregnant while enrolled in NIH-sponsored, international ARV treatment trials.

**REGIMEN:** No HIV-specific ARV treatment will be provided to infants through this study. HIV-1-infected infants will be referred to the local standard of care and pediatric treatment trials as they become available.
1.0 HYPOTHESIS AND STUDY OBJECTIVES

Specific, combination ARV regimens used in clinical trials in diverse areas of the world are safe and well tolerated during pregnancy and breast-feeding periods, and are not associated with adverse side effects to the fetus, neonate, and/or breast-feeding infant. These regimens are associated with reduction of mother to child HIV transmission.

1.1 Primary Objective

1.1.1 Describe the toxicity and adverse events related to in utero, breast milk and standard of care prophylaxis exposure to ARV drugs in infants during the 18 months post delivery.

1.2 Secondary Objectives

1.2.1 Describe the mother to child HIV-1 transmission rates at birth and throughout the early and late postpartum periods up to 18 months of age.

1.2.2 Describe the morbidity rates of infants born to HIV-1-infected mothers as measured by growth parameters, serious infectious complications, and number of hospitalizations.

1.2.3 Describe the mortality rates of infants born to HIV-1-infected mothers during the 18 months post delivery.

1.2.4 Assess breast milk HIV viral load via RNA PCR, and measure ARV concentrations in breast milk in a subset of mothers who elect to breast-feed.

1.2.5 Assess the ARV concentrations in cord blood in a subset of infant-mother pairs from whom cord blood is collected.

1.2.6 Assess bone mineralization and bone age at birth and 6 and 18 months of age in a subset of infants exposed to ARVs in utero, intrapartum, and through breast-feeding.

1.2.7 Describe pregnancy-related complications among mothers of the infants enrolled in A5190-P1054.

1.2.8 Assess ARV resistance in the plasma of HIV-infected infants. Describe the genetic relatedness of ARV-resistance in mother-infant pairs in which transmissions occurred.
2.0 INTRODUCTION

2.1 Background

Clinical studies comparing different antiretroviral (ARV) treatment regimens for management of HIV-1 infection or for prevention of HIV-1 transmission are being conducted in resource-limited countries. These trials will enroll a significant number of women of childbearing age. Although trials comparing the efficacy of ARV regimens generally preclude enrollment of pregnant women, it is likely that during the conduct of A5190-P1054 some women of childbearing age will become pregnant and some will subsequently breast-feed while receiving combination ARVs as study drugs.

The safety and efficacy of ARV regimens in preventing HIV-1 mother-to-child transmission (MTCT) has been established in a large number of phase III studies (1-5). Smaller phase I/II trials have evaluated the pharmacokinetics (PK) of specific ARVs during pregnancy without noting significant toxicities or adverse events (AEs) either to the woman during pregnancy or to the neonate (6-11). Retrospective cohort trials have demonstrated a significant decrease in perinatal HIV-1 transmission with increased combination ARV use, without noting significant AEs or toxicities in neonates (12-14). Although the impact of ARV use during pregnancy has been dramatic in decreasing MTCT in the developed world, there are still concerns regarding the safety and toxicity profile of specific ARVs. Long-term followup of infants exposed to ARVs in utero has failed to demonstrate any significant side effects; however, these studies are ongoing (15, 16). In addition, as new ARVs become available, continued monitoring and followup of exposed pregnant women and their infants are critical. There are very limited data regarding the use of ARVs in lactating women. While in developed countries breastfeeding is contraindicated for HIV-1-infected women, there are few alternatives to this practice in many resource-limited settings; and it is conceivable that many participants in clinical trials evaluating ARV efficacy may choose to breast-feed. Although there are preliminary data indicating that reduction of breast milk HIV viral load correlates with decreased HIV-1 transmission by breast-feeding (17-19), there are no studies to date evaluating the role of ARVs in reducing breast milk transmission. Very little information is available regarding ARV concentrations in breast milk or potential toxicities to the infant. There is, however, safety and toxicity information regarding ARV use in HIV-1-infected infants (10, 20, 21).

AACTG A5175 and HPTN 052 are clinical trials that will use ARV combinations (including the nucleoside reverse transcriptase inhibitors [NRTIs] zidovudine [ZDV], lamivudine [3TC], didanosine enteric-coated [ddl-EC], and emtricitabine [FTC]; the nonnucleoside reverse transcriptase inhibitors [NNRTIs] efavirenz [EFV] and nevirapine [NVP]; the nucleotide tenofovir disoproxil fumarate [TDF]; and protease inhibitors such as atazanavir [ATV], nelfinavir [NFV], or lopinavir/ritonavir [LPV/RTV], among others)
and will be conducted in resource-limited countries. Likewise, A5207 and A5208 are studies that will be using ARV combinations in women who could become pregnant (A5208) or are breast-feeding (A5207 and A5208).

There is limited information regarding TDF use during pregnancy, although clinical trials evaluating the PK of this drug in this scenario are being initiated (i.e., PACTG 394 and HPTN 057). There are concerns regarding fetal bone density stemming from animal studies that used extremely high concentrations of this drug (22). Therefore, infants who are exposed to this drug in utero or through lactation should be monitored for bone abnormalities. EFV is contraindicated during pregnancy because of data indicating central nervous system (CNS) teratogenicity in animal studies (23) and anecdotal reports of CNS malformations in infants exposed in utero (24, 25). Although limited studies reported a potential link between NRTI use during pregnancy and mitochondrial toxicity in HIV-1-exposed uninfected infants (26), large retrospective trials failed to demonstrate an association (15). Experience with the newly licensed agents FTC and ATV during pregnancy is extremely limited.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine (FTC) and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with FTC should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). Severe, acute exacerbations of hepatitis B have been reported in patients after the discontinuation of FTC. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue FTC and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (Emtricitabine package insert, September 2004)

Currently, there are limited data on pregnancy outcomes among HIV-1-infected women treated with potent, combination ARV therapy in resource-limited settings. The parent studies involved with A5190-P1054 will all assess the safety and efficacy of ARV among the women enrolled in them. However, it will also be important to capture pregnancy-related complications among women with infants enrolled in A5190-P1054, so that the maternal outcomes can be linked with the outcomes of the infants. A5190-P1054 will provide the opportunity to describe pregnancy-related outcomes across a number of different ARV trials conducted in resource-limited settings. In most of these trials women will be receiving highly active antiretroviral therapy (HAART) regimens at the time that they conceive, and this will present a unique opportunity to assess pregnancy-related outcomes in a large cohort of such women receiving HAART.
2.2 Rationale

HPTN 052, A5175, A5207, A5208, and P1032 will provide ARVs in regions of the world where there is limited experience with their use. Except for A5207 and P1032, these studies are not designed for pregnant women, although it is expected that some female participants will become pregnant, give birth, and breast-feed while receiving ARV combinations from A5175, HPTN 052, or A5208. It will be important to follow the infants who are conceived during these or future ARV treatment trials and monitor adverse effects (AEs) (including teratogenicity and untoward side effects) as well as potential benefits, particularly reduction of MTCT.

Previous studies have shown the dramatic effect of ARV therapy in reducing MTCT. Although it is most likely that there will be a significant benefit in reduction of in utero, intrapartum, and breast-feeding HIV-1 transmission, A5190-P1054 will provide an opportunity to assess the impact of ARV agents that have not been extensively studied during pregnancy or lactation or in neonates. A5190-P1054 will monitor (until 18 months of age) the effects of in utero, breast milk, and standard of care prophylaxis ARV-exposure in infants born to HIV-1-infected women who are enrolled in NIH-sponsored, international, ARV treatment trials.

The initial A5175 ARV treatment regimens are (1) ZDV, 3TC, plus EFV, (2) ddI-EC, FTC, plus ATV, and (3) TDF, FTC, plus EFV. The inclusion criteria specify that participants have a CD4+ absolute cell count <300 cells/mm³. Pregnant women will not be allowed to enroll into A5175; and throughout the duration of the study, two forms of birth control will be provided to study participants. Nevertheless, women in A5175 who do become pregnant will be counseled about the risks; and those who decide to continue their pregnancy will be followed on study. If women on the EFV-containing arms become pregnant, EFV will be stopped immediately and replaced with a different drug (i.e. NVP). Women will continue on study postpartum and throughout the lactating period. Participants who do not attain suppression or who do not remain virologically suppressed on the initial regimen will be offered other ARVs at the discretion of the site investigator, dependant on local availability.

For the site phase-in or run-in period (approximately 9 months), HIV-1-infected participants in HPTN 052 who are randomized to ARV therapy will be offered regimens that include ZDV, 3TC, plus ATV or EFV, and the choice of a third drug. Additional ARVs may include NFV, NVP, TDF, ddI-EC, or d4T. The full study drug regimens will be decided at a future date. This study allows enrollment of HIV-1-infected pregnant women who have CD4+ counts between 300 cells/mm³ and 500 cells/mm³. Women who were initially randomized to the observational arm and who become pregnant while on HPTN 052 will be switched to a HAART regimen that is known to be safe during...
pregnancy, at approximately the beginning of the 2nd trimester. Secondary or salvage regimens are not defined by the protocol.

A5207 will evaluate HIV-infected women who have received intrapartum single dose (SD) NVP given with other ARVs for reduction of NVP resistance. The postpartum ARV regimens may include drugs such as ZDV, 3TC, TDF, FTC, or LPV/RTV. In A5208 HIV-infected women will be receiving regimens that include TDF, FTC, and either NVP or LPV/RTV. P1032 will look at the prevention of NVP-resistance mutations in pregnant women who received ZDV during the last trimester, single dose NVP at delivery, and additional antiretrovirals after delivery. Their infants received ZDV during the postpartum period.

Given the provision of ARVs in these international ARV treatment trials, it is expected that the rate of HIV-1 MTCT will be very low. Adverse pregnancy outcomes will be assessed in the parent protocols. HIV-1-infected infants will be referred to pediatric treatment trials as they become available.

Enrollment of infants born to HIV-1-infected women participating in other NIH-sponsored ARV international treatment trials (in addition to A5175, A5207, A5208, P1032, or HPTN 052) will be permitted following review by the protocol team. A5190/P1054 will prospectively monitor infant outcomes exclusively. Pregnancy outcomes will be monitored through the parent protocols. Infant outcomes will be linked to maternal pregnancy outcomes through data sharing between the parent protocols and A5190/P1054. Standardized maternal pregnancy case report forms (CRFs) will be used across the parent protocols to collect the same information. Data on maternal outcomes collected in these ARV treatment trials will be analyzed and related to infant outcomes in A5190-P1054 through a data-sharing plan.

2.3 Efficacy in Preventing MTCT and Potential Adverse Effects of Primary Study ARV During Pregnancy and Lactation

Refer to the most recent ARV package inserts for additional information.

ARV therapy has been shown to be effective in preventing HIV-1 MTCT, with reduction of MTCT to 1.6% (2). Data from women who have received ARV therapy (including ZDV, 3TC, NVP, NFV) during pregnancy are available. Less is known about ddi, d4T, and LPV/RTV during pregnancy. EFV is contraindicated during gestation, and there is very limited experience in pregnancy with the newly licensed ARV agents TDF, FTC, and ATV.

Zidovudine: ZDV is an NRTI and classified by the U.S. Food and Drug Administration (FDA) as Pregnancy Category C. It is the prototype ARV drug for prevention of HIV-1
Since PACTG 076 results were released in 1994 (1), multiple subsequent trials have shown that ZDV is safe for use during pregnancy and in infancy as well as efficacious in preventing MTCT. ZDV crosses the placenta and is also excreted in breast milk. To date no teratogenic effects of ZDV have been reported in humans, and no irreversible short-term adverse events (AEs) have been identified in ZDV-prenatally exposed infants. The major toxicities of ZDV in exposed infants and children are neutropenia and anemia. The long-term AEs of in utero ZDV exposure are unknown. In animal studies, ZDV has not been shown to be carcinogenic when used in standard concentrations. At very high doses, however, ZDV has been shown to induce vaginal epithelial neoplasms in mice.

**Lamivudine:** 3TC is an NRTI and classified by the U.S. FDA as Pregnancy Category C. 3TC crosses the placenta and is also detectable in breast milk. Animal reproductive studies have failed to demonstrate teratogenicity. 3TC has been used widely during pregnancy in combination with ZDV and other ARVs and, to date, no teratogenicity has been reported. One study reported two episodes of severe mitochondrial toxicity in French infants exposed to ZDV and 3TC perinatally (26). Subsequent studies combining large cohorts of ARV-exposed infants have failed to demonstrate an association (15).

**Didanosine:** ddI is an NRTI, classified by the U.S. FDA as Pregnancy Category B. Animal reproductive studies have not demonstrated evidence of impaired fertility or teratogenicity associated with ddI, although at doses 12 times those administered to humans, ddI was found to be slightly toxic to female rats and their pups at mid to late gestation. There is evidence that ddI crosses the placenta in rats. Fatal lactic acidosis has been reported when ddI is used in combination with d4T during pregnancy, and this ARV combination is not recommended during pregnancy unless the potential benefit clearly outweighs the risk. ddI is excreted in breast milk in rat studies. The degree of human breast milk excretion is unknown.

**Stavudine:** d4T is an NRTI and classified by the U.S. FDA as Pregnancy Category C. d4T was not found to be carcinogenic in mice or rats at concentrations up to 168 times that of human doses; however, liver and bladder tumors were found in mice and rats at concentrations 250 times greater than that of humans. Reproductive studies in animals have failed to demonstrate any teratogenicity at d4T levels up to 399 times higher than that of human concentrations. At higher doses, evidence of poor ossification in fetal rats was found. Animal studies have shown that d4T crosses the placenta. There are no well-controlled trials in pregnant women. d4T, when used in combination with ddI, has been shown to have a higher risk of lactic acidosis during pregnancy. This combination is not recommended during gestation, unless the potential benefit clearly outweighs the risk.

**Nevirapine:** NVP is an NNRTI and classified by the U.S. FDA as Pregnancy Category C. NVP readily crosses the placenta and is detectable in breast milk. Animal
Carcinogenicity studies have not demonstrated any evidence of mutagenic or clastogenic activity, nor any evidence of teratogenicity. In pregnant rats exposed to concentrations approximately 50% higher than the recommended human daily dose, a decrease in fetal body weight was noted. To date, no evidence of in utero growth retardation has been found in human fetuses exposed to NVP. NVP has been shown to cause hepatic toxicity and, in some cases, fatal hepatic failure; particularly when used by patients with higher CD4+ cell counts (27). The most frequent AEs related to NVP therapy are rash, fever, nausea, headache, and increase in liver transaminases. NVP has been shown to reduce MTCT of HIV-1 by 50%, when administered single dose (SD) to the mother at the time of labor and delivery and to the infant immediately following birth (3). Based on the results of this trial, SD NVP has been recommended as standard of care for prevention of MTCT in resource-limited-settings when no other ARVs are available. SD NVP, however, does induce the development of NVP-resistant HIV strains in approximately one-fourth of the women exposed to the drug (28) and to approximately two-thirds of the women who receive two doses (29). NVP-resistant strains have also been identified in perinatally exposed infants who acquired HIV-1 infection. To date, studies evaluating the significance of these findings in the long-term prognosis of HIV-1-infected patients are pending.

**Efavirenz**: EFV is an NNRTI and classified by the U.S. FDA as Pregnancy Category C. To date, EFV has not been shown to be carcinogenic in in vitro or in vivo animal studies. Malformations have been observed in 3 of 20 fetuses of EFV-treated cynomolgus monkeys and in none of 20 controls. Pregnant monkeys were dosed with EFV concentrations similar to those used by humans. Malformations included anencephaly, unilateral anophthalmia, microlphthalmia, and cleft palate. In rabbits no teratogenicity was noted. In animals, EFV has been shown to readily cross the placenta and to concentrate in breast milk. EFV use is contraindicated during pregnancy. Central nervous system AEs associated with EFV include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. As with NVP, various forms of rash with varying severity have been reported.

**Tenofovir disoproxil fumarate**: TDF is a nucleotide analogue RTI and classified by the U.S. FDA as Pregnancy Category B. TDF has been shown to be mutagenic in the in vivo mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). Reproductive studies performed in rabbits and rats at doses up to 19 and 14 times the human dose, respectively, have shown no evidence of harm to the fetus. Chronic exposure of fetal monkeys to TDF in doses of 30 mg/kg (25 times higher than the human dose) did not result in gross structural abnormalities, although a slight reduction in fetal bone porosity was observed. Continued administration of TDF at 30 mg/kg/day resulted in growth restriction and bone toxicity in 25% of infant monkeys. At concentrations 8 times that of humans, no clinical or radiologic bone toxicity was noted in juvenile
monkeys. Evidence of nephrotoxicity was noted in juvenile monkeys given TDF at doses 12 to 50 times higher than the human dose. Animal studies have demonstrated that TDF crosses the placenta and is excreted in breast milk. TDF as a single dose has been shown to be effective in reducing HIV-1 MTCT in monkey studies. Studies of TDF use in HIV-1-infected children have demonstrated that a 6% bone demineralization rate may occur, as measured by dual-energy x-ray absorptiometry (DEXA) scans, in prospectively followed children receiving standard TDF dosing. Controlled trial results of TDF in pregnancy are not yet available.

**Optional Bone Study:** A5190-P1054 proposes to obtain x-rays of the left hand, wrist, and thoracic spine from all infants at birth and 6 and 18 months of age (until a total of 55 infants with in utero TDF exposure and 55 infants with in utero exposure to other ARV agents to assess the impact of in utero TDF exposure on bone development. At that time, the bone assessments will stop until the data are evaluated. Plain x-ray films have previously been used to detect abnormalities associated with congenital diseases and other metabolic disorders in childhood (30). After being read locally, the films will be reviewed at a central reading facility in the U.S.A. for evidence of osteoporosis/mineralization and bone age.

**Emtricitabine:** FTC is an NRTI and has been classified by the U.S. FDA as Pregnancy Category B. Reproductive and developmental toxicology studies in mice and rabbits have not shown any effect on fertility, sperm count, or early embryonic development. No increased incidence of malformations was noted. Doses administered were 60 (mice) to 120 (rabbits) times higher than the standard dose of 200 mg QD given to humans. Studies indicated that the drug crosses the placenta at high levels. In a mouse pre- and post-natal study, the development and fertility of progeny were unaffected by FTC (31). There are no controlled trials of FTC use during human pregnancy and lactation. In women receiving FTC in clinical trials, 19 live healthy births were reported.

**Nelfinavir mesylate:** NFV is an inhibitor of HIV protease and has been classified by the U.S. FDA as Pregnancy Category B. In animal studies, there were no maternal toxicities or effects on fetal development when rats were given drug concentrations similar to human therapeutic levels. NFV has been used in recent years for treatment of HIV-1-infected pregnant women with no reported serious AEs; however, no controlled studies have been conducted. Placental crossage of NFV in humans is less than 20%. NFV has been shown to be excreted in breast milk of lactating rats.

**Atazanavir sulfate:** ATV is an inhibitor of HIV protease and has been classified by the U.S. FDA as Pregnancy Category B. At maternal doses that produced systemic drug exposure levels equal to those of a human dose of 400 mg/day in rabbits or two-fold in rats, ATV did not produce teratogenic effects. At maternally toxic drug exposure levels two times those of the human dose; ATV caused body weight loss or weight gain
suppression in the offspring. Asymptomatic unconjugated hyperbilirubinemia occurs in most patients undergoing treatment with ATV. It is unknown whether administration during pregnancy will exacerbate physiological hyperbilirubinemia in neonates. There is insufficient information to be able to determine the appropriate dose of ATV in pregnancy. A number of women, however, became pregnant while receiving ATV in clinical trials. These women received ATV for 4 to 6 weeks throughout gestation, and no AEs were noted in the neonates. Healthy infants were delivered to two women who received ATV for 36 weeks. Data regarding placental concentrations of ATV are lacking.

Phase II and III studies in non-pregnant adults have demonstrated good overall safety and tolerability of ATV. The most frequently seen AEs in the phase II and III studies are infection (46%), nausea (28%), headache (24%), abdominal pain (19%), diarrhea (19%), rash (19%), peripheral neurologic symptoms (15%), vomiting (13%), flu syndrome (12%), increased cough (12%), jaundice (12%), and fever (10%). Elevations in total (predominantly unconjugated) bilirubin and associated jaundice including scleral icterus are the most frequent dose-related AEs attributable to ATV. During study AI424-034 (a phase III study of ATV 400 mg versus EFV, each in combination with fixed dose ZDV+3TC for ARV-naive participants with plasma HIV-1 RNA levels ≥ 2000 copies/mL and CD4+ cell counts ≥ 100 cells/mm³ [≥75 cells/mm³ with no prior history of any AIDS-defining diagnoses]) Grades 3 and 4 hyperbilirubinemia was seen in 33% of ATV participants without hepatic transaminase elevations. ATV was associated with favorable lipid parameters compared with EFV, as assessed by mean percent changes from baseline in total cholesterol, fasting low density lipoprotein (LDL) cholesterol, and fasting serum triglyceride concentrations at week 48. The consequences of maternal elevations in unconjugated bilirubin during pregnancy on fetal outcome are currently unknown (32).

Lopinavir/ritonavir: LPV/RTV is an inhibitor of HIV protease and has been classified by the U.S. FDA as Pregnancy Category C. No treatment-related malformations were observed when LPV/RTV was administered to pregnant rats or rabbits. Embryonic developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations or skeletal ossification delays) occurred in rats that received a dose that produced drug exposures similar to 0.7 times the lopinavir and 1.8 times the ritonavir exposures in humans at the recommended therapeutic dose. No embryonic or fetal malformations were observed in rabbits given maternal toxic dosages. It is unknown to what extent LPV/RTV crosses the placenta, but based on studies of other protease inhibitors placental crossover appears to be reduced in humans. The degree of human breast milk excretion is unknown.

2.4 Monitoring Teratogenicity and ARV Toxicities
In order to evaluate AEs, infants will have clinical visits at which time medical histories will be obtained and complete physical exams performed. Since the most frequent AEs of ARVs in infants are hematologic and biochemical abnormalities, complete blood cell counts with differential and platelets will be performed, as well as serum electrolyte assessments. Liver function tests (ALT, AST); amylase for pancreatic function, BUN, creatinine, and urinalysis for evaluation of renal function and screening for proteinuria will be performed.

2.5 Bone Mineralization and Bone Age Studies

Disorders of bone metabolism, particularly osteopenia have been identified in children with HIV-infection, with or without prior antiretroviral use. It is unclear at this point whether these bone metabolism disorders are attributable to HIV-infection, to antiretroviral ARV treatment, or to both, because prospective data are lacking. The etiology of increased bone resorption and/or decreased mineralization remains to be determined. Recent cross-sectional studies of HIV-1-infected children with short- and long-term exposure to ARVs have demonstrated varying degrees of potential osteopenia (33-37). All of the limited pediatric data available on bone metabolism in HIV stem from studies conducted in HIV-infected children receiving long-term antiretroviral therapy. There is an extreme paucity of data from studies of bone metabolism in HIV (and ARV) exposed infants.

Osteoporosis is characterized by depleted bone mass, which results in bone fragility and increased fracture risk. Bone mineral density (BMD) can be expressed as standard deviation scores, with osteopenia being defined as a standard deviation score between −1 to −2.5 from the mean value for patients of that age. Osteoporosis is defined by a standard deviation score of less than −2.5 from the norm, while severe osteoporosis is defined as the same standard deviation score and the presence of one or more fractures. In children, osteopenia and osteoporosis are not well defined. Imaging methods available for diagnosing these conditions include techniques such as plain x-rays of the thoracic or lumbar spine, assessment of bone age through plain films of the hand and wrist or knees, radiogrammetry, where a plain x-ray with the appropriate software can be used for assessment of bone density, and more sophisticated methods such as DEXA or quantitative computer tomography (qCT). DEXA scans, the most widely used method in developed countries, pose problems for use in children, since the z-scores obtained from measurements with this technique may correct for age and sex, but not for differences in patient size. Presently, the best technique for bone density measurements in children is qCT, which is currently only available at selected centers in developed countries. In resource-limited settings, DEXA scans and digital film technology are nearly universally unavailable; therefore, the only feasible imaging technique for assessing bone mineralization is x-ray. Although plain films of the thoracic spine are less sensitive in
detecting more subtle defects in bone mineralization, osteoporosis is detectable through this technique. X-rays of the hand and wrist can determine bone age and, therefore, identify problems with bone maturation.

Bone mass changes as a function of puberty and race are essentially determined by hereditary factors. A variety of intrinsic and extrinsic factors, such as diseases, hormones, behavioral patterns, diet, and drugs also influence bone mass. Children in resource-limited countries are particularly susceptible to diseases such as rickets and infections such as congenital syphilis, which lead to significant bone abnormalities. It is important to assess specific laboratory markers in order to differentiate between disorders due to specific etiologies or possibly caused by ARV exposure. Studies of bone metabolism in HIV-1-infected children have determined that these children have very high bone formation markers and very high bone resorption markers (34, 36, 37). Because bone resorption is a much more rapid process than bone formation, it appears that the net result is bone loss. The mechanism by which ARVs would impair bone metabolism in children is not well understood. There are studies indicating that protease inhibitors might impair the bioactive form of vitamin D in vitro (38). Osteopenia in children receiving ARV treatment might be explained by the complex interaction between osteoclast cytokines (RANK-ligand) and osteoclast progenitor cells (39). In studies of tenofovir use in HIV-1-infected children, a small number of patients showed some evidence of osteopenia as evidenced by DEXA imaging, and in these patients, these findings appeared to be due to increased bone resorption (40).

Given the current body of evidence pointing towards increased bone resorption in HIV-1-infected children receiving full-dose ARV treatment, it is feasible that in utero ARV exposure could lead to disorders of bone metabolism. To monitor this potential complication, a subset of infants followed in A5190-P1054 will have x-rays of the thoracic spine and left hand and wrist performed at birth and 6 and 18 months of age. Serum calcium, phosphorus, levels of osteocalcin, bone-specific alkaline phosphatase (marker of bone formation), vitamin D levels, and acid phosphatase-tartrate resistant (serum marker of bone resorption) will also be measured in this subset of patients. Venereal disease research laboratory testing (VDRL) and/or rapid plasma reagin (RPR) testing will also be performed on serum samples obtained at the first visit to rule out congenital syphilis for all patients. If a treatable disorder is identified during the process (i.e. syphilis, rickets), appropriate standard of care management will be instituted. Urinary calcium, another marker of bone resorption, will not be routinely performed since it requires 24-hour urine collection, which is not feasible for many of the participants living in remote areas.

Because of variability in study design of parent protocols enrolling patients into A5190-P1054, infants enrolled into this study can have a wide range of ARV exposure, from prolonged exposure to ARVs (in utero, intrapartum, and breastmilk) or only limited
exposure (intrapartum and limited breast milk exposure). In order to minimize radiation exposure, and target infants at greatest risk for development of osteopenia, initially 110 infants will have bone x-rays and laboratory assessments of bone metabolism performed. This will include 55 infants with in utero TDF exposure and 55 infants with in utero exposure to other ARV agents. In the event that no abnormalities are identified after 110 infants are evaluated, bone assessments will be discontinued. Continuation of these assessments will depend on positive clinical, imaging, and/or laboratory findings. Because bone mineralization is of concern particularly with in utero TDF exposure, infants of mothers receiving TDF during pregnancy will be preferentially evaluated and compared to infants of mothers receiving similar exposure to other ARV. X-rays will be limited to three over 18 months and will be localized to the area of the thoracic spine and left hand and wrist. This methodology will not identify potential pathologic fractures; however, more subtle findings of osteoporosis can be detected through this screening process. The amount of radiation exposure to the infants per X-ray will be minimal (i.e., less than one transcontinental flight at 30000 feet), and the potential benefits (i.e., ascertaining potential disorders of clinical importance in bone metabolism from in utero or breast milk exposure to ARV drugs for which there are limited data) outweigh the risks. Interpretation of x-rays will be conducted at a central reading site by a single academic radiologist to standardize the procedure and avoid variations in x-ray reading. All x-rays will be mailed to the central reading site for this purpose, after being read on site for clinical care. Performance of bone mineralization assessments (X-rays and serum markers of bone metabolism) will be voluntary.

2.6 Pharmacokinetic Studies of ARV in Cord Blood and Breast Milk

There are limited data regarding the placental crossage and breast milk concentrations of newer ARV agents. When feasible, cord blood specimens will be collected for PK studies of ARV drugs such as ATV, FTC, TDF, and other ARVs that may be incorporated into treatment trials. Likewise, breast milk will be collected from consenting mothers who choose to breast-feed for determination of viral RNA levels and ARV concentrations. Cord blood and breast milk collections are voluntary.

3.0 STUDY DESIGN

A5190-P1054 is a prospective, observational, cohort study of infants born to HIV-1-infected women while enrolled in NIH-sponsored, international, ARV treatment trials (such as A5175, HPTN 052, A5207, A5208, and P1032). Infants will ideally be enrolled within 48 hours of birth (see section 6.2.1) and followed in order to describe the safety, toxicity, and potential side effects of in utero and breast milk exposure to the ARV regimens used in these protocols. Infants will be followed from birth to 18 months of age with six visits at approximately birth and 3, 6, 9, 12, and 18 months of age.
Cord blood and breast milk samples from the infant’s mother will be obtained whenever possible.

Optional Bone Study for In Utero ARV-Exposed Infants ONLY

Assessments of bone metabolism including imaging studies and serum markers will be performed initially in a total of 55 infants with in utero TDF exposure and 55 infants with in utero exposure to other ARV agents. Continuation of these assessments will depend on positive clinical, imaging, and/or laboratory findings.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Infants born to HIV-1-infected mothers enrolled in NIH-sponsored, international, ARV treatment trials (such as A5175, HPTN 052, A5207, A5208, and P1032) and who have had either in utero or postpartum ARV exposure.

4.1.2 Ability and willingness of legal guardian/representative to give written informed consent.

4.2 Exclusion Criteria

4.2.1 Infants who received either no ART exposure or intrapartum ARV exposure only.

4.3 Study Enrollment Procedures

Prior to implementation of A5190-P1054, sites must have the study and its consent form approved by their local institutional review board (IRB) and other country-specific review boards, as required. All registration materials should be forwarded to ICTUprotocol@s-3.com at the ACTG Operations Center for a preliminary review for completeness. The ACTG Operations Center will forward the original registration packet to the DAIDS Regulatory Compliance Center (RCC) for approval. Sites must registered for A5190-P1054 and be approved by the DAIDS/RCC Protocol Registration Office. Protocol registration must occur before any participants can be enrolled in this study.

The details of A5190-P1054 will be carefully discussed with the infant’s parent(s)/legal guardian. The parent(s)/legal guardian will be asked to read and sign the consent form that was approved by the International AIDS Clinical Trials Unit’s (IACTU’s) IRB and
the DAIDS/RCC Protocol Registration Office. The mother’s patient identification number and study number will be recorded.

To ensure compliance with data sharing requirements, all studies interested in collaboration must first receive approval from the A5190-P1054 team. Research staff at each approved site (e.g., sites participating in A5175, A5207, A5208, HPTN 052, P1032, A5190-P1054 as well as other future treatment protocols) will need to coordinate efforts to collect and share appropriate information. A Memorandum of Agreement (MOA) must be signed by the chairs of the participating studies and, prior to enrollment of participants, sites must complete a protocol implementation plan (PIP).

Women with repeat pregnancies during participating in a collaborative ARV treatment study may enroll subsequent infants into A5190-P1054.

4.4 AACTG-PACTG Data Management Registration

All eligible infants will be registered to A5190-P1054 with the ACTG Data Management Center (FSTRF) according to standard procedures.

4.5 Coenrollment

Coenrollment into other studies will be decided on a case-by-case basis. Permission must be requested of the A5190-P1054 study chairs/vice chair prior to enrollment of the infant into other studies.

5.0 STUDY TREATMENT

Regimens, Administration, and Duration

No ARV drugs are available through this trial. HIV-1-infected infants will be referred to the local standard of care and to pediatric ARV treatment trials as they become available.

5.1 Prophylaxis for MTCT and Pneumocystis Carinii Pneumonia (PCP) Prophylaxis

Infants born to HIV-1-infected mothers enrolled in collaborative, NIH-sponsored, international ARV treatment trials will receive either the local standard of care ARV prophylaxis provided by the site or ARV prophylaxis provided through treatment trials for the prevention of MTCT and the prevention of PCP.
5.2 Treatment of HIV-1-Infected Infants

No ARVs are provided by this study. Initiation of ARV therapy for HIV-1-infected infants will be at the discretion of the site investigator and according to the local standard of care and available ARVs; taking into account clinical findings, growth parameters, and plasma HIV-1 RNA levels. Each participating site will be required to provide information about the current access to care as well as the local standard of care ARV treatment for HIV-1-infected infants.

5.3 Breast-Feeding

Breast-feeding will be discouraged at sites where alternative feeding options are feasible and available. Otherwise, women will be counseled regarding safer breast-feeding alternatives according to the World Health Organization (WHO) guidelines (refer to the A5190-P1054 Manual of Operations).
### 6.0 CLINICAL AND LABORATORY EVALUATIONS

#### 6.1 Schedule of Events

<table>
<thead>
<tr>
<th>Infant Evaluations</th>
<th>Visit 1 (Ideally within 48 hours of birth)</th>
<th>Visit 2 (3 months +/- 6 weeks)</th>
<th>Visit 3 (6 months +/- 6 weeks)</th>
<th>Visit 4 (9 months +/- 6 weeks)</th>
<th>Visit 5 (12 months +/- 6 weeks)</th>
<th>Visit 6 (18 months +/- 6 weeks)</th>
<th>Final Study Visit</th>
<th>Premature Discontinuation before 12 months</th>
<th>Premature Discontinuation after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History/Concomitant Medications Update</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Assessments</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Hematology</td>
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<td>X</td>
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<td>Liver Function Test</td>
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<td>X</td>
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</tr>
<tr>
<td>Chemistries</td>
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<td>X</td>
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<tr>
<td>Urinalysis</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>VDRL/RPR Testing</td>
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<tr>
<td>Vitamin D Levels + PTH</td>
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<tr>
<td>Whole Blood Collection on Filter Paper (Guthrie cards)</td>
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<td></td>
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<tr>
<td>HIV-1 (EIA)</td>
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<tr>
<td>Cord Blood</td>
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<td></td>
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<tr>
<td>Stored Plasma</td>
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</tr>
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<td>X-Ray of Thoracic Spine and Left Hand &amp; Wrist</td>
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<td></td>
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<td>Maternal Evaluations</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1) Lipase levels will be performed at the next visit if amylase levels are abnormal
2) Only for Bone Study participants (only those infants with in utero ARV exposure) (optional)
3) HIV-1 RNA PCR to be repeated immediately if the results are positive. If confirmed positive, no further diagnostic PCR assessments will be performed.
4) Obtained if blood is drawn for other purposes.
6.2 Definitions for Schedule of Events – Timing of Evaluations

6.2.1 On-Study Evaluations

Visit 1 (Entry)

Within 48 hours after birth (+ 6 weeks)

This visit ideally occurs within 48 hours after birth. Since, a number of infants will not be born in a setting allowing enrollment within this time frame; they may be enrolled up to 6 weeks after birth.

Visits 2 through Visit 5

These visits should occur as noted in the Schedule of Events in section 6.1 (+/- 6 weeks).

Visit 6

This is the final study visit and will occur 18 months after birth (+/- 6 weeks).

6.2.2 Premature Discontinuation Evaluations

The mothers will be encouraged to continue their infants’ participation in A5190-P1054 until the completion of all study visits. However, if the mother withdraws the infant from the study before the final visit (for any reason), she will be asked that all evaluations indicated in the Schedule of Events for the premature discontinuation visit be obtained. No further study evaluations are required.

6.3 Special Instructions and Definitions of Evaluations


6.3.1 Medical History/Concomitant Medications Update

Birth History and Obstetric Events
To be collected at entry and recorded on the case report forms (CRF).
Peripartum history, mode of delivery, Apgar scores (when available), weight, length, and head circumference at birth, approximate gestational age, duration of labor, signs of fetal distress (presence of meconium), summary of events in first days of life (including feeding, breathing patterns, jaundice, lethargy, or any additional abnormal findings), duration of admission if delivered in hospital.

Feeding Practices
Feeding practice information will be obtained at each study visit and recorded on the CRF.

Medical History and Concomitant Medications
A medical history including, medical events that occurred at and since birth (prior to entry) is to be recorded in the source documents and on the CRFs. Medical events include pneumonia, draining ears, skin rash, diarrhea, febrile illnesses, hospitalizations, developmental milestones, and allergies.

All immunizations and currently prescribed medications should be recorded on the CRFs and source documents. All prescription and nonprescription medications including actual or estimated start and stop dates must also be recorded in the source documents.

Current alternative therapies and traditional treatments are to be recorded as yes/no in the source documents and on the CRFs. If answered yes, the alternative therapy or traditional treatment will be listed in the source documents.

6.3.2 Clinical Assessments

These assessments must be recorded in the source documents and on the CRFs, unless otherwise indicated.

Diagnoses
Report diagnoses identified according to the ACTG criteria for clinical events and other diseases. Refer to the CRF for current ACTG Appendix.

Infant Complete Physical Exam
A complete physical exam will be performed at each study visit to detect congenital anomalies, lymphadenopathy, hepatomegaly, splenomegaly, infections of the ears, mouth, pharynx, or skin, and pulmonary, cardiac, neurologic, or skeletal abnormalities. Length, weight, and head circumference are to be recorded on a CRF at each study visit.
A developmental exam will be performed at each study visit, recorded on the CRF, and include the following motor and cognitive milestones:

Visit 1 (birth): Symmetric movements
Visit 2 (three months): Smiles, coos, holds head steady in sitting position
Visit 3 (six months): Turns to voice, sits without support, brings hands to mouth
Visit 4 (nine months): Babbles, stands holding on, pulls to stand
Visit 5 (twelve months): Indicates wants, stands alone briefly
Visit 6 (eighteen months): Walks well, runs, has at least six words

**Signs and Symptoms**
At entry, record all signs/symptoms regardless of Grade on the CRFs. For post-baseline assessments only Grade ≥ 3 must be recorded on the CRFs.

**Vital Signs**
Temperature, pulse, blood pressure, and respiratory rate are collected at all visits and recorded on the CRF.

**6.3.3 Laboratory Evaluations**
Methodology for the collection and processing of samples is included in the A5190-P1054 Manual of Operations and the Laboratory Processing Chart (LPC).

At entry, record all laboratory values on the CRF.

Post-entry laboratory values must be documented in the source documents, but only laboratory values Grade ≥ 3 must be recorded on the CRFs.

**Hematology**
Complete blood cell count with differential and platelets will be performed on site.

**Liver Function Tests (LFTs)**
AST (SGOT) and ALT (SPGT) will be performed on site.

**Serum Chemistries**
Sodium, potassium, chloride, calcium, phosphorus, bicarbonate, amylase, blood urea nitrogen (BUN), and creatinine will be performed on site.
NOTE: Lipase will be performed at the next visit if amylase levels are abnormal, as clinically warranted.

Urinalysis

Urinalysis and dip stick for hematuria and proteinuria will be performed on site.

Serum VDRL/RPR Testing

VDRL and/or RPR testing will be performed on site to test for congenital syphilis. Sites are encouraged to collect the sample for this assessment from the cord blood if possible.

VIROLOGIC STUDIES

HIV-1 RNA PCR
- To be performed on site using the Roche Amplicor Monitor Test, Version 1.5.
- Positive infection is defined as a confirmed (two positive tests from two separate blood samples collected on different dates) HIV-1 RNA PCR level > 10,000 copies/mL.
- The viral load will be repeated once, even if positive. After confirmation of HIV-1-infection, no further HIV-1 RNA PCR testing is required.

If there are two indeterminate levels (two, separate, positive HIV-1 RNA PCR levels <10,000 copies/mL), HIV-1 DNA PCR will be run from the Guthrie card specimen. This will be performed by the central lab.

Guthrie/Filter Paper Cards for DNA PCR
Whole blood will be collected by heel-stick on filter paper (Guthrie cards) and stored for batched HIV-1 DNA testing of infants who are found to be HIV-1-infected.

NOTE: HIV-1 DNA PCR may also be run on these samples for infants with indeterminate HIV-1 RNA PCR levels and as a backup for resistance and subtype testing if stored plasma doesn’t have sufficient quantities.

HIV-1 Enzyme Immunoassorbant Assay (EIA)

An HIV-1 EIA will be performed on all infants at the final study visit or if the infant prematurely discontinues participation in the study after 12 months of age.
Cord Blood
Cord blood will be obtained only if feasible and if delivery occurs in a clinic/hospital setting. Samples will be stored for future studies of HIV-1 phenotype, genotype, and subtype.

Stored Plasma

Plasma will be stored at visits 1 and 2 for future resistance testing and subtype determination. Additional samples will be stored at subsequent visits if enough blood is left over after all other study-required testing is completed.

• HIV-1 Resistance Testing

Resistance testing will be performed retrospectively, and results will not be used to guide the treatment of individual infants. HIV-1 genotyping will be performed and, in addition, a subset of samples may also be examined using minority variants, phenotypic resistance, or viral fitness assays. If maternal samples and/or ARV resistance data are available from other trials, data from mother-infant pairs will be analyzed.

• HIV-1 Subtype Determination

Phylogenetic subtyping will be performed. Sequences obtained from HIV-1 resistance testing (genotyping) will be used to determine HIV-1 subtype. Additional analyses of sequences from other regions of the HIV-1 genome may be performed for more detailed subtype determination and analysis of inter-subtype recombination.

Optional Bone Study for In Utero ARV-Exposed Infants ONLY

NOTE: The following bone studies will be performed on 55 infants with in utero TDF exposure and 55 infants with in utero exposure to other ARV agents.

Serum Vitamin D Levels and Parathyroid Hormone (PTH)

These samples will be frozen on site and batch shipped to a central laboratory for evaluations of disorders of bone metabolism.
Serum Bone Marker Assessments

These samples will be frozen on site and batch shipped to a central laboratory for tartrate resistance acid phosphatase levels, bone-specific alkaline phosphatase levels, and osteocalcin testing.

X-Rays

X-rays of the left hand, wrist, and thoracic spine will be performed and read on-site for clinical care and quality assurance purposes and then sent to a central reading facility in the U.S.

6.3.5 Breast Milk Samples

Samples will be collected, when available, from consenting mothers of the participating infants either by manual expression or by breast pumps. The samples will be used to assess ARV and HIV-1 RNA levels. All women who choose to breast-feed are eligible to provide these samples; however, this collection is not required.

Information on mastitis and other potential breast pathology will be collected during study visits and recorded on the CRFs.

7.0 TOXICITY MANAGEMENT

7.1 Toxicity Management of Infants

Most infants enrolled in this study will have had in utero exposure to maternal ARV therapy, and it is possible that a subset of infants will continue to be exposed to ARVs via breast milk. Appropriate medical management will be instituted according to the local standard of care for both infected and uninfected infants. HIV-1-infected infants will be referred to pediatric treatment trials as they become available.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Criteria for Participant Discontinuation

- The legal guardian refuses followup evaluations.
- Request by the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
8.2 Criteria for Study Discontinuation

- At the discretion of the AACTG/PACTG, NIAID, NICHD, or investigator.

NOTE: NICHD provides funding to some PACTG sites.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

A5190-P1054 is an observational study with the general objective of assessing the safety and toxicity of HIV-specific ARV exposure among infants born to HIV-1-infected women who are enrolled in ARV treatment protocols in diverse areas of the world. The study plans to enroll infants born to HIV-1-infected women participating in A5175, HPTN 052, A5207, A5208, P1032, and other, future NIH-sponsored, international, ARV treatment trials. Enrollment should occur within 48 hours of birth (+ 6-week window).

The study will monitor and describe birth outcomes and toxicity and adverse event rates following in utero exposure to ARVs. The study will follow all infants through 18 months postpartum and describe long-term mortality and morbidity in relation to ARV exposure through breast milk, site standard of care ARV prophylaxis, or ARV treatment trial-provided prophylaxis for prevention of MTCT.

Due to the observational nature of the design, the study has the following limitations: 1) there is no control group of unexposed infants; 2) the exposure is not blinded; 3) the participants are not randomized; and 4) the study might be subject to confounding factors.

9.2 Endpoints

9.2.1 Primary endpoints

9.2.1.1 Infant toxicity and adverse events at birth:

- Estimated birth weight (low birth weight <2500 grams; very low birth weight <1500 grams [not collected for home deliveries])
- Gestational age (by physical exam) <32 weeks; 32- ≤37 weeks; >37 weeks
- Congenital anomalies
9.2.1.2 Toxicity and adverse events at birth and during the 18 months post-delivery:
- Worst reported grade of any toxicity in infants at birth and during the 18 months post-delivery.
- Diagnoses in infants at birth and during the 18 months post delivery.

9.2.2 Secondary endpoints

9.2.2.1 Infant HIV-1 status at each visit

9.2.2.2 Infant growth measurements at each visit

9.2.2.3 Serious infectious complications

9.2.2.4 Number of overall infant hospitalizations

9.2.2.5 Mortality of infants born alive to HIV-1-infected mothers during the 18 months post-delivery

9.2.2.6 Breast milk HIV-RNA PCR copy numbers and ARV concentrations in breast milk at each visit in a subset of mothers who elect to breast-feed.

9.2.2.7 ARV concentrations in cord blood in a subset of infants from whom cord blood collection is feasible.

9.2.2.8 Bone x-rays measurements at birth and 6 and 18 months of age

9.2.2.9 Vitamin D and PTH levels at 6 and 18 months of age

9.2.2.10 Tartrate resistance acid phosphatase levels at birth and at 6 and 18 months of age

9.2.2.11 Bone-specific alkaline phosphatase levels at birth and at 6 and 18 months of age

9.2.2.12 Osteocalcin levels at birth and at 6 and 18 months of age

9.2.2.13 Pregnancy-related complications among mothers of the infants

9.2.2.14 HIV-1 resistance and HIV-1 subtype in HIV-1-infected infants
9.3 Sample Size and Accrual

A5190-P1054 is a protocol with an open sample size because it will be run in parallel to parent ARV treatment trials. The initial parent protocols to enroll into A5190-P1054 will be A5175, HPTN 052, A5207, A5208, and P1032. A5175 will have about 1520 participants, 760 of whom may be women of childbearing age. HPTN 052 has a sample size of 1750 HIV-1-infected participants, approximately one third (600) of whom are potentially women of childbearing age. A5207 is a study conducted in pregnant women with a sample size of 300, 20% (60) of whom are potentially breastfeeding. A5208 is a study conducted exclusively in women of childbearing age with a sample size of 640. P1032 is a study conducted in pregnant women/infant pairs with a sample size of 150, and all 150 infants are eligible for A5190-P1054. Estimating that 2000 women with a potential for becoming pregnant are enrolled in the A5175, HPTN 052, A5208 trials and that 3% to 10% of these women will become pregnant during the trial, 60 infants from A5207 and 150 infants from P1032 are enrolled, the estimate is that 270 to 410 HIV-1-exposed infants will be born to these mothers. Taking into consideration that repeat pregnancies may occur in about 30% of females enrolled in the first three trials, a sample size of 270 to 410 might increase to 288 to 470 over the followup period for the first trials to enroll into A5190-P1054. Infants will be followed for approximately 18 months post-enrollment.

With regard to detection of bone abnormalities associated with TDF, assuming bone toxicity rate (based on both x-rays and serologic bone marker assays) of 10% for ARV exposed infants in general, a sample size of 110 will allow us to detect bone abnormalities associated with TDF (or other ARVs) if the bone toxicity rate increases from 10% to around 30% (see Table 1). Table 1 lists the number of infants needed to detect the corresponding rate difference. The calculation was based on two-sided Chi-square tests with type-I error of 0.10 and power of 80%, after adjusting for 10% lost-to-followup rate. It is also assumed half of infants had in utero exposure to TDF. If the proportion of infants with in utero TDF exposure is far from 50% (much larger or much smaller) then the power of detecting this rate difference is smaller.
Table 1:

<table>
<thead>
<tr>
<th>Detectable Rate Difference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>From 10% to 18%</td>
<td>512</td>
</tr>
<tr>
<td>From 10% to 20%</td>
<td>345</td>
</tr>
<tr>
<td>From 10% to 23%</td>
<td>218</td>
</tr>
<tr>
<td>From 10% to 25%</td>
<td>170</td>
</tr>
<tr>
<td>From 10% to 27%</td>
<td>137</td>
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<tr>
<td>From 10% to 30%</td>
<td>104</td>
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<td>From 10% to 40%</td>
<td>52</td>
</tr>
<tr>
<td>From 10% to 50%</td>
<td>30</td>
</tr>
</tbody>
</table>

9.4 Monitoring

9.4.1 Cumulative toxicity reports showing the accumulation of all primary endpoints will be generated by SDAC for review by the study chairs and medical officer on a monthly basis. These will not include information regarding the mother's ARV treatment but will be broken down by site.

9.4.2 Cumulative toxicity reports showing the accumulation of all primary endpoints will be generated by SDAC for review by the DAIDS medical officer on an every 3 month basis. This report will be broken down by the mother’s ARV treatment, if appropriate. Again this report will be broken down by site.

9.4.3 Subsequent to accrual of the first infant, the study will be reviewed for safety by the DSMB at the same time as A5175. For this safety review the rates of all primary and secondary endpoints (overall and broken down by a mother's ARV therapy when appropriate) will be presented. Where appropriate, this report will be broken down by site. As a safety review there are no formal stopping guidelines. Expedited adverse events of A5190 infants will be reported through the parent studies. A5190 infant safety data will also be available for parent study DSMB reviews.

9.5 Analyses

Since this is an observational study, the analyses will involve interval estimation. No significance testing is planned. The analyses will be stratified according to whether infants have in utero ARV exposure (as opposed to postpartum ARV exposure only). The analyses will also be stratified by the enrolling site. Overall summary statistics regardless of the mother's ARV treatment will be the primary focus, but in the event of an
ARV-specific effect, detected through exploratory analysis, they will also be broken down by the mother's ARV treatment experience during pregnancy and the period 18 months postpartum. Analyses of bone data will occur after at least 55 infants with in utero TDF exposure and 55 infants with in utero exposure to other ARV agents are measured. Summary statistics of bone x-ray measurements and bone markers will be broken down by in utero TDF exposure. In the event of a breast milk ARV exposure effect detected through exploratory analyses, analyses will also be broken down by the breast-feeding status. In the event of interactions by site, detected through exploratory analysis, site-specific incidence rates will also be calculated.

HIV-1-infected infants receiving ARV therapy through participation in treatment studies or through standard of care will be excluded from all postpartum analyses after initiation of ARV, since it is not possible to separate out the cause of toxicities. Separate summaries of events occurring following the initiation of ARVs will be performed. Toxicities and followup time of HIV-1-infected infants prior to initiation of ARV therapy will be counted when incidence rates are calculated.

9.5.1 Primary Analyses

9.5.1.1 Toxicity and adverse events at birth: Estimation of the incidence rates of experiencing at least one of endpoints listed in 9.2.1.1; endpoint-specific rates will also be estimated.

9.5.1.2 Toxicity and adverse events at birth and during the 18 months post-delivery: Summaries of all toxicities and adverse events listed in 9.2.1.2 by type and grade, with estimation of the cumulative incidence of experiencing at least one Grade >2, Grade >3, and Grade >4 targeted toxicity and diagnoses.

9.5.2 Secondary analyses (for each of the endpoints described in 9.2.2)

Appropriate summaries of each of the endpoints described in section 9.2.2 including:

9.5.2.1 Mother-to-infant HIV-1 transmission rate

9.5.2.2 Incidence of abnormal infant growth

9.5.2.3 Incidence of serious infectious complications

9.5.2.4 Median number of infant hospitalizations
9.5.2.5 Cumulative incidence of infant mortality

9.5.2.6 Median HIV-1 RNA PCR copy numbers and ARV concentrations in breast milk at each visit in a subset of mothers who elect to breast-feed, stratified based on the presence or absence of breast pathology.

9.5.2.7 Median ARV concentrations in cord blood in a subset of infants from whom cord blood collection is feasible

9.5.2.8 Cumulative incidence of osteoporosis and abnormal bone maturation by in utero TDF exposure

9.5.2.9 Median vitamin D and PTH levels at 6 and 18 months of age

9.5.2.10 Median tartrate resistance acid phosphatase levels at birth and 6 and 18 months of age

9.5.2.11 Median bone-specific alkaline phosphatase levels at birth and at 6 and 18 months of age

9.5.2.12 Median osteocalcin levels at birth and at 6 and 18 months of age

9.5.2.13 Pregnancy-related complications among mothers of the infants

9.5.2.14 Summary of HIV-1 resistance and HIV-1 subtype in HIV-infected infants

10.0 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

A5190-P1054 is a prospective, observational cohort study that will examine the safety, toxicity, and AEs in infants related to ARV exposure through their HIV-1-infected mother’s ARV treatment. The objective of the pharmacology plan is to measure select ARV drugs in cord blood and breast milk to 1) better gauge drug transfer into these compartments, and 2) generate concentration-time data for further safety and toxicity analyses.
10.2 Study Design

No treatment is provided through this study. HIV-1-infected infants will be referred to pediatric treatment trials as they become available at their site. Infants enrolled into A5190-P1054 will have been exposed to the ARVs their mothers are receiving, or had received, in NIH-sponsored, international, ARV treatment protocols. Therefore, the drugs to be studied will vary across participants. A5190-P1054 will initially focus on TDF in the cord blood and breast milk, but other drugs may also be examined such as ATV and FTC. Study visits will occur at birth, at 3, 6, 9, 12, and 18 months of age.

Cord blood samples will be collected at birth when feasible. Breast milk samples will also be collected from a subset of consenting mothers and stored. Dose and dose-timing information of the mothers’ ARV treatment will be recorded.

It is anticipated that between 360 and 500 infants will be enrolled into this study. Since repeat pregnancies may occur, a sample size of 360 to 500 might increase to 378 to 560 (see section 9.3 for further details). Therefore the anticipated maximum number of cord blood and breast milk samples will be 560 each (1120 total), although this number is subject to change. It is unlikely that this many breast milk samples will be collected, since not all women will be breast feeding. In addition cord blood samples will be collected only if feasible and if delivery occurred in a clinic/hospital setting.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

Raw concentration-time data for the drug being examined will be tabulated and presented using descriptive statistics only. Safety and/or toxicity data analyses that utilize the concentration-time data will be at the discretion of the protocol statistician. Information to be recorded includes the dose amount of all drugs administered, the time of the most recent doses, the time of the previous doses, and the time the cord blood or breast milk sample was collected.

Drug determination in cord blood or breast milk will likely be completed at more than one Adult or Pediatric ACTG Pharmacology Laboratory. The protocol pharmacologist will be responsible for determining which labs will be involved; ensuring samples are shipped in a timely manner to the laboratories, and coordinating results with the Data Management Center. Assays are currently available to measure most if not all ARVs in plasma from cord blood. NNRTI, NRTI, and PI assays in breast milk are currently under development at several AACTG and PACTG laboratories.
10.4 **Anticipated Outcomes**

Results from this study will further elucidate ARV drug transfer to the fetus of HIV-1-infected women who are receiving ARV drugs as well as the penetration into the breast milk compartment. The goal is that these data will translate into better drug selection for treating HIV-1-infected women during pregnancy and while breast feeding. Additional statistical analyses using the concentration-time results may also yield important information regarding relationships between drug exposure and safety or toxicity.

11.0 **DATA COLLECTION AND MONITORING AND ADVERSE EXPERIENCE REPORTING**

11.1 **Records to Be Kept**

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs, but will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG Data Management Center upon registration.

11.2 **Role of Data Management**

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG Data Management Center. Each IACTU is responsible for submitting the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG Data Management Center to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 **Clinical Site Monitoring and Record Availability**

11.3.1 Site monitors under contract to the National Institute of Allergy and Infectious Diseases (NIAID) will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians’ progress notes, nurses’ notes, individuals’ hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites’ regulatory files to ensure that regulatory requirements are being followed.
11.3.2 The investigator will make study documents (e.g., consent forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRBs, ethics committees, or local ministries of health, the site monitors, the NIAID, and the Office for Human Research Protections (OHRP) for confirmation of the study data.

11.4 Expedited Adverse Experience (EAE) Reporting

No EAEs will be reported in A5190-P1054. Instead, all EAE reporting for infants enrolled in A5190-P1054 will occur through collaborating ARV treatment protocols, for example, A5175, HPTN 052, A5207, A5208, or P1032.

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol document and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the parent, legal guardian, or person with power of attorney for the infant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent or legal guardian, and this fact will be documented in the infant’s record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant’s parent or legal guardian, except as necessary for monitoring by IRB, the NIAID, NICHD, local ministry of health, ethics committees, or OHRP.

12.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIAID, NICHD, local ministry of health, or other government agencies as part of their duties to ensure that research participants are protected.
13.0 **PUBLICATION OF RESEARCH FINDINGS**

Publication of the results of this trial will be governed by ACTG and PACTG policies.

14.0 **BIOHAZARD CONTAINMENT**

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

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g., FedEx, Airborne, for specific instructions.


REFERENCES (Cont’d.)


REFERENCES (Cont’d.)


REFERENCES (Cont’d.)


REFERENCES (Cont’d.)


APPENDIX I

DIVISION OF AIDS
ADULT AIDS CLINICAL TRIALS GROUP (AACTG)/PEDIATRIC AIDS CLINICAL
TRIALS GROUP (PACTG) SAMPLE INFORMED CONSENT FOR

PROTOCOL A5190-P1054

TITLE: Assessment of Safety and Toxicity Among Infants Born to HIV-1-infected Women
Enrolled in Antiretroviral Treatment Protocols in Diverse Areas of the World (FINAL
VERSION 1.0, dated 01/06/05)

SHORT TITLE FOR THE STUDY: A5190-P1054, Safety and Toxicities in Infants Born to
HIV-1-Infected Mothers in Antiretroviral Treatment Studies

INTRODUCTION

You and your baby are being asked to participate in this research study because you are infected
with the HIV virus and were pregnant while participating in an antiretroviral (anti-HIV drug)
treatment study such as A5175, HPTN 052, A5207, A5208, or P1032. A5190-P1054 is
sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this
site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this
study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

HIV-infected pregnant women are given antiretrovirals (anti-HIV drugs) for their HIV disease
and/or to decrease the chances of passing HIV to the baby. Antiretrovirals taken during
pregnancy may affect the baby. Therefore, it is important to look at whether these drugs taken
during your pregnancy affect your baby. Long-term followup is recommended for a baby whose
mother takes antiretrovirals during pregnancy.

This study will look at whether babies have any side effects from exposure to antiretrovirals
while in the mothers’ womb or through breast milk. This study will also look at whether
pregnancy-related or antiretroviral-related events that happened to the mother, while pregnant, affected the baby.

WHAT DOES MY BABY HAVE TO DO IN THIS STUDY?

This is an observational study, which means that no HIV treatment will be provided to your baby by this study. If your baby becomes infected with HIV, the research study staff will discuss options with you concerning treatment or enrollment of your baby into antiretroviral trials if and when they become available.

You will be asked to bring your baby to the clinic six times during this study. This study will last about 18 months (1 ½ years). You will receive the results of your baby’s tests that can be used for routine clinical care as soon as they become available.

Your baby should be brought for the study visits at the following times:

Visit 1: If possible, within 2 days after birth or within the first 6 week after birth.
Visit 2: At about 3 months of age.
Visit 3: At about 6 months of age.
Visit 4: At about 9 month of age.
Visit 5: At about 12 months of age.
Visit 6: At about 18 months of age.

Each visit will last about one hour.

Entry (visit 1)
You will be asked to bring your baby for visit 1 within 2 days after birth. If this is not possible, you will be asked to bring your baby for the first visit within the first 6 weeks after his/her birth.

At this first visit your baby’s medical and birth information will be collected. A physical exam will be performed. Urine will be collected, and about 1 teaspoon of blood will be taken for routine safety blood tests, to see if your baby has syphilis (a bacterial infection that may be passed to your baby while in the womb), and to see whether there is any HIV virus in your baby’s blood. If the results show that your baby is infected with HIV and a followup test confirms it, then this test will not be repeated during the study.

There will be an optional Bone Study for some infants. If you agree to have your baby participate in the Bone Study, your baby will have less than 1 teaspoon of additional blood taken to measure the amount of vitamin D in your baby’s blood and to check for bone abnormalities.
An x-ray of your baby’s spine and left hand and wrist will be performed to look for bone disorders such as loss of bone.

**On-Study Visits**

After the first study visit, you will be asked to bring your baby to the clinic about once every 3 months for five more visits.

At all study visits your baby’s medical information will be collected, a physical exam will be performed, and urine will be collected. About 1 teaspoon of blood will be taken for routine safety blood tests.

If your baby is participating in the Bone Study, an additional teaspoon of blood will be taken for vitamin D levels and to test for bone disorders at visits 3 and 6. X-rays of your baby’s spine and left hand and wrist will also be performed at visits 3 and 6 or if your baby leaves the study early.

Less than 1 teaspoon of blood will be drawn to see if the HIV virus is in your baby’s blood. If at any time during the study the results of this test show that your baby is infected with HIV, then no more testing will be done to look at levels of HIV virus in your baby’s blood. Some blood collected and stored during the study will be used for other HIV testing.

At the final visit, 1 tsp of blood will be taken as a final check to see if your baby has HIV infection.

About 1 teaspoon of the blood collected from your baby will also be stored (with usual protectors of identity) for future virology tests, including resistance tests (to see whether the virus in your baby’s body is likely to respond to certain antiretrovirals). These blood samples will be tested at a later date. The results of these tests will be kept confidential and will not be available to you or your primary care provider. (For those participants at NICHD sites, there is a separate consent form that explains this and asks for your consent.)

**Other**

As the sample collections below are optional, please indicate your choice (by initialing the appropriate line below) whether you agree to participate in the optional cord blood, breast milk, bone evaluation assessments, and storage of left-over blood for future use. These samples may be held for an indefinite length of time. No matter what you decide, it will not affect your baby’s participation in the study.
APPENDIX I (Cont'd)

You may be asked to allow collection of umbilical cord blood at delivery, which may be used to measure the levels of the HIV virus and antiretrovirals in the blood and possibly a blood test for syphilis.

I agree to the collection and storage of umbilical cord blood:

Yes_____ No_____  

If you decide to breast-feed your baby, you may be asked to provide samples of breast milk, which will be stored for future testing. These samples may be used to measure the concentration of the HIV virus and the levels of antiretrovirals in the milk.

I agree to the collection and storage of breast milk samples:

Yes_____ No_____  

If you agree to the collection of blood from your baby’s umbilical cord and the collection of breast milk, specimens will be stored anywhere from six months to three years for future testing.

You may be asked to have your baby evaluated for his/her bone health if you received tenofovir or other antiretrovirals while pregnant. This means additional blood tests performed on your baby during the same study visit and three sets of x-rays of the left hand and wrist and the upper portion of the spine during the first 18 months of life. The purpose of these evaluations is to see whether these specific antiretroviral drugs affect the baby’s bones.

I agree to bone studies (blood tests and X-rays):

Yes_____ No_____  

Blood left-over after all study testing is done may be stored for future ACTG-approved AIDS-related research. We cannot ensure that you will be told of the results of the research done on these samples. Your identity and the identity of your baby will be protected with an identification number, and all assurances of confidentiality described below are in place for this work.

Yes_____ No_____
APPENDIX I (Cont'd)

Premature Discontinuation/Early Withdrawal

If you decide to stop your baby’s participation before all study visits have been done, you will be asked to bring your baby in for a final visit. At that final visit, your baby’s medical information will be collected and a physical exam will be performed. About 1 teaspoon of blood will be taken for safety tests. Less than 1 teaspoon of blood may also be taken to measure the HIV level in the blood and to check for an immune response to the HIV virus. A urine sample will be collected for safety testing. If you are breastfeeding, you will be asked to provide a sample of breast milk. The sample will be stored and tested some time in the future. If your baby is participating in the Bone Study, an x-ray of your baby’s spine and left hand and wrist will be done to look for broken bones and other bone disorders.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 270 to 500 babies may take part in this study throughout the world.

HOW LONG WILL MY BABY BE IN THIS STUDY?

Your baby will be in this study until about 18 months of age (about 1 ½ years).

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

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

- The study is cancelled by the site’s institutional review board (IRB), ethics committee (EC), or local ministry of health, National Institute of Allergy and Infectious Diseases (NIAID), the Office for Human Research Protections (OHRP), or the National Institute of Child Health and Human Development (NICHD). (An IRB, EC, and the OHRP are committees that watch over the safety and rights of research participants.)
- A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)
- Your baby is not able to attend the study visits as required by the study.
- Study participation is no longer in the best interest of your baby.
WHAT ARE THE RISKS OF THE STUDY?

Breast-Feeding

A mother who is infected with HIV may infect her baby through breast milk. HIV-infected mothers who are able to obtain baby formula and clean water should not breast-feed their babies. It is not known whether the antiretrovirals that you are taking pass through your breast milk and cause harm to your infant. It is also unknown whether these drugs reduce the chances that HIV can pass from your breast milk to your baby.

Risks of Blood Draws

There may be some discomfort when blood is drawn. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site.

Risks Related to X-Rays

An x-ray (like taking a picture) is a commonly used diagnostic procedure that exposes your baby to a small dose of radiation. The amount of radiation that your baby will be exposed to in this study less than a full chest x-ray.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

It is unlikely that your baby will receive any direct benefit from participating in this study. Information learned from this study may help other women, especially those receiving antiretroviral drugs and are either pregnant or planning to become pregnant.

Information learned may help mother/infant pairs who have HIV/AIDS in your own and other countries by identifying the rate of transmission of HIV from mother to baby and the effects of the mothers’ antiretroviral drugs on babies.

WHAT OTHER CHOICES ARE THERE BESIDES THIS STUDY?

[Insert general information about HIV/AIDS treatment availability in your country or locale.]

Laboratory tests and quality medical care for HIV/AIDS may or may not be available to your baby. The clinic staff will discuss with you treatment choices in your area and the risks and the benefits of these choices.
WHO WILL SEE MY BABY’S MEDICAL INFORMATION?

The study team will provide your baby with an identification number. The identification number (not your baby’s name or other information that could be used to identify your baby) will be used for laboratory tests or blood stored for testing in future studies. Your baby’s medical records and the list of names, addresses, and identification numbers will be kept locked. Any publication of this study will not use your baby’s name or identify your baby personally.

Efforts will be made to keep your baby’s personal information confidential. We cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Your baby’s records may also be reviewed by (insert name of site IRB or Ethics Committee), your country’s national health agency, NICHD, the National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), study staff, and study monitors supporting this study.

WHAT ARE THE COSTS TO ME?

There will be no cost for your baby to take part in this study. No antiretrovirals will be provided by this study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants]

WHAT HAPPENS IF MY BABY IS INJURED?

If your baby is injured as a result of being in this study, he/she will be given immediate treatment for any injuries, and will be referred for further treatment, if necessary. The cost for this treatment may be charged to you [or to the program which normally pays for your medical care]. There is no program for compensation either through [this institution] or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.
WHAT ARE MY BABY'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or to leave this study at any time. Your baby will be treated the same no matter what you decide.

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

Your baby may be withdrawn from the study if continued participation is no longer in the baby’s best interest.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research subject, contact:
- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above
If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to your baby taking part in this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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</thead>
<tbody>
<tr>
<td>Participant’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
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APPENDIX II

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET

When your child joins this NICHD sponsored Study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child’s name.)

WHY HAVE A REPOSITORY?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board (IRB), a separate group of people overseeing the repository, examines the study and makes sure that your child’s rights are being protected.

HOW WILL MY CHILD’S PRIVACY BE PROTECTED?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The specimens will have a special study code. It will be the same code that is on your child’s information in the NICHD sponsored Study from your child’s interviews and examinations. Again, none of this information will have your child’s name on it.

HOW WOULD A RESEARCHER GET TO USE THE SPECIMENS IN THE REPOSITORY?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded
information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

WHY WOULDN’T I FIND OUT THE RESULTS OF THE RESEARCH USING MY CHILD’S SPECIMENS?

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

WOULD I EVER BE CONTACTED IN THE FUTURE ABOUT RESEARCH USING MY CHILD’S SPECIMENS?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I GAVE MY PERMISSION TO TESTING MY CHILD’S SPECIMENS IN THE REPOSITORY, BUT WHAT IF I CHANGE MY MIND?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.
WHAT TYPE OF RESEARCH WILL BE DONE WITH MY CHILD’S SPECIMENS?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (A5190-P1054: Assessment of Safety and Toxicity Among Infants Born to HIV-1-infected Women Enrolled in Antiretroviral Treatment Protocols in Diverse Areas of the World), your child is being asked to have some blood taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.

You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.
APPENDIX II (Cont'd)

TEMPLATE CONSENT FORM

WHAT ARE THE GENERAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The blood specimens would be collected as part of your child’s study visits. There may be some discomfort when blood is drawn. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site. Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________ ___________________________ ________
Parent or Legal Guardian Signature  Witness Signature  Date

WHAT ARE THE SPECIAL HIV-RELATED STUDIES THAT CAN BE DONE WITH THE REPOSITORY SPECIMENS?

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless
APPENDIX II (Cont'd)

supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The blood specimens would be collected as part of your child’s study visits. There may be some discomfort when blood is drawn. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site. Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.

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<thead>
<tr>
<th>I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).</th>
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<td>Parent or Legal Guardian Signature</td>
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WHAT IF I HAVE MORE QUESTIONS?

If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

<table>
<thead>
<tr>
<th>I refuse to have any specimen collected from my child stored in the repository.</th>
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<td>Parent or Legal Guardian Signature</td>
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