

HPTN 057
A Phase I Open Label Trial of the Safety and Pharmacokinetics of
Tenofovir Disoproxil Fumarate in HIV-1 Infected
Pregnant Women and their Infants
(DAIDS Document ID 10143)

A Multicenter Study of the International Maternal Pediatric Adolescent AIDS Clinical
Trials Group (IMPAACT)

Sponsored by:

US National Institute of Allergy and Infectious Diseases (NIAID)
And
The Eunice Kennedy Shriver
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INVESTIGATOR OF RECORD SIGNATURE PAGE

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Final Version 2.0, dated 28 October 2009

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Gilead Sciences, Inc.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be submitted to the IMPAACT Manuscript Review Committee, DAIDS, and the product Co-Sponsors for review prior to submission.

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

Name of Investigator of Record

Signature of Investigator of Record

Date

LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|------------------|--|
| AE | adverse event |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT [SGPT] | alanine aminotransferase |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| AUC | steady-state exposure |
| AZT | zidovudine |
| CBC | complete blood count |
| CORE | (HPTN) Coordinating and Operations Center |
| DAIDS | Division of AIDS |
| DAIDS EAE Manual | The Manual for Expedited Reporting of Adverse Events to DAIDS |
| DEXA | dual-energy absorptiometry |
| EAE | Adverse event requiring expedited reporting to DAIDS (Expedited Adverse Event) |
| EC | ethics committee |
| FDA | (United States) Food and Drug Administration |
| HAART | Highly Active Antiretroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| HIVNET | HIV Network for Prevention Trials |
| HPTN | HIV Prevention Trials Network |
| IMPAACT | International Maternal Pediatric Adolescent AIDS Clinical Trials Group |
| IRB | institutional review board |
| LDMS | Laboratory Data Management System |
| MTCT | mother-to child HIV transmission |
| NIAID | (United States) National Institute of Allergy and Infectious Diseases |
| NICHD | (United States) National Institute of Child Health and Development |
| NIH | (United States) National Institutes of Health |
| NL | (HPTN) Network Lab |
| NNRTI | non- nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| PACTG | Pediatric AIDS Clinical Trials Group |
| pk | pharmacokinetic |
| pMTCT | prevention of mother-to child HIV transmission |
| PSRT | Protocol Safety Review Team |
| SAE | serious adverse event |
| SIV | Simian Immunodeficiency Virus |
| SDMC | (HPTN) Statistical and Data Management Center |
| SMC | (HPTN) Study Monitoring Committee |
| SSP | study-specific procedures |
| TDF | tenofovir disoproxil fumarate |
| TFVpp | tenofovir diphosphate |
| US | United States |
| ULN | upper limit of normal |
| WHO | World Health Organization |

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SCHEMA

HPTN 057: A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir Disoproxil Fumarate in HIV-1 Infected Pregnant Women and their Infants

PURPOSE: To evaluate the safety and pharmacokinetics of tenofovir disoproxil fumarate (TDF) administered to human immunodeficiency virus (HIV) infected pregnant women during labor and to their infants during the first week of life.

DESIGN: Phase I, open label, non-controlled trial

STUDY POPULATION: *Mothers:* HIV-infected pregnant women; *Infants:* born to HIV-1 infected enrolled mothers

STUDY SIZE: 110 fully evaluable mother/infant pairs

STUDY DRUG REGIMEN: Eligible women and their infants will be enrolled in one of four cohorts outlined below. Irrespective of and outside of this Phase I study of TDF, all participating women and infants will be offered the local standard of care antiretroviral regimen for prevention of mother to child HIV transmission. Cohort 4 was added after reviewing the pharmacokinetic and safety data from Cohorts 1 – 3.

| | <i>Maternal Dosing Regimen</i> | <i>Infant Dosing Regimen</i> |
|--------------------|--|---|
| Cohort 1 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section. | The infant will not receive study drug. |
| Cohort 2 N = 20 | The mother will not receive study drug. | 4 mg/kg of the TDF oral suspension at birth. The dose must be administered as soon as possible; within 12 hours of birth. Repeat the dose on Days 3 and 5 of life. |
| Cohort 3 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section* | 4 mg/kg of the TDF oral suspension at birth. The dose must be administered as soon as possible; within 12 hours of birth**. Repeat the dose on Days 3 and 5 of life. |
| Cohort 4 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section | 6 mg/kg of the TDF oral suspension for 7 days initiated at birth. The birth dose must be administered as soon as possible; within 12 hours of birth. The second dose must be administered within 16 to 32 hours after the birth dose and five subsequent doses should be administered daily (every 24 hours +/- 2 hours). |

*dose may be adjusted to 900 mg based on results of cohort 1

**dose may be adjusted to 6 mg/kg based on results of cohort 2

STUDY DURATION: The duration of Cohorts 1 – 3 will be approximately two years. Enrollment is expected to take approximately 6-9 months, with enrollment of Cohort 3 beginning after all mothers and infants in Cohort 1 and 2 have been followed for a minimum 6 weeks postpartum.

Cohort 4 will begin after Cohorts 1 – 3 have completed follow-up and is expected to take approximately 6 months. Mothers and infants in all four cohorts will be followed through 12 months post delivery.

PRIMARY OBJECTIVES:

- (1) To evaluate the safety and tolerability of intrapartum/neonatal TDF in HIV-infected women and their infants.
- (2) To evaluate the pharmacokinetics of intrapartum/neonatal TDF in HIV-infected women and their infants and to determine maternal plasma exposure with a single-dose of 600 mg and, if necessary, 900 mg.

SECONDARY OBJECTIVES:

- (1) To evaluate the effect of a single dose of TDF on maternal HIV-1 RNA levels, and to determine if there is RNA rebound above baseline following washout of the drug in study participants at 5 to 7 days and 6 weeks postpartum.
- (2) To evaluate viral resistance to TDF in HIV isolates from maternal plasma, infant plasma, and breastmilk
- (3) To determine the infection status of participating infants.
- (4) To measure TDF concentration in amniotic fluid and breastmilk following maternal exposure to intrapartum TDF.

STUDY SITES: The study will be conducted at the following locations and/or additional NIAID or NICHD Clinical Trial Sites:

Malawi: Queen Elizabeth Central Hospital, Blantyre
Brazil: Federal University of Minas Gerais, Belo Horizonte
Irmandade Santa Casa de Misericordia, Porte Alegre
Hospital Nossa Senhora da Conceicao Servico de Infectologia, Porte Alegre
Hospital dos Servidores do Estado – Servico de Doencas, Rio de Janeiro

1.0 INTRODUCTION

Evaluation of alternative antiretroviral (ARV) agents that can be used in simple perinatal regimens suitable for the prevention of mother to child HIV transmission (pMTCT) in the developing world is a high priority. Tenofovir is a potent ARV with proven animal model efficacy, a favorable resistance profile and pharmacokinetic (PK) properties that make it attractive for use in short course regimens for prevention of intrapartum and early postpartum/breastfeeding mother-to-child HIV transmission (MTCT). This study will provide PK and safety data needed to identify a tenofovir regimen that can be used, if indicated, in a subsequent evaluation of the efficacy of tenofovir for prevention of mother to child HIV transmission (pMTCT).

Tenofovir disoproxil fumarate (TDF), the oral pro drug of tenofovir, is the first nucleotide analogue approved by the United States (US) Food and Drug Administration (FDA) for use in HIV infection. TDF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide), which in turn is converted intracellularly to tenofovir diphosphate, its active form. Animal studies have shown that pre- and post- exposure tenofovir regimens are effective in preventing HIV transmission.^{1,2,3} TDF's resistance profile and PK properties as determined from adult human studies suggest that it would be a suitable agent for use in regimens to prevent MTCT.^{4,5,6,7} For these reasons, TDF is an attractive agent for investigation of pMTCT. With favorable resistance and safety profiles, oral administration and a relatively long half-life, TDF holds the promise of a simple yet effective peripartum regimen for prevention of mother to child transmission (pMTCT) that will be practical for use in resource-limited settings.

HPTN 057 is designed to evaluate the safety, tolerance and pharmacokinetics of TDF when administered to HIV-infected pregnant women during labor and/or to their infants during the first week of life.

1.1 BACKGROUND AND RATIONALE

The major mode of acquisition of HIV in children worldwide is through mother-to-child-transmission (MTCT). Prior to the development of effective specific interventions to reduce the risk of MTCT, the estimated rates of transmission ranged from 15-25% in the U.S. and Europe and 25-40% in African populations. In resource-rich countries, MTCT of HIV-1 has decreased to less than 2% following recommendations for universal prenatal HIV counseling and testing, widespread implementation of ARV prophylaxis, elective cesarean delivery, and avoidance of breastfeeding.

The dramatic public health success in resource-rich countries following the results of PACTG 076 contrasts with the continued perinatal epidemic in resource-limited countries, where the PACTG 076 zidovudine (AZT) prophylaxis regimen is too expensive and complex to implement, operative delivery may not be safe and could threaten the health of the mother, women often present for the first time late in pregnancy or at delivery, widespread use of highly active antiretroviral therapy (HAART) or women who do not require therapy for their own health may not be feasible, and HIV-infected women continue to breastfeed due to lack of safe, sustainable, affordable, and acceptable alternatives to breastfeeding. Several randomized clinical trials conducted in

breastfeeding populations have demonstrated that a variety of short, simple, effective, and inexpensive ARV regimens including AZT alone, AZT plus lamivudine (3TC), or nevirapine (NVP) alone can also reduce early MTCT by 38-63%, although there is some diminution of this reduction with continued breastfeeding, particularly with the AZT and AZT/3TC regimens.⁸⁻¹³

HIVNET 012 – Single-dose Nevirapine

NVP is a highly potent ARV drug with a long-half life and excellent transplacental passage and tissue penetration. HIVNET 012 employed the simplest approach to ARV prophylaxis of MTCT to date – maternal single-dose NVP during labor followed by single-dose NVP to her newborn.^{11, 12} MTCT was reduced by 42% at age 6-8 weeks and maintained significant efficacy of 41% at age 18 months in a breastfeeding population, when compared to an ultra-short AZT regimen of intrapartum AZT combined with 7 days of neonatal AZT. Transmission rates in the single-dose NVP arm were 11.7% and 15.7% at 6-8 weeks and 18 months of age, respectively. The SAINT trial demonstrated that intrapartum/postpartum single-dose NVP had similar efficacy to intrapartum/postpartum AZT/3TC.¹⁴ More recently, a short-course AZT regimen combined with single-dose NVP in a non-breastfeeding population in Thailand was associated with a transmission rate under 2%.¹⁵

The low cost, ease of implementation, and remarkable efficacy of the single-dose NVP approach in preventing MTCT, including in breastfeeding settings, has resulted in its strong endorsement by the World Health Organization (WHO) and by countries with the combination of high HIV infection rates and limited health care resources.

Single-Dose Nevirapine and Drug Resistance

However, a complicating feature of the single-dose NVP prophylactic regimen is the frequent emergence of NVP resistance in women within days to weeks of NVP administration, and in infants who become infected despite NVP prophylaxis. Concerns have been expressed related the potential for such resistance to diminish response to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ARV therapy, which is the first-choice regimen recommended for initial therapy by WHO for resource-limited settings, when therapy is subsequently needed by the mother or the infected infant.

Two factors favor selection of NVP-resistant virus in women and infants receiving single-dose NVP. First, only a single mutation is necessary to result in high-level resistance to NVP as well as cross-resistance to other NNRTI drugs. Secondly, NVP has a prolonged half-life in pregnant women and infants, with detectable levels of drug present for 2-3 weeks or longer following a single-dose. Furthermore, infected infants are effectively exposed to two doses: one *in utero*, and one after birth. Thus, the prolonged plasma NVP decay curve most likely accounts for the remarkable efficacy of NVP in preventing MTCT, including early breast milk transmission, but also its propensity to select for resistant viral mutants.

Several studies have examined the rate of detection of NVP-resistant HIV-1 following single-dose NVP. In HIVNET 012, NVP-resistant variants were detected in 25% of women 6-8 weeks after single-dose NVP using the ViroSeq genotyping assay.^{16, 17} Emergence of NVP resistance following single-dose NVP was also observed in other studies, regardless of whether single-dose NVP was administered alone or in combination with other ARV drugs.^{18, 19, 20}

NVP resistance was also detected in infants from the HIVNET 012 cohort.¹⁶ Mutations associated with NVP resistance were detected by 6-8 weeks of age in 11 (46%) of 24 evaluable infants who were infected with HIV-1. In addition, one of nine evaluable infants with late HIV-1 infection (after 6-8 weeks of age) had detectable NVP resistance, which appeared to be transmitted from the mother. Additional studies of single-dose NVP alone or in combination with other antiretrovirals have demonstrated rates of NVP resistance in infected infants ranging between 17%-52%.

Limited available data suggest some compromise of the effectiveness of subsequent treatment with an NNRTI-based regimen following single-dose NVP prophylaxis.^{15, 21} Several larger observational as well as randomized clinical trials are ongoing or planned that will evaluate this question in a rigorous fashion in women and infants infected despite single-dose NVP prophylaxis, as well as interventions to potentially reduce the development of resistance. It is not clear whether these findings will have long-term implications for the continued use of NVP as a way to prevent perinatal transmission. However, evaluation of alternative ARV agents that can be safely used in simple, short regimens for the pMTCT in resource-limited countries that are similar to single-dose NVP but without the problem of inducing drug resistance is a high priority.

1.2 STUDY PRODUCT PHARMACOLOGY

Tenofovir disoproxil fumarate (TDF), 9-[(R)-2-[[bis[[isopropoxycarbonyl]oxy] methoxy] phosphinyl]methoxy]propyl]adenine fumarate, is the oral pro-drug of the intravenous compound 9-[2-(phosphonomethoxy) propyl] adenine (tenofovir, PMPA)1-3. TDF is converted in vivo by diester hydrolysis to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir is phosphorylated by cellular enzymes to tenofovir diphosphate (TFVpp), which inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. The bioavailability of tenofovir in nonpregnant adults on an empty stomach is 25% and increases to around 40% when administered with a meal. Tenofovir is eliminated primarily by renal excretion and has an estimated terminal half-life of approximately 6-8 hours. In non-pregnant adults, the intracellular half-life for the disappearance of tenofovir diphosphate, the active metabolite, has been 12 to 15 hours in activated lymphocytes and 33 to 50 hours in resting lymphocytes.²² More recently, an intracellular half life of ≥ 60 hours was observed, with 8/8 adult patients having measurable intracellular concentrations of tenofovir diphosphate at 60 to 72 hours.²³

The serum concentration of tenofovir necessary for antiviral efficacy is difficult to define. For all nucleoside or nucleotide reverse transcriptase inhibitors, the intracellular amounts

of the phosphorylated anabolites (i.e., TFVpp for tenofovir) are responsible for antiviral activity. However, while intracellular concentrations of the nucleoside reverse transcriptase inhibitors do not correlate with extracellular concentrations, the intracellular concentration of TFVpp does correlate with extracellular concentrations.^{24,25} This provides a frame of reference for determining the concentrations necessary for antiviral activity in-vitro and tenofovir serum concentrations expected to be effective in vivo. Based on laboratory data using the HIV-1 IIIB strain in PBMCs, the IC50 is 0.18 μ M or ~52 ng/mL. The mean IC50 for clinical isolates in primary PBMC cultures ranged from 0.55 to 2.2 μ M (159-636 ng). In adult patients receiving 300 mg tenofovir daily, end of dose interval concentrations are approximately 50 to 70 ng/mL.^{24,25} These data provide a reference point for selecting tenofovir concentrations in maternal and cord blood that are likely to be safe and provide antiviral activity.

1.3 PRIOR RESEARCH: ANIMAL DATA

Tenofovir has demonstrated significant prophylactic efficacy against perinatal transmission of Simian Immunodeficiency Virus (SIV) infection in macaques, a primate model of acquired immune deficiency syndrome (AIDS).^{1,2,3} Animal studies provide strong support for both the pre-exposure as well as post-exposure efficacy of tenofovir in preventing retroviral infections. These studies include challenge by both the intravenous and intravaginal modes of SIV infection as well as the vertical transmission to neonate macaques. Tenofovir is active against HIV-2 as well as HIV-1, whereas NVP is active only against HIV-1. Additionally, unlike NVP, there appears to be a very low prevalence of the most important tenofovir-associated mutation, K65R. Genotypic analyses performed in patients enrolled in two clinical trials showed that the K65R mutation developed in just 2-3% of patients who were treated with TDF over periods of 24-48 weeks.^{4,5} In addition, no subject developed detectable resistance to the drug during 4 weeks of monotherapy. *In vitro* data suggest that there may be a fitness barrier for the K65R mutation that may explain the low frequency of this mutation.²⁶ Tenofovir is cleared from the body by the kidneys and is not metabolized by the liver. Therefore, tenofovir has limited potential to have pharmacokinetic interactions with other hepatically metabolized drugs.

The major toxicities of tenofovir predicted from animal studies include the kidney and bone. Pre-clinical toxicological studies of tenofovir and/or TDF in rats, dogs, and monkeys have identified the kidney as the primary target organ for toxicity. Histopathologic changes have included renal tubular karyomegaly, degeneration/regeneration, necrosis, dilatation, casts, and interstitial nephritis. The incidence and severity of these events were related to dose and duration of treatment.²⁵ Animal studies in rats and dogs treated with daily tenofovir for \geq 13 weeks have shown evidence of hypercalciuria and/or hyperphosphaturia, elevations in serum alkaline phosphatase, alterations in serum and urine markers of bone metabolism, with concomitant abnormalities in bone (e.g., decreases in bone mineral content, density, thickness and periosteal circumference, and increases in the endosteal circumference).²⁵ These findings are consistent with an increase in bone resorption during chronic dosing.

Preclinical efficacy studies in infant, juvenile and adult rhesus monkeys have demonstrated that prolonged administration of a *high*-dose tenofovir regimen (30 mg/kg daily via subcutaneous route) resulted in renal toxicity (proximal renal tubular disorder) which resulted in hyperphosphaturia, hypophosphatemia, elevated serum alkaline phosphatase levels and bone changes that are consistent with hypophosphatemic rickets/osteomalacia (i.e., overall decreased bone density, enlarged growth plates, bone deformities including fractures; histology: irregular hyperplastic growth plates and trabecular hyperplasia with widened osteoid seams).^{25, 27} In contrast, when a range of tenofovir doses (4-30 mg/kg body weight, administered subcutaneously once daily) were administered for a short period of time (ranging from 1 day to 8 weeks) to 39 newborn or infant macaques as part of SIV prophylaxis/therapy studies, no adverse events on their health or growth were observed, including for 12 animals that were monitored for more than two years. In addition, prolonged administration of a *low* dose of tenofovir (10 mg/kg per day, subcutaneously) starting at birth did not have any detectable effects on growth and bone density after more than 3.5 years of daily treatment (Van Rompay, unpublished data). This 10 mg/kg subcutaneous dosage regimen to a newborn macaque gives steady-state exposure (AUC) approximately 18-fold higher than the 300 mg TDF regimen currently used in HIV-infected adults.

In rats, tenofovir had no adverse effects on fertility or general reproductive performance at doses up to 600 mg/kg/day (exposure equivalent to approximately 10 times the human dose based on body surface area comparisons). Placental transfer of tenofovir has been studied in rhesus monkeys; following daily subcutaneous administration of 30 mg/kg/day, the fetal/maternal C_{max} was 17%.²⁷ After a single 30 mg/kg subcutaneous dose near term, the tenofovir level in the cord blood collected during cesarean delivery 2 hours later was 60% that of maternal blood.¹ No adverse effects on embryo/fetal development were seen when tenofovir was given in doses up to 450 mg/kg/day to pregnant rats and 300 mg/kg/day to pregnant rabbits. When tenofovir was administered to pregnant rats in doses of 450-600 mg/kg/day, which are maternally toxic doses, peri- and postnatal development studies of their offspring showed reduced survival and slight delay in sexual maturation. However, there were no adverse effects on growth, development, behavior, or reproductive parameters when tenofovir was administered to pregnant rodents at doses that were not associated with maternal toxicity (150 mg/kg/day). Chronic exposure of fetal monkeys to tenofovir at a high dose of 30 mg/kg (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) from days 20-150 of gestation did not result in gross structural abnormalities.²⁸ Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible. In a different study, two of nine rhesus neonates receiving tenofovir in utero beginning on day 80 of gestation (via 30 mg/kg/d daily subcutaneous injections of gravid monkeys) and who continued chronic, high dose tenofovir (30 mg/kg/d) beginning on day 2 of life had evidence of drug-related bone toxicity at 2 and 7.5 months of age postnatally.²⁷ However, as noted earlier, chronic administration of *low* dose of tenofovir (10 mg/kg per day, giving exposure 18-fold higher than in an adult human receiving 300 mg daily TDF) to neonatal macaques starting at birth did not have any evidence of bone toxicity after >3.5 years of daily treatment.²⁵ The data from the macaque studies suggest that tenofovir -associated

bone abnormalities are associated with very high doses and prolonged treatment durations.

1.4 PRIOR RESEARCH: HUMAN TRIALS

No studies of TDF have been completed in pregnant women or neonates, although PACTG 394, a phase I pharmacokinetic study similar to HPTN 057 is underway in the US. The safety profile in humans for TDF is derived primarily from four clinical studies in HIV-1 infected adults and 2 in children. The adult trials involved approximately 1050 subjects who received TDF alone or in combination with other ARV agents for HIV treatment. The majority of clinical and laboratory adverse events were of mild intensity. The frequencies of these events in patients who received TDF were similar to those in patients receiving placebo.

In a randomized, double-blind, placebo-controlled, phase I/II trial, HIV-infected adults with HIV RNA $\geq 10,000$ copies/mL and CD4+ counts $\geq 200/\text{mm}^3$ were enrolled and studied at four different dosages, 75, 150, 300, or 600 mg as monotherapy for 4 weeks.²⁹ In each dose cohort, approximately eight patients received active drug and two received placebo. In the 75 mg cohort, an additional 5 patients were enrolled (4 active drug and 1 placebo) to confirm safety prior to dose escalation. Subjects received a single daily dose in the fasting state on day 1 followed by pharmacokinetic analysis. Drug was dosed with food on days 8 to 35. When compared to placebo, all dosages of TDF demonstrated reduction in viral load following completion of dosing. Following the single dose of 300 mg, the licensed adult daily dose of TDF administered on day 1, there was a 0.33 log₁₀ copies/mL reduction in viral load measured at day 4. The reduction in viral load after the chronic dosing phase was related to dose. At day 35, reductions were -0.33 log₁₀ for the 75 mg dose, -0.44 log₁₀ for the 150 mg dose, -1.22 log₁₀ for the 300 mg dose, and -0.80 log₁₀ for the 600 mg dose (ref). Serious adverse events included reversible elevations in creatinine kinase in 5 of 28 (18%) active vs. 1 of 7 (14%) placebo recipients. There was also exacerbation of pre-existing sensory neuropathies in 2 subjects (1 active drug and 1 placebo). One subject had an isolated rise in creatinine that returned to baseline on the following day. There was no demonstrated emergence of genotypic mutations in the HIV isolates harvested on day 35, as compared with baseline.²⁹

In another study, 189 ARV experienced patients with plasma HIV-1 RNA levels between 400 and 100,000 copies/mL and on stable ARV therapy (ART) were randomly assigned to add TDF, 75 mg, 150 mg, or 300 mg, or placebo.³⁰ Patients were assessed after 4, 24, and 48 weeks of blinded therapy. Reductions in baseline viral load were seen in all TDF groups with the 300 mg group demonstrating the greatest reduction (0.58 log at 24 weeks and 0.62 log at 48 weeks). Compared to placebo, TDF recipients had more diarrhea. Other adverse events, including renal function abnormalities, were not different between the groups.

Although there is no information about the safety and tolerance of an oral 900 mg dose of TDF, review of the available adult TDF pharmacokinetic data are reassuring that a single-dose of this size is likely to be safe. As discussed above, patients receiving oral doses of TDF of 75 to 600 mg daily for 28 days had few adverse events (5 events in 28 patients)

and there were no adverse events in 10 patients receiving the 600 mg dose. The AUC at 600 mg was 5.2 mcg/mL*hrs and was increased proportional to the lower doses. There is safety information available following administration of intravenous doses of 1 and 3 mg/kg to adults for 7 days. In this trial, eight patients at each dose level displayed no significant adverse events. The AUC for the 3 mg/kg dose was 22.5 mcg/mL*hr or approximately 4 times higher than with the 600 mg oral dose because the absorption fraction for TDF is approximately 25%. Thus a single dose of 900 mg given orally will have an AUC less than 50% of that shown to be safe when 3 mg/kg was given intravenously for 7 days.

Three phase I safety and pharmacokinetic trials of TDF in a small number of HIV-infected, treatment-experienced pediatric patients are ongoing in France and the US (studies 926, 927 and 983); two are chronic dosing studies and one is a single-dose study. In the US chronic dosing study, patients are receiving TDF at a dose of about 175 mg/m² body surface area once daily for 96 weeks; in the French chronic dosing study, patients receive TDF at a dose of about 5 mg/kg once daily. (Note that the 4 mg/kg dose of TDF to be used in HPTN 057 is lower.) Preliminary data indicate TDF exposure at these doses is similar to that in adults receiving 300 mg once daily. Lumbar spine densitometry measured by dual-energy absorptiometry (DEXA) scan is being evaluated in the US study. Over half of the 12 HIV-infected children had lumbar bone density that was at least 1 standard deviation from the norm at baseline prior to receiving TDF, indicating a high prevalence of background osteopenia. Preliminary data indicated a decrease in bone mineral density of >6% from baseline in 4 children at week 24. These data suggest that HIV-infected, treatment-experienced older children have a significant prevalence of osteopenia, and that chronic TDF treatment may exacerbate this in some children.²⁵

PACTG 394 was a phase I study initiated in 2004 in the US to evaluate the pharmacokinetics and safety of a single dose of TDF given to mother during labor and a single dose to the infant at age 24 hours. Pk and safety of 900 mg TDF alone plus 600 mg FTC (given as Truvada®) in mothers and 4 mg/kg TDF alone and plus 3 mg/kg FTC administered to their newborns. In conclusion, TDF is safe and demonstrated an acceptable absorption profile. Single dose TDF administration results in CB/M ratios of approximately 65% regardless of maternal dose. There was a trend to lower AUC (↓38%) and C_{max} (↓62%) in women delivering by vaginal delivery (n=9) compared to C-section (n=6) but sample size was small resulting in limited power. TFV C_{max} increased by 83% compared to 600 mg dosing but AUC was similar. TFV exposures were lower in infants suggesting either altered absorption or more rapid clearance. Single dose TDF did not result in detection of the K65R mutation in the 8 women who were assessed for resistance. However, the remaining 8 women and all of the infants had undetectable levels of viremia that precluded resistance testing. The appropriate dosing schedule in infants to maintain effective concentrations over the first days of life remains to be determined.³¹

HPTN 057 differs from PACTG 394 in that TDF for Cohorts 2 and 3 for infants will be given at birth, and at days 3 and 5, instead of only once at 24 hours post-partum. A fourth Cohort has been added in which TDF will be given to infants at birth (within 12

hours) for 7 days. Considering the pharmacology of TDF, the HPTN 057 regimen more closely replicates the HIVNET 012 intrapartum/neonatal regimen of NVP in duration of coverage (intrapartum through the first week of life). Importantly, HPTN 057 will also begin to explore whether there are any unusual toxicities or pk differences in these non-US populations in which a subsequent efficacy trial, if indicated, would be most appropriate and for which an intervention of this nature would be most applicable. Background nutritional deficits, dietary differences, and disease burden may alter the metabolism of and response to the study drug compared to that observed in US populations, making it important to evaluate the safety and pharmacokinetics in the populations for which the intervention is primarily targeted. The TDF regimen to be tested may be applicable to both developed and developing world settings for women who have not received any antenatal ART for reasons such as late presentation and lack of availability. Also, in many developing countries like Malawi, most HIV-infected women begin breastfeeding their infants soon after birth and, although the risk of breast milk transmission continues for the duration of breastfeeding, data indicate that the highest risk of breast milk transmission may be the first few weeks of life.³²⁻³⁵ While HPTN 057 is not designed to test a breastfeeding intervention, the regimen to be tested was chosen to closely replicate the two-dose neonatal/intrapartum regimen of NVP that significantly reduced the rate of mother to infant HIV transmission in a breastfeeding population in Uganda and that is now the standard of care in many resource limited settings. Also, in many countries - even those in which prenatal ART is available - a significant proportion of women do not present for pre-natal care (e.g. 20-30% in Brazil);^{36,37,38} therefore the proposed intrapartum/neonatal regimen of TDF would be relevant in these settings as well. Concurrent conduct of PACTG 394 in the US and HPTN 057 in non-US/developing country settings mirrors the evaluation path followed for NVP, which included PACTG 250 in the US and HIVNET 006 in Africa followed by HIVNET 012. Careful and expedient evaluation of a simple, inexpensive ARV regimen that has the potential to confer a similar level of protection as the two-dose intrapartum/neonatal regimen of NVP but without the same concerns regarding resistance is of highest priority for the populations at the greatest risk of mother to infant HIV transmission.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 PRIMARY OBJECTIVES

- (1) To evaluate the safety and tolerability of intrapartum/neonatal TDF in HIV-infected women and their infants.
- (2) To evaluate the pharmacokinetics of intrapartum/neonatal TDF in HIV-infected women and their infants and to determine maternal plasma exposure with a single dose of 600 mg and, if necessary, 900 mg.

2.2 SECONDARY OBJECTIVES

- (1) To evaluate the effect of a single dose of TDF on maternal HIV-1 RNA levels, and to determine if there is RNA rebound above baseline following washout of the drug in study participants at 5 to 7 days and 6 weeks postpartum.
- (2) To evaluate viral resistance to TDF in HIV isolates from maternal plasma, infant plasma and breastmilk.
- (3) To determine the infection status of participating infants.
- (4) To measure TDF concentration in amniotic fluid and breastmilk following maternal exposure to intrapartum TDF.

2.3 STUDY DESIGN

HPTN 057 is a Phase I, open-label, non-controlled study to evaluate the safety and pharmacokinetics of TDF administered to HIV-1 infected pregnant women in active labor and/or to their infants. The goal is to identify a simple intrapartum/neonatal regimen of TDF suitable for resource poor settings that would be appropriate for subsequent efficacy evaluation, if indicated. This study will include careful toxicity monitoring through clinical evaluation and laboratory monitoring of TDF in each group of study subjects, with special attention to possible development of renal and bone toxicity.

Three cohorts will be enrolled in approximately equal numbers at the two participating study countries (Malawi and Brazil), with no more than seven deliveries by elective caesarean section per cohort per country. The first two cohorts may be enrolled concurrently; the third will be enrolled after all mothers and infants in Cohorts 1 and 2 have reached six weeks postpartum and the safety and pk data from these cohorts have been carefully reviewed by the study team; any available data from PACTG 394 will also be considered.

Note: Cohort 4 was added after reviewing pk and safety data from Cohorts 1–3 (See Section 2.4) and will enroll an additional 30 mother/infant pairs in approximately equal numbers at the two participating countries (Malawi and Brazil). There is no restriction on the number of C-section deliveries for Cohort 4.

During the last trimester of pregnancy, women who have documented HIV infection based on the results of standard HIV testing and counseling services and who provide written informed consent will be screened for the study. Those found eligible on the initial screening tests will be asked to provide informed consent for study enrollment. Eligible, consenting women will then be enrolled upon presentation at study site for delivery. As standard of care, all women and infants will be offered the local standard ARV regimen for pMTCT in addition to the study TDF regimen to which they are assigned. In Brazil, the specific ARV regimen provided for pMTCT is the use of triple ART consisting of a protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs) or a NNRTI (NVP) and two NRTIs starting at 14 to 28 weeks of gestation. During labor, women are typically given IV AZT infusion and infants are

given six weeks of AZT initiated at birth. Women, who do not come for antenatal care, typically receive IV AZT during labor and six weeks of AZT to the infant initiated shortly after birth. In Malawi, the specific ARV regimen provided for pMTCT depends on when and if a women presents for antenatal care. Women who present for antenatal care are given AZT starting at 28 weeks. During labor women are typically given AZT + 3TC and single-dose NVP. Postpartum women are given AZT + 3TC for 7 days. All infants are given single-dose NVP at birth. Infants whose mothers started AZT at 28 weeks are given AZT for 7 days initiated at birth. Infants whose mothers did not start AZT at 28 weeks are given 4 weeks of AZT initiated at birth. Also, participants in HPTN 057 will not be precluded from receiving available HIV treatment, as described in Section 8.0.

In Cohort 1, women will receive a single oral dose of TDF 600 mg in active labor, defined as cervical dilation of > 3 cm or regular uterine contractions, or 4-hours prior to a scheduled C-section. Data from Cohort 1 will allow evaluation of the safety and pharmacokinetics of TDF in women following intrapartum dosing and in their newborns following transplacental TDF exposure. Maternal-fetal transport will be evaluated by the ratio of TDF concentration in cord blood and maternal samples obtained at delivery.

In Cohort 2, there will be no maternal TDF dosing. However, infants will receive a 4 mg/kg dose at birth (as soon as possible and no later than 12 hours after delivery), as well as, on Days 3 and 5 of life. Based on the TDF serum concentration time profiles from these infants, the TDF dose size and timing for infants in Cohort 3 may be modified. The data obtained from Cohort 2 will allow evaluation of safety and the absorption, distribution and elimination characteristics of TDF in newborns following administration immediately after birth and during the first week of life, when the infant is recovering from the rigors of labor and adapting to the extrauterine environment. A cohort with no maternal dosing is clinically relevant. Experience with implementation of the intrapartum/neonatal NVP regimen has shown that many infants are born before the maternal dose can be given. In this situation, the best alternative is to dose the neonate as soon as possible after birth. It is important to study TDF pharmacokinetics in the neonate under these circumstances, as there are no data describing the absorption of orally administered drugs to neonates immediately following the stress of delivery and during the period of adaptation to the extrauterine environment, both of which may compromise gastrointestinal function. In addition, TDF absorption is less rapid and less complete than that of NVP. It is not known whether, after TDF administration to a mother in labor, the rate of absorption and transfer across the placenta to the fetus will be rapid enough to achieve adequate fetal TDF concentrations before delivery. If not, then the way to get adequate TDF concentrations in the neonate as soon as possible after delivery may be direct administration to the neonate immediately after birth.

In Cohort 3, women will receive a single dose of TDF (dose size to be determined from Cohort 1 data) during active labor, defined as cervical dilation of > 3 cm or regular uterine contractions, or 4-hours prior to a scheduled C-section and infants will receive a dose of TDF as soon as possible after birth and no later than 12 hours after delivery, as well as, on Days 3 and 5 of life. Serial serum samples will be collected from mother,

infant and cord blood for evaluation of TDF pharmacokinetic parameters. The goal of Cohort 3 is to define a simple mother-infant TDF regimen that will maintain adequate fetal and newborn TDF exposure from labor through the end of the first week of life to protect against intrapartum and early postpartum/breast feeding HIV transmission. Based on cord blood levels and safety profile, the maternal dose of TDF may either remain the same or be increased to 900 mg in Cohort 3. Criteria for dose/regimen modification are specified in Section 2.3.1.

In Cohort 4, women will receive a single 600 mg dose of TDF (dose size was determined from data from Cohort 1 and 3 and PACTG 394) during active labor, defined as cervical dilation of > 3 cm or regular uterine contractions, or 4-hours prior to a scheduled C-section and infants will receive a dose of TDF as soon as possible after birth and no later than 12 hours after delivery, a second dose will be given within 16 to 32 hours after the first dose and then 5 additional doses will be given every 24 hours (+/- 2 hours). A serum sample will be collected from the mother at delivery and cord blood and serial serum samples will be collected from the infant at birth, after the fourth dose and after the seventh dose for evaluation of TDF pharmacokinetic parameters. The goal of Cohort 4 is to define a simple mother-infant TDF regimen that will maintain adequate fetal and newborn TDF exposure from labor through the end of the first week of life to protect against intrapartum and early postpartum/breast feeding HIV transmission.

In Cohorts 1, 3, and 4, TDF concentration following intrapartum maternal exposure will be measured in amniotic fluid among women delivering via elective C-section for further evaluation of placental transport and in breastmilk for those who choose to breastfeed.

Mothers and infants in all four cohorts will be closely followed for safety and toxicity through 12 months postpartum (See Schedules of Evaluations, Appendix I A and B). Women with detectable virus at 5-7 days and 6 weeks post-partum will have viral resistance testing performed. Should TDF virus resistance mutations be identified, duration of expression in these women will be measured thereafter at 6-month intervals. The 12 month duration of follow-up was chosen after careful consideration because lengthier follow-up would expose participants to additional participation/assessment risks beyond their utility is therefore not justified.

2.3.1 Criteria for Maternal Dose Adjustment in Cohort 3

An initial maternal intrapartum dose of 600 mg has been selected for Cohort 1. The rationale for selecting an initial dose higher than the current adult recommended daily dose of 300 mg is an anticipated lower absorption fraction, higher systemic clearance, and larger volume of distribution for women during pregnancy or labor as well as less than complete transfer across the placenta. The dose of 600 mg daily for up to 28 days in HIV-1 infected adults has been assessed in clinical trials with no increase in adverse events compared to lower doses, supporting the safety of a single maternal dose.²⁹

If no safety concerns arise, the maternal and cord blood serum concentrations sufficient for activity will determine whether the initial maternal dose will remain the same or increase to 900 mg in Cohort 3. Escalation to the higher dose will occur if the median value for infant 4-hour blood samples in Cohort 1 is <50 ng/mL. This threshold was selected based on safe and effective trough concentrations for HIV-infected adults receiving TDF 300 mg daily, serum concentrations consistent with antiviral activity, and estimates of achievable drug levels in cord blood. The efficacy of this threshold has not been demonstrated nor will it be assessed in this Phase I trial. Currently, there is no information about the safety and tolerance of a single 900 mg oral dose of TDF. However, there is safety information available on intravenous doses of 1 and 3mg/kg.³⁹ In that study, eight participants at each dose level displayed no significant adverse events. Relative AUC from the 300 mg and 600 mg oral doses of TDF were approximately 63% and 116% of that produced by the 1.0 mg/kg intravenous dose. Thus, a single oral dose of 900 mg would likely produce AUCs less than the 3 mg/kg intravenous dose that was not associated with significant adverse events.

2.3.2 Criteria for Infant Dose Adjustment in Cohort 3

The goal of Cohort 2 is to describe TDF pharmacokinetics in infants immediately after birth in the absence of maternal dosing. Maternal intrapartum oral TDF dosing may not provide adequate fetal exposure prior to delivery if TDF absorption is slow during labor and/or transplacental passage is poor. In addition, experience acquired from implementation of the two-dose mother-infant NVP regimen has demonstrated that many mothers deliver before the maternal intrapartum dose can be administered. While administration of an oral NVP dose to the infant as soon as possible after birth has been advocated as providing the earliest possible protection to the infant, no PK data are available describing the rate and extent of NVP absorption and distribution during this period of adaptation to the extrauterine environment and of recovery from the physiologic stress of labor and delivery. Cohort 2 will provide these data for TDF.

Maintenance of infant serum concentrations of TDF above 50 ng/mL throughout the first week of life is the goal. If this level is not maintained in six or more of the 20 infants in Cohort 2, the dose in Cohort 3 may be increased to 6 mg/kg.

In addition to data from Cohorts 1 and 2, any available maternal and infant data from PACTG 394 will also be considered before proceeding to Cohort 3 in HPTN 057.

2.4 PK AND SAFETY DATA FROM COHORTS 1-3: RATIONALE FOR COHORT 4

Cohorts 1-3 enrolled a total of 89 mother/infant pairs - 30 in Cohort 1, 23 in Cohort 2, and 36 in Cohort 3. The safety and toxicity data from these cohorts have been followed routinely by the HPTN 057 Protocol Safety Review Team (PSRT) and was evaluated by

the HPTN Study Monitoring Committee (SMC) in August 2007 and February 2008. No safety concerns have been identified by either the PSRT or the SMC.

Summaries of the maternal pk parameters and the TDF concentrations in maternal blood at delivery and in cord blood from Cohorts 1 and 3 are presented in Tables 1 and 2:

Table 1: Mean (SD) Maternal PK Parameters

| Dose | Tmax (hrs) | Cmax (ng/mL) | t _{1/2} (hrs) | AUC _{0-∞} (ng*hr/mL) |
|---|------------|---------------|------------------------|-------------------------------|
| 600 mg | 2.0 (1.6) | 480.0 (199.3) | 19.5 (4.2) | 4979.0 (3950.5) |
| 900 mg | 2.9 (2.4) | 489.2 (224.2) | 17.3 (3.8) | 5627.6 (1682.8) |
| Nonpregnant Adults - 300 mg ³⁹ | 3.0 | 303 | 13.7 | 2937 |

Table 2: Maternal Delivery and Cord Blood TDF Concentrations (ng/mL)

| | Cohort 1 (600 mg) | | | Cohort 3 (900 mg) | | |
|---------------------|-------------------|-------|----|-------------------|-------|----|
| | mean | SD | n | mean | SD | n |
| Maternal Delivery | 156.4 | 135.2 | 30 | 209.8 | 131.4 | 30 |
| Cord Blood | 77.6 | 57.7 | 29 | 133.6 | 106.0 | 31 |
| Cord:Maternal Ratio | 0.57 | .34 | 27 | 0.62 | 0.54 | 30 |

Infant pk parameters and a plot of the median infant TDF concentrations for Cohort 2 (no maternal dosing and 4 mg/kg infant doses) are presented in Table 3:

Table 3: Mean (SD) Infant PK Parameters – Cohort 2 (4 mg/kg doses)

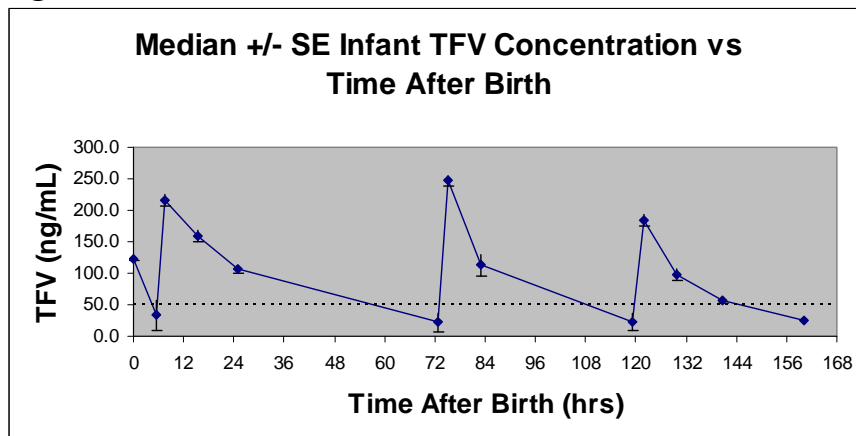
| | Day 0 (n=21) | Day 3 (n=21) | Day 5 (n=20) | Adults 300 mg qd (median) [†] |
|-------------------------------|--------------|--------------|--------------|--|
| Tmax (hr) | 3.7 (3.4) | 6.5 (9.5) | 4.3 (4.4) | 3.0 |
| Cmax (ng/ml) | 220.0 (99.3) | 110.4 (81.5) | 99.9 (58.3) | 303 |
| AUC _{0-τ} (ng*hr/ml) | 4795 (1907) | 2805 (1695) | 2006 (1063) | 2937 |
| t _{1/2} (hrs) | 27.1 (22.0) | 21.6 (9.0) | 23.5 (14.6) | 13.7 |
| # with trough <50 ng/mL | 19 | 18 | 18 | ----- |

Infant pk parameters and a plot of the median infant TDF concentrations for cohort 3 (900 mg maternal doses and 6 mg/kg infant doses) are presented below in Table 4 and Figure 1:

Table 4: Mean (SD) Infant PK Parameters – Cohort 3 (6 mg/kg/doses)

| | Day 0 (n=34) | Day 3 (n=31) | Day 5 (n=31) | Adults 300 mg qd (median) [†] |
|-------------------------------|---------------|---------------|---------------|--|
| Tmax (hr) | 5.3 (3.5) | 3.4 (2.8) | 3.2 (2.5) | 3.0 |
| Cmax (ng/ml) | 292.4 (175.0) | 256.7 (148.4) | 204.5 (121.1) | 303 |
| AUC _{0-τ} (ng*hr/ml) | 5723 (2180) | 3728 (1625) | 3002 (1282) | 2937 |
| T1/2 (hrs) | 23.2 (5.0) | 17.1 (4.0) | 18.1 (5.0) | 13.7 |
| # with trough <50 ng/mL | 32 | 29 | 27 | ----- |

Figure 1:



As can be seen from these data, maternal TDF exposure was very similar with either 600 mg or 900 mg intrapartum doses and exceeded TDF exposure seen with single 300 mg doses in nonpregnant adults⁴⁰. The infant data show that the infants eliminated TDF nearly as fast as adults, and almost all infants in Cohorts 2 and 3 had trough TDF concentrations below 50 mg/mL, the trough concentration target for the protocol. These data suggest that daily infant dosing will be necessary in order to exceed the trough concentration target. Therefore an additional cohort of mothers and infants will be enrolled with maternal intrapartum dosing of 600 mg and daily infant dosing of 6 mg/kg for 1 week.

Cohort 4 will be modeled after the recently completed Cohort 3 in terms of number of mother-infant pairs (n=30), pk sampling scheme, safety and other assessments, visit schedule and duration of follow-up, with the only major difference being the change in infant dosing to daily dosing for 1 week.

3.0 STUDY POPULATION

A total of 110 fully evaluable mother/infant pairs will be enrolled including a total of 30, 20, 30 and 30 in each of the four study cohorts, respectively.

Mother/infant pairs will be enrolled in approximately equal numbers across the two sites – with about half of each cohort in Brazil and half in Malawi. A fully evaluable mother/infant pair is defined as one for which a complete set of pk samples is obtained as specified in Section 5.6 and in the Schedules of Evaluations (Appendix I A and B).

For Cohorts 1 and 3, no more than seven women with a scheduled Caesarean section may be enrolled in each cohort per country. As Cohort 2 involves only infant dosing, route of delivery will not be a consideration for enrollment. There is no restriction on the number of Caesarean section deliveries in Cohort 4.

3.1 INCLUSION CRITERIA FOR WOMEN

- ≥ 18 years of age
- Documented HIV-1 infection
- Willing and able to provide written informed consent for screening and study participation
- Stated intent to deliver at the study site
- Stated willingness to be contacted or visited at home
- Stated willingness to be admitted to and remain in delivery facility through Day 3 postpartum (Cohort 1)
- Stated willingness to be admitted to and remain in delivery facility through Day 7 postpartum (Cohorts 2, 3, and 4)

3.2 EXCLUSION CRITERIA FOR WOMEN

- Prior treatment with TDF
- Active opportunistic infection and/or serious bacterial infection
- Laboratory values as follows on the most recent test prior to study entry: hemoglobin < 8 gm/dL, alanine aminotransferase (ALT [SGPT]) > 3 x upper limit of normal (ULN), serum creatinine > 1.5 mg/dL
- Chronic malabsorption or diarrhea during current pregnancy, according to WHO definitions
- Evidence of clinically significant disease or condition that would compromise the ability of the participant to complete the study or the study requirements as determined by the study clinician
- Known multiple gestation this pregnancy (prior to enrollment)
- Participation in any other therapeutic or vaccine trial during the current pregnancy
- Use of any of the following disallowed medications within two weeks of anticipated delivery date: investigational agents, heparin, highly nephrotoxic drugs (such as amphotericin B, cidofovir, ganciclovir, or valganciclovir), or dideoxyinosine.
- Use of atazanavir or lopinavir/ritonavir (Kaletra®) within 2 weeks of anticipated delivery date (Cohorts 1, 2 and 3)
- Any other condition or situation that, in the opinion of the investigator, would interfere with study participation or interpretation.

Note: Mothers found eligible during screening based on the criteria above will not be enrolled until presentation in active labor for delivery. If at that time, any of the above conditions are known to be present (developed since initial screening assessments), based

on medical history since and lab results from the previous screening visit the mother will not be enrolled. However, a physical examination and results of tests on specimens obtained at the labor and delivery visit are not required for eligibility determination.

Note: If the mother in Cohort 1 is not dosed with the study drug for any reason, then the mother infant/pair will be terminated from the study, and no further assessments will be done. If the infant in Cohort 2 does not receive the first study drug dose then the mother/infant pair will be terminated from the study and no further assessments will be done. If the mother in Cohort 3 or 4 is not dosed with the study drug for any reason then infant will not be dosed and the mother infant/pair will be terminated from the study, and no further assessments will be done. All mothers and infants exposed to study drug will remain in the study throughout the follow-up period for safety monitoring even if study drug dosing is discontinued early.

Note: While stated willingness to remain in the hospital for the period specified above is a criterion for inclusion and is the goal, it is acknowledged that there may be circumstances in which the woman and/or infant may need to be discharged early. This will not disqualify a woman or infant from further participation in the study. In such a case, every effort would be made to have the participants return to the site for completion of the scheduled assessments.

Note: For Cohorts 1 and 3, if the maximum allowed number of caesarean section deliveries (7) has been reached for a country, and an enrolled mother who received study drug has a previously unscheduled caesarean section, the mother and her infant will remain in the cohort into which she was enrolled and have all scheduled assessments including collection of pk specimens. This mother/infant pair will not count toward the target number of vaginal deliveries in the cohort.

3.3 INCLUSION CRITERION FOR INFANTS

- Born to HIV-infected mother enrolled in the study

3.4 EXCLUSION CRITERIA FOR INITIAL INFANT DOSING (COHORTS 2, 3, AND 4)

- Birth weight <2000 gm
- Severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the examining clinician
- Grade 2 or higher serum creatinine level or any other Grade 3 or higher toxicity if known prior to dosing. (Note: test results not required prior to dosing initiation).
- Multiple birth

3.5 RECRUITMENT PROCESS

As standard of care (outside of the study), all women presenting for antenatal care at the participating sites will be offered HIV counseling and testing by a trained nurse/counselor

or physician. Also as standard of care, HIV-1 infected women will be offered the local standard ARV regimen for pMTCT transmission (described in Section 2) and counseled about the risks and benefits of breastfeeding.

Screening for the study will proceed in a stepwise manner over two or more clinic visits and will include assessment of medical history, physical exams and laboratory tests. Written informed consent for initial screening (Appendix IIA for Cohorts 1-3) and Appendix IIC for Cohort 4) - including confirmatory HIV testing if documentation is not already available - will be obtained before any study specific screening procedures are undertaken. Informed consent for screening may be obtained any time during pregnancy; however, protocol-specified clinical and laboratory screening tests must be performed during the last trimester. Women who meet the initial eligibility criteria and remain interested in participating in the study will receive intensive study informed consent counseling, including detailed information on the study procedures, risks and benefits. If the woman agrees to participate in the study, she will be asked to provide written informed consent for final screening procedures and study enrollment (Appendix IIB for Cohorts 1-3 and Appendix IID for Cohort 4). If at any point during this process, a mother is found ineligible, screening will be discontinued.

Only consenting, eligible women who present at the study facility for labor and delivery will be enrolled in the study. Therefore, the point of enrollment will be considered the time of presentation for delivery. If any exclusionary condition becomes known before or at the time of presentation for delivery, the woman will not be enrolled; however, eligibility assessments are not expected to be repeated at that point.

Women may be enrolled in Cohorts 1 and 2 concurrently however for logistical and procedural simplicity, Cohort 1 will be opened at each site first. If the quota of C-section deliveries in Cohort 1 has been met, then eligible consenting women scheduled to deliver by C-section may be enrolled in Cohort 2 while Cohort 1 remains open for vaginal deliveries. Cohort 3 will be enrolled after all mothers and infants in Cohorts 1 and 2 have reached six weeks postpartum and the safety and pk data from these cohorts have been carefully reviewed by the study team; any available data from PACTG 394 will also be considered.

Cohort 4 will be open for enrollment after Cohorts 1, 2 and 3 have completed follow-up. The safety and pk data from Cohorts 1 – 3 were reviewed by the study team indicating a need to enroll a fourth cohort to reach the target trough TDF concentrations. Please see Section 2.4.

Study screening, enrollment and follow-up procedures are outlined in Section 5 and Schedules of Evaluations (Appendix I A and B) and will be detailed in the study-specific procedures (SSP) manual.

3.6 CO-ENROLLMENT GUIDELINES

The eligibility criteria specified above preclude participation of women who have been enrolled in any other therapeutic or vaccine trial during the current pregnancy and those

using investigational agents within two weeks of the anticipated delivery date. During follow-up, co-enrollment in other trials of investigational agents that may interfere with participation in or interpretation of HPTN 057 will be discouraged, but cannot be prohibited. For example, an HPTN 057 participant would not be prevented from joining another study through which proven treatment to which she would otherwise not have access is provided. Regardless, all mothers and infants exposed to study drug will be asked to continue follow-up in HPTN 057 as scheduled, even if the study dosing regimen is not completed or if they enroll in another study.

Note: All mothers and HIV-infected infants may receive ARV (excluding dideoxyinosine within two weeks of anticipated delivery date) or other available therapy for treatment of HIV/AIDS and related illnesses. For Cohorts 1 – 3 mothers will be excluded if they receive atazanavir or lopinavir/ritonavir (Kaletra[®]) within 2 weeks of anticipated delivery date. Receipt of ARVs and all other concomitant medications will be recorded in the participant's study records.

3.7 PARTICIPANT WITHDRAWAL/EARLY TERMINATION

A mother may withdraw herself or her child from the study at any time for any reason. Extensive follow-up procedures used successfully in other studies at the sites will be employed to maximize study retention and schedule adherence. Participants may be withdrawn from the study if the study sponsor or local government or regulatory authorities terminate the trial prior to its planned end date.

The site investigator also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, the NIAID and US National Institute of Child Health and Development (NICHD) Medical Officers, and the Protocol Statistician.

If a mother in Cohort 1, 3, or 4 is not dosed with the study drug for any reason, then the mother/infant pair will be terminated from the study and no further assessments will be done. If an infant in Cohort 2 does not receive the first dose of study drug as scheduled, then the mother/infant pair will be terminated from the study and no further assessments will be done. If an infant who receives the study drug in Cohort 2 dies before the end of the scheduled follow-up period, his/her mother will be terminated from the study and no further assessments will be done.

All participants exposed to the study drug will be asked to remain in the study and complete follow-up as scheduled, even if the study drug regimen is not completed for any reason.

4.0 STUDY PRODUCT

4.1 STUDY PRODUCT REGIMEN

Eligible women and their infants will be enrolled in one of four cohorts as outlined below. (Note: Cohort 4 was added after Cohorts 1 -3 completed follow-up.) Irrespective of and outside of this Phase I study of TDF, all participating women and infants will be offered the local standard of care ARV regimen for pMTCT as described in Section 2.0.

| | <i>Maternal Dosing Regimen</i> | <i>Infant Dosing Regimen</i> |
|--------------------|--|---|
| Cohort 1 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section. | The infant will not receive study drug. |
| Cohort 2 N = 20 | The mother will not receive study drug. | 4 mg/kg of the TDF oral suspension at birth. The dose must be administered as soon as possible; within 12 hours of birth. Repeat the dose on Days 3 and 5 of life. |
| Cohort 3 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section* | 4 mg/kg of the TDF oral suspension at birth. The dose must be administered as soon as possible; within 12 hours of birth**. Repeat the dose on Days 3 and 5 of life. |
| Cohort 4 N = 30 | Single 600 mg oral dose of TDF at onset of labor defined as cervical dilation of > 3 cm or regular uterine contractions or 4 hours prior to a scheduled C-section | 6 mg/kg of the TDF oral suspension for 7 days initiated at birth. The birth dose must be administered as soon as possible; within 12 hours of birth. The second dose must be administered within 16 to 32 hours after the birth dose and five subsequent doses should be administered daily (every 24 hours +/- 2 hours). |

*dose may be adjusted to 900 mg based on results of cohort 1

**dose may be adjusted to 6 mg/kg based on results of cohort 2

4.2 STUDY PRODUCT ADMINISTRATION

For the mothers in Cohorts 1 and 4, the 600 mg dose will be administered as two- 300mg tablets of TDF by study staff with two ounces milk or nutritional supplement.

Depending on the results of the first two cohorts, the mothers in Cohort 3 will receive a 600 mg dose or a 900 mg dose. The 900mg dose will be administered as three- 300mg tablets of TDF. The dose will be administered by the study staff with two ounces milk or nutritional supplement.

For the infants in Cohorts 2, 3 and 4 the TDF oral suspension will be administered to infants by study staff with a feeding; using an oral syringe calibrated in 0.1 mL increments.

The exact volume of suspension to be administered for Cohort 2 will be based on body weight of 4 mg/kg.

Depending on the results of Cohort 2, the dose administered to the infants in Cohort 3 will be based on the body weight of 4 mg/kg or may be increased to 6 mg/kg.

Based on the results of Cohorts 2 and 3, the dose administered to infants in Cohort 4 will be based on body weight of 6 mg/kg.

If there is a problem with dosing of the mother in Cohort 1, 3 or 4 (e.g. she vomits within 1 hour of dosing or does not deliver within 24 hours of dosing) the infant will not be dosed. If one scheduled infant dose is missed (Cohorts 2, 3 and 4) due to toxicities (as specified in Section 4.6.1) or for any other reason, all further dosing will be permanently discontinued.

For Cohort 4, if an infant vomits within 1/2 hour of study drug administration on a pk sampling day then the infant should not be re-dosed and no further dosing or sampling should be done. If an infant vomits within 1/2 hour of study drug administration on a non-pk sampling day then he/she should be re-dosed one time and continue with dosing and pk sampling as scheduled.

4.3 STUDY PRODUCT FORMULATION

TDF for the mothers in Cohorts 1 and 3 were supplied as 300 mg tablets in blister packs. The TDF tablets for the mothers in Cohort 4 will be supplied as 300 mg tablets in bottles. The TDF tablets must be stored in its original packaging at 25°C (75°F), with excursions permitted 15°-30°C (59° - 86°F). Detailed instructions for the dispensing of the TDF oral tablets will be provided in the SSP manual.

TDF for infants will be supplied as a powder for oral suspension, packaged in a natural high-density polyethylene (HDPE) bottle. TDF powder should be refrigerated at 2°- 8° C (36°- 46°F). After reconstitution, final concentration is 20 mg/mL of oral suspension and is refrigerated at 2°- 8° C (36°- 46°F). The suspension is stable for 30 days. Detailed instructions for the preparation and dispensing of the TDF oral suspension will be provided in the SSP manual.

4.4 PRODUCT SUPPLY AND ACCOUNTABILITY

Study product will be supplied by Gilead Sciences Inc. and will be prepared and shipped to the study sites by the NIAID Clinical Research Products Management Center (CRPMC). Instructions for obtaining the study product on site will be provided in the *Pharmacy Guidelines and Instructions for Division of AIDS (DAIDS) Clinical Trials Networks*. The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed. All unused study products must be returned to the CRPMC after the study is completed or terminated, unless otherwise instructed by the sponsor. The procedures to be followed are in the

Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks and will be detailed in the study-specific procedures manual.

4.5 ADHERENCE ASSESSMENT

Assessment of adherence will be through documentation of direct observation (all doses will be administered at the study facility by study staff) and by evaluation of TDF serum concentration levels in study participants.

4.6 TOXICITY MANAGEMENT/SEVERITY GRADING

The severity (the clinician’s evaluation of intensity) of all adverse events (AEs) will be classified based upon the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 and Clarification dated August 2009 (which can be found at the following website address: <http://rcc.tech-res.com>) with the following exception: calcium which will be graded using the following parameters which include correction for albumin:

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE- THREATENING |
|--|---|---|--|--|
| Calcium, serum, high (corrected for albumin) | | | | |
| Adult and Pediatric ≥ 7 days | 10.6 – 11.5 mg/dL 2.65 – 2.88 mmol/L | 11.6 – 12.5 mg/dL 2.89 – 3.13 mmol/L | 12.6 – 13.5 mg/dL 3.14 – 3.38 mmol/L | > 13.5 mg/dL > 3.38 mmol/L |
| Infant*†, < 7 days | 11.5 – 12.4 mg/dL 2.88 – 3.10 mmol/L | 12.5 – 12.9 mg/dL 3.11 – 3.23 mmol/L | 13.0 – 13.5 mg/dL 3.245 – 3.38 mmol/L | > 13.5 mg/dL > 3.38 mmol/L |
| Calcium, serum, low (corrected for albumin) | | | | |
| Adult and Pediatric ≥ 7 days | 7.8 – 8.4 mg/dL 1.95 – 2.10 mmol/L | 7.0 – 7.7 mg/dL 1.75 – 1.94 mmol/L | 6.1 – 6.9 mg/dL 1.53 – 1.74 mmol/L | < 6.1 mg/dL < 1.53 mmol/L |
| Infant*†, < 7 days | 6.5 – 7.5 mg/dL 1.63 – 1.88 mmol/L | 6.0 – 6.4 mg/dL 1.50 – 1.62 mmol/L | 5.50 – 5.90 mg/dL 1.38 – 1.51 mmol/L | < 5.50 mg/dL < 1.38 mmol/L |

Note: The measurement of albumin is only for determination of severity grade for calcium levels, which calls for correction for albumin. Corrected calcium levels will be monitored for safety, therefore, separate reporting of AEs for albumin is not required.

In addition, grading of malnutrition (failure to thrive) will follow the scale below:

- Grade 1 - Underweight: 60-80% of the 50th percentile expected weight for age *and* edema absent
- Grade 2 - Marasmas: <60% of 50th percentile expected weight for age *and* edema absent
- Grade 3 - Kwashiorkor: 60-80% of the 50th percentile expected weight for age *and* edema present
- Grade 4 - Marasmic-kwashiorkor: <60% of 50th percentile expected weight for age *and* edema present

Axillary measured fever will be graded as follows:

Grade 1: 37.1 - 38.0 °C
Grade 2: 38.1 - 38.7 °C
Grade 3: 38.8 - 39.9 °C
Grade 4: >39.9 °C

Any exceptions to the severity grading procedures specified above must be approved by the sponsor and the Institutional Review Boards (IRBs)/ethics committees (ECs) in advance of implementation. When grading laboratory values, normal limits will be defined according to local age-specific institutional values.

All abnormal clinical events and laboratory values occurring in enrolled mothers and infants will be followed closely. The urgency and frequency of repeat evaluations will depend on the clinical significance of the specific abnormality. Study clinicians will provide appropriate clinical management of AEs according to their best medical judgment and local practice. For grade 3 or 4 laboratory abnormalities, repeat evaluations will be performed within 3 days, if possible. If any grade 3 or 4 clinical or laboratory abnormality is thought to be potentially due to the study drug, evaluations should be repeated approximately weekly until toxicity falls below grade 2.

Because the duration of TDF regimen being used in this study is very short, study drug treatment in an individual will either be continued as specified or permanently discontinued; there will be no dose adjustment in individuals and no resumption of treatment if interrupted due to occurrence of a toxicity as specified below or for any other reason. Neither mothers nor infants will be re-dosed for any reason (e.g. if they vomit shortly after dosing).

4.6.1 Toxicity Criteria for Permanent Study Drug Discontinuation in Infants

Study drug dosing will be permanently discontinued in infants with a grade 2 or higher serum creatinine level or any Grade 3 or Grade 4 clinical or laboratory adverse event, regardless of relatedness.

For Grade 1 or 2 adverse events (other than Grade 2 serum creatinine adverse event), no interruption in the study dosing is necessary, even if possibly related, unless otherwise directed by the Protocol Safety Review Team (PSRT), as described in Section 6.1.

All mothers and infants exposed to the study will be asked to remain in the study for the full follow-up period, even if study drug dosing is discontinued early for any reason; they will undergo all scheduled follow-up procedures and assessment with the exception of pk sampling which will be discontinued following the first missed dose.

Additional safety monitoring procedures are specified in Section 6.1.

4.7 CONCOMITANT MEDICATIONS

All mothers (Cohorts 1-4) who use any of the following medications within two weeks of anticipated delivery date: investigational agents, heparin, highly nephrotoxic drugs (such as amphotericin B, cidofovir, ganciclovir, or valganciclovir), or dideoxyinosine will not be enrolled. In addition Mothers in Cohorts 1 – 3 who receive atazanavir or lopinavir/ritonavir (Kaletra[®]) within two weeks of anticipated delivery date will not be enrolled. Enrolled participants may receive all medications needed for their health throughout the follow-up period; however, if a participant needs one of the following medications during the study drug dosing period the study drug would be discontinued: heparin, highly nephrotoxic drugs (such as amphotericin B, cidofovir, ganciclovir, or valganciclovir) or dideoxyinosine and in addition for cohorts 1 – 3 atazanavir or lopinavir/ritonavir (Kaletra[®]).

All medications taken by mothers within 2 weeks before delivery and by mothers and infants through the duration of follow-up will be recorded in the participant's source records and on DataFax Case Report Forms for entry into the study database. In addition to prescribed and over-the-counter medication, vitamins, herbal remedies, and other traditional preparations will be recorded.

5.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule for mothers and infants is presented in Schedules of Evaluations (Appendix I A and B). Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in a SSP manual.

Note: For the purposes of visit and assessment scheduling, time and day of birth are considered Time 0 and Day 0, respectively. Visit and assessment windows will be specified in the study-specific procedures manual.

5.1 MATERNAL SCREENING EVALUATIONS

5.1.1 Maternal Screening Evaluations (anytime during pregnancy, ideally in the last trimester)

Clinical Evaluations

- Screening consent (prior to any screening evaluations)
- Demographics

Laboratory Evaluations

Confirmatory HIV Test, if documented confirmation is not available

5.1.2 Maternal Screening Evaluations: ≥ 34 weeks gestation

Clinical Evaluations

- Enrollment informed consent (may be completed prior to this time)
- Medical/Obstetric History
- Full Physical Exam

Laboratory Evaluations

- Complete blood count (CBC) with differential and platelet count
- Chemistries (bilirubin, aspartate aminotransferase (AST), ALT [SGPT], creatinine, calcium, albumin, phosphorus, alkaline phosphatase)
- HIV RNA PCR
- Plasma Storage for TDF resistance testing

5.2 MATERNAL ENROLLMENT EVALUATIONS: LABOR AND DELIVERY

Note: Mothers who have consented and are determined to be eligible will be enrolled at the time of presentation for delivery. If at that time, any of the conditions specified in Section 3.2 are known to be present (i.e. developed since initial screening assessments), based on medical history since and lab results from the previous screening visit the mother will not be enrolled. However, a physical examination and results of tests on specimens obtained at the labor and delivery visit are not required for eligibility determination. See Section 3.4 for exclusion criteria for initiation of infant dosing.

Clinical Evaluations

- Interim medical history

Laboratory Evaluations

- CBC with differential and platelet count
- CD4+ cell count
- Chemistries (bilirubin, AST, ALT [SGPT], creatinine, calcium, albumin, phosphorus, alkaline phosphatase)
- HIV RNA PCR (collected during active labor, prior to TDF dosing)
- Amniotic fluid storage for TDF concentration (only from mothers who deliver by C-section)
- Plasma Storage for TDF resistance testing
- Pharmacokinetics sampling as specified in Section 5.6.

5.3 POST-DELIVERY EVALUATIONS

5.3.1 Infant Birth and Follow-up Evaluations

Clinical Evaluations

- Birth and neonatal medical history (prior to dosing in Cohorts 2 and 3; within 24 hours of birth in Cohort 1)
- Interim medical history (3 and 5-7 days; 6 and 12 weeks; 6, 9, and 12 months)
- Physical Exam (prior to dosing in Cohorts 2 and 3 and within 24 hours of birth in Cohort 1 then at 3 and 5-7 days; 6 and 12 weeks; 6, 9, and 12 months)

Laboratory Evaluations

- CBC with differential and platelet count (within 24 hours of birth; 5 -7 days; 6 and 12 weeks)
- Chemistries [bilirubin, AST, ALT [SGPT], creatinine, calcium, albumin, phosphorus, alkaline phosphatase] (at birth within 24 hours; 5-7 days; 6 and 12 weeks)
- HIV DNA or RNA PCR (at birth within 24 hours; 5-7 days; 6 and 12 weeks (and 6 and 12 months-if breastfeeding)). If positive confirm with a HIV DNA PCR or RNA PCR on a different specimen
- Plasma Storage for TDF resistance testing (at birth within 24 hours; 5-7 days; 6 and 12 weeks; and 6 and 12 months)
- Dried Blood Spot Storage (at birth within 24 hours; 5-7 days; 6 and 12 weeks; and 6 and 12 months)
- Radiologic bone assessments [X-rays of thoracic spine and left wrist] (at 3 days \pm 2 days; and 3 months) – Cohorts 1, 2, and 3 only)
- Pharmacokinetics sampling as specified in Section 5.6.

5.3.2 Maternal Post-Delivery Follow-up Evaluations

Clinical Evaluations

- Interim medical history (at 24 to 48 hours; 5 to 7 days; 6 and 12 weeks; and 6 and 12 months)
- Symptom directed physical exam (at 24 to 48 hours; 5 to 7 days; 6 and 12 weeks; and 6 and 12 months)

Laboratory Evaluations

- CBC with differential and platelet count (at 24 to 48 hours; 5 to 7 days; and 6 weeks)
- Chemistries [bilirubin, AST, ALT [SGPT], creatinine, calcium, albumin, phosphorus, alkaline phosphatase] (at 24 to 48 hours; 5 to 7 days; and 6 weeks)
- HIV RNA PCR (at 5 to 7 days; 6 and 12 weeks, 6 and 12 months postpartum)
- Plasma Storage for TDF resistance testing (at 5 to 7 days; 6 and 12 weeks; and 6 and 12 months)
- Breastmilk Storage for TDF concentration and viral studies [breastfeeding mothers only] (at 24 to 48 hours; 5 to 7 days; and 6 and 12 weeks)

- Pharmacokinetics sampling as specified in Section 5.6.

5.4 RESISTANCE TESTING

Resistance testing will be performed retrospectively (not in real time) and results will not be routinely provided to study participants. While mothers and infants may have access to ART through local programs, patient management in these settings depends on prospective evaluation of HIV viral load and other laboratory markers, clinical evaluation, and adherence behavior. Resistance testing is not performed for patient management as a standard of care, nor is it clear that this technology could be used cost-effectively in these settings in the future. In addition, interpretation of resistance testing in a population is complex because: 1) not all genotypic resistance is associated with phenotypic resistance, 2) the magnitude of resistance observed in different countries where ART is used is changing rapidly and in some cases in unexplained ways, 3) resistant variants may on occasion be less fit for transmission or less pathogenic, 4) continued ART in the face of resistance may have a salutary effect, 5) resistant variants cannot be easily detected in the absence of selective pressure, and their re-emergence at a later time is only now being studied; and 6) resistance mutations have been characterized predominantly in subtype B; there is less information about how to interpret resistance mutations in other subtypes.

5.5 RADIOLOGIC BONE ASSESSMENTS

DEXA scan is not readily available in the HPTN 057 study sites and is not indicated with the short duration of study drug dosing. Standard radiologic bone assessments (X-rays) of thoracic spine and left wrist will be performed in infants in Cohorts 1-3. These radiologic assessments will be done at two timepoints only to minimize infant exposure. Radiologic bone assessments will be read locally, in real-time, and any abnormalities identified will be treated according to the local standard of care. However, assessments for the study endpoint will be batched and read centrally by a single pediatric radiologist in the US, so that the assessments will be standardized.

5.5.1 Radiologic Bone Assessment Data from Cohorts 1 – 3

Standard radiologic bone assessments (X-rays) of thoracic spine and left wrist were performed for Cohort 1-3 infants at birth and at 3 months of age. X-ray abnormalities were present in 7/52 (13.5%) of infants at birth and 13/51 (25.4%) at 3 months. One infant had periosteitis on X ray and serologic findings of congenital syphilis. Other abnormalities seen were osteopenia, metaphyseal lucencies and abnormal bone age. These findings were thought to be related to nutritional and environmental factors. No fractures or findings with clinical repercussions were seen except for the case of congenital syphilis, which was serologically diagnosed before the X-ray interpretations were available. The lack of standards for normal wrist and spine X rays and bone age assessments for Brazilian and Malawian infants at these ages limited the usefulness of the Cohort 1-3 X- rays. Since the X-rays were difficult to interpret and were of limited value in assessing TDF bone toxicity, wrist and spine X rays will not be performed on the Cohort 4 infants.

5.6 PHARMACOKINETICS SAMPLING

5.6.1 Maternal (Cohort 1)

Before dosing (pre-dose), at + 1, 2, 4, 8, 12, 18 to 24, and 36 to 48 hours post dose and at delivery. The pre-dose sample should be collected < 1 hour before dosing. If collection of the pre-dose sample falls within one hour of another scheduled pk specimen collection time point, the previously scheduled specimen need not be collected.

5.6.2 Maternal (Cohort 2)

No pharmacokinetics sampling will be performed.

5.6.3 Maternal (Cohort 3)

If 600 mg: Delivery only

If 900 mg: Before dosing (pre-dose), at + 1, 2, 4, 8, 12, 18 to 24, and 36 to 48 hours post dose and at delivery. The pre-dose sample should be collected < 1 hour before dosing. If collection of the pre-dose sample falls within one hour of another scheduled pk specimen collection time point, the previously scheduled specimen need not be collected.

5.6.4 Maternal (Cohort 4)

Delivery only

5.6.5 Infant (Cohort 1)

Cord blood sample and +4, 12, 18 to 24, 36 to 48 hours post delivery.

5.6.6 Infant (Cohort 2)

Birth: Cord blood sample, before dosing (pre-dose) and +2, 10, 18 to 24 hours post dose. Cord blood sample may serve as pre-dose sample if the initial TDF dose is given ≤ 2 hours after birth. If the initial TDF dose will be given > 2 hours after birth then a separate pre-dose sample should be collected ≤ 1 hour before dosing. If the cord blood specimen is not obtained then the pre-dose sample should be collected < 1 hour before dosing.

Day 3: Before dosing (pre-dose) and +2, 10 hours post dose. The pre-dose sample should be collected < 1 hour before dosing.

Day 5: Before dosing (pre-dose) and +2, 10, 18 to 24, 36 to 48 hours post dose. The pre-dose sample should be collected < 1 hour before dosing.

5.6.7 Infant (Cohort 3)

Birth: Cord blood sample, before dosing (pre-dose) and +2, 10, 18 to 24 hours post dose. Cord blood sample may serve as pre-dose sample if the initial TDF dose is given ≤ 2 hours after birth. If the initial TDF dose will be given > 2 hours after birth then a separate pre-dose sample should be collected ≤ 1 hour before dosing. If the cord blood specimen is not obtained then the pre-dose sample should be collected < 1 hour before dosing.

Day 3: Before dosing (pre-dose) and +2, 10 hours post dose. The pre-dose sample should be collected < 1 hour before dosing.

Day 5: Before dosing (pre-dose) and +2, 10, 18 to 24, 36 to 48 hours post dose. The pre-dose sample should be collected < 1 hour before dosing.

5.6.8 Infant (Cohort 4)

Birth Dose: Cord blood sample, before dosing (pre-dose) + 2, 10 hours post dose + just prior to next dose. Cord blood sample may serve as pre-dose sample if the initial TDF dose is given ≤ 2 hours after birth. If the initial TDF dose will be given > 2 hours after birth then a separate pre-dose sample should be collected ≤ 1 hour before dosing. If the cord blood specimen is not obtained then the pre-dose sample should be collected < 1 hour before dosing.

Dose 4: Pre-dose, + 2, 10 hours post dose + just prior to next dose.

Dose 7: Pre-dose, + 2, 10, 24 hours post dose

5.7 CRITERIA FOR DISCONTINUATION OF PK SAMPLING

Pk sampling will be discontinued (specimens not taken) in the following circumstances:

- If there is a problem with study drug dosing of the mother in Cohort 1, 3 or 4 (she vomits within 1 hour or does not deliver within 24 hours of dosing), the infant will not be dosed and only the cord pk specimen will be taken. The mother will not receive any additional doses. Mothers and infants will remain in follow-up and undergo all other procedures.
- If an infant study drug dose is missed (Cohorts 2, 3 and 4) for any reason, the pk specimens associated with (following) that dose should not be obtained and subsequent dosing and pk sampling will not be done. Mothers and infants will remain in follow-up and undergo all other study procedures.

- If an infant pk specimen (Cohorts 1, 2, 3 and 4) is missed for any reason, no further study drug dosing or pk sampling will be done on the mother and infant. The mother and infant will remain in follow-up and undergo all other study procedures.
- Cohort 4: If an infants birth, 4th or 7th study drug dose is missed for any reason or if the infant vomits within 1/2 hour of administration of those study drugs, the pk specimens associated with (following) that dose should not be obtained and subsequent dosing and pk sampling will not be done. Mothers and infants will remain in follow-up and undergo all other study procedures.

5.8 ENROLLMENT OF ADDITIONAL MOTHER/INFANT PAIRS

For each mother/infant pair that is not fully evaluable, another pair may be enrolled in the same cohort after consultation with the Protocol Safety Review team (PSRT), described in Section 6.1. A fully evaluable mother/infant pair is defined as one for which a complete set of pk specimens is obtained as specified in Section 5.6 and in the Schedules of Evaluations (Appendix I A and B). Mother/infant pairs that are not fully evaluable are technically not ‘replaced’ in the study, as all participants exposed to the study drug will remain in the study for safety monitoring and complete follow-up as originally scheduled, even if dosing is discontinued early; however these mother infant pairs will not count toward the targets specified for each cohort.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 SAFETY MONITORING

Close cooperation between the Protocol Chairs and co-Chairs, the study site Investigators, the NIH Medical Officers and other study team members will be necessary to monitor participant safety and respond to occurrences of toxicity in a timely manner.

The study site Investigators are responsible for continuous close monitoring of all adverse events that occur among study participants and for alerting the Protocol Chair and other members of the study team if unexpected concerns arise.

A Protocol Safety Review Team (PSRT) will routinely review clinical and laboratory safety data reports prepared by the Statistical and Data Management Center (SDMC). The PSRT will include the Protocol Chair and Co-Chairs, the NIAID Medical Officer, the NICHD Medical Officers and the Protocol Statistician. The content, format and frequency of the safety data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. The PSRT will convene via conference call routinely throughout the study to review the data and discuss any potential safety concerns - at least every other week during the dosing phases and at least once a month thereafter and on an ad hoc basis between routine calls. The PSRT will also provide rapid consultation with site clinicians regarding management of toxicities as needed.

If any mother or infant experience a life-threatening toxicity which is judged to be possibly, probably, or definitely related to study drug; or 2 or more women receive a dose of TDF experience the same Grade 3 or higher adverse event that is judged to be possibly, probably, or definitely related to study drug, further enrollment into the study may be paused by the PSRT; or if two or more infants who are exposed to the study product experience the same Grade 3 or higher adverse event (AE) judged to be possibly, probably or definitely related, further enrollment and dosing of additional infants may be paused by the PSRT. The PSRT and other members of the protocol team will carefully review all relevant safety data and determine whether further accrual and product administration should be stopped. Such a decision may be made at any time that unacceptable type and/or frequency of adverse events have been observed and will involve consultation with the pharmaceutical company representatives and other members of the study team.

6.2 ADVERSE EVENT REPORTING REQUIREMENTS

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6). Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above may also be considered to be serious. (October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: <http://rcc.tech-res-intl.com> and will be included in the Study Specific Procedures Manual.

Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: <http://rcc.tech-res-intl.com>, and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC.

Specifically, the ‘intensive’ level of reporting defined in the DAIDS EAE manual will be followed for the entire duration of each participant’s follow-up period (from study enrollment until the participant completes the study or is terminated from study participation for any reason).

After the end of a participant’s follow-up period stated above, sites must report unexpected, serious adverse drug reactions if the study site staff become aware of the events on a passive basis, i.e., from publicly available information.

The study product in HPTN 057 is the TDF regimen given to mothers during labor and/or to infants within the first week of life; therefore it is the relationship of all AEs to this product that is to be considered in determining the reporting requirements for each AE (e.g., whether the AE must be reported in an expedited manner to DAIDS). Conditions or illnesses in mothers or infants occurring before exposure to the study product will be reported as pre-existing conditions. Mothers in Cohort 2 are not exposed to study drug; therefore, AE reporting in this cohort is required only for infants.

The severity (intensity) of all AEs will be graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 and the additional grading scales for malnutrition and fever specified in Section 4.6.

Information on all AEs occurring in mothers and infants during the duration of follow-up, regardless of seriousness, severity or relatedness, will be recorded in the source documentation and on standard DataFax AE case report forms (CRFs) for entry into the study database.

Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities, according to their requirements. The investigators will report information on adverse events and serious adverse events to all responsible local and US-based IRBs/ECs in accordance with applicable regulations and individual IRB/EC requirements.

Note: Bone abnormalities identified locally (on site) based on radiologic assessment (X-ray) will only be reported as AEs if the site deems the local findings as clinically significant. All bone abnormalities identified locally (on site) or centrally based on radiologic assessment (X-ray) will be recorded in the infant’s source documentation and on the appropriate case report form (CRF) for entry into the study database. X-rays will not be done Cohort 4 participants.

7.0 STATISTICAL CONSIDERATIONS

7.1 REVIEW OF STUDY DESIGN

HPTN 057 is a Phase I, open label, non-controlled trial with four mother/infant cohorts. The primary aim is to provide therapeutic levels of TDF throughout the first week of life to interrupt vertical HIV transmission. This study is designed to determine the dosing regimen needed to accomplish this aim and to evaluate its safety. The primary objectives of this Phase I trial are identification of major toxicities occurring at high frequencies and evaluation of plasma concentration levels of TDF. Results of the trial will guide selection of a TDF regimen to be tested in a subsequent efficacy trial, if indicated. To simultaneously maximize considerations of convenience, cost and acceptability, there is interest in determining the lowest dose and frequency that will achieve minimally required levels by pk assessments and yield an acceptable safety profile.

7.2 ENDPOINTS

7.2.1 Primary Endpoints

- (1) Frequency of adverse events with a severity grade 3 or higher attributable to receipt of the study product.
- (2) Maintenance of infant serum concentrations of TDF above 50 ng/mL throughout the first week of life. The primary dosing outcome measure will be cord blood and trough TDF concentrations during the first week of life.

7.2.2 Secondary Endpoints

- (1) Maternal HIV-1 RNA levels at screening (\geq 34 weeks gestation), during labor and delivery before TDF dosing, and at 5 to 7 days and 6 weeks postpartum.
- (2) Viral resistance to TDF in all HIV-1 infected infants, all of the corresponding mothers (transmitters) and a subset of mothers whose infants are not infected (non-transmitters). Analysis of TDF in mothers may include testing of breastmilk samples, if collected.
- (3) HIV infection in infants \leq 12 months of age.
- (4) TDF concentration in amniotic fluid and breast milk.

7.3 ACCRUAL, FOLLOW-UP, AND SAMPLE SIZE

Four groups comprising a total of 110 evaluable mother/infant pairs will be enrolled. An evaluable mother/infant pair is one for which a complete set of TDF concentration samples

have been collected from the mother and infant as specified in Section 5.6 and in the Schedules of Evaluations (Appendix I A and B).

Cohort 1, with maternal dosing only, will include 30 mother/infant pairs. Cohort 2, with infant dosing only, will include 20 mother/infant pairs. These cohorts may be enrolled concurrently. Cohort 3, with both maternal and infant dosing, will include 30 mother/infant pairs. Enrollment in Cohort 3 will proceed after all mother and infants in the first two cohorts have reached 6 weeks postpartum and the study team has carefully evaluated the safety and pk data from these cohorts and any available data from PACTG 394 to determine the regimen to be used in Cohort 3. No more than seven mothers scheduled for Caesarean section at the time of enrollment will be included in Cohort 1 or in Cohort 3 at each site. (Route of delivery is not a factor for Cohort 2 as only infants are dosed.) Cohort 4, which was added after enrollment and follow-up of Cohorts 1-3 was completed, will include 30 mother/infant pairs. There is no restriction on the number of C-section deliveries for Cohort 4. All mothers and infants who receive one or more doses of TDF will be asked to remain in the study throughout the scheduled follow-up period for safety monitoring, even if dosing is discontinued early for any reason.

7.3.1 Sample Size Justification

Traditional sample size calculations are difficult to perform in a phase I study when there is no prior experience with the agent in the study population. Typical sample sizes for phase I protocols of this type generally range between 10 and 20 subjects per arm. The larger end of this spectrum has been selected as the sample size for Cohort 2 of this study because the study is being conducted in populations characterized by different modes of infant feeding and different clades of circulating HIV. The sample size has been further expanded by 10 mother/infant pairs in Cohorts 1, 3 and 4 to enable enrollment of adequate numbers of women delivering vaginally and by cesarean section, so that the sample size for those arms will be 30 evaluable mother/infant pairs for each.

For each mother/infant pair that is not fully evaluable, another pair will be enrolled in the same cohort. Mother/infant pairs that are not fully evaluable are technically not 'replaced' in the study, as all participants exposed to the study drug will remain in the study for safety monitoring and complete follow-up as originally scheduled, even if dosing is discontinued early; however these mother infant pairs will not count toward the targets specified for each cohort.

Table 5 below presents the probabilities that 0, 1+, 3+, 5+ or 6+ subjects in a cohort of size 30 experience adverse events at different levels of true event rates. For example, if the underlying rate of adverse events is 20%, then there is a 74.5% chance that 5 or more events will be observed. Likewise, if the true event rate is 30% and 20% is the maximum acceptable adverse event rate for the intervention, there is a 7.7% (1-.923) chance that there would be an inadequate number of events to conclude that the intervention has an unacceptable level of harm.

Table 5:

| Event rate | P(No events n=30) | P(1 or more events n=30) | P(3 or more events n=30) | P(5 or more events n=30) | P(6 or more events n=30) |
|------------|--------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| 1% | 0.740 | 0.260 | 0.003 | 0.000 | 0.000 |
| 5% | 0.215 | 0.785 | 0.188 | 0.016 | 0.003 |
| 10% | 0.042 | 0.958 | 0.589 | 0.175 | 0.073 |
| 20% | 0.001 | 0.999 | 0.956 | 0.745 | 0.572 |
| 30% | 0.000 | 1.000 | 0.998 | 0.970 | 0.923 |
| 40% | 0.000 | 1.000 | 1.000 | 0.998 | 0.994 |
| 50% | 0.000 | 1.000 | 1.000 | 1.000 | 0.999 |

7.4 MONITORING AND ANALYSIS

The study team will monitor rates of accrual, adherence, follow-up, and AE incidence closely. Routine conference calls will be held in which general site and laboratory operations, participant accrual, and operational issues and toxicity data will be discussed. As described in Section 6.1, the PSRT will closely monitor clinical and laboratory safety data on a routine basis.

In addition to the close oversight of the Study Chair, NIH Medical Officers and other members of the protocol team and PSRT, the HPTN Study Monitoring Committee (SMC) will monitor the study regularly with a focus on issues relating to quality of trial conduct, including rates of recruitment, adherence to study treatment and visit schedules, and overall retention.

7.4.1 Safety Assessment Procedures

The safety criteria will be considered to have failed in HPTN 057 if:

- a. Any of the mother/infant pairs experiences a life-threatening toxicity after TDF dosing that is judged to be possibly, probably or definitely related to study drug after consultation with the PSRT and other members of the protocol team.
- b. Two or more of the mothers or infants who have received TDF dosing have the same non life-threatening Grade 3 or 4 toxicity that is judged to be definitely, probably or possibly related to study drug after consultation with the PSRT and other members of the protocol team.

If the above safety criteria (a or b) are failed, the study may be suspended immediately following an evaluation by the PSRT of whether the current dosing regimen or a modified dosing regimen is likely to be safe. If these safety criteria are satisfied in Cohort 1 and 2 after at least 6 weeks of follow-up of all infants have been obtained, then the dosing for Cohort 3 will be determined by review of the pk parameters (see Section 7.5.1). Adverse events will continue to be monitored throughout follow-up of all subjects. If the PSRT determines at any

time that there are any treatment related toxicities, which may compromise participant safety, the PSRT will decide if the study needs to be suspended or modified.

7.5 DATA ANALYSIS

7.5.1 Primary Analyses

Primary Objective 1 – Safety Analysis

All adverse events occurring in each cohort will be tabulated overall and by site according to severity grade and seriousness and distinguishing between those deemed definitely not related to the study drug and those deemed potentially related according to the definitions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS.

Primary Objective 2 – Pk Data Analysis

Pk Parameter Estimation - Initial pk evaluation will be done using standard non-compartmental analysis to determine AUC and elimination half-life for the mothers in Cohort 1. If these data are sufficient they may also be analyzed using compartmental models to determine estimates of oral clearance, elimination half-life, and apparent volume of distribution. TDF concentrations will be determined by a LC-MS/MS assay developed by Dr. Walter Hubbard of the Johns Hopkins Mass Spectrometry Laboratory. The assay uses a C18 reversed phase bonded column (4.6mm x 150 mm). A gradient of 0.1% formic acid containing 5 millimolar ammonium formate to 0.1% formic acid in methanol containing 5 millimolar ammonium formate is employed for elution of adefovir and TDF. The solvent flow rate is 0.5 mL per minute. The assay requires a sample size of 50 uL and has a lower limit of quantification of 0.5 ng/mL. Measured TDF concentrations in maternal plasma at the time of delivery and cord blood will be used to determine a cord blood/maternal TDF ratio as a measure of placental transfer. The relationship between cord blood TDF concentration and the time from maternal dosing to delivery will be investigated. The serial TDF concentrations from the infants in Cohort 1 will be used to determine the elimination half life of transplacentally acquired TDF. The pre-dose plasma TDF concentrations from the infants in Cohort 2 and Cohort 4 will be inspected to determine if plasma TDF concentrations remain above 50 ng/mL throughout the first week of life. Relationships between participant characteristics and TDF pk parameters will be examined. Maternal pk parameters (oral clearance and apparent volume) will be examined initially in a univariate analysis against age, ideal body weight, weight at the time of onset of labor, and estimated creatinine clearance.

Pk modeling and dosing adjustments for Cohort 3 - pk parameter estimates will be used to model TDF concentrations in mothers and infants following maternal and/or infant dosing. The goal will be to develop a simple dosing regimen that will keep infant TDF concentrations above the target plasma concentration of 50

ng/mL from birth through the first week of life. The constraints of relatively few samples for both maternal and infant studies for fitting a model to the data are acknowledged and both population and Bayesian approaches may be utilized.

Decision Criteria for Cohort 3 Maternal and Infant Doses - The pk criteria for Cohort 3 maternal and infant doses presume that the safety criteria have been met. A primary goal for Cohort 1 is to select a single TDF maternal dose given during labor that is safe and yields maternal plasma concentrations sufficient to provide adequate TDF cord blood concentrations. The threshold median cord blood concentration will be 50 ng/mL. There are several possible outcomes for Cohort 3 based on the pk data from Cohorts 1 and 2:

1. If median cord blood TDF concentration in Cohort 1 fails to reach 50 ng/mL, the maternal TDF dose in Cohort 3 will be increased to 900 mg. Dose escalation is precluded if either of the following conditions are met:
 - i. median AUC for maternal TDF concentrations exceeds by more than 1.5 times the value for adults given 600 mg maternal TDF concentrations
 - ii. significant maternal safety concerns have been identified.
2. If median 4-hour blood TDF concentration in Cohort 1 infants exceeds the target concentration of 50 ng/mL, then Cohort 3 will continue with the 600 mg maternal dose.
3. If infant concentrations in Cohort 2 are maintained above the target concentration of 50 ng/mL after the initial infant dose through the end of the first week of life, the Cohort 2 infant regimen will be used in Cohort 3.
4. If infant concentrations in Cohort 2 are not maintained above the target concentration of 50 ng/mL after the initial infant dose through the end of the first week of life, infant dose size for Cohort 3 may be increased to 6 mg/kg. pk modeling will be used to estimate the effect of the increased dose on infant TDF concentrations prior to the initiation of Cohort 3 with an increased infant dose.

7.5.2 Secondary Analyses

1. *Maternal HIV-1 RNA levels at screening (≥ 34 weeks gestation), during labor and delivery before TDF dosing, and at 5 to 7 days and 6 weeks postpartum.*

For evaluating an antiviral effect of TDF, the values at screening and at labor and delivery will be compared to the value obtained at 5 to 7 days postpartum. For evaluating rebound, the change from 5 to 7 days to 6 weeks postpartum will be used.

2. *Viral resistance to TDF in women (plasma and breastmilk) and in all HIV-1 infected infants, all of the corresponding mothers (transmitters) and a subset mothers whose infants are not infected (non-transmitters).*

HIV-1 genotyping will be performed for all mothers whose infants are HIV-infected (plasma and breastmilk) and for all HIV-infected infants; HIV-1 genotyping will also be performed for a subset of women whose infants are not HIV-1 infected. HIV-1 genotyping will be performed using the ViroSeq HIV-1 Genotyping System (Celera Diagnostics). The ViroSeq system is an FDA-cleared system for evaluation of HIV-1 drug resistance mutations based on population sequencing. If TDF resistance is detected at 5-7 days, genotyping will be performed on baseline samples (from screening and labor and delivery for mothers, and from birth for infants). The duration of resistance will also be measured by performing genotyping on samples collected after 6 weeks (up to month 12, if resistance persists). Resistance to TDF will be defined as the detection of the K65R mutation in RT. If other mutations are identified that decrease susceptibility to TDF, they will be examined as well. If TDF resistance is detected using the ViroSeq system, more sensitive assays may be performed on selected samples to quantify TDF-resistant variants at baseline and analyze fading of those variants over time.

3. *HIV infection in infants < = 12 months of age*

HIV infection is defined as a positive HIV-1 DNA PCR or RNA PCR (> 10,000 copies) confirmed by a positive assay on a second specimen drawn on a different day.

4. *TDF concentration in amniotic fluid and breast milk.*

8.0 HUMAN SUBJECTS CONSIDERATIONS

The evaluation of new ARV agents for the pMTCT transmission appropriate for use in resource poor settings is a high priority. Though there is no guarantee, mothers and infants in this study may benefit from additional protection against MTCT from receipt of TDF, a potent ARV, which will be added to the ARV regimen that is the background standard of care for prevention of vertical HIV transmission in each locale. The main risks to which study participants will be exposed are from TDF toxicity, which will be monitored closely. Other minimal physical risks will be those associated with study-mandated procedures, such as drawing of blood. In addition, there may be social risks if others learn that a woman is participating in the study and assume that she and/or her infant is infected with HIV. The purpose of the study, the risks and procedures will be thoroughly explained to potential volunteers and they will be encouraged to ask questions before being asked to provide written informed consent for participation.

At all study sites, HIV counseling and testing and infant feeding counseling are provided as part of standard of care. Both sites also have existing programs through which a proven regimen for prevention of mother to infant transmission is offered as standard of care to all pregnant women

known to be HIV-infected (described in Section 2.0). All participants in HPTN 057 will be offered the standard of care ARV regimen for PMTCT; the choice to accept or decline this regimen will not affect a woman's eligibility for this study in any way. Therefore, no participant will be deprived of a proven regimen to which they would otherwise have access. All women will receive counseling regarding infant feeding options according to WHO/UNAIDS/ UNICEF and local Ministry of Health guidelines. Infant feeding choice will not affect a woman's eligibility for participation in this study in any way.

Clinical care provided to HIV-infected mothers and infants may vary by site. At a minimum, mothers and infants will be offered a number of therapeutic benefits including free diagnosis and treatment for their infections, malaria, tuberculosis, and other illnesses. Mothers of infants determined to be HIV-infected will be offered bactrim prophylaxis for their infants to prevent pneumocystis pneumonia and bacterial infections. All study women or children who require admission to the hospital will receive close monitoring and follow-up. Mothers will be offered nutritional counseling, multivitamins including vitamin D, iron and folate. Each site will develop a plan for the provision of medical care and support to mothers that is consistent with host country standards and policies.

Participants in HPTN 057 will not be precluded from receiving available treatment with ARVs. In Brazil, outside of pregnancy, triple ART is recommended for all HIV-infected individuals with a CD4+ cell count <350. Patients with CD4+ cells between 350 and 500 are eligible for treatment at the discretion of their physician; any patient presenting with an opportunistic infection or an AIDS-defining condition should initiate ARV treatment. Individuals are able to receive ARVs dispensed by the Brazilian government at the institutions where they receive medical care. The institutions providing HIV care are all affiliated with the Brazilian National AIDS Program.

ARVs for the treatment of HIV/AIDS are not widely available in Malawi. Limited programs are being introduced through which ARVs are provided to individuals who meet certain HIV disease stage criteria. National Guidelines for Antiretroviral Therapy were issued jointly by the Malawi Ministry of Health and the National AIDS Commission in October 2003. These guidelines specify criteria for initiating ARVs which include WHO Clinical Disease Stage 3 and Stage 4 or CD4+ count below 200/mm³. The first line regimen is daily TRIOMUNE, a fixed dose combination of 150 mg Lamivudine, 30 mg Stavudine and 200 mg NVP. The second line regime is AZT plus Didanosine plus Nelfinavir. Since July 2004, ARVs are provided free under sponsorship of the Global Fund, beginning in three pilot hospitals. The Johns Hopkins Project (where the study site is headquartered) is on the grounds of Queen Elizabeth Central Hospital (QECH), one of the hospitals where provision of ARVs is being piloted. Due to the difficulties of procuring reagents to monitor patients on ARVs by the main hospital lab, these routine tests are not done. The site will therefore offer quarterly CD4+ counts, CBCs and chemistries for participants to help monitor their progress on treatment.

In both Malawi and Brazil, study clinicians will be familiar with the criteria being applied in available programs for access to care and treatment and will refer study participants accordingly through established links.

Regarding future availability of the study drug, should subsequent larger-scale trials demonstrate its safety and efficacy for pMTCT, TDF is currently available by prescription in Brazil through the Single Health System, the government health insurance program which provides antiretrovirals at no cost. TDF will be available in Malawi through the Gilead Global Access Program at a no profit price. Therefore, a pathway for expanded accessibility, if indicated, will have been established in advance.

Prisoners will not be included or followed in this study.

8.1 ETHICAL REVIEW

This protocol and the site informed consent documents (including local language versions and back-translations) and any subsequent modifications will be reviewed and approved by the sponsor, IRBs and ECs responsible for oversight of the study with respect to scientific content and compliance with applicable research and human subjects regulations prior to implementation.

Subsequent to initial review and approval, the responsible local IRBs/ECs will review the study at least annually. Documentation of continuing/annual review will be submitted to the DAIDS Protocol Registration Office, via the HPTN CORE, in accordance with the current DAIDS Protocol Registration Policy and Procedures Manual. The Investigator will make safety and progress reports to the IRBs/ECs at least once a year and within three months of study termination or completion at the site. All changes to the informed consent forms must be approved by the responsible IRBs/ECs prior to use. All protocol amendments and changes to informed consent forms associated with protocol amendments must be approved by the sponsor (DAIDS) and the IRBs/ECs before implementation.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study sites.

8.2 INFORMED CONSENT

Written informed consent will be obtained from each study participant for screening and study enrollment (or the parents or legal guardians of participants who cannot consent for themselves). Each study site is responsible for developing a study informed consent form for local use, based on the templates in Appendix II A-D, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Written informed consent will first be obtained from mothers for initial screening. The study will then be thoroughly explained to all women who are found eligible based on those initial screening tests, before a mother is asked to sign the informed consent form

for final screening and enrollment. A copy of the consent forms will be offered to the mother. If he is reasonably available at the study clinic, the study will also be thoroughly explained to the father and his written informed consent obtained; however, the father's written consent is not required for enrollment of the mother or infant, unless otherwise directed by the IRB/EC. Pending IRB/EC approval, sites may also use additional written materials/illustrations to aid in the informed consent process.

Participants who are able will document their informed consent by signing the informed consent forms. Those who are not able to sign the consent form, will be asked to document informed consent by marking the informed consent forms with an X, thumbprint, or other mark in the presence of a literate third party witness. (Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the DAIDS Standard Operating Procedure for Source Documentation.) Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants (or their parents or legal guardians) will be provided with a copy of their informed consent forms if they are willing to receive them. Study staff will document the informed consent process as instructed in the study-specific procedures manual.

8.3 RISKS

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others; for example, participants are asked to stay in the hospital for a longer time than typical (5-7 days after delivery). Social harms may result because participants could become known as HIV-infected. Participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

The following side effects have been associated with the use of TDF, though in higher doses and for greater duration than used in this study:

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness
- Abdominal pain
- Lack of energy
- Inflammation or swelling and possible damage to the pancreas
- Increase of creatinine or decrease of phosphate in blood, which could possibly mean kidney damage or kidney failure
- Shortness of breath
- Rash
- Increase of liver function tests in children
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness.

Lactic acidosis and severe hepatomegaly with steatosis that may result in liver failure, other complications and death have been reported with the use of TDF, as well as ARV nucleoside analogues alone or in combination. The liver complications and death have been seen more often when receiving chronic and prolonged therapy with these drugs.

Some problems with kidneys and bone growth were seen in animal and human studies of TDF. These problems were seen with long term dosing. HPTN 057 involves only very short term dosing. In children, some decrease in bone density has been seen with longer periods and higher levels of dosing, although this finding is not conclusive. The risks of TDF use in pregnant women are not known. Multiple blood draws are required, particularly in the first week after delivery.

8.4 BENEFITS

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe, effective, and appropriate ARV regimen that prevents intrapartum/neonatal HIV infection.

In addition, participants will receive more frequent physical exams and closer overall health monitoring than they would ordinarily receive outside of the study.

8.5 INCENTIVES

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or will be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms or otherwise approved by the IRB/EC.

8.6 CONFIDENTIALITY

All study-specific records will be stored securely with access limited to authorized personnel only. Study-specific laboratory specimens, case report forms or documents that are transferred or transmitted off-site for processing will be identified by a coded number only to maintain participant confidentiality. All local databases must be secured with password-protected access systems. The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.

Individual clinical information will not be released without the written permission of the participant, except as necessary for monitoring by the study sponsor (the U.S. National Institute of Allergy and Infectious Diseases), representatives of their or the National Institute of Child Health and Developments authorized contractors (the DAIDS Clinical Site Monitoring Contractor (CSMC), Westat, the HPTN Coordinating and Operations Center (CORE), the HPTN Statistical and Data Management Center (SDMC), and the HPTN Network Laboratory (NL)), the U.S. Food and Drug Administration, the study

drug manufacturer (Gilead Sciences), the IRBs and/or representatives of local regulatory authorities.

8.7 STUDY DISCONTINUATION

The study may be discontinued at any time by NIAID, Gilead Sciences, the US FDA, the IRBs/ECs, or other host country government or regulatory authorities.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 LOCAL LABORATORY SPECIMENS

Each site will be responsible for completing the following local laboratory tests:

- routine clinical chemistries
- hematology evaluations
- HIV-1 RNA PCR and DNA PCR

In addition the local laboratory will be responsible for the preparation and shipping of specimens to the NL in a timely manner.

Each study site will adhere to standards of good laboratory practice, the NL Manual; and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the local laboratories. Specimen collection, testing, and storage at the local laboratories will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the study-specific procedures manual.

9.2 NETWORK LABORATORY SPECIMENS

The NL will perform viral resistance and TDF serum concentration testing and will conduct quality assurance testing on a subset of samples tested locally for HIV RNA and HIV DNA. Further characterization of HIV in plasma and breastmilk may involve HIV viral load testing or testing with other genotypic or phenotypic assays (e.g. HIV replication capacity) performed at the NL or at a designated commercial laboratory.

The NL will adhere to standards of good laboratory practice and the NL Manual for proper collection, processing, labeling, and transport of specimens for the NL. Any specimens shipped will be done in accordance with IATA specimen shipping regulations. All shipments will be documented using the LDMS as described in the study-specific procedures manual.

9.3 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The NL has established a proficiency testing program at each study site. NL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. NL staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

Throughout the course of the study, on a quarterly basis, the NL or SDMC will select a random sample of stored specimens to test for quality assurance (QA) purposes. The total number of specimens undergoing QA testing will represent at least 10 percent of all specimens collected.

The SDMC or NL will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the NL. The NL will test the specimens and compare the results of their tests with the results obtained by the local labs. NL staff will follow up directly with site staff to resolve any quality assurance problems identified through this process.

9.4 SPECIMEN STORAGE AND POSSIBLE FUTURE RESEARCH TESTING

Study site staff will store all specimens collected in this study at least through the end of the study and completion of all study specified testing and quality assurance procedures. Any specimens left over after completion of study specified testing and quality assurance procedures will be destroyed.

9.5 BIOHAZARD CONTAINMENT

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

10.0 ADMINISTRATIVE PROCEDURES

10.1 STUDY ACTIVATION

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the study-specific procedures manual — to the HPTN CORE. CORE staff will work with study site staff and complete DAIDS protocol registration in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual. Included in this step will be CORE and DAIDS review of each site-specific study informed consent form.

10.2 STUDY COORDINATION

DAIDS will hold the Investigational New Drug (IND) application for this study. Gilead Sciences, Inc. will provide TDF 300 mg tablets and TDF powder for oral suspension for the study. Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to Gilead Sciences, Inc. for cross-referencing with the company's other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and Gilead Sciences, Inc.

Pending successful protocol registration and submission of all required documents, HPTN CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

This protocol will direct study implementation. In addition, a SSP manual will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. The study-specific procedures manual will be submitted to the sponsor prior to implementation of the study, will be posted on the following website: <http://www.HPTN.org> and will be made available to the IRBs/ECs, the US FDA and other regulatory authorities upon request.

Close cooperation between the Study Investigators, site staff, NIAID Medical Officer, HPTN CORE Protocol Specialist, SDMC Protocol Operations Coordinator, Biostatistician, Data Managers, and other study team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The study team will monitor rates of accrual, adherence, follow-up, and AE incidence closely. Routine telephone conference calls will be held in which general site operations, participant accrual, and operational issues and toxicity data will be discussed.

Case report forms will be developed by the protocol team and the SDMC. Data will be transferred to the SDMC using DataFax for quality control checking, pooling and analysis. Quality control reports and queries will be routinely sent back to the sites for verification and resolution of inconsistencies. All physical case report forms and other individual study related documents will remain securely stored on site. Site investigators will have access to data files maintained by the SDMC. Data processing and management procedures will be included in the study-specific procedures manual.

Procedures for specimen collection, preparation, processing, testing and shipping will be included in the study-specific procedures manual. Oversight and direction for laboratory procedures, including QA/QC, will be provided by the NL at Johns Hopkins University.

In addition to the close oversight of the Study Chair, NIAID and NICHD Medical Officers and other members of the protocol team, the HPTN SMC will monitor the study regularly with a focus on issues relating to quality of trial conduct, including rates of recruitment, adherence to study treatment and visit schedules, and retention. As described in Section 6.1, the PSRT will closely monitor clinical and laboratory study data on a routine basis.

10.3 STUDY MONITORING

On-site study monitoring will be performed in accordance with NIAID or NICHD policies. Study monitors will visit the site to

- verify compliance with human subjects and other research regulations and guidelines;

- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the sponsor (NIAID), NICHD, IMPAACT leadership, the HPTN CORE, SDMC and NL, Gilead Sciences, Inc., the US FDA, the IRB/ECs and host country government and regulatory authorities.

10.4 PROTOCOL COMPLIANCE

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the sponsor. All protocol amendments must be submitted to and approved by the sponsor and the relevant IRBs/ECs and prior to implementation.

10.5 INVESTIGATORS' RECORDS

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with US federal regulations, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.6 USE OF INFORMATION AND PUBLICATIONS

Publication of the results of this study will be governed by IMPAACT policies. Any presentation, abstract, or manuscript must adhere to IMPAACT, DAIDS, and Gilead Sciences publication policies.

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APPENDICES

- I. Schedules of Study Visits and Procedures
 - A. Schedule of Maternal Evaluations
 - B. Schedule of Infant Evaluations
- II. Sample Informed Consent Form(s)
 - A. Sample Informed Consent for Screening
 - B. Sample Informed Consent For Enrollment
 - C. Sample Informed Consent For Screening Cohort 4
 - D. Sample Informed Consent For Enrollment Cohort 4

APPENDIX I A
SCHEDULE OF MATERNAL EVALUATIONS

| Activities/Evaluations | Screening | | Labor and Delivery (Enrollment ¹) | 24-48 hrs pp | 5 to 7 days pp | 6 wks pp | 12 wks pp | 6 mos pp | 12 mos pp |
|--|--------------------------|----------------------|---|--------------|----------------|----------|----------------|----------------|----------------|
| | Anytime during pregnancy | ≥ 34 weeks gestation | | | | | | | |
| Screening Informed Consent | X | | | | | | | | |
| Enrollment Informed Consent | | X | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical/obstetric history | | X | | | | | | | |
| Interim medical history | | | X | X | X | X | X | X | X |
| Physical examination | | X | | | | | | | |
| Symptom-directed physical exam | | | | X | X | X | X | X | X |
| Confirmatory HIV test (if documentation not available) | X | | | | | | | | |
| Hematology: CBC w/ differential and platelet count | | X | X | X | X | X | | | |
| CD4+ cell count | | | X | | | | | | |
| Chemistries: bilirubin, AST, ALT [SGPT], creatinine, calcium, albumin, phosphorus, alkaline phosphatase) | | X | X | X | X | X | | | |
| HIV RNA PCR | | X | X ² | | X | X | X ³ | X ³ | X ³ |
| Viral resistance | | X ⁴ | X ^{2,4} | | X | X | X ⁴ | X ⁴ | X ⁴ |
| TDF concentration: Breast milk ⁵ | | | | X | X | X | X | | |
| TDF concentration: amniotic fluid ⁶ | | | X | | | | | | |

| Dosing Arm | | TDF plasma concentration (2 mL blood specimen required) |
|-----------------|-----------|--|
| Cohort 1 | | Pre-dose ⁷ , +1, 2, 4, 8, 12, 18-24, 36-48 hours post dose and at delivery ⁸ |
| Cohort 3 | If 600 mg | Delivery only |
| | If 900 mg | Pre-dose ⁷ , +1, 2, 4, 8, 12, 18-24, 36-48 hours post dose and at delivery ⁸ |
| Cohort 4 | | Delivery Only |

¹ The effective point of enrollment is when a mother presents for delivery.

² Blood sample collected during active labor, prior to TDF dosing

³ Stored for later assay, if necessary

⁴ Specimens to be stored; resistance testing to be performed on selected samples

⁵ Only in mothers who are currently breastfeeding

⁶ Only in mothers who deliver by C-section

⁷ Collected < 1 hour before dose

⁸ If collection of the pre-dose sample falls within one hour of another scheduled PK specimen collection time point, the previously scheduled specimen need not be collected.

APPENDIX I B SCHEDULE OF INFANT EVALUATIONS

| Evaluations | Before Dosing (Cohorts 2,3,4) | Within 24 hrs of birth | Day 3 | Day 5-7 | Wk 6 | Wk 12 | Mos 6 | Mos 9 | Mos 12 |
|--|-------------------------------|------------------------|-------------|----------------|----------------|----------------|----------------|-------|----------------|
| Birth and neonatal medical history | X | X ¹ | | | | | | | |
| Interim medical history | | | X | X | X | X | X | X | X |
| Physical examination | X | X ¹ | X | X | X | X | X | X | X |
| Hematology (CBC, differential, platelet count) | | X | | X | X | X | | | |
| Chemistries: ALT [SGPT] AST, bilirubin, creatinine, CPK, calcium, albumin, phosphorous, alkaline phosphatase, total protein, glucose | | X | | X | X | X | | | |
| HIV DNA or RNA PCR ² | | X | | X | X | X | X | | X |
| Viral resistance | | X ³ | | X ³ | X ³ | X ³ | X ³ | | X ³ |
| Dried Blood Spot Storage (for back-up) | | X | | X | X | X | X | | X |
| Radiologic bone assessments (x-ray of thoracic spine and left wrist) Cohorts 1, 2 and 3 only | | | X ±2days | | | X | | | |
| Total Blood Volume | | 3 - 4 mL | | 3 - 4 mL | 3 - 4 mL | 3 - 4 mL | 3 - 4 mL | | 3 - 4 mL |

| Dosing Arm | TDF plasma concentration (0.5 mL BLOOD SPECIMEN REQUIRED) |
|---|---|
| Cohort 1 (maternal dose at labor only) | Cord +4, 12, 18-24, 36-48 hours post delivery |
| Cohort 2 (infant dose at birth, days 3 & 5) | Birth: cord, pre-dose ^{4,5} , +2, 10, 18-24 hours post dose Day 3: pre-dose ⁵ , +2, 10 hours post dose Day 5: pre-dose ⁵ , +2, 10, 18-24, 36-48 hours post dose |
| Cohort 3 (maternal dose at labor and infant dose at birth, days 3 & 5) | Birth: cord, pre-dose ^{4,5} , +2, 10, 18-24 hours post dose Day 3: pre-dose ⁵ , +2, 10 hours post dose Day 5: pre-dose ⁵ , +2, 10, 18-24, 36-48 hours post dose |
| Cohort 4 (Maternal dose at labor and infant dose daily from birth for 7 days) | Birth Dose: Cord blood, pre-dose ^{4,5} + 2, 10 hours post dose + just prior to next dose. 4 th Dose: Pre-dose, + 2, 10 hours post dose + just prior to next dose. 7 th Dose: Pre-dose, + 2, 10, 24 hours post dose |

¹ Cohort 1 only; these assessments must be done prior to dosing for Cohorts 2 and 3, and 4 and need not be repeated.

² If positive confirm with a DNA PCR or RNA PCR on a different specimen.

³ Specimens to be stored; resistance testing to be performed on selected samples

⁴ If cord blood is collected and infant receives the initial dose of TDF ≤ 2 hours after birth then this specimen can be omitted.

⁵ To be collected within 1 hour before dose

APPENDIX II A
SAMPLE INFORMED CONSENT FORM FOR SCREENING
(COHORTS 1, 2, AND 3)

DIVISION OF AIDS, NIAID, NIH

HPTN 057

A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir
Disoproxil Fumarate in HIV-1 Infected
Pregnant Women and their Infants

Version [2.0], Dated [28 Oct 09]

Principal Investigator: [insert name and contact information for site PI]

Introduction

You are being asked to take part in screening tests for the research study named above because you are pregnant and infected with HIV, the virus that causes AIDS. The research study will test a drug named tenofovir for use in pregnant women with HIV and their newborn babies. The screening tests will determine if you qualify to participate in the research study. The study is sponsored by the United States National Institutes of Health (NIH). The person in charge of the study at this site is [insert name of site investigator].

Before you decide whether or not to take part in this screening, we would like to explain the purpose of the research study and give you some information about what would be required if you were to participate in the study. We also want to explain the procedures involved in the screening process, any risks and benefits to you, and what is expected of you if you agree to participate in this screening. You are free to ask any questions. After the screening process has been fully explained to you, and if you agree to participate in the screening, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy of this form to keep.

What should you know about the screening for the research study?

- Your participation in the screening is entirely voluntary.
- You may decide not to take participate in the screening tests or to withdraw from the screening at any time without losing the benefits of your standard medical care.
- If you decide not to participate in the screening, you and your baby cannot participate in this research study, but you can still join another research study later, if one is available and you qualify.
- Even if you agree to participate in the screening, it does not mean that you have agreed to participate in the research study.

Why is this research being done?

This research study is being done to test a drug named tenofovir. There are two purposes for the study. One purpose is to see if tenofovir is safe for use in HIV-infected pregnant women and their newborn babies. The other purpose is to see how much tenofovir should be used for the mother during delivery and for the baby in the first week after birth to try to prevent passing of HIV from a mother to her baby. In this research study, tenofovir is considered investigational. This means that we do not know if the study drug can help protect your baby from getting HIV. It also means that the drug can only be used in a small number of women and babies to make sure it is safe and to see how it works. A similar study is currently being done with the same drug in pregnant women and their babies in America. Tenofovir has been approved by the [insert name of local drug authority] in this country and the United States Food and Drug Administration for the treatment of HIV/AIDS in adults, but it has not been approved for use to prevent HIV from being passed from an HIV-infected mother to her baby. However, they have allowed the use of tenofovir in this study.

The purpose of the screening process is to see if you and your baby are able to join the main study. If the screening tests show that you are able to participate in the research study and you are still interested, you will be given more information about the study at a later visit. If you agree to participate in the research study, you will be asked to sign or make your mark on another consent form after the study has been fully explained to you. You are encouraged to bring the baby's father to the study clinic so that we can also explain the study to him. If the father is available and comes to the study clinic to participate in the informed consent discussion, he will be asked to sign the consent form also. If you agree that you and your baby can participate in the study, you will go to the [insert name of local study facility] to deliver your baby. You must be willing to stay in the clinic/hospital for up to 7 days following the birth of your baby. During this time, you and your baby will have blood drawn several times. Participants in the study will be divided into three groups. If you and your baby are assigned to the first group, only you will receive the study drug, tenofovir; you baby will not get the study drug. If you are assigned to the second group, only your baby will be given tenofovir. If you are in the third group, both you and your baby will receive tenofovir. You will not know which group you will be assigned to until you join the study. Which group you are assigned to will depend on when your baby is delivered. Mothers and babies in all three groups will come to the clinic to participate in the study for 1 year after the baby is born.

What will happen if you agree to the study screening?

The study staff will ask you some questions about yourself, your health and pregnancy. They will review your recent medical records, including your HIV test results. You will have a physical examination. The study staff will ask if you are in any other studies and what medicines you have been taking. The study staff will draw about 1 teaspoon (5 mL) of blood from you. Your blood will be tested to check your health. Your blood may also be tested to confirm that you have HIV infection, if needed. You will be asked to return to the clinic to get the results of these blood tests. These screening tests are the first step in determining if you will be able to join the research study.

Some women will not be able to join the study because of information learned during the screening. If the screening tests show that you are not able to participate in the study, or if you choose not to participate, any leftover blood taken from you will be destroyed. If these screening tests show that

you may be able to join the study, more detailed information about the study will be given to you. You will be able to decide if you want for you and your baby to participate in the study or not. After the study has been fully explained to you, and you have asked all of your questions, the study worker will ask you some questions about the study to be sure that you understand. If you agree that you and your baby will participate in the study, you will be asked to sign another consent form. We will not know for sure whether you can join the study until you come to the hospital for delivery.

What are the risks of study screening?

Taking blood from you may cause slight pain, swelling, a light headed feeling, and bruising at the place where the blood is taken. Drawing blood can also cause fainting or infection, but this is rare. If you are screened for this study, some hospital and study staff will know that you have HIV. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatments or attend a special clinic, it may make others wonder if you have HIV.

What are the possible benefits of study screening?

These screening tests may not be of direct benefit to you. The results of the screening tests will be shared with you and with the medical staff providing your antenatal care at this clinic and may help them know more about what care you need. They may refer you for additional care if they find that your body's system for fighting infections is weak.

What are the choices if you do not want to be screened for the study?

You do not have to agree to be screened for this research study. If you do not agree to the screening, your care at [insert name of clinic] will not be affected. However, you and your baby will not be able to join the research study. If you agree to take part in the screening, you can change your mind at any time without losing the benefits of your standard medical care.

At this clinic, there is a special program for all pregnant women who are infected with HIV. You are advised to follow the [insert name] program for HIV infected women whether or not you decide to be screened for these studies.

What about confidentiality?

The study doctors and staff will protect information about you and your baby, and your participation in these screening tests to the best of their ability. On your study screening records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the (Malawi/Brazil) Ministry of Health, the institutional review boards and ethical committees, the United States Food and Drug Administration, the company that makes the study drug, the study sponsor (the United States National Institutes of Health), and their authorized representatives will be allowed to inspect your screening records.

Will there be any costs or payments to you?

The clinic visits, procedures and blood tests will be free - at no cost to you. You will not receive any payment for having the screening tests done.

Antiretroviral treatment for HIV will not be provided through this study, however, study staff will refer you to available care and treatment programs (outside of the study) for which you may qualify.

What happens if you are injured during the screening?

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

You will not give up your legal rights by signing this consent form.

What should you do if you have problems or questions about the screening?

If you ever have questions about this screening or if you have a study-related medical problem or injury, you should contact the study investigator, [insert name of site investigator] at the [insert physical and mailing address]. You may also ring [insert name of site investigator] at [insert phone number].

If you have questions about your rights or your baby's rights as a research volunteer, you may contact

- [insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [insert telephone number and physical address of above]

APPENDIX II B
SAMPLE INFORMED CONSENT FORM FOR ENROLLMENT
(COHORTS 1, 2, AND 3)

DIVISION OF AIDS, NIAID, NIH

HPTN 057

A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir
Disoproxil Fumarate in HIV-1 Infected
Pregnant Women and their Infants

Version [2.0], Dated [28 Oct 09]

Principal Investigators: [insert name and contact information of site PI]

Introduction

You are being asked to participate and to allow your baby to participate, in the research study named above because you agreed to participate in the screening tests and, so far, these test show that you and your baby may be able to participate in the research study. The research study will test a drug named tenofovir for use in pregnant women with HIV and newborn babies. The study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of site investigator].

Before you decide whether or not you and your baby will participate in the study, we would like to explain the purpose of the study, the risks and benefits of participating, and what is expected of you and your baby. This informed consent form gives you information about this study. This information will also be discussed with you. You are free to ask any questions. After the study has been fully explained to you, and if you agree that you and your baby will participate in the study, you will be asked some questions to determine whether you fully understand what is involved. You will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy of this form to keep. You are encouraged to bring the baby's father to the study clinic so that we can also explain the study to him. If the father is available and comes to the study clinic to participate in the informed consent discussion, he will be asked to sign the consent form also.

What should you know about the research?

- Your participation in the research is entirely voluntary.
- You may decide not to participate in the study or to withdraw from the study at any time without losing the benefits of your standard medical care.
- If you decide not to participate in this research study, you can still join another research study later, if one is available and you and/or your baby qualify.

Why is this research being done?

This research study is being done to test a drug named tenofovir. There are two purposes for the study. One purpose is to see if tenofovir is safe for use in HIV-infected pregnant women and their newborn babies. The other purpose is to see how much tenofovir should be used for the mother during delivery and for the baby in the first week after birth to try to prevent passing of HIV from a mother to her baby. In this research study, tenofovir is considered investigational. This means that we do not know if the study drug can help protect your baby from getting HIV. It also means that the drug can only be used in a small number of women and babies to make sure it is safe and to see how it works. A similar study is currently being done with the same drug in pregnant women and their babies in America. Tenofovir has been approved by the [insert name of local drug authority] in this country and the United States Food and Drug Administration for the treatment of HIV/AIDS in adults, but it has not been approved for use to prevent HIV being passed from an HIV-infected mother to her baby. However, they have allowed the use of tenofovir in this study.

Mothers who have HIV can pass HIV to their babies before delivery, during delivery, and after delivery through breastfeeding. Other research studies have shown that giving drugs to the mother and the baby before and soon after birth can cut the chances of passing HIV to the baby. Every woman with HIV who comes to this clinic is offered drugs to help prevent passing HIV to her baby. You and your baby will be offered these drugs regardless of your decision to participate in this research study.

We continue to look for more and better treatments that are safe, easy to give to mothers and babies in local hospitals, and that preventing passing of HIV from mothers to their babies. We do not know if tenofovir, the drug we are testing in this study, is safe for HIV-infected pregnant women and newborns. The studies that have been done in animals and with HIV-infected adults and children make us think that it will be safe in the amounts that will be given in this study. This study will help us find that out. Studies in animals also make us hope that tenofovir may help prevent passing of HIV from a mother to her baby. This study is an important first step in finding out if it will work.

This study will include about 80 mothers and their babies from Malawi and Brazil. About half (40) of the mothers and their babies will come from this country.

What will happen if you agree to participate in the study?

If you agree that you and your baby can be in this study, there are things that you will be asked to do. You will be asked to come to the [insert name of local study facility] for delivery of your baby. You will be asked to stay in the delivery facility for up to seven days following the delivery of your baby. You and your baby will be put into one of three groups, depending on when you deliver. You and your baby will be part of the study until your baby is one year old. If you join the study, some of your blood and your baby's blood will be stored during the study period for later testing related to the study. Some of your blood will be shipped to the United States for testing. After the study and all related testing are completed, any leftover specimens will be destroyed.

The study staff may need to contact or visit you at home or work to remind you of study visits. To participate in the study, you must be willing to tell us how to contact you at home.

No matter whether you decide to participate in the study or which group you are in, staff at the clinic will offer you the standard study drugs used in this clinic to decrease the chance of passing HIV to your baby.

Mother's Procedures

Labor, delivery and first week after delivery

You will be asked come to [insert name of local study facility] as soon as your labor begins. When you arrive, the study staff will ask you some questions about your health to make sure you are still eligible for the study. We will ask you to give about 2 teaspoons of blood (10 mL) to check your health. Depending on what group you are assigned to, you may receive the study drug and give more samples of blood as explained below. If you deliver your baby by C-section, the study staff will take a small sample of the fluid that surrounds the baby during delivery. If you are breastfeeding, we will take a sample of breastmilk (about 1 tablespoon - 15 mL) from you about two days after delivery to test for the study drug in your breast milk. Before you leave the hospital (5-7 days after birth) you will have a physical exam and will be asked to give another sample of blood to check your general health. If you are breastfeeding, you will also be asked to give another sample of breast milk.

If you are in Group 1:

During labor, you will give blood (less than one teaspoon (about 2-3 mL) before receiving study drug to compare the level of drug in your blood with blood taken after you receive drug. We will give you 2 tablets of the study drug to take with a small amount of milk or other liquid. Your baby will not receive the study drug. If you have a C-section a sample of the fluid that surrounds the baby during delivery will be taken about 2 to 3 mls which is less than 1 teaspoon,.

In the two days after delivery, you will give blood samples 7 or 8 more times (less than one teaspoon (about 2-3 mL) each time. These blood tests will help us check your health and will also give us important information about how much of the drug is in your blood.

If you are in Group 2:

You will not be given any tablets of the study drug, but your baby will receive the study drug in the form of a liquid.

If you are in Group 3:

During labor, you will give blood (less than one teaspoon (about 2-3 mL) before receiving study drug to compare the level of drug in your blood with blood taken after you receive drug. We will give you 2 or 3 tablets of the study drug to take with a small amount of milk or other liquid. If you have a C-section a sample of the fluid that surrounds the baby during delivery will be taken about 2

to 3 mLs which is less than 1 teaspoon. In the two days after delivery, you may be asked to give blood samples 7 or 8 more times (less than one teaspoon (2-3 mL) each time). These blood tests will help us check your health and will also give us important information about how much of the drug is in your blood.

After discharge from the hospital

After you leave the hospital (5 to 7 days after delivery), you will be asked to come to the clinic at least 5 times during the next 12 months with your baby. At most of these study visits, you will give a blood sample to check your health. If you are breastfeeding, you will also be asked to give a breast milk sample. Study staff will ask you questions about your health and the health of your baby, and you will have a physical examination. We will give you any information that we learn from these tests and physical exams that relates to your health or the health of your baby.

Baby's Procedures

First week of life

After your baby is born, he or she will have a physical exam and his or her birth records will be reviewed. When blood is taken from your baby it will be taken through a needle inserted into a vein or a prick with a needle on his or hers heel. A blood specimen of less than one teaspoon (5ml) each time will be taken to check the baby's health and to test for HIV infection within 24 hours of birth and again before he or she leaves the hospital (5-7 days after birth). Your baby will have two more physical exams during the first week of life, and a picture (X-ray) will be taken of your baby's spine and left wrist bone. You will be given any information learned related to your baby's health.

If you and your baby are in Group 1:

Your baby will not receive the study drug. A small amount of blood will be taken from the baby 4 times (less than one teaspoon - about 0.5 mL – each time) during the two days following delivery for testing. Information from these tests will give us important information about how much study drug passed from you to the baby. In total, blood will be taken from your baby about 5 times during the first week of life.

If you and your baby are in Group 2 or Group 3:

Your baby will be given the study drug (tenofovir) in the form of a liquid solution three times: as soon after birth as possible and again at Day 3 and at Day 5 after delivery. A small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby before each dose of the study drug. After the first dose of the study drug, a small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby 3 times. After the second dose of the study drug, a small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby two times. After the third dose of the study drug, a small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby 4 times. Information from these tests will give us important information about how much tenofovir passed from you to the baby. In total, blood will be taken from your baby about 14 times during the first week of life.

After the first week of life

After leaving the hospital, we will ask you to bring your baby to the clinic about 5 more times during the 12 months of the study. You will bring your baby to the clinic for study visits when he or she is 6 weeks old, 12 weeks old, 6 months old, 9 months old and 1 year old. During these visits we will ask questions about your baby's health and we will do a physical exam. We will take small blood samples to check your baby's health (no more than 10 mL, which is about 2 teaspoons). You will be told the results of all the tests performed during the study that affect your baby's health. During the first 3 months we will also test for HIV infection about 2 more times. If you are breastfeeding past 3 months then we will test again for HIV infection 2 more times when your baby is 6 months and 1 year old. If your baby's HIV tests show that he or she may be infected with HIV, we will take another blood sample to confirm the first result. If we learn that your baby is infected with HIV, we will tell you in person as soon as possible.

What are the risks of the study?

Study Drug Risks

The study drug has been tested in animals (adult and baby), human adults, and older children. The testing included routine safety tests to see if the drug was harming or having bad effects on the animals or people taking it.

Animal and human studies of study drug (tenofovir) found some problems with kidneys and bones. Whether the animals or humans had these problems and how bad the problems were depended on how much of the drug was given and for how long. In all cases, problems were only seen with very high doses and long term treatment.

Most of the studies done in humans included adults who are infected with HIV. Over 1000 people participated in these studies, and only minor problems were seen. The problems were not different from problems seen in the people in the studies who did not receive tenofovir. The following side effects have been seen in patient being treated with tenofovir: upset stomach, vomiting, gas, loose or watery stools, dizziness, stomach pain, lack of energy, kidney damage or failure, inflammation or swelling and possible damage to the pancreas, shortness of breath, rash, low phosphate, a chemical in blood, increase of liver function tests in children, allergic reaction which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness. These side effects were seen in patients receiving the drug for much longer periods of time and with much higher doses of than in this study. These are not all the side effects seen with this drug. These are the more serious or common side effects with a known or possible relationship. If you have questions concerning additional side effects please ask the clinical study staff.

This study drug (tenofovir) and other similar drugs used to treat HIV infection may cause serious liver problems and other diseases that can rarely lead to liver failure or death. These problems happen more often in women receiving these drugs for treatment of HIV for a long time. Signs of these problems may be: unexplained weight loss, stomach pain, nausea, vomiting, tiredness, weakness and being short of breath.

Research has recently begun in the United States to see if the study drug (tenofovir) is safe in pregnant women and their babies when given to try to prevent passing HIV to the baby. We do not yet know the results of this research. However, tests in animals showed that the study drug is may help in stopping mothers from passing HIV to their babies. This research also showed that high doses of the drug affected the babies' growth and bones (bone toxicity). No problems with the babies' growth or bones were seen when lower doses were given, even if the drug was given every day for a long time,.

If we learn more from this or other research while you are participating in this study that may affect your decision to continue participation, we will let you know.

We do not know if giving the study drug (tenofovir) for a short time to mothers during labor and to babies during the first week of life to try to stop passing HIV to the baby will make this drug, or others like it, less likely to work to treat HIV in the future. This is because the HIV virus may adjust to the drug and become resistant to it. This means that drug may not be as useful as part of a possible treatment for you or for your baby if he or she becomes infected with HIV.

Blood Drawing Risks

Taking blood may cause slight pain, a light headed feeling, swelling and bruising at the place where the blood is taken. Drawing blood can also cause infection, but this is rare. Being in this study requires that you and your baby have many blood samples taken during the first week after your baby is born. Sometimes it causes mothers to be stressed when their baby's blood is being taken.

Social Risks

If you join this study, some hospital staff and all study staff will know that you have HIV. They will also know that it is possible that your baby may be infected with HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatment, such as staying in the hospital longer than usual after having a baby, or attend a special clinic, it may make others wonder if you or your baby have HIV.

What are the possible benefits of being in the study?

You and your baby may receive no benefit from this study. However, knowledge gained from this study may in the future help others not become infected with HIV. You will receive information about your health and your baby's health from the study examinations and laboratory tests that you might otherwise not have. This information will be shared with the health care workers at this clinic so that they may know better what care you or your baby may need.

What if the researchers learn something new?

The study doctors or staff will tell you any new information learned during the study that may cause you to change your mind about you and your baby continuing to participate in the study. Near the end of the study you will be told when the study results will be available and how to learn about them.

What could make us take you out of the study early?

You and your baby may be withdrawn from the study before the study is done if the study is canceled by the study sponsor, the [Malawi/ Brazil] Ministry of Health, the Ethics Committees overseeing the research, the U.S. Food and Drug Administration, or the company that makes the study drug.

You and your baby may be removed from the study if for some reason you or your baby does not receive the study drug as you are supposed to. Your baby may not be given the study drug if the study staff decide that the drug might harm your baby.

If you or your baby receive any study drug, we will ask you to remain in the study and complete your visits, even if all of the study drug has not been given for any reason.

What are the choices if you do not want to be in the study?

You do not have to agree for you and your baby to be in this study. If you choose not to participate, your care and your baby's care at [fill in name of clinic/hospital] will not be affected.

If you agree to take part in the study, you can change your mind at any time without losing the benefits of your standard medical care.

What about confidentiality?

The study doctors and staff will protect information about you and your baby, and your participation in this study to the best of their ability. On your study records (and on your baby's study records), a code will be used instead of your names. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the (Malawi/Brazil) Ministry of Health, the Institutional Review Boards (IRBs) and Ethical Committees, the United States Food and Drug Administration, the company that makes the study drug, the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your records.

Will there be any costs or payments to you?

The study drug, clinic visits, hospital stay, examinations and laboratory tests will be provided free of charge. We will not pay you or your baby to be in the study. However, we will reimburse you for your time and travel to the clinic for scheduled visits, or visits that we ask you to make.

Antiretroviral treatment for HIV will not be provided through this study, however, study staff will refer you to available care and treatment programs (outside of the study) for which you may qualify.

What happens if you or your baby are injured during the study?

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

You are not giving up your legal rights by signing this form.

What should you do if you have problems or questions about the study?

If you ever have questions about this study or if you have a study related medical problem or injury, you should contact the study investigator, [insert name of site investigator] at the [insert physical address for contact]. You may also ring [insert name of site investigator] at [insert phone number].

If you have questions about your rights or your baby's rights as a research volunteer, you may contact

- [insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

The study counselors and other staff would be happy to help you contact the right person to answer any questions you have.

APPENDIX II C
SAMPLE INFORMED CONSENT FORM FOR SCREENING (COHORT 4)
DIVISION OF AIDS, NIAID, NIH

HPTN 057
**A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir
Disoproxil Fumarate in HIV-1 Infected
Pregnant Women and their Infants**

Version [2.0], Dated [28 Oct 09]

Principal Investigator: [insert name and contact information for site PI]

Introduction

You are being asked to take part in screening tests for the research study named above because you are pregnant and infected with HIV, the virus that causes AIDS. The research study will test a drug named tenofovir for use in pregnant women with HIV and their newborn babies. The screening tests will determine if you qualify to participate in the research study. The study is sponsored by the United States National Institutes of Health (NIH). The person in charge of the study at this site is [insert name of site investigator].

Before you decide whether or not to take part in this screening, we would like to explain the purpose of the research study and give you some information about what would be required if you were to participate in the study. We also want to explain the procedures involved in the screening process, any risks and benefits to you, and what is expected of you if you agree to participate in this screening. You are free to ask any questions. After the screening process has been fully explained to you, and if you agree to participate in the screening, you will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy of this form to keep.

What should you know about the screening for the research study?

- Your participation in the screening is entirely voluntary.
- You may decide not to participate in the screening tests or to withdraw from the screening at any time without losing the benefits of your standard medical care.
- If you decide not to participate in the screening, you and your baby cannot participate in this research study, but you can still join another research study later, if one is available and you qualify.
- Even if you agree to participate in the screening, it does not mean that you have agreed to participate in the research study.

Why is this research being done?

This research study is being done to test a drug named tenofovir. There are two purposes for the study. One purpose is to see if tenofovir is safe for use in HIV-infected pregnant women and their newborn babies. The other purpose is to see how much tenofovir should be used for the mother during delivery and for the baby in the first week after birth to try to prevent passing of HIV from a mother to her baby. In this research study, tenofovir is considered investigational. This means that we do not know if the study drug can help protect your baby from getting HIV. It also means that the drug can only be used in a small number of women and babies to make sure it is safe and to see how it works. A similar study is currently being done with the same drug in pregnant women and their babies in America. Tenofovir has been approved by the [insert name of local drug authority] in this country and the United States Food and Drug Administration for the treatment of HIV/AIDS in adults, but it has not been approved for use to prevent HIV from being passed from an HIV-infected mother to her baby. However, they have allowed the use of tenofovir in this study.

The purpose of the screening process is to see if you and your baby are able to join the main study. If the screening tests show that you are able to participate in the research study and you are still interested, you will be given more information about the study at a later visit. If you agree to participate in the research study, you will be asked to sign or make your mark on another consent form after the study has been fully explained to you. You are encouraged to bring the baby's father to the study clinic so that we can also explain the study to him. If the father is available and comes to the study clinic to participate in the informed consent discussion, he will be asked to sign the consent form also. If you agree that you and your baby can participate in the study, you will go to the [insert name of local study facility] to deliver your baby. You must be willing to stay in the clinic/hospital for up to 7 days following the birth of your baby. During this time, you and your baby will have blood drawn several times. Both you and your baby will be given Tenofovir. You will be given Tenofovir when you are in labor and your baby will be given Tenofovir once each day for 7 days starting soon after birth. Mothers and babies will come to the clinic to participate in the study for 1 year after the baby is born.

What will happen if you agree to the study screening?

The study staff will ask you some questions about yourself, your health and pregnancy. They will review your recent medical records, including your HIV test results. You will have a physical examination. The study staff will ask if you are in any other studies and what medicines you have been taking. The study staff will draw about 1 teaspoon (5 mL) of blood from you. Your blood will be tested to check your health. Your blood may also be tested to confirm that you have HIV infection, if needed. Some of your blood will be stored to see if you become resistant to tenofovir later on. You will be asked to return to the clinic to get the results of these blood tests. These screening tests are the first step in determining if you will be able to join the research study. Each screening visit may take approximately *[insert approximate length of visit(s)]* to complete.

Some women will not be able to join the study because of information learned during the screening. If the screening tests show that you are not able to participate in the study, or if you choose not to participate, any leftover blood taken from you will be destroyed. If these screening tests show that you may be able to join the study, more detailed information about the study will be given to you.

You will be able to decide if you want for you and your baby to participate in the study or not. After the study has been fully explained to you, and you have asked all of your questions, the study worker will ask you some questions about the study to be sure that you understand. If you agree that you and your baby will participate in the study, you will be asked to sign another consent form. We will not know for sure whether you can join the study until you come to the hospital for delivery.

What are the risks of study screening?

Taking blood from you may cause slight pain, swelling, a light headed feeling, and bruising at the place where the blood is taken. Drawing blood can also cause fainting or infection, but this is rare. If you are screened for this study, some hospital and study staff will know that you have HIV. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatments or attend a special clinic, it may make others wonder if you have HIV.

What are the possible benefits of study screening?

These screening tests may not be of direct benefit to you. The results of the screening tests will be shared with you and with the medical staff providing your antenatal care at this clinic and may help them know more about what care you need. They may refer you for additional care if they find that your body's system for fighting infections is weak.

What are the choices if you do not want to be screened for the study?

You do not have to agree to be screened for this research study. If you do not agree to the screening, your care at [insert name of clinic] will not be affected. However, you and your baby will not be able to join the research study. If you agree to take part in the screening, you can change your mind at any time without losing the benefits of your standard medical care.

At this clinic, there is a special program for all pregnant women who are infected with HIV. You are advised to follow the [insert name] program for HIV infected women whether or not you decide to be screened for these studies.

What about confidentiality?

The study doctors and staff will protect information about you and your baby, and your participation in these screening tests to the best of their ability. On your study screening records, a code will be used instead of your name. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the (Malawi/Brazil) Ministry of Health, the institutional review boards and ethical committees, the United States Food and Drug Administration, the company that makes the study drug, the study sponsor (the United States National Institutes of Health), and their authorized representatives will be allowed to inspect your screening records.

Will there be any costs or payments to you?

The clinic visits, procedures and blood tests will be free - at no cost to you. You will not receive any payment for having the screening tests done.

Antiretroviral treatment for HIV will not be provided through this study, however, study staff will refer you to available care and treatment programs (outside of the study) for which you may qualify.

What happens if you are injured during the screening?

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

You will not give up your legal rights by signing this consent form.

What should you do if you have problems or questions about the screening?

If you ever have questions about this screening or if you have a study-related medical problem or injury, you should contact the study investigator, [insert name of site investigator] at the [insert physical and mailing address]. You may also ring [insert name of site investigator] at [insert phone number].

If you have questions about your rights or your baby's rights as a research volunteer, you may contact

- [insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [insert telephone number and physical address of above]

APPENDIX II D
SAMPLE INFORMED CONSENT FORM FOR ENROLLMENT (COHORT 4)
DIVISION OF AIDS, NIAID, NIH

HPTN 057
**A Phase I Open Label Trial of the Safety and Pharmacokinetics of Tenofovir
Disoproxil Fumarate in HIV-1 Infected
Pregnant Women and their Infants**

Version [2.0], Dated [28 Oct 09]

Principal Investigators: [insert name and contact information of site PI]

Introduction

You are being asked to participate and to allow your baby to participate, in the research study named above because you agreed to participate in the screening tests and, so far, these test show that you and your baby may be able to participate in the research study. The research study will test a drug named tenofovir for use in pregnant women with HIV and newborn babies. The study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of site investigator].

Before you decide whether or not you and your baby will participate in the study, we would like to explain the purpose of the study, the risks and benefits of participating, and what is expected of you and your baby. This informed consent form gives you information about this study. This information will also be discussed with you. You are free to ask any questions. After the study has been fully explained to you, and if you agree that you and your baby will participate in the study, you will be asked some questions to determine whether you fully understand what is involved. You will be asked to sign this consent form or make your mark in front of a witness. You will be offered a copy of this form to keep. You are encouraged to bring the baby's father to the study clinic so that we can also explain the study to him. If the father is available and comes to the study clinic to participate in the informed consent discussion, he will be asked to sign the consent form also.

What should you know about the research?

- Your participation in the research is entirely voluntary.
- You may decide not to participate in the study or to withdraw from the study at any time without losing the benefits of your standard medical care.
- If you decide not to participate in this research study, you can still join another research study later, if one is available and you and/or your baby qualify.

Why is this research being done?

This research study is being done to test a drug named tenofovir. There are two purposes for the study. One purpose is to see if tenofovir is safe for use in HIV-infected pregnant women and their newborn babies. The other purpose is to see how much tenofovir should be used for the mother during delivery and for the baby in the first week after birth to try to prevent passing of HIV from a mother to her baby. In this research study, tenofovir is considered investigational. This means that we do not know if the study drug can help protect your baby from getting HIV. It also means that the drug can only be used in a small number of women and babies to make sure it is safe and to see how it works. A similar study was done with the same drug in pregnant women and their babies in America. Approximately 89 mother/infant pairs have already participated in this study in Malawi and Brazil. The results up to now show that the drug is safe. Tenofovir has been approved by the [insert name of local drug authority] in this country and the United States Food and Drug Administration for the treatment of HIV/AIDS in adults, but it has not been approved for use to prevent HIV being passed from an HIV-infected mother to her baby. However, they have allowed the use of tenofovir in this study.

Mothers who have HIV can pass HIV to their babies before delivery, during delivery, and after delivery through breastfeeding. Other research studies have shown that giving drugs to the mother and the baby before and soon after birth can cut the chances of passing HIV to the baby. Every woman with HIV who comes to this clinic is offered drugs to help prevent passing HIV to her baby. You and your baby will be offered these drugs regardless of your decision to participate in this research study.

We continue to look for more and better treatments that are safe, easy to give to mothers and babies in local hospitals, and that prevent passing of HIV from mothers to their babies. We do not know if tenofovir, the drug we are testing in this study, is safe for HIV-infected pregnant women and newborns. The studies that have been done in animals and with HIV-infected adults and children make us think that it will be safe in the amounts that will be given in this study. This study will help us find that out. Studies in animals also make us hope that tenofovir may help prevent passing of HIV from a mother to her baby. This study is an important first step in finding out if it will work.

This study will include about 110 mothers and their babies from Malawi and Brazil. About half (55) of the mothers and their babies will come from this country.

What will happen if you agree to participate in the study?

If you agree that you and your baby can be in this study, there are things that you will be asked to do. You will be asked to come to the [insert name of local study facility] for delivery of your baby. You will be asked to stay in the delivery facility for up to seven days following the delivery of your baby. You and your baby will be part of the study until your baby is one year old. If you join the study, some of your blood and your baby's blood will be stored during the study period for later testing related to the study. Some of your blood will be shipped to the United States for testing. After the study and all related testing are completed, any leftover specimens will be destroyed.

The study staff may need to contact or visit you at home or work to remind you of study visits. To participate in the study, you must be willing to tell us how to contact you at home.

No matter whether you decide to participate in the study or not staff at the clinic will offer you the standard study drugs used in this clinic to decrease the chance of passing HIV to your baby.

Mother's Procedures

Labor, delivery and first week after delivery

You will be asked to come to [insert name of local study facility] as soon as your labor begins. When you arrive, the study staff will ask you some questions about your health to make sure you are still eligible for the study. We will ask you to give about 2 teaspoons of blood (10 mL) to check your health. During labor, you will give blood (less than one teaspoon (about 2-3 mL)) before receiving study drug to compare the level of drug in your blood with blood taken after you receive drug. We will give you 2 tablets of the study drug to take with a small amount of milk or other liquid. If you have a C-section a sample of the fluid that surrounds the baby during delivery will be taken (about 2 to 3 mLs, which is less than 1 teaspoon). You will have blood taken after you deliver about 10 mLs, which is about 2 teaspoons. These blood tests will help us check your health and will also give us important information about how much of the drug is in your blood. If you are breastfeeding, about two days after you deliver, you will be asked to give a sample of breastmilk for HIV related tests. Before you leave the hospital (about 7 days after delivery) you will have a physical exam and will be asked to give another sample of blood to check your general health. If you are breastfeeding, you will also be asked to give another sample of breast milk for HIV related tests.

After discharge from the hospital

After you leave the hospital (about 7 days after delivery), you will be asked to come to the clinic at least 5 times during the next 12 months with your baby. Each of these visits may take approximately [insert approximate length of each visit] to complete. At most of these study visits, you will give a blood sample to check your health. If you are breastfeeding, you will also be asked to give a breast milk sample for HIV related tests. Study staff will ask you questions about your health and the health of your baby, and you will have a physical examination. We will give you any information that we learn from these tests and physical exams that relates to your health or the health of your baby.

Baby's Procedures

First week of life

After your baby is born, he or she will have a physical exam and his or her birth records will be reviewed. When blood is taken from your baby it will be taken through a needle inserted into a vein or a prick with a needle on his or hers heel. A blood specimen of less than one teaspoon (5ml) each time will be taken to check the baby's health and to test for HIV infection within 24 hours of

birth and again before he or she leaves the hospital (about 7 days after birth). Your baby will have two more physical exams during the first week of life.

Your baby will be given the study drug (tenofovir) in the form of a liquid solution once each day for 7 days starting as soon after birth as possible. A small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby before the first, fourth and seventh (last) dose of the study drug. After the first, fourth and seventh (last) dose of the study drug, a small amount of blood (less than one teaspoon – 0.5 mL) will be taken from the baby 3 times. Information from these tests will give us important information about how much tenofovir passed from you to the baby. In total, blood will be taken from your baby about 12 times during the first week of life.

After the first week of life

After leaving the hospital, we will ask you to bring your baby to the clinic about 5 more times during the 12 months of the study. You will bring your baby to the clinic for study visits when he or she is 6 weeks old, 12 weeks old, 6 months old, 9 months old and 1 year old. During these visits we will ask questions about your baby's health and we will do a physical exam. We will take small blood samples to check your baby's health (no more than 4 mL, which is about 1 teaspoon). You will be told the results of all the tests performed during the study that affect your baby's health. During the first 3 months we will also test for HIV infection about 2 more times. If you are breastfeeding past 3 months then we will test again for HIV infection 2 more times when your baby is 6 months and 1 year old. If your baby's HIV tests show that he or she may be infected with HIV, we will take another blood sample to confirm the first result. If we learn that your baby is infected with HIV, we will tell you in person as soon as possible.

What are the risks of the study?

Study Drug Risks

The study drug has been tested in animals (adult and baby), human adults, older children and infants. The testing included routine safety tests to see if the drug was harming or having bad effects on the animals or people taking it.

Animal and human studies of study drug (tenofovir) found some problems with kidneys and bones. Whether the animals or humans had these problems and how bad the problems were depended on how much of the drug was given and for how long. In all cases, problems were only seen with very high doses and long term treatment.

Most of the studies done in humans included adults who are infected with HIV. Over 1000 people participated in these studies, and only minor problems were seen. The problems were not different from problems seen in the people in the studies who did not receive tenofovir. The following side effects have been seen in patients being treated with tenofovir: upset stomach, depression, muscle pain, muscle weakness, vomiting, gas, loose or watery stools, dizziness, stomach pain, lack of energy, kidney damage or failure, inflammation or swelling and possible damage to the pancreas, shortness of breath, rash, low phosphate, a chemical in blood, increase of liver function tests in children, allergic reaction which may include a potentially serious swelling of the face, lips and or tongue, fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness,

shortness of breath or a general feeling of illness. These side effects were seen in patients receiving the drug for much longer periods of time and with much higher doses of than in this study. These are not all the side effects seen with this drug. These are the more serious or common side effects with a known or possible relationship. If you have questions concerning additional side effects please ask the clinical study staff.

This study drug (tenofovir) and other similar drugs used to treat HIV infection may cause serious liver problems and other diseases that can rarely lead to liver failure or death. These problems happen more often in women receiving these drugs for treatment of HIV for a long time. Signs of these problems may be: unexplained weight loss, stomach pain, cramps, nausea, vomiting, tiredness, weakness, being short of breath, lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver).

Note: If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped.

Research has recently begun in the United States to see if the study drug (tenofovir) is safe in pregnant women and their babies when given to try to prevent passing HIV to the baby. Tests in animals showed that the study drug may help in stopping mothers from passing HIV to their babies. This research also showed that high doses of the drug affected the babies' growth and bones (bone toxicity). No problems with the babies' growth or bones were seen when lower doses were given, even if the drug was given every day for a long time.

If we learn more from this or other research while you are participating in this study that may affect your decision to continue participation, we will let you know.

We do not know if giving the study drug (tenofovir) for a short time to mothers during labor and to babies during the first week of life to try to stop passing HIV to the baby will make this drug, or others like it, less likely to work to treat HIV in the future. This is because the HIV virus may adjust to the drug and become resistant to it. This means that drug may not be as useful as part of a possible treatment for you or for your baby if he or she becomes infected with HIV.

Blood Drawing Risks

Taking blood may cause slight pain, a light headed feeling, swelling and bruising at the place where the blood is taken. Drawing blood can also cause infection, but this is rare. Being in this study requires that you and your baby have many blood samples taken during the first week after your baby is born. Sometimes it causes mothers to be stressed when their baby's blood is being taken.

Social Risks

If you join this study, some hospital staff and all study staff will know that you have HIV. They will also know that it is possible that your baby may be infected with HIV. These workers are very serious about your privacy. Study staff will make every possible effort to be sure that others do not learn your HIV status. However, sometimes if you receive special treatment, such as staying in the hospital longer than usual after having a baby, or attend a special clinic, it may make others wonder if you or your baby have HIV. You may also feel anxious as you await the results of your baby's HIV test.

What are the possible benefits of being in the study?

You and your baby may receive no benefit from this study. However, knowledge gained from this study may in the future help others not become infected with HIV. You will receive information about your health and your baby's health from the study examinations and laboratory tests that you might otherwise not have. This information will be shared with the health care workers at this clinic so that they may know better what care you or your baby may need.

What if the researchers learn something new?

The study doctors or staff will tell you any new information learned during the study that may cause you to change your mind about you and your baby continuing to participate in the study. Near the end of the study you will be told when the study results will be available and how to learn about them.

What could make us take you out of the study early?

You and your baby may be withdrawn from the study before the study is done if the study is canceled by the study sponsor, the [Malawi/ Brazil] Ministry of Health, the Ethics Committees overseeing the research, the U.S. Food and Drug Administration, or the company that makes the study drug.

You and your baby may be removed from the study if for some reason you or your baby does not receive the study drug as you are supposed to. Your baby may not be given the study drug if the study staff decide that the drug might harm your baby.

If you or your baby receive any study drug, we will ask you and your baby to remain in the study and complete your visits, even if all of the study drug has not been given for any reason.

What are the choices if you do not want to be in the study?

You do not have to agree for you and your baby to be in this study. If you choose not to participate, your care and your baby's care at [fill in name of clinic/hospital] will not be affected.

If you agree to take part in the study, you can change your mind at any time without losing the benefits of your standard medical care.

What about confidentiality?

The study doctors and staff will protect information about you and your baby, and your participation in this study to the best of their ability. On your study records (and on your baby's study records), a code will be used instead of your names. Only the study staff will know this code. The study staff will not give out any information that identifies you without your written consent. However, the (Malawi/Brazil) Ministry of Health, the Institutional Review Boards (IRBs) and Ethical Committees, the United States Food and Drug Administration, the company that makes the study drug, the study sponsor (the U.S. National Institutes of Health), and their authorized representatives will be allowed to inspect your records.

Will there be any costs or payments to you?

The study drug, clinic visits, hospital stay, examinations and laboratory tests will be provided free of charge. We will not pay you or your baby to be in the study. However, we will reimburse you for your time and travel to the clinic for scheduled visits, or visits that we ask you to make.

Antiretroviral treatment for HIV will not be provided through this study, however, study staff will refer you to available care and treatment programs (outside of the study) for which you may qualify.

What happens if you or your baby is injured during the study?

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

You are not giving up your legal rights by signing this form.

What should you do if you have problems or questions about the study?

If you ever have questions about this study or if you have a study related medical problem or injury, you should contact the study investigator, [insert name of site investigator] at the [insert physical address for contact]. You may also ring [insert name of site investigator] at [insert phone number].

If you have questions about your rights or your baby's rights as a research volunteer, you may contact

- [insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

The study counselors and other staff would be happy to help you contact the right person to answer any questions you have.

