IMPAACT 2010

Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants

"VESTED"
Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG

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

Sponsored by:
National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver
National Institute of Child Health and Human Development
National Institute of Mental Health

Study Drugs Provided by:
Gilead Sciences
Mylan
ViiV Healthcare Ltd

DAIDS Study ID #30129
IND # 133,438 Held by DAIDS

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DAIDS Study ID #30129

Version 2.0
Protocol Signature Page

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ACTG	AIDS Clinical Trials Group
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV/r	ritonavir-boosted atazanavir
AUC	area under the curve
BID	twice a day
BMC	bone mineral content
CFR	(US) Code of Federal Regulations
CHAI	Clinton Health Access Initiative
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CMC	clinical management committee
CNS	central nervous system
COBI	cobicistat
CrCl	creatinine clearance
CRF	case report form
CRMS	Clinical Research Management System
CRPMC	Clinical Research Products Management Center
d4T	staduvine
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DHHS	(US) Department of Health and Human Services
DILI	drug-induced liver injury
DMC	Data Management Center
DNA	deoxyribonucleic acid
DRV/r	ritonavir-boosted darunavir
DSMB	Data and Safety Monitoring Board
DTG	dolutegravir
DXA	dual-energy x-ray absorptiometry
EAE	expedited adverse event
EC	ethics committee
eCRF	electronic case report form
EFV	efavirenz
EIA	enzyme immunoassay
EPDS	Edinburgh Postnatal Depression Scale
EUROCAT	European Surveillance of Congenital Anomalies

EVG	elvitegravir
FDA	(US) Food and Drug Administration
FDAAA	(US) Food and Drug Administration Amendments Act
FDC	fixed-dose combination
FTC	emtricitabine
GCLP	good clinical laboratory practice
HBV	hepatitis B virus
HDL	high-density lipoprotein
HESDE	Historical Evidence of Sensitivity to Drug Effects
HIV	human immunodeficiency virus
ICF	informed consent form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
INR	international normalized ratio
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
ITT	intention to treat
LDMS	laboratory data management system
LFT	liver function test
LPC	laboratory processing chart
LPV/r	ritonavir-boosted lopinavir
MOP	manual of procedures
NAT	nucleic acid test
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	(US) National Institutes of Health
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
PACTG	Pediatric AIDS Clinical Trials Group
PCR	polymerase chain reaction
PI	protease inhibitor
PID	participant identification number
PK	pharmacokinetic
PRO	(DAIDS) Protocol Registration Office
PT	prothrombin time
QD	once a day
QTc	corrected QT interval
RAL	raltegravir
RNA	ribonucleic acid
RR	relative risk
RSC	(DAIDS) Regulatory Support Center
SAE	serious adverse event
SDMC	Statistical and Data Management Center
SES	subject enrollment system
SID	study identification number
SOP	standard operating procedure
SRG	safety review group
SUSAR	suspected unexpected serious adverse reaction
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate

TFV-DP	tenofovir diphosphate
ULN	upper limit of normal
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
VL	viral load
VQA	Virology Quality Assurance
WHO	World Health Organization
ZDV	zidovudine

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SCHEMA

Purpose: To compare the virologic efficacy and safety of three antiretroviral regimens for HIV-1-infected pregnant women and to compare the safety of these regimens for their infants

Design: Phase III, three-arm, randomized, open-label study

Study Population: HIV-1-infected pregnant women initiating antiretroviral therapy at 14-28 weeks gestation, and their infants

Sample Size: 639 mother-infant pairs (approximately 213 per arm) with possible adjustment at first interim analysis

Study Drug:

Arm 1: Maternal dolutegravir plus emtricitabine/tenofovir alafenamide [DTG+FTC/TAF]

Arm 2: Maternal dolutegravir plus emtricitabine/tenofovir disoproxil fumarate [DTG+FTC/TDF]

Arm 3: Maternal efavirenz/emtricitabine/tenofovir disoproxil fumarate [EFV/ FTC/TDF]

In the objectives below, "a DTG-containing regimen" refers to the combination of both DTG-containing arms (i.e., Arm 1+Arm 2). "Any pairwise regimen comparison" refers to comparisons of Arm 1 to Arm 2, Arm 2 to Arm 3, and Arm 1 to Arm 3.

Study Duration: Up to approximately 31 months total. Accrual is expected to require approximately 12 months (from the date of first enrollment) and enrolled participants will be followed through pregnancy and for approximately 50 weeks postpartum.

Primary Objectives

To determine the following among HIV-1-infected pregnant women and their infants:

- Whether treatment initiated during pregnancy with a DTG-containing regimen is non-inferior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery
- Whether rates of the following safety outcomes differ for any pairwise regimen comparison
  - Adverse pregnancy outcomes (spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
  - Maternal grade 3 or higher adverse events through 50 weeks postpartum
  - Infant grade 3 or higher adverse events through 50 weeks postpartum

Secondary Objectives

To evaluate the following among HIV-1-infected pregnant women and their infants:

- Whether treatment initiated during pregnancy with a DTG-containing regimen is superior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery
- Whether the following differ when comparing a DTG-containing regimen initiated during pregnancy to EFV/FTC/TDF:
  - Proportion of mothers with HIV-1 RNA <50 copies/mL at delivery
  - Proportion of mothers with HIV-1 RNA <200 copies/mL at 50 weeks postpartum
  - Time to maternal HIV-1 RNA <200 copies/mL through delivery
- Whether the following differs for any pairwise regimen comparison:
  - Proportion of mothers with HIV-1 RNA <200 copies/mL at delivery and at 50 weeks postpartum using the standardized FDA snapshot algorithm
- Whether rates of the following differ when comparing a DTG-containing regimen to EFV/FTC/TDF:
  - Adverse pregnancy outcomes (spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
  - Maternal grade 3 or higher adverse events through 50 weeks postpartum
  - Infant grade 3 or higher adverse events through 50 weeks postpartum
- Whether rates of the following differ for any pairwise regimen comparison:
  - A composite outcome of spontaneous abortion, fetal death, preterm delivery, small for gestational age, or major congenital anomaly
  - A ranked composite infant safety outcome measure through 50 weeks postpartum
  - Infant HIV infection through 50 weeks postpartum
  - Infant mortality through 50 weeks postpartum
  - Infant bone toxicity at 26 weeks postpartum
  - Maternal bone toxicity at 50 weeks postpartum
  - Markers of maternal and infant renal toxicity through 50 weeks postpartum
  - Antiretroviral drug resistance observed with each maternal ART regimen:
    - Among mothers who experience virologic failure (at baseline and time of virologic failure)
    - Among HIV-infected infants (at time of HIV diagnosis)
- Whether treatment initiated during pregnancy with each regimen is non-inferior with regard to preterm delivery and, separately, small for gestational age, for any pairwise regimen comparison

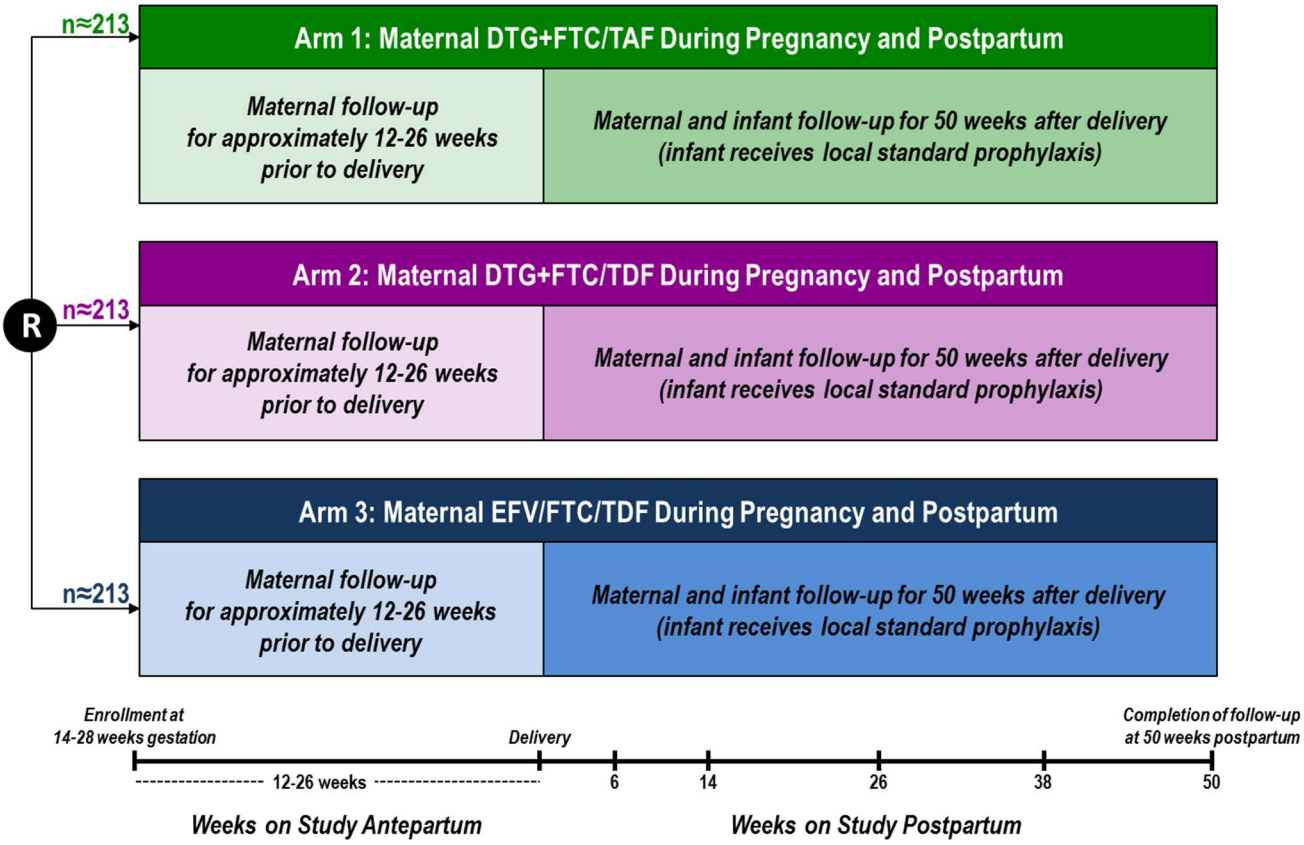
Exploratory Objectives

To:

- Evaluate the following with treatment initiated in pregnancy with a DTG-containing regimen compared to EFV/FTC/TDF:
  - Maternal postpartum depression through 50 weeks postpartum
  - Adverse outcomes of subsequent pregnancies occurring during maternal follow-up
- Evaluate potential immunologic and hormonal predictors of adverse pregnancy outcomes and postpartum maternal health outcomes and the association of these factors with maternal ART regimens
- Assess for associations between maternal antepartum adverse events and adverse pregnancy outcomes
- Assess for associations between maternal antiretroviral drug levels and maternal and infant adverse events
- Assess for mother-to-infant transfer of antiretrovirals during pregnancy and breastfeeding
- Assess adherence to maternal ART regimens in the antenatal and postnatal periods and describe barriers and facilitators of adherence during these periods

IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants

Figure 1
Overview of Study Design



1 INTRODUCTION

1.1 Background

Approximately 1.5 million HIV-infected women deliver annually, with nearly 90% of these births occurring in sub-Saharan Africa (1). Efavirenz/(lamivudine or emtricitabine)/tenofovir disoproxil fumarate [EFV/(3TC or FTC)/TDF] is the preferred first-line antiretroviral treatment (ART) regimen recommended by the World Health Organization (WHO) for adults, including pregnant women (2, 3). For pregnant women who are not able to take EFV, the WHO-recommended alternative first-line regimen includes nevirapine (NVP), which carries known safety concerns when initiated at higher CD4 counts and is not available in fixed-dose combination formulations with TDF/FTC or 3TC. Other alternatives (abacavir (ABC)) or ritonavir-boosted protease inhibitors (PIs)) are often not available or would not be considered by programs due to cost or other concerns. Finding a feasible, safe, and effective alternative first-line regimen to EFV/(3TC or FTC)/TDF during pregnancy is of significant importance, because:

a) Not all women will tolerate (or be ideal candidates for) EFV/(3TC or FTC)/TDF, including women with a history of (or at risk of developing) depression or other psychiatric illness. EFV has been associated with hepatotoxicity (4) and higher rates of suicidal ideation compared with non-EFV based ART (5), and little is known about its potential to exacerbate postpartum depression.
b) An increasing number of women are conceiving while taking ART. Slight concern remains regarding the potential teratogenic effects of first-trimester EFV exposure (6), although EFV is a component of WHO-recommended first-line ART for pregnant women and women of childbearing potential.
c) TDF can cause renal and bone toxicity in a subset of patients taking TDF-containing ART, and may (7) or may not (8) be associated with bone toxicity in perinatally exposed infants.

In addition, it is very important to obtain timely pregnancy efficacy and safety data for antiretrovirals that are currently taken or likely to be taken by large numbers of women of childbearing potential globally within the relatively near future. Unfortunately, pregnancy safety and efficacy data are often late or lacking, leading either to use of suboptimal regimens in pregnant women (or women of childbearing potential), or use in pregnancy of antiretroviral regimens for which minimal pregnancy data exist. Most antiretroviral combinations used thus far have not been demonstrated to result in adverse maternal health, pregnancy, or child health outcomes. However, some ART regimens (e.g., regimens containing lopinavir/ritonavir [LPV/r]) may be associated with increased adverse maternal low grade toxicity and preterm delivery/low birth weight compared to zidovudine (ZDV) plus single dose nevirapine (sdNVP) (9).

It is anticipated that two newer antiretroviral drugs, dolutegravir (DTG) and tenofovir alafenamide (TAF), will be recommended and widely used as first-line in both resource-rich and resource-constrained settings over the next several years because of their favorable potency, safety, and cost profiles. In fact, a modeling exercise undertaken by the Clinton Health Access Initiative (CHAI) suggested that DTG and TAF will replace current ARVs in ≥90% of patients by 2025, and that this may be associated with more than $3 billion in cost savings during that time period (10, 11).

DTG, a once-daily integrase inhibitor, is highly efficacious and generally well tolerated. It appears to have a very high barrier to development of HIV drug resistance. In a head-to-head study comparing DTG combined with ABC and 3TC to EFV/FTC/TDF, the DTG combination had superior virologic activity at 48 weeks (described below) (12). DTG is included in two of the preferred first-line regimens recommended for adults by the US DHHS (13) and is used with increasing frequency in well-resourced settings. DTG was also recently included in WHO guidelines as an alternative first-line agent in non-pregnant adults (3) and is being incorporated into new national program guidelines for first-line use in some resource-limited countries. In 2015, CHAI, UNAIDS, and UNITAID announced a new agreement under which generically-manufactured DTG will be available for $44 /patient per year (a price that is comparable to that of EFV) (14). Hence, it is expected that DTG may soon become a cornerstone of preferred first-line ART treatment globally.

Tenofovir alafenamide fumarate (TAF) is as efficacious as TDF in ART regimens studied thus far, and is associated with less toxicity than TDF as a component of ART (15). Given its favorable toxicity profile, it is likely that TAF will replace TDF in adult ART regimens, assuming that it is competitively priced (16). TAF/FTC received United States Food and Drug Administration (FDA) approval in April 2016 (as Descovy®). TAF/FTC (like DTG) has already been sub-licensed with the Medicines Patent Pool, and TAF is cheaper to manufacture than TDF (requiring fewer raw materials). It will therefore fortunately be possible for generic pharmaceutical producers to manufacture a single combination pill of DTG/TAF/FTC (or 3TC) to be taken once daily that would be affordable and accessible in resource-limited settings.

In sum, it is very likely that both DTG and TAF will be used with increasing frequency in the future, potentially as components of first-line recommended ART globally. The WHO 2015 guidelines update noted that neither DTG nor TAF had been studied in pregnancy (both were pregnancy Category B); however, as described in Sections 1.2.2 and 1.3.2, data from studies in pregnancy are emerging. If DTG and TAF are included in future WHO-recommended first-line regimens in resource-limited settings as anticipated, it will be important to have data regarding their efficacy and safety in pregnancy (given the desire to use the same first-line ART regimens in pregnant and non-pregnant patients, for programmatic simplicity). These data will also be of relevance in the US and other well-resourced settings.

1.2 Prior Research on Dolutegravir (DTG, Tivicay®)

1.2.1 Dolutegravir: Studies in Non-Pregnant Adults

Superior virologic efficacy has been observed in randomized trials of DTG-containing versus EFV- or PI-containing three-drug ART regimens among treatment-naïve adults, in three out of four trials (12, 17-19).

In the SINGLE trial, 833 ART-naive adults (16% women) with HIV-1 RNA ≥1,000 copies/mL were randomized in double-blind fashion to start ART with DTG+ABC/3TC versus EFV/TDF/FTC (and received at least one dose). At week 48, 88% of participants in the DTG arm versus 81% in the EFV arm had HIV-1 RNA <50 copies/mL (per FDA snapshot algorithm) (p=0.003, meeting superiority criterion) (12). A low and similar percentage of participants in both arms had virologic failure; however, 10% of participants in the EFV arm and 2% of the DTG arm discontinued study drug due to adverse events (AEs). No resistance to DTG nor to NRTIs was detected in virus from SINGLE trial participants randomized to DTG and experiencing virologic failure (while five participants in the EFV arm developed drug-resistant virus) (17). In the Phase IIb SPRING-1 trial in ART-naive adults, 205 patients were randomized to start DTG (10 mg, 25

mg, or 50 mg) or EFV (20). Week 16 response rates (HIV-1 RNA ≤50 copies/mL) were 93% for all doses of DTG and 60% (30 of 50) for EFV. Week 48 response rates were 87% (139 of 155) for all doses of DTG and 82% (41 of 50) for EFV.

In another randomized trial among ART-naive adults (the open-label FLAMINGO study, 15% of participants female), once-daily DTG was found to be superior to once-daily darunavir/ritonavir (DRV/r, each in combination with either TDF/FTC or ABC/3TC) at 48 weeks (per FDA snapshot algorithm). Four hundred eighty-four participants were included in the analysis (242 in each arm); 217 (90%) participants in the DTG arm and 200 (83%) in the DRV/r arm had HIV-1 RNA <50 copies/mL (adjusted difference 7.1%, 95% CI 0.9-13.2) (18). DTG was therefore deemed non-inferior (and superior, on pre-specified secondary analysis). Virologic failure occurred in two participants (<1%) in each arm, while a slightly higher proportion of patients in the DRV/r arm discontinued drug (4%) compared with the DTG arm (2%) due to AEs or stopping criteria. No new primary drug resistance mutations were detected in participants in either arm. Ninety-six-week data from the FLAMINGO study showed higher rates of virologic suppression to <50 copies/mL in the DTG arm (80%) compared with the DRV/r arm (68%, p=0.002), with the greatest difference in patients with high viral load at baseline (17).

In the ARIA randomized trial conducted among 495 treatment-naive women, DTG/ABC/3TC had superior virologic efficacy to ritonavir-boosted atazanavir (ATV/r) + TDF/FTC at 48 weeks (19). Using the FDA snapshot algorithm with HIV-1 RNA<50 copies/mL, 82% in the DTG arm versus 71% in the ATV/r arm were deemed to have virologic success at 48 weeks (p=0.005). Two percent versus 6% had virologic non-response due to HIV-1 RNA above threshold, and 4% versus 7% had no virologic data due to an adverse event or death in the DTG and ATV/r arms, respectively.

DTG was also found to be non-inferior to raltegravir (RAL) in the double-blind SPRING-2 Study conducted in North America, Australia, and Europe (21). In this trial, 822 ART-naive adults with HIV-1 RNA ≥1,000 copies/mL were randomized to start ART with DTG or RAL and received at least one dose (each in combination with either investigator-selected TDF/FTC or ABC/3TC. At 96 weeks, 81% of participants in the DTG arm and 76% of participants in the RAL arm had HIV-1 RNA <50 copies/mL (adjusted difference 4.5%, 95% CI -1.1% to 10.0%). Virologic non-response occurred in fewer participants in the DTG arm versus the RAL arm (5% versus 10% respectively). Only 2% of participants in each arm discontinued study drug due to AEs (most of which occurred by week 48). At 48 weeks, no new drug resistance mutations were found in participants failing DTG.

The most common adverse events reported with DTG-containing ART are insomnia, headache, dizziness, abnormal dreams, and depression (in 6-11% of patients) (22-24); anxiety, transaminitis, diarrhea, and rash (in less than 5% of patients); hypersensitivity and drug-induced liver injury (DILI) are very rare. DTG inhibits the tubular excretion of creatinine, and may thus cause a small (~0.1-0.15 mg/dL), non-pathologic increase in serum creatinine within the first few weeks of DTG initiation that does not reflect renal injury.

1.2.2 Dolutegravir: Studies in Pregnancy

DTG was classified as FDA pregnancy Category B (when this classification scheme was used).

Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented. In the most recent version of the Antiretroviral Pregnancy Registry report (issued 30 June 2017), 2/77 women with first trimester exposure to DTG had a live-born child with a reported birth defect and 2/56 women with second or third trimester exposure had a live-born child with a reported birth defect (25).

IMPAACT P1026s has reported pharmacokinetic outcomes in 13 women taking DTG during pregnancy, and their neonates, with these data more recently updated for 21 women, all enrolled in the United States (26, 27). Median third trimester DTG levels were somewhat lower than second trimester (or postpartum) levels in these 11 participants. However, second and third trimester DTG C_{min} concentrations (0.86 mcg/mL in both cases) exceeded the IC90 for the drug (which is approximately 0.064 mcg/mL), and third trimester AUC and trough levels were similar to those in non-pregnant adults. Infant DTG drug levels at birth (C_{max} was approximately 2 mcg/mL) were also well above the IC90. DTG pregnancy pharmacokinetic data are still being collected in additional participants in P1026s (9 of whom are already enrolled). Maternal HIV-1 RNA was <50 copies/mL at delivery in 15 of 15 women (100%) in whom it was measured. In sum, data from P1026s thus far suggest that while third trimester DTG levels may be lower, reasonable DTG levels (and transplacental transfer of DTG) will nevertheless be achieved in pregnancy with standard dosing, although final data are awaited. It is anticipated that sufficient DTG pregnancy pharmacokinetic data will be available prior to the opening of IMPAACT 2010 (these data will be reviewed by the 2010 Protocol Team prior to study initiation, to verify that it is appropriate to move forward with the study as planned). Of note, as of June 2016, five babies were reported to have congenital anomalies (and two babies with findings deemed to be "normal variants") of approximately 15 born (see Table 1).

Table 1
Reported Congenital Anomalies in IMPAACT P1026s Dolutegravir Arm

Anomaly	Other Findings	Gestational Age DTG Started	Relatedness
Multicystic dysplastic right kidney	Cystic fibrosis	11 4/7 weeks	Possibly related
Cyst left kidney	None	12 2/7 weeks	Possibly related
Total anomalous pulmonary venous return	None	16 6/7 weeks	Not related
Congenital filum terminale fibrolipoma	Normal conus, sacral dimple	18 3/7 weeks	Not related
Hereditary chin tremors	None	28 6/7 weeks	Resolved
Two vessel umbilical cord	None	Prior to conception	Normal variant
Post-axial supernumerary digit	None	9 weeks	Normal variant

Based on the nature of the anomalies and the timing of first exposure in pregnancy, possible association with DTG can be ruled out for all but two of the five anomalies (the renal cysts). Given the gestational age at which DTG was initiated and the nature of the renal cysts, they are also unlikely to be related to exposure to DTG (of note, in both instances the renal cysts were incidentally detected during routine antenatal fetal ultrasound, rather than due to any clinical concern or finding – because of this, and because they are not likely to have medical or surgical

significance, these renal cysts would not generally be described as major congenital malformations).

An observational surveillance study of birth outcomes in women starting ART during pregnancy (in the context of the national HIV treatment program) showed similar rates of adverse pregnancy outcomes (stillbirth, neonatal death, preterm or very preterm birth, small for gestational age or very small for gestational age) among 845 women initiating DTG/TDF/FTC (at median 19 weeks gestation) compared with 4593 women initiating EFV/TDF/FTC (at median 21 weeks gestation) in pregnancy. Among 512 women initiating ART in the first trimester of pregnancy (116 DTG/TDF/FTC, 396 EFV/TDF/FTC), one major congenital abnormality was identified (skeletal dysplasia in an EFV-exposed infant). (28)

Several smaller studies of DTG in pregnancy are planned. The DolPHIN1 study in Uganda (NCT02245022) will evaluate DTG pharmacokinetics in pregnancy. This study will enroll 60 women, 30 in the DTG arm and 30 in standard of care arm (NVP or EFV + 2 NRTI). The planned DolPHIN2 study will enroll 250 women late in pregnancy (approximately half of whom will take DTG-containing ART) and will evaluate maternal HIV-1 RNA at delivery, safety and tolerability. In addition, women who become pregnant while taking the DTG/ABC/3TC fixed dose combination tablet while participating in the ARIA trial (described in Section 1.2.1) will have DTG PK testing (NCT02075593).

1.2.3 Animal Studies of Dolutegravir

The following information was obtained from the US DHHS Perinatal Guidelines, last updated 6 August 2015 (13).

Carcinogenicity

DTG was not genotoxic or mutagenic *in vitro*. No carcinogenicity was detected in 2-year long-term studies in mice at exposures up to 14-fold higher than that achieved with human systemic exposure at the recommended dose, or in rats at exposures up to 10-fold higher in males and 15-fold higher in females than human exposure at the recommended dose.

Reproduction/Fertility

DTG did not affect fertility in male and female rats and rabbits at exposures approximately 27-fold higher than human clinical exposure, based on area under the curve, at the recommended dose.

Animal Teratogenicity/Developmental Toxicity

Studies in rats and rabbits have shown no evidence of developmental toxicity, teratogenicity, or effect on reproductive function with DTG.

Placental and Breast Milk Passage

Studies in rats have demonstrated that DTG crosses the placenta in animal studies and is excreted into breast milk in rats.

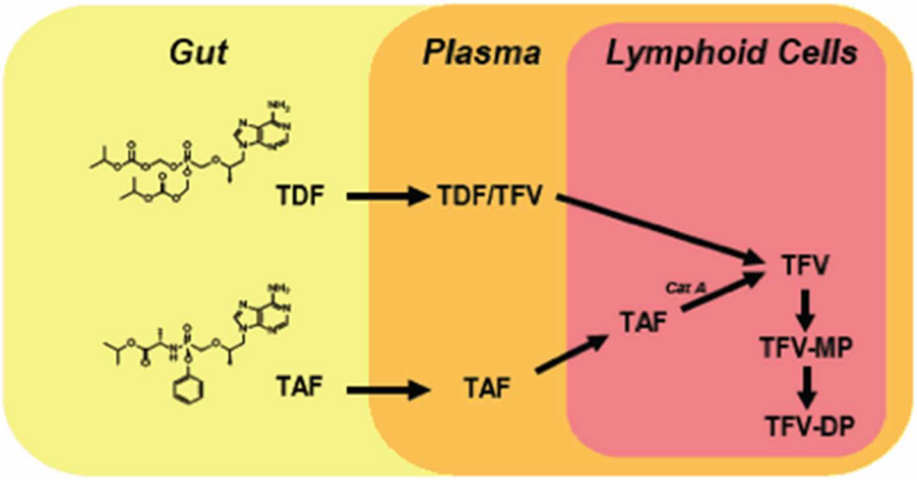
1.3 Prior Research on Tenofovir Alafenamide (TAF)

1.3.1 Tenofovir Alafenamide: Studies in Non-Pregnant Adults

TDF, a prodrug of tenofovir (TFV), is associated with renal and bone toxicity in adults (29, 30) and may be associated with bone toxicity in perinatally exposed infants (8). The PROMISE trial did not find that TDF-containing ART was associated with lower newborn bone mineral content compared with non-TDF (ZDV) containing ART, when NRTIs were used in combination with LPV/r during pregnancy, but did find that both of these ART regimens were associated with significantly lower bone mineral content than ZDV+sdNVP (7). The PROMISE results also revealed the puzzling finding of higher rates of severe adverse pregnancy outcomes and 14-day infant mortality among women who received LPV/r+TDF/FTC compared with LPV/r+ZDV/3TC during pregnancy, although the rates of severe adverse pregnancy outcomes did not differ significantly between women who received LPV/r+TDF/FTC versus ZDV/sdNVP (9). Reassuringly, a different (observational) study did not demonstrate higher rates of adverse pregnancy outcomes with use of EFV/TDF/FTC compared with other 3-drug ART (or with ZDV) during pregnancy (31).

Tenofovir alafenamide fumarate, another prodrug of TFV, results in approximately 10-fold lower plasma concentration of drug but at least 4-fold higher intracellular drug concentration (32), and requires a smaller quantity of raw materials to produce. This is because after absorption from the gut, only a small fraction of TAF is metabolized in the plasma to TFV (Figure 2). Instead, the TAF prodrug is predominantly metabolized intracellularly into TFV, which is then phosphorylated to become the active drug tenofovir diphosphate (TFV-DP). In contrast, after gut absorption, the majority of the TDF prodrug is converted to TFV in the plasma; TFV is then taken up into cells, and converted into the active TFV-DP intracellularly. It is thought that the ~90% lower systemic exposure to TFV leads to its lower toxicity (as TFV levels have been associated with renal and bone toxicity).

Figure 2
Absorption of TAF and TDF in Gut, Plasma, and Lymphoid Cells



The virologic efficacy of ART with elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF is non-inferior to that of EVG/COBI/FTC/TDF in several large trials (15, 33). In two controlled, double-blind Phase III studies conducted in 1,744 ART-naive HIV-infected adults from 16 countries (15% women), participants were randomly assigned (1:1) to receive once-daily EVG/COBI/FTC/TAF or EVG/COBI/FTC/TDF with matching placebo. At 48 weeks, 92% of 866 patients in the TAF group and 90% of 867 patients in the TDF group had plasma HIV-1 RNA <50 copies/mL (per FDA snapshot algorithm)—adjusted difference 2.0%, 95% CI -0.7 to 4.7 (15). Patients in the TAF arm had significantly smaller mean serum creatinine increases than those in the TDF arm (0.08 versus 0.12 mg/dL; p <0.0001), significantly less proteinuria (median percent change -3 versus. 20; p <0.0001), and a significantly smaller decrease in bone mineral density at spine (mean % change, -1.30 versus -2.86; p <0.0001) and hip (-0.66 versus -2.95; p<0.0001) (15).

In a Phase II study, 103 ART-naive adults were randomized to start darunavir/COBI/FTC/TAF and 50 were randomized to start darunavir/COBI/FTC/TDF once daily with matched placebos. At week 48, the proportions with HIV-1 RNA <50 copies/mL were similar (77% in the TAF versus 84% in the TDF arms); the difference was driven by higher rate of discontinuations in TAF (6.8%) versus TDF (2%) (33). The safety profiles of both arms (TAF versus TDF) were similar, with 92% versus 94% of participants reporting any treatment-emergent adverse events, and 7% versus 8% reporting a grade 3 or 4 adverse event (33). The TAF arm had significantly better renal and bone safety parameters than the TDF arm: less proteinuria and less change in hip and spine bone mineral density.

Of note, TAF appears to have similar activity against hepatitis B as TDF (34, 35), although Phase III trial results are not yet published.

TAF PK in Non-Pregnant Adults

Standard TAF dosing results in at least four-fold higher intracellular concentrations of the active TFV-DP drug compared with standard TDF dosing (32). Based on existing data, plasma TAF levels can be used to accurately predict intracellular TFV-DP levels in non-pregnant individuals and it is unlikely that pregnancy would affect this relationship (36). Adherence preceding the observed TAF dose (prior to PK testing in P1026s) should not substantially affect plasma TAF levels, given its short plasma half-life. The IC90 from 10-day monotherapy studies for TAF is <50 ng*h/mL.

Table 2 shows plasma TAF area under the curve (AUC) in non-pregnant adults from Phase III studies of TAF (36). Both TAF 25 mg and TAF 10 mg with COBI yield similar AUC parameters.

Table 2
Plasma TAF AUC in Non-Pregnant Adults

	Genvoya + Descovy (TAF 10 & 25 mg) AUC (ng*h/mL) N=831 (292-0104, 292-0111, 311-1089)	**Descovy only (TAF 25 mg) AUC (ng*h/mL) N=161 (311-1089)**
Mean	182	167
Median	167	158
Min	30.3	77.6
Max	1869	406
10% percentile	74.30	111.7

1.3.2 Tenofovir Alafenamide: Studies in Pregnancy

TAF was classified as FDA pregnancy Category B (when this classification scheme was used).

Thus far, minimal safety or efficacy data for TAF in pregnancy have been published or presented. In the most recent version of the Antiretroviral Pregnancy Registry report (issued 30 June 2017), 1/8 women with first trimester exposure to TAF had a live-born child with a reported birth defect and 0/10 women with second or third trimester exposure had a live-born child with a reported birth defect. (25)

The Phase IV WAVES study of EVG/COBI/FTC/TAF versus ATV/r + TDF/FTC (NCT01705574) enrolled only women (n=583). The extension phase of the study randomizes those in the ATV/r arm to remain on their current regimen or switch to EVG/COBI/FTC/TAF. Women who become pregnant in this study are encouraged to remain on their study drugs, and pregnancy outcomes are captured. Among 14 women with pregnancy in the EVG/COBI/FTC/TAF arm thus far, three had a live birth, four had an elective abortion, five had a spontaneous abortion, and two were pending their pregnancy outcome (37). Among six women with pregnancy in the ATV/r + FTC/TDF arm thus far, three had a live birth, one had an elective abortion, one had a spontaneous abortion, and one was pending her pregnancy outcome (37). These numbers are too small to permit meaningful interpretation of findings; it is also important to note that spontaneous abortion rates in women followed prospectively from conception, as in this study, are not available for most ART regimens, and that spontaneous abortion may occur in up to one third of the general population) (38).

As noted in Section 1.6.2, tenofovir (the metabolite of both TAF and TDF) crosses the placenta well. Given approximately 10-fold higher plasma concentrations of tenofovir with the use of TDF (compared with TAF), placental concentrations of tenofovir may well be lower with TAF than with TDF. However, no data on this exist to date.

TAF PK in Pregnancy

IMPAACT P1026s is currently evaluating TAF PK in pregnancy. As of November 2017, 65 women taking TAF during pregnancy had enrolled in P1026s (27 taking 25 mg unboosted, 8 taking 25 mg boosted with COBI or RTV, and 30 taking 10 mg boosted with COBI).

Version 1.0 of this protocol specified that TAF pregnancy PK data from IMPAACT P1026s would be reviewed to determine whether standard TAF dosing in pregnancy yields drug exposures exceeding a minimum level above which the drug is likely to maintain efficacy in pregnancy. Plasma TAF AUC in second and third trimesters was specified as the PK parameter of interest, to be reviewed when six or more women in P1026s had TAF PK data available through pregnancy outcome (with either the 25 mg TAF doing or the 10 mg TAF dosing boosted with COBI). Pre-specified decision rules for this data review were as follows:

- If at least 50% of women had TAF AUC >10th percentile (i.e., >74 ng*hr/mL) on all measurements, IMPAACT 2010 would be permitted to open. The IMPAACT 2010 team, in collaboration with the IMPAACT P1026s team, would summarize the TAF PK results and the decision to open IMPAACT 2010 to enrollment in a memorandum to the study sites.

- If <50% of women reach this AUC target, the IMPAACT 2010 team would discuss next steps, which might include waiting for additional TAF pregnancy PK data. The team would also review any available virologic suppression data from P1026s participants taking TAF-containing regimens.

As documented in a protocol Clarification Memorandum issued under protocol Version 1.0, the protocol-specified review of data from IMPAACT P1026s was completed in mid-June 2017. The review included data from 11 women, seven of whom were receiving 25 mg TAF (unboosted) and four of whom were receiving 10 mg TAF boosted with COBI. Among the 11 women, two had PK samples collected only in the second trimester of pregnancy, four had samples collected in both the second trimester and the third trimester, and five had samples collected only in the third trimester. The resulting fifteen AUC values during pregnancy ranged from 119 to 524 ng*hr/mL, with a median of 152 ng*hr/mL in the second trimester and a median of 176 ng*hr/mL in the third trimester. All AUC values were greater than 74 ng*hr/mL. Based on these results, the TAF PK criteria for opening IMPAACT 2010 to accrual were met.

1.3.3 Animal Studies of Tenofovir Alafenamide

Embryonic fetal development studies of TAF have been performed in rats and rabbits. These revealed no evidence of impaired fertility or harm to the fetus due to TAF. The embryo-fetal studies showed no observed adverse effect levels in rats and rabbits occurred at TAF exposures similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose. TAF is rapidly converted to tenofovir. The observed tenofovir exposure in rats and rabbits were 59 and 93 times higher than human tenofovir exposures at the recommended daily doses, respectively. The information above was obtained from the Genvoya® package insert (39).

Although there are no preclinical data available regarding the penetration of TAF into the placenta or breast milk, data from animal (rat) and *in vitro* models suggest that it is unlikely that intact TAF-prodrug crosses the placental barrier at significant levels, due to the expression of efflux transporters (40), as is the case with TDF, also a prodrug of tenofovir (41).

1.4 Prior Research on Dolutegravir + Emtricitabine/Tenofovir Alafenamide (DTG + FTC/TAF) in Non-Pregnant Adults

DTG and FTC/TAF have not yet been studied in combination. However, two studies have evaluated DTG/3TC as two-drug therapy in ART-naïve adults, given the high potency and high barrier to emergence of resistance with DTG:

a. A pilot study of DTG/3TC as initial therapy in 20 ART-naive adults with baseline HIV-1 RNA ≤100,000 copies/mL and CD4 count ≥200 cells/mm^3 (the PADDLE study, NCT02211482). Results were encouraging: after 8 weeks of DTG/3TC, all 20 study participants had a viral load below 50 copies/mL, all 20 maintained HIV-1 RNA below 50 copies through week 24, and 18 of 20 had HIV-1 RNA <50 copies/mL at 48 weeks (one had low-level viremia, one died) (12, 42).

b. The AIDS Clinical Trials Group (ACTG) conducted A5353, a Phase II single-arm open-label study of two-drug treatment with DTG/3TC in 120 ART-naive adult men and women with HIV-1 RNA ≥1,000 copies/mL and <500,000 copies/mL (at entry, median HIV-1 RNA was 4.6 $\log_{10}$ copies/mL and CD4 count was 387 cells/mm^3). At 24 weeks, 108/120 (90%, CI [83%, 95%]) had HIV-1 RNA <400 copies/mL, with no significant difference in suppression

rates between persons with entry HIV-1 RNA ≤100,000 copies/mL versus >100,000 copies/mL: 90% [82%, 96%] and 89% [75%, 97%], respectively. In the as-treated population, 108/112 (96% [91%, 99%]) had HIV-1 RNA < 50 copies/mL at 24 weeks, with no difference between the HIV-1 RNA strata (99% [93%, 100%] versus 92% [78%, 98%], p=0.10). The three participants (two in low, one in high HIV-1 RNA strata) with virologic failure had plasma DTG levels below the limit of quantification around the time of failure, and no integrase mutations were detected (M184V was detected in one participant). (43)

The fact that DTG/3TC alone (without a third drug such as TAF) may be sufficiently potent ART in first-line treatment of adults provides some further assurance of the potency of three-drug ART with DTG+FTC/TAF in pregnant women, although there are insufficient data on DTG/3TC alone in non-pregnant adults to warrant testing this approach in pregnant women.

1.5 Prior Research on Emtricitabine (FTC, Emtriva™)

1.5.1 Emtricitabine: Studies in Non-Pregnant Adults

Emtricitabine (FTC) is a synthetic nucleoside analogue with activity against HIV reverse transcriptase. FTC is widely used globally, and is included in the first-line recommended regimen by the WHO for adults, including pregnant women (2, 3). It is also included in recommended agents to be used during pregnancy by the US DHHS (13).

Two Phase III controlled studies (FTC-301A and FTC-303) provide the most information concerning the safety and efficacy of FTC in HIV-infected adults treated for extended periods with combinations of ART (44).

Study FTC-301A was a 48 week, double-blind, active-controlled, multicenter study comparing FTC (200 mg) once daily to d4T in combination with once daily open-label didanosine and EFV in 571 ARV-naïve patients with plasma HIV RNA >5,000 copies/mL. At week 48, FTC was statistically superior to d4T with 81% of the patients in the FTC treatment group achieving and maintaining plasma HIV RNA <400 copies/mL compared with 68% of the patients in the d4T treatment group. Likewise, the proportion of patients who achieved and maintained plasma HIV RNA <50 copies/mL was statistically significantly different with 78% of patients in the FTC treatment group compared with 59% of patients in the d4T treatment group. Additionally, FTC-treated patients had a statistically greater increase in CD4 cell count at Week 48 with a mean increase from baseline of +168 cells/mm^3 for the FTC group and +134 cells/mm^3 for the d4T group. The proportion of patients with virologic failure was 3% in the FTC group and 11% in the d4T group. A statistically greater proportion of patients in the d4T group experienced an AE that led to study drug discontinuation through Week 48 than in the FTC group (13% versus 7%).

Study FTC-303 was a 48 week, open-label, active-controlled, multicenter study comparing FTC to 3TC in combination with d4T or ZDV and a PI or NNRTI in 440 patients who were on a 3TC-containing triple-ARV regimen for at least 12 weeks prior to study entry and had plasma HIV RNA <400 copies/mL (44). Patients were randomized 1:2 to continue therapy with 3TC (150 mg BID) or to switch to FTC (200 mg QD). All patients were maintained on their stable background regimen. Through 48 weeks of therapy, there was no statistically significant difference between treatment groups in efficacy outcomes. The proportion of patients with virologic failure was 7% in the FTC arm and 8% in the 3TC arm. Through 48 weeks of therapy, the proportion of patients who achieved and maintained plasma HIV RNA <400 copies/mL was 77% in the FTC arm and 82% in the 3TC arm. The difference was largely attributed to attrition from the study and not loss of virologic activity. Likewise, the proportion of patients who achieved and maintained plasma

HIV RNA <50 copies/mL was 67% in the FTC arm and 72% in the 3TC arm. The mean increase from baseline in CD4 cell counts was +29 cells/mm^3 in the FTC arm and +61 cells/mm^3 in the 3TC arm. These findings support equivalent efficacy of FTC 200 mg once daily and 3TC 150 mg administered twice daily (45).

More than 2,000 adult patients with HIV infection have been treated with FTC alone or in combination with other ARVs for periods of 10 days to 200 weeks in Phase I-III clinical trials. Assessment of AEs is based on data from studies FTC-301A and FTC-303 in which 571 treatment naïve (FTC-301A) and 440 treatment experienced (FTC-303) patients received FTC 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving FTC with other ARVs in clinical trials were headache, diarrhea, nausea, and rash event, which were generally mild to moderate in severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All AEs were reported with similar frequency in FTC and control treatment groups with the exception of skin discoloration, which was reported with higher frequency in the FTC-treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. Laboratory abnormalities in these studies occurred with similar frequency in the FTC and comparator groups.

1.5.2 Emtricitabine: Studies in Pregnancy

FTC was classified as FDA pregnancy Category B (when this classification scheme was used). There are sufficient data in the Antiretroviral Pregnancy Registry to rule out at least a 1.5-fold increase in overall birth defects and a 2-fold increase in the risk of cardiovascular and genitourinary birth defects with FTC (46).

In a study of 35 pregnant women given a dose of 400 mg FTC at the onset of labor, median cord/maternal drug ratio was 0.73, indicating significant placental transfer. Median AUC after a 400 mg dose in labor was 15.5 mg*h/L, similar to levels in non-pregnant adults after a 200 mg dose. Among 18 women receiving standard FTC dosing (200 mg/day) during the third trimester, median AUC of 8.6 µg*h/mL was above the target of >7 µg*h/mL, but only 12 of 18 women were above the target (47). Mean cord/maternal blood ratio at delivery was 1.17.

Emtricitabine is excreted into human breast milk, achieving median minimal and maximal breast milk concentrations of 177 and 679 ng/mL, well above the estimated emtricitabine IC50 for HIV-1. The median dose of FTC that was estimated to be delivered by breast milk represented only 2% of the recommended infant treatment dose. (48)

1.5.3 Animal Studies of Emtricitabine

Carcinogenicity

In long-term oral carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or mouse micronucleus assays. (49)

Reproduction/Fertility

FTC did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose. (49)

Teratogenicity/Developmental Toxicity

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. (49)

Placental and Breast Milk Passage

FTC has been shown to cross the placenta in mice and rabbits; the average fetal/maternal drug concentration was 0.4 in mice and 0.5 in rabbits (47).

1.5.4 Emtricitabine and Hepatitis B Infection

Exacerbations of hepatitis B (HBV) have been reported after discontinuation of FTC (50, 51). Patients who are co-infected with HBV and HIV may have increased values on liver function tests (LFTs) and exacerbation of hepatitis symptoms when FTC is stopped. Usually these symptoms are self-limiting; however, serious complications have been reported. The threshold for stopping antiretrovirals with activity against HBV (including FTC) should be high, and patients co-infected with HBV and HIV should be closely monitored with both clinical and laboratory assessments for several months after stopping FTC treatment.

1.6 Prior Research on Tenofovir Disoproxil Fumarate (TDF, Viread®)

1.6.1 Tenofovir Disoproxil Fumarate: Studies in Non-Pregnant Adults

TDF is one of the most widely-used antiretrovirals globally, and is included in the first-line recommended regimen by the WHO for adults, including pregnant women (2, 3).

Although TDF is a nucleotide analogue, it has the same mechanism of action and resistance pattern as NRTIs. Therefore, for simplification of discussion, TDF will be referred to as an NRTI in this study.

Efficacy in Treatment Naïve Patients

Study 903 was a 144-week randomized, double-blind trial designed to compare the efficacy and safety of a treatment regimen of TDF, 3TC, and EFV to a regimen of d4T, 3TC and EFV in 600 ART-naive adults with HIV infection. Following the completion of the double blind portion of the trial, there was an additional two-year single arm open-label portion of the trial in selected sites, wherein all patients received TDF, 3TC and EFV as once daily regimen. (Patients originally randomized to the d4T arm switched to receive TDF.)

In a 144-week analysis, when missing observations in the intent to treat (ITT) analysis were treated as having plasma HIV RNA concentrations greater than 400 copies/mL, 76% of participants in the TDF group and 72% of participants in the d4T active control group achieved plasma HIV RNA concentrations <400 copies/mL. Plasma HIV RNA concentrations <50 copies/mL at week 144 were seen in 73% and 69% of participants in the TDF and d4T active control groups, respectively. The mean increases in CD4 cell count from baseline to week 144 were 263 cells/mm^3 and 283 cells/mm^3 for the TDF and d4T active control groups, respectively. The assessments of safety and tolerability indicate that the safety profile of TDF 300 mg/day was similar to that of the d4T active control (52).

FTC-TDF compared to 3TC-ZDV

Study 934 was a Phase III, randomized, open-label, multicenter study designed to compare a regimen of EFV with either TDF 300 mg/FTC 200 mg once daily or ZDV 300 mg/3TC 150 mg twice daily as fixed dose combination (FDC) Combivir® (52). Interim analysis at 48 weeks revealed discontinuation occurred more frequently in the 3TC-ZDV group (9%) than FTC-TDF (4%), mostly because of AEs such as anemia and nausea. The 48-week data demonstrated that, using the time to loss of virologic suppression as the primary analysis in which missing or switching is counted as a failure, the proportion of participants with plasma HIV RNA levels less than 400 copies/mL in an ITT analysis (n=487) was 84% in the FTC-TDF group compared to 73% in the 3TC-ZDV-treated participants (p=0.002). The proportion of participants with plasma HIV RNA levels <50 copies/mL was 80% in the FTC-TDF group versus 70% in the 3TC-ZDV group (p=0.021). These results are supported by 96-week data (53).

Tenofovir and TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) between 6- and 12-fold higher than observed in humans caused bone toxicity. In monkeys, the bone toxicity was diagnosed as osteomalacia, and appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Studies to assess loss of bone density among patients receiving tenofovir are described below.

More than 1,200 patients have received TDF 300 mg once daily alone or in combination with other ARVs in Phase I-III clinical trials. Over 11,000 patients have received TDF in expanded access programs. The cumulative patient exposure to marketed TDF from first approval to 31 December 2003 is estimated to be approximately 200,000 patient-years of treatment.

In clinical trials in treatment-experienced patients (Studies 902 and 907), the safety profile of TDF 300 mg/day was similar to that of placebo. There were no clinically significant AEs attributable to TDF 300 mg once daily other than a slightly higher incidence of mild to moderate gastrointestinal AEs (nausea, diarrhea, vomiting, and flatulence). Few adverse laboratory events were documented other than mild or moderate transient hypophosphatemia. Clinically significant events considered by the investigators to be related to TDF were uncommon and none suggested potential adverse drug reactions or drug-drug interactions (54, 55).

Study 910 was initiated to observe the long-term safety effects of TDF, in combination with other ARVs, in participants who have completed prior TDF studies 901, 902, and 907. The long-term safety and tolerability of TDF were monitored using periodic assessments of concomitant medications, AEs, serial laboratory tests, and bone densitometry (in select participants). A total of 687 participants received TDF 300 mg either initially or through rollover. Long-term follow up shows that the incidence of AEs or laboratory abnormalities leading to discontinuation of TDF remained low despite mean treatment duration of more than two years, and extending to nearly

four years in some participants. None of the AEs or laboratory abnormalities that led to study drug discontinuation had a reported incidence of more than 1%. Furthermore, there was no indication of nephrotoxicity in this highly treatment-experienced population (56). In a large cohort of HIV-infected adults in Zambia, only 0.25% of patients with no or mild renal dysfunction at pre-ART baseline experienced severe renal dysfunction after 12 months of TDF-containing ART (and 1.8% developed moderate or severe renal dysfunction) (57).

1.6.2 Tenofovir Disoproxil Fumarate: Studies in Pregnancy

TDF was classified as FDA pregnancy Category B based on animal and clinical data (when this classification scheme was used).

In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester TDF exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects but no such increase in birth defects has been observed. The prevalence of birth defects after first trimester TDF exposure was 2.3% (60 of 2,608 births; 95% CI, 1.8%-3.0%), which is within the range of congenital anomalies reported in the general US population (46).

TDF pharmacokinetics during pregnancy among 19 pregnant women was assessed in P1026s in the last trimester between weeks 30-36 and also at 6-12 weeks post-delivery. The proportion of pregnant women with AUC exceeding the target of 2 µg hour/mL was slightly lower in the third trimester (74%) than postpartum (86%) but trough levels were comparable at both time points. A recent case series found TDF to be well tolerated among 76 pregnant women, with two stopping therapy, one for rash and one for nausea. All 78 infants were healthy with no signs of toxicity, and all were HIV-uninfected (58).

In three studies of pregnant women, the cord-to-maternal blood ratio ranged from 0.60 to 0.99, indicating high placental transfer (59-61). A dose of 600 mg of TDF in labor resulted in levels in the women similar to levels in non-pregnant adults after a 300 mg dose, suggesting higher doses are required for adequate levels during labor in term pregnant women (62).

Tenofovir does not penetrate well into human breast milk (breast milk/maternal plasma ratio=0.08) (63).

An observational study of 74 TDF-exposed (DXA at median 13 days) and 69 TDF-unexposed infants (DXA at median 19 days) showed that the mean (standard deviation) bone mineral content (BMC) of TDF-exposed infants was 12% lower than for TDF-unexposed infants (56.0 [11.8] versus 63.8 [16.6] g; p=0.002); and that the adjusted mean bone mineral content was 5.3 g lower (95% CI, -9.5, -1.2; p=0.013) in the TDF-exposed infants (8).

The P1084s substudy of the PROMISE trial sought to compare newborn BMC by randomized exposure to maternal ZDV+sdNVP with brief TDF/FTC tail; LPV/r+ZDV/3TC or LPV/r+TDF/FTC. Infant DXA was performed from 0-21 days of life. Mean infant whole body BMC was significantly lower in both LPV/r arms compared to the ZDV arm, but was not significantly worse in the TDF/FTC arm compared with the ZDV/3TC arm (in the context of LPV/r exposure in both of these arms). Lumbar spine BMC did not differ significantly between regimens. (7)

1.6.3 Animal Studies of Tenofovir Disoproxil Fumarate

Chronic dosing of rats in pregnancy noted no growth or reproductive problems when TDF was administered at doses not associated with maternal toxicity. At high doses of exposure (25 times the AUC achieved with therapeutic dosing), no fetal structural changes were seen.

Chronic exposure of fetal monkeys to TDF at a high dose of 30 mg/kg (25 times the AUC levels achieved with therapeutic doses in humans) from days 20-150 of gestation was associated with maternal monkey toxicity but did not result in gross structural abnormalities (64). However, significantly lower fetal circulating insulin-like growth factor levels were reported and were associated with body weights 13% lower than untreated controls. A slight reduction in fetal bone porosity was also observed within two months of maternal treatment. However, a macaque treated for over 10 years with 10 mg/kg/day of TDF has given birth over several years to three infant macaques, all of whom were normal and had no bone abnormalities at birth (65).

Studies of intravenous TDF administration in pregnant cynomolgus monkeys reported a fetal/maternal concentration of 17% indicating some placental transfer (64).

1.6.4 Tenofovir Disoproxil Fumarate and Hepatitis B Infection

Exacerbations of HBV have been reported in patients after discontinuation of TDF (66). Patients who are co-infected with HBV and HIV may have increased values on LFTs and exacerbation of hepatitis symptoms when TDF is stopped. Usually these symptoms are self-limiting; however, serious complications have been reported. The threshold for stopping antiretrovirals with activity against HBV (including TDF) should high, and patients co-infected with HBV and HIV should be closely monitored with both clinical and laboratory assessments follow-up for several months after stopping TDF.

1.7 Prior Research on Emtricitabine and Tenofovir Disoproxil Fumarate Fixed-Dose Combination Tablet (FTC/TDF, Truvada®)

Gilead Sciences developed Truvada, a product containing FTC 200 mg and TDF 300 mg in a fixed-dose combination (FDC) tablet formulation that was approved by the FDA in August 2004. As a component of the New Drug Application, two Phase I studies evaluating the pharmacokinetics of co-administered FTC and TDF tablet formulation were completed.

Overall, Study GS-US-104-172 demonstrated bioequivalence between the FTC-TDF combination tablet and the FTC capsule and TDF tablet formulations when administered separately. Administration of the FTC-TDF combination tablet with either a high-fat meal or light meal increased tenofovir exposure by approximately 30% compared with fasted-state administration. Clinical experience with TDF indicates that the effect of food on tenofovir exposure is not of clinical relevance. FTC and TDF, either administered as a combination tablet (containing FTC 200 mg/ TDF 300 mg) or co-administered as FTC 200 mg capsule and TDF 300 mg tablet were well tolerated.

Among women becoming pregnant while taking part in pre-exposure prophylaxis trials, no significant difference in adverse pregnancy outcomes (including preterm delivery or congenital anomalies) were observed between the TDF, TDF/FTC, and placebo arms (67, 68).

1.8 Prior Research on Efavirenz (EFV, Sustiva®, Stocrin®)

1.8.1 Efavirenz: Studies in Non-Pregnant Adults

EFV is a potent NNRTI that is approved by the FDA and that has been widely used in combination with other antiretroviral agents for the treatment of HIV-1 infection throughout the world. It is included in the first-line preferred regimen by the WHO for adults, including pregnant women and women of childbearing age (2, 3). The US HHS perinatal guidelines also include EFV among recommended agents for use in pregnancy, but starting after 8 weeks' gestation.

Clinical Experience with EFV

EFV is a once daily NNRTI that has been shown to be effective in the treatment of HIV disease, demonstrating high and durable levels of virologic suppression (in combination with two NRTIs) in multiple large studies conducted among ART-naive patients. EFV was superior to LPV/r in the ACTG A5142 trial (69), but comparable to ATV/r in the ACTG A5202 study (70). In the 2NN study, NVP did not meet non-inferiority criteria when compared to EFV (71). In the ECHO and THRIVE studies, EFV was non-inferior to RPV; EFV was associated with lower rates of virologic failure (particularly among participants with pre-ART HIV-1 RNA >100,000 copies/mL) (72).

In more recent studies, some regimens have been found to be superior to EFV, primarily due to fewer discontinuations because of AEs in non-EFV regimens. As noted earlier, the SINGLE trial showed that a DTG-based regimen was superior to EFV for the primary endpoint of viral suppression at Week 48 (12). In the STARTMRK trial, raltegravir was superior to EFV at 4 and 5 years (73, 74).

Safety Profile

The most significant side effects associated with EFV are central nervous system (CNS) symptoms and rash. CNS symptoms include, but are not limited to, dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. Symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks of therapy. Symptoms may also be less noticeable if EFV is taken at bedtime. Potential for additive symptoms may occur if used concomitantly with alcohol or psychoactive drugs.

In multi-study comparisons of EFV-treated versus controls, severe acute depression (1.6% versus 0.6%) and suicidal ideation (0.6% versus 0.3%) were reported. Patients with a history of psychiatric disorder are at greater risk. There have been occasional post-marketing reports of delusions and aberrant behavior, predominantly in those with a history of mental illness or substance abuse. An analysis including data from four ACTG trials showed a higher rate of suicidality (reported suicidal ideation or attempted or completed suicide) among patients taking EFV-containing regimens compared with non-EFV comparator regimens (5), although this association was not found in two large observational cohorts (75, 76).

Rash is usually mild to moderate and occurs within the first two weeks of initiating therapy. In most participants, rash resolves with continuing EFV therapy within one month. However, EFV can be associated with erythema multiforme/Stevens-Johnson syndrome. Among approximately 2,200 treated individuals in studies and expanded access programs, the incidence of grade 4 rash (e.g., erythema multiforme and Stevens-Johnson syndrome) was 0.14%. The median time to onset of rash in adults was 11 days, and the median duration was 16 days. EFV should be permanently

discontinued in persons developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. (77)

Other side effects associated with EFV include upset stomach, diarrhea, anorexia, headache, tiredness, pancreatitis, elevated cholesterol (including HDL), elevated triglycerides, and elevated transaminases. EFV has also been associated with severe drug-induced liver injury in South Africa, with higher CD4 count at ART initiation, younger age, and possibly female gender associated with these liver events (4). Finally, EFV has been associated with prolonged QTc, particularly in individuals with slower EFV metabolism (78).

More information can be found in the most recent Sustiva or Stocrin package insert (77).

1.8.2 Efavirenz: Studies in Pregnancy

The following section has been taken from the US DHHS Guidelines, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (13).

The FDA advises women to avoid becoming pregnant while taking EFV and health care providers to avoid administration in the first trimester of pregnancy as potential fetal harm may occur. However, EFV remains a cornerstone of the preferred first-line antiretrovirals recommended by the WHO, regardless of trimester (and for women of childbearing potential), and is used by millions of women globally.

Pharmacokinetics

A recent review of an intensive pregnancy PK study plus four others that measured single EFV concentrations in pregnant women found that EFV concentrations were not significantly affected by pregnancy and that high rates of HIV RNA suppression at delivery were achieved with EFV-containing regimens (79).

Placental and Breast Milk Passage

In a study of 25 mother-infant pairs, median EFV cord blood/maternal blood concentration was 0.49 (range 0.37–0.74) (80). In a study of 13 women in Rwanda, EFV concentration was significantly higher in maternal plasma than skim breast milk (mean breast milk to mean maternal plasma concentration ratio 0.54) and higher in skim breast milk than in infant plasma (mean skim breast milk to mean newborn plasma concentration ratio 4.08) (81). Mean infant plasma EFV concentrations were 860 ng/mL; the mean infant plasma EFV concentration was 13.1% of maternal plasma concentrations. All infants had detectable plasma concentrations of EFV, and eight of 13 newborns had plasma EFV concentrations below the minimum therapeutic concentration of 1,000 ng/mL recommended for treatment of HIV-infected adults. In a study of plasma and hair drug concentration in 56 mother-infant pairs receiving EFV-based therapy during pregnancy and breastfeeding, infant plasma levels at delivery and hair levels at age 12 weeks suggested moderate ***in utero*** transfer during pregnancy and breastfeeding, with approximately one-third of transfer occurring postpartum (40% cumulative with 15% during breastfeeding) (82). All mothers and infants had detectable EFV plasma levels at 0, 8, and 12 weeks and mean infant-to-maternal-hair concentration at 12 weeks postpartum was 0.40 for EFV.

Teratogenicity Data

This section is adapted from the US DHHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (13).

In pregnancies with prospectively reported exposure to EFV-based regimens in the Antiretroviral Pregnancy Registry through January 2016, birth defects were observed in 21 of 883 live births with first-trimester exposure (2.4%, 95% confidence interval [CI], 1.5% to 3.6%) (46). Although these data provide sufficient numbers of first-trimester exposures to rule out a two-fold or greater increase in the risk of overall birth defects, the low incidence of neural tube defects in the general population means that a larger number of exposures are still needed to be able to definitively rule out an increased risk of this specific defect. Prospective reports to the Antiretroviral Pregnancy Registry of defects after first-trimester EFV exposure have documented one neural tube defect case (sacral aplasia, myelomeningocele, and hydrocephalus with fetal alcohol syndrome) and one case of bilateral facial clefts, anophthalmia, and amniotic band. Among retrospective cases, there are six reports of CNS defects, including three cases of meningomyelocele in infants born to mothers receiving EFV during the first trimester. Retrospective reports can be biased toward reporting of more unusual and severe cases and are less likely to be representative of the general population experience.

In an updated meta-analysis of 23 studies (including the Antiretroviral Pregnancy Registry data) reporting on birth outcomes among women exposed to EFV during the first trimester, there were 44 infants with birth defects among 2,026 live births to women receiving first-trimester EFV (rate of overall birth defects (1.63%, 95% CI, 0.78% to 2.48%) (83). The rate of overall birth defects was similar among women exposed to EFV-containing regimens and non-EFV-containing regimens during the first trimester (pooled relative risk [RR] 0.78, 95% CI, 0.56–1.08). Across all births, one neural tube defect (myelomeningocele) was observed, giving a point prevalence of 0.05% (95% CI, <0.01 to 0.28), within the range reported in the general population. The number of reported first-trimester EFV exposures (>2000) are sufficient to rule out more than a 2-3 fold increase in neural tube defects (83) (the incidence of neural tube defects in the general U.S. population is very low — 0.02% to 0.2% — so the incidence of defects even with a 2-3 fold increase would still be well under 1%).

A French study of 13,124 live births between 1994 and 2010 included an analysis of 372 infants born after first-trimester EFV exposure (6). In the primary analysis using the European Surveillance of Congenital Anomalies (EUROCAT) classification system, no increase in birth defects after first trimester EFV exposure was detected compared to those without EFV exposure in pregnancy (adjusted odds ratio 1.16, 95% CI, 0.73–1.85). In a secondary analysis using the modified Metropolitan Atlanta Congenital Defect Program classification used by the Antiretroviral Pregnancy Registry, an association was found between first-trimester EFV exposure and neurologic defects. However, none of the four defects (i.e., ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst, and pachygyria) were neural tube defects, and none of the defects had common embryology (84). First-trimester EFV exposure was not associated with an increased risk of defects in a Pediatric HIV/AIDS Cohort Study analysis that included 2,580 live births, 94 after first-trimester EFV exposure (85) or an analysis of a national cohort in Italy that included 1,257 pregnancies, 80 after first-trimester EFV exposure (86).

Although two small studies (Pediatric AIDS Clinical Trials Group [PACTG] protocol 219/219C and PACTG protocol P1025) reported a higher rate of birth defects among infants with first-trimester exposure to EFV compared with those without exposure, the number of exposures was small (35 exposures in PACTG 219/219C and 42 in P1025) and there is overlap in defect cases between the two studies (87-89). Thus, additional data are needed on first-trimester EFV exposures to more conclusively determine if risk of neural tube defects is elevated.

The FDA advises women to avoid becoming pregnant while taking EFV and health care providers to avoid administration in the first trimester of pregnancy. However, given that the risk of neural tube defects is restricted to the first 5 to 6 weeks of pregnancy (the neural tube closes at 36 to 39 days after last menstrual period), pregnancy is rarely recognized before 4 to 6 weeks of pregnancy, and ARV drug changes in pregnancy may be associated with loss of viral control, EFV can be continued in pregnant women receiving EFV-based antiretroviral therapy who present for antenatal care in the first trimester (as recommended in the US perinatal ARV guidelines (90)). Since 2012, the British HIV Guidelines recommend that EFV can be used regardless of the trimester of pregnancy, stating that "...efavirenz can be used in pregnancy without additional precautions and considerations over and above those of other antiretroviral therapies" (91).

1.8.3 Animal Studies of Efavirenz

This section is adapted from the US DHHS Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (13).

Carcinogenicity

EFV was neither mutagenic nor clastogenic in a series of ***in vitro*** and animal ***in vivo*** screening tests. A study evaluating genotoxicity of EFV in mice noted DNA damage in brain cells after daily dosing for 36 days; no damage was seen in liver, heart, or peripheral blood cells (92). Long-term animal carcinogenicity studies with EFV have been completed in mice and rats. At systemic drug exposures approximately 1.7-fold higher than in humans receiving standard therapeutic doses, no increase in tumor incidence above background was observed in male mice, but in female mice, an increase above background was seen in hepatocellular adenomas, carcinomas, and pulmonary alveolar/bronchiolar adenomas. No increase in tumor incidence above background was observed in male and female rats with systemic drug exposures lower than that in humans receiving therapeutic doses.

Reproduction/Fertility

No effect of EFV on reproduction or fertility in rodents has been seen.

Teratogenicity/Developmental Toxicity

An increase in fetal resorption was observed in rats at EFV doses that produced peak plasma concentrations and area under the curve (AUC) values in female rats equivalent to or lower than those achieved in humans at the recommended human dose (600 mg once daily). EFV produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans administered EFV (600 mg once daily). Central nervous system (CNS) malformations and cleft palate were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving EFV

from gestational days 20 to 150 at a dose of 60 mg/kg/day (resulting in plasma concentrations 1.3 times that of systemic human therapeutic exposure, with fetal umbilical venous drug concentrations approximately 0.7 times the maternal values) (93). The malformations included anencephaly and unilateral anophthalmia in one fetus, microphthalmia in another fetus, and cleft palate in a third fetus.

Placental and Breast Milk Passage

EFV readily crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. Maternal and fetal blood concentrations in pregnant rabbits and cynomolgus monkeys are equivalent, while fetal concentrations in rats exceeded maternal concentrations.

1.9 Rationale for the Study and its Objectives

1.9.1 Overall Rationale

While current ART regimens achieve very low rates of perinatal HIV transmission when started early enough in pregnancy and adhered to, there is need for a safe, effective, and affordable alternative to EFV-containing ART for pregnant HIV-infected women in resource-constrained settings. Furthermore, it is very important to obtain pregnancy efficacy and safety data for antiretroviral regimens that are being adopted in newer first-line treatment regimens due to their better potency, tolerability, and resistance profiles. This study aims to ascertain the safety and virologic efficacy of DTG-containing ART during pregnancy and to obtain data on the efficacy and safety of DTG+FTC/TAF. These data will be relevant to well-resourced as well as resource-constrained settings.

1.9.2 Rationale for Studying Virologic Efficacy

Studies powered to detect differences in risk of perinatal HIV transmission require very large sample sizes. Maternal HIV-1 RNA at delivery is the strongest predictor of perinatal HIV transmission measured in studies thus far (94-96) and much of the transmission risk reduction associated with use of maternal ART regimens is achieved through reducing maternal viral burden. Therefore, virologic suppression at delivery, a surrogate for perinatal transmission rates, was chosen as the primary virologic efficacy outcome for this study. While it is acknowledged that there may be residual transmission risk not captured through measurement of maternal virologic suppression, virologic efficacy outcomes from this study will provide randomized clinical trial data needed to optimize choice of ART regimen during pregnancy.

An HIV-1 RNA threshold of <200 copies/mL was chosen for the primary virologic endpoint (rather than <50 copies/mL) due to more reliable (and less variable) detection at 200 copies/mL, particularly when HIV-1 RNA is being tested at multiple different laboratories (even using the same testing platform). Use of the <200 copies/mL threshold (rather than <50 copies/mL) is also expected to lead to fewer "false calls" for clinical management of virologic failure and optimize the likelihood of correctly defining virologic success versus failure for statistical analysis. The primary virologic efficacy analysis will therefore use 200 copies/mL as the threshold, based upon testing that will be run in real time at each site. For a secondary objective, batched testing at one centralized VQA-certified laboratory will be performed to assess virologic suppression at delivery using a threshold of 50 copies/mL.

Non-inferiority was hypothesized for the primary virologic study objective, in order to establish that DTG-based ART does not have appreciably worse virologic efficacy in pregnant women compared with the current most frequently-used ART regimen globally.

1.9.3 Rationale for Studying Adverse Pregnancy Outcomes

HIV-infected women, particularly women starting three-drug ART, experience higher rates of adverse pregnancy outcomes (preterm delivery, small for gestational age, and stillbirth) than HIV-uninfected women (9, 31, 97, 98). Certain antiretroviral drugs may be associated with specific adverse birth outcomes (e.g., PIs have been associated with preterm delivery in some studies, including one randomized controlled trial (99), but not in others (100-102)). However, observational data can be potentially misleading (e.g., due to residual confounding), and data from large randomized trials reflecting pregnancy outcomes by antiretroviral regimen are scarce. In the PROMISE trial, rates of preterm delivery (<37 weeks) were not significantly different between TDF/LPV/r and ZDV/LPV/r (19.7% versus 18.5%); rates of very preterm delivery (<34 weeks) were higher with TDF/LPV/r than ZDV/LPV/r (6.0% versus 2.6%, p=0.04) but not when compared with ZDV/sdNVP (3.2%, p=0.10) (9).

In sum, it is possible that particular regimens or drug classes (and/or timing of ART use during pregnancy) are associated with adverse pregnancy outcome, but insufficient data exist to predict which antiretrovirals will be associated with lower/higher risk. It is important to ascertain rates of adverse pregnancy outcomes with new regimens that may be used in a widespread fashion in pregnant women (and women of childbearing potential).

The upper gestational age limit specified for this study (28 weeks) was selected for appropriate evaluation of adverse pregnancy outcomes, as women enrolled at later gestational ages may be at lower risk for these outcomes (i.e., some women who already experienced these adverse pregnancy outcomes would not enroll in the study if enrollment at later gestational age were permitted). Women with known multiple pregnancies (e.g., twins) will be excluded from the study because of association of such pregnancies with fetal growth restriction, preterm delivery, and fetal demise, which are components of the primary adverse pregnancy outcome for this study.

Congenital anomalies are excluded from the primary composite endpoint of adverse pregnancy outcomes because events that are associated with chromosomal abnormalities or with organogenesis (collectively, the vast majority of major congenital anomalies) cannot be related to study drug due to timing of first drug exposure. Thus, inclusion of these "pre-randomization" events may bias us toward not being able to detect a difference between arms. Secondary analyses will include congenital anomalies, however.

The outcomes of any new pregnancies that occur during maternal follow-up will also be evaluated in this study. Although the number of new pregnancies is expected to be small, the planned exploratory analyses will provide some data on the outcomes that follow exposure to the study ART regimens during the first trimester of pregnancy.

1.9.4 Rationale for Comparing Toxicity/Tolerability

In the only trial to directly compare treatment with EFV-based versus DTG-based ART thus far (the SINGLE study), 10% of participants in the EFV arm and 2% in the DTG arm discontinued study drug due to AEs (although rates of serious adverse events did not differ between arms) (12). Based upon this (and upon other data from other trials showing DTG to be well tolerated (17, 21)), it is anticipated that DTG will be at least as well tolerated as EFV in pregnant women. However, a higher proportion of patients stopped DTG in a clinical setting than in the trials published thus far (103), and data do not yet exist on the safety/tolerability of DTG in pregnant women. The safety and tolerability of DTG (and TAF) in pregnant women, compared to the current global standard of care regimen, EFV/FTC/TDF, will be important for decisions to be made by policy makers, clinicians and patients around the use of these drugs in pregnancy.

Similarly, it is important to ascertain the general safety of newer maternal ART regimens for infants. For example, in the PROMISE trial, mortality among infants through one week of age was found (unexpectedly) to differ between randomized ARV arms: 1-week infant mortality was 4.4% in TDF/LPV/r-exposed infants, 3.2% in ZDV/sdNVP-exposed infants (p=0.43) and 0.6% in ZDV/LPV/r-exposed infants (p=0.001 versus TDF/LPV/r); most infant mortality was likely mediated through preterm birth (9). Data are inconclusive regarding effects of *in utero* exposure to different ART combinations on infant growth (104, 105), neurodevelopment (106, 107), and hematological outcomes (with most data being reassuring) (108-110).

Chronic treatment with TDF-containing ART is associated with more renal and bone toxicity than TAF is, in non-pregnant adults (15, 33). As noted earlier, the effects (if any) of *in utero* TDF exposure on infant bone development, growth, and renal function remain unclear. No data exist on the relative bone and renal toxicities of TDF versus TAF in postpartum women nor their newborns. This randomized trial represents an important opportunity to learn more about the effects of the 3 regimens on maternal and infant bone and renal outcomes. The rationale for conducting DXA once in infants at 26 weeks of age is to assess bone mineral density/content (BMD/BMC) at the latest time point on-study at which it is still practicable to perform high-quality infant DXA, in order to capture potential longer-term effects of exposure to each regimen on infant BMD/BMC while minimizing infant radiation exposure. The rationale for conducting maternal DXA once at 50 weeks postpartum is to assess maternal BMD after the longest possible period of exposure to ART on-study.

1.9.5 Rationale for a Three-Arm Trial

It is anticipated that DTG+FTC/TAF will be one of the most commonly used first-line ART regimens within the next few years, globally. One option would be to conduct a two-arm trial, comparing this new regimen (DTG+FTC/TAF) with the current global standard first-line regimen (EFV/FTC/TDF). The primary rationale for including the third arm (DTG+FTC/TDF) is to investigate effect modification of DTG in the presence of either TAF or TDF. This analysis will be highly informative in the event that there is an unexpected excess of safety events associated with exposure to DTG. Without the DTG+FTC/TDF arm, if there is an unexpected excess of safety events, it would be impossible to assess whether DTG+FTC/TAF is safer than DTG+FTC/TDF and it would be difficult to determine whether the safety signal was due to the DTG or the TAF.

Inclusion of the DTG+FTC/TDF arm will also provide data on this specific regimen in pregnancy. These data may be important if FTC/TAF is not adopted as rapidly or widely in HIV treatment guidelines as currently expected (or as rapidly as DTG).

1.9.6 Rationale for Exploratory Objectives

Maternal Postpartum Depression

EFV (and less commonly DTG) can be associated with development of depression; however, very little is known about the interplay between treatment with EFV and postpartum depression, and no data exist regarding the incidence of depression in postpartum women taking DTG-based regimens. This study offers an important opportunity to assess rates of postpartum depression by randomized regimen (with referral of women with possible signs/symptoms of depression for further evaluation/treatment). The study will also assess sleep disturbances and anxiety, as these are fairly common side effects of both EFV and DTG.

Predictors of Adverse Pregnancy Outcomes

Progesterone is a critical hormone in pregnancy that maintains the pregnancy state and works as an anti-inflammatory, smooth muscle relaxer and vasodilator (111). Murine and human studies have shown a relationship between progesterone levels and birth weight in the presence of antiretrovirals (112). At present, it is unknown whether specific ART regimens impact progesterone directly or via other regulatory hormones including prolactin (113); whether all ART regimens can impact progesterone levels or if this is restricted to PIs (112); or whether the timing of ART exposure in pregnancy matters. It is also unknown whether low progesterone levels impact birth outcomes directly (at the level of the cervix and placenta) or by allowing immunologic shifts away from a Th2-dominated environment (leading to systemic effects and possible placental damage). In addition, HIV-infected pregnant and postpartum women have been shown to have higher mortality than HIV-uninfected women, with higher reported rates of malaria, tuberculosis, and bacterial infections (114, 115). Many of these studies have been observational and performed in the era prior to the use of three-drug ART during pregnancy and postpartum, and the majority of data on chronic inflammation in HIV have focused on men. Levels of inflammation and associations with infectious morbidity and pregnancy complications have not been well described, particularly in resource-limited settings. Understanding the nature of residual inflammation in this unique population can provide targets for interventions designed to optimize clinical outcomes.

Stored samples will be used to characterize ante- and postpartum inflammation, including IDO-1, monocyte activation, and other plasma markers of inflammation, and to evaluate the relationship between progesterone/prolactin/markers of inflammation and pregnancy outcomes. The study will evaluate changes over time and will compare women receiving the three different ART regimens. The primary analyses will be designed to understand the extent to which residual inflammation in women on ART is associated with infectious morbidity, pregnancy and delivery complications, and non-infectious morbidity. Analyses will advance our understanding of possible targets for anti-inflammatory clinical therapies that can reduce morbidity and optimize outcomes in pregnant and postpartum women.

Mother-to-Infant Transfer of ARVs during Pregnancy and Breastfeeding

Studies such as IMPAACT P1026s provide maternal pregnancy and postpartum PK data (as well as data on neonatal elimination of some ARVs). However, P1026s does not assess penetration of ARVs into breast milk, nor levels of ARVs acquired by breastfeeding infants. This study provides the opportunity to collect samples that will permit assessment of DTG and TAF levels in breast milk (and in breastfeeding infants). Analysis of ARV levels in maternal and infant hair samples collected at delivery/birth will permit comparison of degree of maternal-infant ARV transfer (for the different ARVs).

Maternal ART Adherence

Maternal adherence to ARVs during the antepartum period tends to be very high, but some studies (particularly in programmatic settings) have reported loss to follow-up and/or drop-off in ART adherence in the postpartum period (116-118). Little is known about reasons for (and interventions to prevent) this decline in postpartum adherence (119). This study offers an opportunity to assess adherence overall, by antepartum versus postpartum periods, and by ARV regimen and study site. Hair levels of ARVs reflect drug uptake from the systemic circulation over weeks to months (120), reflecting cumulative exposure to medications over time (and therefore serving as an objective biomarker of antiretroviral adherence during pregnancy) (121). Adherence will be assessed in this study by HIV-1 RNA level, maternal and infant hair levels, and maternal self-report (122).

1.10 Hypotheses

Among HIV-1-infected pregnant women initiating ART between 14 and 28 weeks gestation, and their infants:

- A DTG-containing regimen will be non-inferior to EFV/FTC/TDF with regard to virologic efficacy at delivery
- Rates of adverse pregnancy outcomes will not significantly differ between the three study ART regimens
- Rates of maternal and infant grade 3 or higher adverse events will not significantly differ between the three study ART regimens

2 OBJECTIVES

Note: In the objectives below, "a DTG-containing regimen" refers to the combination of both DTG-containing arms (i.e., Arm 1+Arm 2). "Any pairwise regimen comparison" refers to comparisons of Arm 1 to Arm 2, Arm 2 to Arm 3, and Arm 1 to Arm 3.

2.1 Primary Objectives

The primary objectives of this study are to determine the following among HIV-1-infected pregnant women and their infants:

2.1.1 Whether treatment initiated during pregnancy with a DTG-containing regimen is non-inferior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery

2.1.2 Whether rates of the following safety outcomes differ for any pairwise regimen comparison:

- Adverse pregnancy outcomes (spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
- Maternal grade 3 or higher adverse events through 50 weeks postpartum
- Infant grade 3 or higher adverse events through 50 weeks postpartum

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the following among HIV-1-infected pregnant women and their infants:

2.2.1 Whether treatment initiated during pregnancy with a DTG-containing regimen is superior to EFV/FTC/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery

2.2.2 Whether the following differ when comparing a DTG-containing regimen initiated during pregnancy to EFV/FTC/TDF:

- Proportion of mothers with HIV-1 RNA <50 copies/mL at delivery
- Proportion of mothers with HIV-1 RNA <200 copies/mL at 50 weeks postpartum
- Time to maternal HIV-1 RNA <200 copies/mL through delivery

2.2.3 Whether the following differs for any pairwise regimen comparison:

- Proportion of mothers with HIV-1 RNA <200 copies/mL using the standardized FDA snapshot algorithm at delivery and at 50 weeks postpartum

2.2.4 Whether rates of the following differ when comparing a DTG-containing regimen to EFV/FTC/TDF:

- Adverse pregnancy outcomes (spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
- Maternal grade 3 or higher adverse events through 50 weeks postpartum
- Infant grade 3 or higher adverse events through 50 weeks postpartum

2.2.5 Whether rates of the following differ for any pairwise regimen comparison:
- A composite outcome of spontaneous abortion, fetal death, preterm delivery, small for gestational age, or major congenital anomaly
- A ranked composite infant safety outcome measure through 50 weeks postpartum
- Infant HIV infection through 50 weeks postpartum
- Infant mortality through 50 weeks postpartum
- Infant bone toxicity at 26 weeks postpartum
- Maternal bone toxicity at 50 weeks postpartum
- Markers of maternal and infant renal toxicity through 50 weeks postpartum
- Antiretroviral drug resistance observed with each maternal ART regimen:
  - Among mothers who experience virologic failure (at baseline and time of virologic failure)
  - Among HIV-infected infants (at time of HIV diagnosis)

2.2.6 Whether treatment initiated during pregnancy with each regimen is non-inferior with regard to preterm delivery and, separately, small for gestational age for any pairwise regimen comparison

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

2.3.1 Evaluate the following with treatment initiated in pregnancy with a DTG-containing regimen compared to EFV/FTC/TDF:
- Maternal postpartum depression through 50 weeks postpartum
- Adverse outcomes of subsequent pregnancies occurring during maternal follow-up

2.3.2 Evaluate potential immunologic and hormonal predictors of adverse pregnancy outcomes and postpartum maternal health outcomes and the association of these factors with maternal ART regimens

2.3.3 Assess for associations between maternal antepartum adverse events and adverse pregnancy outcomes

2.3.4 Assess for associations between maternal antiretroviral drug levels and maternal and infant adverse events

2.3.5 Assess for mother-to-infant transfer of antiretrovirals during pregnancy and breastfeeding

2.3.6 Assess adherence to maternal ART regimens in the antenatal and postnatal periods and describe barriers and facilitators of adherence in these periods

3 STUDY DESIGN

This is a Phase III, three-arm, randomized, open-label study to compare the virologic efficacy and safety of three antiretroviral regimens for HIV-1-infected pregnant women and their infants. Refer to Figure 1 for an overview of the study design and to Section 4 for the study eligibility criteria. A total of 639 mother-infant pairs are expected to be enrolled at study sites in Botswana, Brazil, Haiti, India, Malawi, South Africa, Thailand, Uganda, the United States, Tanzania, and Zimbabwe.

Mother-infant pairs will be screened for eligibility during pregnancy and enrolled at 14-28 weeks gestation. Mothers will be ART-naïve, defined as having not received prior antiretroviral therapy, other than ARVs received during previous pregnancies or previous periods of breastfeeding (stopped at least six months prior to study entry). Mothers will be permitted to have taken ARVs during previous pregnancies and/or periods of breastfeeding to optimize the generalizability of study findings to the relevant population of interest. Mothers will be permitted (but not required) to receive up to 14 days of non-study ART in the current pregnancy prior to study entry as part of local standard management. This period of non-study ART use was selected to ensure that initiation of ART is not delayed while mothers are being screened for the study while also keeping the period of non-study ART exposure as short as is feasible to minimize potential impacts on study outcomes.

Upon enrollment, mothers will be randomly assigned in a 1:1:1 ratio to receive either DTG+FTC/TAF (Arm 1), DTG+FTC/TDF (Arm 2), or EFV/FTC/TDF (Arm 3) during pregnancy, through delivery, and postpartum. Infants will not receive ARVs as part of the study but are expected to receive non-study ARV prophylaxis consistent with local standards of care. Mothers will be counseled on infant feeding options consistent with local standards of care; both breastfeeding and formula feeding mother-infant pairs may take part in the study.

Mothers will complete study visits every four weeks during pregnancy; mothers and infants will complete study visits at delivery and at 6, 14, 26, 38, and 50 weeks postpartum. Study-specific visits and procedures will be performed as described in Section 6 and the Schedule of Evaluations in Appendix I. Safety outcomes will be assessed throughout follow-up, with standard evaluations performed at all sites; at selected sites, infant DXA scans will additionally be performed at 26 weeks postpartum, and maternal DXA scans will be performed at 50 weeks postpartum. Primary and secondary virologic efficacy outcomes will be assessed at delivery and at 50 weeks postpartum, using a single HIV-1 RNA testing platform at all sites. All HIV-1 RNA assays performed at site laboratories will be performed in real time. For the secondary objective evaluating viral suppression to less than 50 copies/mL at delivery, however, the assay will be performed centrally (batched) after all specimens have collected.

Safety and efficacy will be routinely monitored by an independent data and safety monitoring board (DSMB) as described in Section 9.5.3. The DSMB will also re-evaluate the study sample size and make recommendations regarding potential sample size adjustments following a pre-specified algorithm. Primary virologic efficacy analyses will compare participants randomized to either DTG-containing regimen (Arm 1 + Arm 2 combined) to participants randomized to the EFV-containing regimen (Arm 3). Primary safety analyses will compare participants randomized to each DTG-containing regimen to participants randomized to the EFV-containing regimen and to participants randomized to the other DTG-containing regimen. Refer to Section 9 for a complete description of statistical considerations, data monitoring, and data analysis plans.

4 STUDY POPULATION

This study will be conducted among approximately 639 mother-infant pairs who will be selected for the study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to participant retention and withdrawal from the study are provided in Sections 4.5 and 4.6, respectively.

4.1 Inclusion Criteria

All of the criteria listed below must be met in order for mother-infant pairs to be included in this study.

4.1.1 Mother is at least 18 years of age and willing and able to provide written informed consent for her and her infant's participation in this study

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

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay (EIA) OR Western blot OR immunofluorescence assay OR chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Sample #2 may be tested using any of the following:

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

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

4.1.3 At screening, mother is ART-naïve, defined as having not received prior antiretroviral therapy other than ARVs received during prior pregnancies or prior periods of breastfeeding (i.e., receipt of any single, dual, or triple ARV regimen during prior time-limited periods of pregnancy and breastfeeding is permitted). Receipt of up to 14 days of ARVs during the current pregnancy is permitted prior to study entry so that initiation of ARVs during the current pregnancy is not delayed during the study screening period.

Note: Non-study ART may be initiated in the current pregnancy prior to initiation of the study screening process. For eligible participants, enrollment must occur within 14 days of non-study ART initiation.

Note: Consistent with criterion 4.2.4, receipt of ARVs during a prior pregnancy or prior period of breastfeeding must have concluded at least six months prior to study entry. Receipt of TDF or FTC/TDF for pre-exposure prophylaxis at any time in the past is not exclusionary (even if received within six months prior to study entry).

4.1.4 At screening, mother has the following laboratory test results (based on testing of samples collected within 14 days prior to study entry):

- Grade 1 or lower (<2.5 x ULN) ALT and AST
- Grade 2 or lower (≤1.8 x ULN) creatinine
- Grade 2 or lower (≥60 mL/min) estimated creatinine clearance (CrCl; Cockcroft-Gault formula)

See Section 7.3.3 for guidance on severity grading. Laboratory tests may be repeated during the study screening period, with the latest result used for eligibility determination.

4.1.5 At screening and at study entry, no evidence of multiple gestation or fetal anomalies, as assessed by best available method

4.1.6 At study entry, gestational age of 14-28 weeks, defined as greater than 13 weeks plus six days and less than 28 completed weeks gestation, estimated by best available method

Note: For criteria 4.1.5 and 4.1.6, fetal ultrasound is preferred but not required for purposes of eligibility determination. If ultrasound cannot be performed during the study screening period prior to study entry, it must be performed within 14 days after study entry. As further explained in Section 6.1, enrolled participants will not be withdrawn from the study based on ultrasound findings obtained after study entry.

4.1.7 At study entry, mother expects to remain in the geographic area of the study site during pregnancy and for 50 weeks postpartum

4.2 Exclusion Criteria

Mother-infant pairs must be excluded from the study if any of the following are identified at any time prior to study entry:

4.2.1 Mother is currently incarcerated or involuntarily confined in a medical facility

4.2.2 Mother is currently receiving:
- A psychoactive medication for treatment of a psychiatric illness
- Treatment for active tuberculosis
- Treatment for active hepatitis C infection

4.2.3 Mother is expected to require treatment with interferon and/or ribavirin for hepatitis C infection during the study follow-up period

4.2.4 Mother has a history of any of the following, as determined by the site investigator or designee based on maternal report and available medical records:
- Hypersensitivity or clinically significant adverse reaction to any of the ARVs included in the three study drug regimens (ever)
- Antiretroviral drug resistance mutations that would impact selection of ART regimen (ever)
- Clinically significant heart disease and/or known prolonged QTc interval (ever)
- Suicidal ideation or attempt (ever)
- HIV-2 infection (ever)
- Zika virus infection, diagnosed or suspected, during the current pregnancy
- Receipt of any antiretroviral medication within six months prior to study entry, with two exceptions: receipt of any duration of TDF or FTC/TDF for pre-exposure prophylaxis or receipt of up to 14 days of ARVs during the current pregnancy
- Receipt of any prohibited medication within 14 days prior to study entry (see Section 5.9)
- Clinically significant acute illness requiring systemic treatment and/or hospitalization within 14 days prior to study entry
- Unstable liver disease (defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice) or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) within 14 days prior to study entry

4.2.5 Mother or fetus has any other condition that, in the opinion of the site investigator or designee, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

4.3 Co-Enrollment Considerations

Co-enrollment in other studies is not precluded, although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies. Requests for such approval should be emailed to the Clinical Management Committee (CMC; refer to Sections 7.1.2 and 9.5.1 for more information regarding the role of the CMC for this study).

4.4 Recruitment, Screening, and Enrollment Process

Recruitment methods for this study may vary across sites but are expected to rely on active identification and referral of HIV-1-infected pregnant women who are not taking ART at the time of presenting for antenatal care. Based on current standards of care, it is expected that many such women will be started on a non-study ART regimen at the time of presenting for antenatal care. This is permitted by the study eligibility criteria. However, recruitment and eligibility screening procedures will need to be performed in a timely manner to ensure that eligible women are enrolled within 14 days of starting non-study ART. Upon enrollment, women will discontinue their non-study ART regimen (if they had started a non-study regimen) and initiate a study drug regimen.

Upon identification of a potentially eligible pregnant woman, study staff will provide information about the study to her. Women who express interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process may be initiated at any time during pregnancy but — based on the required timing of study entry described above — is generally not expected before approximately 12 weeks gestation or after approximately 26 weeks gestation. The process will include detailed review of the study informed consent form, time to address any questions or concerns the woman may have, and an assessment of the woman's understanding before proceeding to her informed consent decision. The process will be fully documented and only women who are able to demonstrate understanding will be asked to provide written informed consent for study screening and enrollment.

Eligibility screening will be initiated after written informed consent is provided. Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrolment. Screening evaluations must be performed within 14 days prior to enrollment and enrollment must occur within 14 days of (non-study) ART initiation during the current pregnancy (for example, a woman who starts (non-study) ART on the first day of the month must be enrolled by the fourteenth day of the month). Screening evaluations may be repeated during the 14-day screening period, with the latest outcome used for eligibility determination. In the event that the 14-day screening period is exceeded, the screening process may be repeated, provided the mother is still within 14 days of non-study ART initiation; in this case, most but not all screening evaluations must be repeated, as specified in Section 6.1.

Women who are found to meet the study eligibility criteria will be enrolled in the study in pairs with their infants. The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, participant identification numbers (PIDs) will be assigned to the mother and (unborn) infant, and a study-specific screening number will be obtained for the pair through the SES. For pairs found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate study identification numbers (SIDs) for the mother and infant and prescribing information for the maternal study drug regimen. For pairs who are screened and found to be ineligible, or who do not otherwise enroll in the study for any reason, an electronic case report form (eCRF) will be entered to record the screening outcome. Refer to Section 9.5 for more information on monitoring participant accrual in this study.

Successful entry into the SES will result in generation of SIDs as well as generation the random assignment for the pair; for these pairs, generation of the SIDs with the random assignment is the effective point of enrollment in the study. The prescribing information generated by the SES will detail the randomly assigned regimen — DTG+FTC/TAF, DTG+FTC/TDF, or EFV/FTC/TDF — consistent with Sections 5.1 and 5.2, below. For all mother-infant pairs, the relevant study drug regimen will be prescribed and dispensed on the day of enrollment, with the first dose expected to be taken on the day of enrollment or the following day.

4.5 Participant Retention

Once a mother-infant pair is enrolled, study staff will make every effort to retain both mother and infant for the protocol-specified duration of follow-up (through 50 weeks postpartum), thereby maximizing statistical power and minimizing potential biases associated with loss to follow-up. Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.6 Participant Withdrawal from the Study

Regardless of the participant retention procedures referenced above, mothers may voluntarily withdraw themselves and/or their infants from the study. Participants may also be withdrawn from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site and cannot be transferred to another site or is otherwise determined to be lost-to-follow-up
- Site investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs

Mother-infant pairs in which the mother discontinues use of study drug for any reason will not be withdrawn from the study; any such pairs should ideally be retained through the scheduled duration of follow-up. Likewise, any mother who does not deliver a live born infant or whose infant dies during follow-up should ideally be retained through the scheduled duration of follow-up.

Should the consenting mother of an enrolled infant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study-specific infant evaluations should be performed until informed consent for continued study participation is obtained from the infant's authorized guardian, as defined locally. Study sites may continue to provide care for the infant as needed and appropriate (outside of the study), consistent with local standards of care, but no study-specific procedures (outside of the standard of care) may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the infant must be withdrawn from the study. Refer to Section 12.3 for further guidance on guardian consent for infant study participation.

For any participant who is withdrawn from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal in detail and will make every effort to complete final evaluations as described in Section 6.9. In the event that the circumstances that led to a participant's withdrawal change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

5 STUDY DRUG CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

Study drug is defined for this study as the ARVs included in the maternal regimens specified in Section 5.1. Mothers will be exposed to study drug through direct ingestion; infants may be exposed to study drug *in utero* and through breastfeeding. Refer to the relevant Package Inserts for each of the ARVs and fixed dose combinations thereof for more information about these drugs.

5.1 Study Drug Regimens

Mother-infant pairs will be randomly assigned in a 1:1:1 ratio to receive one of the following maternal ART regimens during pregnancy, through delivery, and for 50 weeks postpartum:

Arm 1 **Dolutegravir (DTG) + emtricitabine/tenofovir alafenamide (FTC/TAF)** during pregnancy, through delivery, and for 50 weeks postpartum

Arm 2 **Dolutegravir (DTG) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF)** during pregnancy, through delivery, and for 50 weeks postpartum

Arm 3 **Efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF)** during pregnancy, through delivery, and for 50 weeks postpartum

As noted in Section 4.4, the first dose of each regimen is expected to be taken on the day of enrollment or the following day.

5.2 Study Drug Administration

Dolutegravir (DTG) will be administered orally as one 50 mg tablet once daily, with or without food.

Refer to the IMPORTANT INTERACTION sub-section of Section 5.8.1 for additional information on administration of DTG for mothers who require cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications.

Refer to Section 8.4 for additional information on management of DTG dosing for mothers who require rifampin-containing treatment for active tuberculosis.

Emtricitabine/tenofovir alafenamide (FTC/TAF) will be administered orally as one fixed-dose combination tablet (FTC 200 mg/TAF 25 mg) once daily, with or without food.

Refer to Section 8.4 for additional information on management of FTC/TAF dosing for mothers who require rifampin-containing treatment for active tuberculosis.

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) will be administered orally as one fixed-dose combination tablet (FTC 200 mg/TDF 300 mg) once daily, with or without food.

Efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) will be administered orally, as one fixed-dose combination tablet (EFV 600 mg/FTC 200 mg/TDF 300 mg) once daily, on an empty stomach, preferably at bedtime.

5.3 Study Drug Formulation

Dolutegravir (DTG): 50 mg tablets. Store at 25°C (77°F) with excursions between 15° and 30°C (59°-86°F) permitted (see USP Controlled Room Temperature).

Emtricitabine/tenofovir alafenamide (FTC/TAF): Fixed-dose combination tablets (FTC 200 mg/TAF 25 mg). Must be dispensed in original bottle; keep container tightly closed. Store below 30°C (86°F).

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF): Fixed-dose combination tablets (FTC 200 mg/TDF 300 mg). Must be dispensed in original bottle with the desiccant provided. Store at 20°-25°C (68°-77°F) with excursions between 15° and 30°C (59°-86°F) permitted.

Efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF): Fixed-dose combination tablets (EFV 600 mg/FTC 200 mg/TDF 300 mg). Store per manufacturer's storage instructions.

5.4 Study Drug Supply

DTG will be supplied by ViiV Healthcare Ltd.

FTC/TAF and FTC/TDF will be supplied by Gilead Sciences.

EFV/FTC/TDF will be supplied by Mylan.

All of the above-listed study drugs will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, these study drugs may be obtained by the site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

Study-supplied study drugs are expected to be provided to mothers in Arms 1, 2, and 3 consistent with their random assignments as specified in Section 5.1. However, for mothers in all arms, ART regimens may be modified as specified in Section 8 and Appendix II. As indicated in these sections, all regimen changes involving DTG, EFV, TAF, or TDF should be made in consultation with the CMC.

All available study-supplied study drugs, as well as ARVs available from non-study sources, may be used when constructing regimens for mothers in all arms. In the event that study supplies of DTG, FTC/TAF, FTC/TDF, or EFV/FTC/TDF are not available, these ARVs may be provided from non-study supplies, with approval in advance from the CMC. If non-study-supplied ARVs are provided, the ARVs should ideally be dispensed through study site pharmacies. If this is not possible, other options may be considered in consultation with the CMC; CMC review and approval of the operational plan is required. Any ARV supplied from non-study sources must comply with the DAIDS policy on use of drug products not marketed in the US, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management.

5.5 Study Drug Accountability

Site pharmacists must maintain complete records of all study drugs received from the CRPMC and subsequently dispensed.

5.6 Final Disposition of Study Drug

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

5.7 Study Drug Adherence Assessment and Counseling

Study staff will provide adherence counseling to enrolled mothers throughout the period of study participation. Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs; site SOPs must also meet for minimum requirements specified in the study-specific Manual of Procedures (MOP) with respect to initial and ongoing counseling and support. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each mother. Information on correct use of study drugs will be provided, particularly at the time of enrollment and in the early stages of follow-up, as well as at the time of any regimens changes. Counseling will also address challenges to consistent use of study drug over time, with the aim of supporting mothers in identifying strategies to address any such challenges.

Adherence to the maternal study drug regimen will be assessed by questionnaire as indicated in the Schedule of Evaluations in Appendix I. These data will not be used as a basis for adherence counseling. The results of HIV viral load testing performed throughout follow-up provide a biologic measure of adherence and may be used to guide feedback to mothers and associated adherence counseling. Refer to Section 8.3 for more information on virologic monitoring and management.

5.8 Concomitant Medications

The term concomitant medications is used in this study to refer to medications other than the study drugs that comprise the maternal ART regimens listed in Section 5.1.

5.8.1 Maternal Concomitant Medications

All concomitant medications received by enrolled mothers throughout the duration of study participation must be source documented as part of the medical and medication histories obtained at each study visit (see Section 6.11). This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; contraceptives; antacids, antenatal vitamins and other nutritional supplements; and alternative, complementary, and traditional medications and preparations. Requirements for entering maternal concomitant medications into eCRFs are specified in Section 6.11.

IMPORTANT INTERACTIONS WITH COMMONLY USED CONCOMITANT MEDICATIONS

Mothers who have not initiated cotrimoxazole or isoniazid prophylaxis prior to study entry should preferably defer initiation of these medications until at least two weeks after initiation of their study drug regimen, if eligible to initiate such prophylaxis per local standards of care.

Mothers in Arms 1 and 2 (i.e., the DTG-containing arms) who require cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications will be counseled to take these medications at least six hours before or at least two hours after taking DTG. Alternatively, DTG and supplements containing calcium or iron can be taken together with food.

Refer to Section 8.4 for additional information on management of mothers who require rifampin-containing treatment for active tuberculosis.

5.8.2 Infant Concomitant Medications

All concomitant medications received by enrolled infants must be source documented as part of the medical and medication histories obtained at each study visit (see Section 6.14). This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; therapeutic foods and nutritional supplements; and alternative, complementary, and traditional medications and preparations. Requirements for entering infant concomitant medications into eCRFs are specified in Section 6.14.

5.9 Prohibited Medications

Any mother who requires a medication considered prohibited while on study drug must have the study drug held or permanently discontinued. A list of prohibited medications will be posted on the study-specific website: http://impaactnetwork.org/studies/IMPAACT2010.asp. Upon identification of the need for a prohibited medication, the site investigator should consult the CMC for further guidance on study drug management.

5.10 Precautionary Medications

A list of medications that should be used with caution while on study drug will be posted on the study-specific website: http://impaactnetwork.org/studies/IMPAACT2010.asp.

6 STUDY VISITS AND PROCEDURES

An overview of the maternal and infant schedule of study visits and evaluations is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures. Information related to scheduled visits is presented in Sections 6.1-6.5; information related to event-driven visits for maternal ARV switches, maternal virologic failure, and infant HIV infection is presented in Sections 6.6-6.8; and information on early discontinuation and post-study contacts is presented in Sections 6.9-6.10. Additional details related to study-specific procedures, such as physical exams, ultrasound scans, and DXA scans are provided in Sections 6.11-6.17. Additional considerations for laboratory procedures are provided in Section 6.18.

All visits and procedures must be performed at the approved clinical research site or approved associated facilities. All visits should be conducted as close as possible to the specified target visit dates and within the specified allowable visit windows. Unless otherwise specified, visits may be split, with required procedures performed on more than one day within the allowable visit window if necessary. Some visit windows overlap by a period of one day; the day of overlap should be prioritized, when applicable, for completion of the earlier of the two visits. For example, there is one day of overlap between the allowable windows for the Antepartum Week 4 and Week 8 Visits. If a participant were to present to the study site on this day, the Antepartum Week 4 Visit should be conducted on this day, if not previously conducted; otherwise, the Antepartum Week 8 Visit may be conducted on this day. In the event that a scheduled visit is missed (i.e., not completed within the allowable window), the missed evaluations should be completed, if possible, at the next scheduled visit. For example, if the Antepartum Week 12 Visit is missed, the ALT, AST, creatinine, creatinine clearance, and HIV-1 RNA evaluations specified for that visit should be performed, if possible, at the Antepartum Week 16 Visit. Further operational guidance on prioritization of evaluations is provided in the study-specific MOP.

All visits and procedures must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 10 for more information on documentation and data management requirements. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent; providing contraception counseling (see Section 8.6) and other relevant types of counseling; scheduling telephone contacts and visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff may also perform additional evaluations if required per the participant management guidance in Section 8, if clinically indicated, and/or if such evaluations would otherwise be expected according to local standards of care. Study staff should inform mothers of clinically meaningful physical examination findings and laboratory test results when available.

6.1 Screening Visits

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

Screening may be initiated after written informed consent is obtained. Screening procedures may be performed on multiple days, including on the date of enrollment (see Section 6.2). Further operational guidance for the required screening procedures is as follows:

- Maternal HIV testing may or may not be required to meet the eligibility criteria in Section 4.1.2. One of the required maternal HIV tests must be performed in an appropriately certified laboratory setting; the other required test may be performed in other (non-certified) settings.

- Maternal pregnancy testing may or may not be required to meet the eligibility criteria in Section 4.1.6. If available maternal medical records document a positive pregnancy test result, or if pregnancy is confirmed by ultrasound scan prior to enrollment, no pregnancy testing is required. Otherwise, a blood or urine pregnancy test should be performed, with results available for eligibility determination prior to enrollment.

- Maternal ALT, AST, and creatinine testing is required in relation to the eligibility criteria in Section 4.1.4; as soon as the screening creatinine test result is obtained, the mother's estimated CrCl rate should be calculated using the Cockcroft-Gault formula, and all results should be graded for severity as specified in Section 7.3.3.

- Every effort should be made to perform fetal ultrasound to estimate gestational age and assess for multiple gestation and fetal anomalies prior to study entry. However, if this is not possible, the best available method should be used to perform these assessments for eligibility determination. In these cases, ultrasound must be performed as soon as possible and within 14 days after study entry and the ultrasound findings will subsequently be used in algorithms to calculate gestational age at study entry and gestational age at delivery. If ultrasound is performed prior to study entry, results must be considered for purposes of eligibility determination. For example, if ultrasound performed prior to study entry indicates multiple gestation, the mother (and her fetuses) should not be enrolled. However, if ultrasound is performed after study entry, enrolled participants will not be withdrawn from the study if the ultrasound identifies an exclusionary condition.

  Note: In the event that fetal ultrasound was performed prior to the study screening period, and a result report meeting all requirements specified in Section 6.13 is available, it is not necessary to perform another scan for study purposes.

- Screening evaluations may be repeated, with the latest outcome used for eligibility determination.

For potential participants who do not meet eligibility criteria, screening should be discontinued once ineligibility is determined (enter the relevant eCRF to record the screening outcome).

Screening Visit Procedures (within 14 days prior to study entry)		
Administrative and Regulatory		• Obtain written informed consent for IMPAACT 2010 • Assign PIDs to mother and (unborn) infant • Obtain screening number from SES • Obtain available documentation of mother's HIV status
Clinical		• Obtain available maternal medical records and maternal medical and medications history • Assess documentation of HIV infection and of current pregnancy in relation to study requirements • Assess maternal ARV history in relation to study requirements • Perform complete maternal physical exam • Perform fetal ultrasound *if possible (and if not performed prior to the study screening period)* • Assess current gestational age based on best available method
Laboratory	**Blood**	Collect maternal blood for: • Confirmatory HIV testing *if needed per Section 4.1.2* • ALT, AST, creatinine, CrCl • Complete blood count • Stored plasma for antiretroviral resistance testing
	Blood or Urine	Collect blood or urine for: • Pregnancy test *if needed per Section 4.1.6 (see above for further guidance)*

All screening procedures are expected to be performed within 14 days prior to study entry. In the event that the 14-day screening period is exceeded, the screening process may be repeated, provided that adequate time remains to permit enrollment within 14 days of non-study ART initiation. In this case, all of the screening procedures listed above must be repeated, with the exception that:

- New PIDs should not be assigned
- Confirmatory HIV testing need not be repeated
- Fetal ultrasound need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

6.2 Entry Visit

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

For eligible mother-infant pairs, enrollment must occur at 14-28 weeks gestation and within 14 days of the mother initiating ART in the current pregnancy.

All Entry Visit procedures are expected to be performed on the day of enrollment; procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical examination) should be performed first, prior to final eligibility determination. In the event that a mother-infant pair is found to be ineligible on the scheduled day of entry, enrollment must not occur.

Additional guidance for sequencing of procedures at the Entry Visit is as follows:

- Final eligibility determination and confirmation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing must precede dispensing of study drug
- Blood collection must precede ingestion of the first dose of study drug

As noted in Section 6.1, fetal ultrasound should be performed prior to study entry if possible. If this is not possible, ultrasound must be performed as soon as possible and within 14 days after study entry. Participants will not be withdrawn from the study if ultrasound performed after entry identifies an exclusionary condition (i.e., multiple gestation, fetal anomaly, or gestational age outside of the allowable range of 14-28 weeks). For any multiple gestation identified after enrollment, pregnancy outcomes will be ascertained for all fetuses and all live born infants will be followed per the Schedule of Evaluations.

Note: In the event that fetal ultrasound is not performed prior to or within 14 days after study entry, the CMC must be informed immediately. The mother-infant pair will be retained in follow-up and available information will be used to estimate gestational age at study entry; this will be done by the site investigator or designee in consultation with the CMC. Please refer to Section 9.5.1 for more information on monitoring for completeness and timeliness of ultrasound and actions to be taken in response to missed or delayed ultrasound scans.

Entry Visit Procedures (Day 0)		
Administrative and Regulatory		• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file
Clinical		• Update medical and medications history since last visit* • Perform complete maternal physical exam* • Perform fetal ultrasound *if not done previously and if possible prior to enrollment (if not done prior to enrollment, must be done within 14 days after enrollment)* • Administer Pittsburgh Sleep Quality Index (PSQI) • Administer Generalized Anxiety Disorder 7-Item Scale (GAD-7)
Study Drug		• Prescribe and dispense ARVs • Provide ARV use instructions and adherence counseling
Laboratory	**Blood**	Collect blood for: • Hepatitis B surface antigen • CD4+ cell count • HIV-1 RNA (real-time; store residual plasma) • Stored plasma and cell pellets for immunologic and hormonal markers of adverse pregnancy outcomes
	Urine	Collect urine for: • Storage for markers of renal toxicity

*Perform prior to enrollment

6.3 Maternal Antepartum Follow-Up Visits

After study entry, mothers will complete scheduled follow-up visits every four weeks prior to delivery. Between scheduled visits, particularly in the first month of study participation, study site staff are encouraged to contact mothers to address any issues or questions about their study participation, clarify instructions for use of study drugs, and/or provide adherence counseling as needed.

Given that mother-infant pairs will be enrolled at 14-28 weeks gestation, up to seven or eight antepartum visits may be completed by each mother, depending on the gestational age at entry and the gestational age at delivery. For example, a mother who enrolls at 14 weeks gestation and delivers at 40 weeks gestation would be expected to complete antepartum visits at 18, 22, 26, 30, 34, and 38 weeks gestation; the corresponding study weeks for these visits would be Antepartum Follow-Up Weeks 4, 8, 12, 16, 20, and 24. Mothers who enroll in the study later, or deliver earlier, would have fewer visits than in this example.

The target dates for all maternal antepartum follow-up visits are counted from the date of enrollment as Day 0, with an allowable window of ± 2 weeks. There is no required sequencing of procedures at these visits.

Maternal creatinine and CrCl evaluations are required at Antepartum Follow-Up Weeks 4, 12, and 24. As soon as the creatinine results from these visits are obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

6.3.1 Antepartum Follow-Up Week 4 Visit

Antepartum Follow-up Week 4 Visit Procedures (Day 28 ± 2 weeks)		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma)

6.3.2 Antepartum Follow-Up Week 8 Visit

Antepartum Follow-up Week 8 Visit Procedures (Day 56 ± 2 weeks)		
Clinical		• Obtain interval medical and medications history • Administer PSQI • Administer GAD-7 • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire and barriers and facilitators questionnaires • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA (real-time; store residual plasma) • Stored plasma and cell pellets for immunologic and hormonal markers of adverse pregnancy outcomes

6.3.3 Antepartum Follow-Up Week 12 Visit

Antepartum Follow-up Week 12 Visit Procedures (Day 84 ± 2 weeks)		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma)

6.3.4 Antepartum Q4 Week Follow-Up Visits

After completion of the Antepartum Follow-up Week 12 visit, mothers will continue to complete scheduled follow-up visits every four weeks (Q4) prior to delivery. Depending on the date of delivery, these visits may take place at Antepartum Follow-up Weeks 16, 20, 24, and 28. For example, a mother enrolled at 14 weeks gestation who delivers at 40 weeks gestation would complete the Week 4, 8, and 12 visits described above, as well as Q4 visits at study Weeks 16, 20, and 24 prior to delivery. In contrast, a mother enrolled at 24 weeks gestation who delivers at 37 weeks gestation would complete the Week 4, 8, and 12 visits described above, but would not completed any Q4 visits prior to delivery.

Antepartum Follow-up Week 16 (Day 112 ± 2 weeks), Week 20 (Day 140 ± 2 weeks), Week 24 (Day 168 ± 2 weeks), and Week 28 (Day 196 ± 2 weeks) Visit Procedures		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	*At Week 24 only,* collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time, store residual plasma)

6.4 Maternal and Infant Delivery Visit

Mothers and infants should complete a study visit **as soon as possible after delivery**, and within a targeted window of 14 days after delivery.

In addition to other evaluations, the primary study outcomes are ascertained at this visit. **As such, every effort should be made to conduct this visit within the targeted window.** If the visit cannot be conducted within the targeted window, it may be conducted within an allowable window of 27 days after delivery. The timeliness of visit completion at each site will be closely monitored and corrective actions taken when needed, as described in Section 9.5.1.

In the event that an enrolled mother does not deliver a live born infant, or that a live born infant dies soon after delivery, the mother should still complete the Delivery Visit and all subsequent postpartum visits if she is willing to do so.

Maternal Delivery Visit Procedures (as soon as possible and within 14 (targeted) or 27 (allowable) days after delivery or other pregnancy outcome)		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire and record details of last two ARV doses • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma) • Stored plasma for HIV-1 RNA at central laboratory • Stored plasma and cell pellets for immunologic and hormonal markers of adverse pregnancy outcomes • *Only if mother is at risk for Zika virus infection (due to local transmission, travel, or other exposure) and maternal Zika virus infection during the current pregnancy is suspected:* stored serum for Zika diagnostic testing
	Hair	Collect hair for: • Storage for ARV drug levels

Infant Delivery Visit Procedures (as soon as possible and within 14 (targeted) or 27 (allowable) days after birth)		
Clinical		• Obtain birth history, interval medical and medications history since birth, and feeding history since birth • Perform complete physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (store remnant samples) • ALT and creatinine • Complete blood count • *Only if mother is at risk for Zika virus infection (due to local transmission, travel, or other exposure) and maternal Zika virus infection during the current pregnancy is suspected:* stored serum for Zika diagnostic testing
	Hair	Collect hair for: • Storage for ARV drug levels

As soon as the maternal creatinine result from this visit is obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

In the event that the infant HIV NAT performed at this visit is positive, the infant should be recalled to the clinic as soon as possible for confirmatory testing. See also Section 6.8.

6.5 Maternal and Infant Postpartum Follow-Up Visits

Following delivery, mothers and infants will complete scheduled follow-up visits at 6, 14, 26, 38, and 50 weeks postpartum. For both mothers and infants, the target dates for all postpartum visits are counted from the date of delivery (or other pregnancy outcome) as Day 0. The Week 6 Visit may be conducted within an allowable window of ± 2 weeks. For all other visits, the allowable window is ± 6 weeks. There is no required sequencing of procedures at these visits.

All infants will undergo HIV testing at Weeks 6, 14, and 50, regardless of feeding method. Breastfed infants will additionally undergo testing at Weeks 26 and 38 if they were exposed to breast milk since the date of their last test. In the event of any positive test, the infant should be recalled to the clinic as soon as possible for confirmatory testing. See also Section 6.8.

Maternal creatinine and CrCl evaluations are required at Postpartum Follow-Up Weeks 14, 26, and 50. As soon as the creatinine results from these visits are obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

6.5.1 Postpartum Follow-Up Week 6 Visit

Maternal Postpartum Follow-up Week 6 Visit Procedures (Day 42 ± 2 weeks)		
Clinical		• Obtain interval medical and medications history • Administer Edinburgh Postnatal Depression Scale (EPDS) • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer adherence routine questionnaire and record details of last two ARV doses • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • Stored plasma for ARV drug levels
	Breast milk	*If currently breastfeeding,* collect breast milk for: • Storage for ARV drug levels

Infant Week 6 Visit Procedures (Day 42 ± 2 weeks)		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (store remnant samples) • Stored plasma for ARV drug levels

6.5.2 Postpartum Follow-Up Week 14 Visit

Maternal Postpartum Follow-Up Week 14 Visit Procedures (Day 98 ± 6 weeks)		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma)

Infant Week 14 Visit Procedures (Day 98 ± 6 weeks)		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (store remnant samples)

6.5.3 Postpartum Follow-Up Week 26 Visit

Maternal Postpartum Follow-Up Week 26 Visit Procedures (Day 182 ± 6 weeks)		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • Complete blood count • CD4+ cell count • HIV-1 RNA (real-time; store residual plasma)

Infant Week 26 Visit Procedures (Day 182 ± 6 weeks)		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	*If ever exposed to breast milk,* collect blood for: • HIV NAT (store remnant samples) • ALT and creatinine • Complete blood count
Radiology *(at selected sites)*		*At DXA sites only,* DXA scan of whole body and lumbar spine

6.5.4 Postpartum Follow-Up Week 38 Visit

Maternal Postpartum Follow-Up Week 38 Visit Procedures (Day 266 ± 6 weeks)		
Clinical		• Obtain interval medical and medications history • Administer PSQI • Administer GAD-7 • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) • Provide information, counseling, and referrals (as needed) in preparation for study exit at Week 50
Study Drug		• Administer routine adherence questionnaire and barriers and facilitators questionnaires • Prescribe and/or dispense ARVs as needed • Provide ARV use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA (real-time; store residual plasma)

Infant Week 38 Visit Procedures (Day 266 ± 6 weeks)		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	*If ever exposed to breast milk,* collect blood for: • HIV NAT (store remnant samples)

At this visit, information and counseling should be provided to the mother to begin to prepare for study exit at the Week 50 Visit. Referrals to non-study care and treatment should be discussed as needed, with emphasis on the importance of retention in care following study completion.

6.5.5 Postpartum Follow-Up Week 50 Visit

The Week 50 Visit is the final scheduled study visit for mothers and infants.

Maternal Postpartum Follow-Up Week 50 Visit Procedures (Day 350 ± 6 weeks)		
Clinical		• Obtain interval medical and medications history • Administer EPDS • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated) • Provide information, counseling, and/or referrals (as needed) in relation to study exit at this visit
Study Drug		• Administer routine adherence questionnaire • Collect any remaining study drug supplies
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • Complete blood count • CD4+ cell count • HIV-1 RNA (real-time; store residual plasma) • Stored plasma and cell pellets for immunologic and hormonal markers of adverse pregnancy outcomes
	Urine	Collect urine for: • Storage for markers of renal toxicity
	Blood or Urine	*At DXA sites only*, collect blood or urine for: • Pregnancy test on same day (preferably) or within 14 days prior to DXA scan
Radiology *(at selected sites)*		*At DXA sites only,* DXA scan of lumbar spine and hip

Infant Week 50 Visit Procedures (Day 350 ± 6 weeks)		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (store remnant samples)

At this visit, prior discussions of transition to non-study care and treatment should be reviewed, with information, counseling, and/or referrals provided as needed. Study drug cannot be dispensed to mothers at or after this visit; therefore, operational plans must be in place to permit transition to non-study care and treatment at this visit. Arrangements should be made to provide the infant's HIV NAT result and all other clinically meaningful results to the mother. The mother should also be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

6.6 Additional Procedures Following Maternal ARV Switch

For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch, according to the "Post ARV Switch" column of the Schedule of Evaluations, to assess tolerance and monitor virologic response to the modified regimen. In addition to the procedures listed below, other evaluations may be performed at the discretion of the site investigator and/or if recommended by the CMC. These procedures may be combined with regularly scheduled visit procedures if they are performed within the allowable window of a regularly scheduled visit.

Post Maternal ARV Switch Visit Procedures (Four Weeks after Switch ± 1 week)		
Clinical		• Obtain interval medical and medications history • Administer EPDS • Administer PSQI • Administer GAD-7 • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Prescribe and/or dispense ARVs as needed • Provide instructions and adherence counseling as needed
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma)

As soon as the maternal creatinine test result for this visit is obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

6.7 Additional Procedures for Confirmation of Maternal Virologic Failure

Refer to Section 8.3 for more information on monitoring maternal HIV viral load and managing virologic failure.

Maternal virologic failure is defined as two successive plasma HIV-1 RNA test results ≥200 copies/mL, with specimen collection for the first test occurring at or after 24 weeks on study (counted from the date of enrollment).

In the event that a mother has an HIV viral load ≥200 copies/mL at or after at least 24 weeks on study, the mother should be recalled to the clinic for confirmatory HIV-1 RNA testing as soon as possible and ideally within 28 days of the date of specimen collection for the initial test. Other procedures should also be performed according to the "Confirmation of Virologic Failure" column of the Schedule of Evaluations, and clinical management should proceed consistent with Section 8.3. All procedures should be performed regardless of reported adherence to study drug and any other factors that may affect HIV-1 RNA test results. These procedures may be combined with regularly scheduled visit procedures if they are performed within the allowable window of a regularly scheduled visit.

It is generally not expected that mothers will meet the criteria for confirmation of virologic failure (≥200 copies/mL at or after at least 24 weeks on study) during antepartum follow-up; however, if these criteria are met prior to delivery, the Confirmation of Virologic Failure evaluations should be performed.

Maternal Confirmation of Virologic Failure Visit Procedures		
Clinical		• Obtain interval medical and medications history (targeted physical exam may be performed if clinically indicated) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Assess adherence in relation to HIV-1 RNA test results and provide adherence counseling as needed
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA (real-time; store residual plasma) • Antiretroviral resistance testing (real-time if virologic failure is confirmed, with storage of residual plasma; otherwise store plasma)

6.8 Modified Procedures for Infants Identified as HIV-Infected

Any infant with a positive HIV NAT result should be recalled to the clinic for confirmatory testing **as soon as possible** and within 28 days of specimen collection for the initial test. As is the case at other visits when HIV NAT is performed, 3 mL of blood should be collected for the testing and remnant samples will be stored; an additional 3 mL should also be collected and stored for antiretroviral resistance testing. In the event that the second test does not confirm the initial result, the CMC should be consulted for guidance on next steps to clarify the infant's HIV status. Pending confirmatory testing, infant ARVs should be managed consistent with local standards of care.

All infants identified with HIV infection will remain in study follow-up but will be referred to non-study sources of HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that no further HIV tests will be performed and stored plasma will be used for antiretroviral resistance testing. Study sites may perform additional laboratory testing as needed to facilitate rapid initiation of ART for infected infants.

6.9 Early Discontinuation Visit

Refer to Section 4.6 for criteria for withdrawal from the study. For any mother or infant who is withdrawn or terminated from the study prior to the scheduled completion of follow-up at Week 50, every effort should be made to perform a final series of study evaluations, if possible, according to the "Early D/C" column of the Schedule of Evaluations. However, any evaluations performed within the 28 days prior to the Early Discontinuation Visit need not be repeated at the visit.

Maternal Early Discontinuation Visit Procedures		
Clinical		• Obtain interval medical and medications history • Perform targeted physical exam • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer routine adherence questionnaire • Collect any remaining study drug supplies
Laboratory	**Blood**	Collect blood for: • ALT, AST, creatinine, CrCl • HIV-1 RNA (real-time; store residual plasma)
	Urine	Collect urine for: • Storage for markers of renal toxicity

Infant Early Discontinuation Visit Procedures		
Clinical		• Obtain interval medical, medications, and feeding history • Perform targeted physical exam with growth evaluation • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	**Blood**	Collect blood for: • HIV NAT (store residual plasma)

As soon as the maternal creatinine test result for this visit is obtained, the estimated CrCl rate should be calculated using the Cockcroft-Gault formula, graded for severity, and assessed for clinical significance concurrent with all other laboratory test results.

Arrangements should be made to provide the mother clinically meaningful test results from the Early Discontinuation Visit. The mother should be provided information on how to remain in contact with study staff (if desired) and learn about the results of the study when available. The mother should also be provided information, counseling, and referrals to non-study sources of care and treatment for herself and her infant, as applicable.

6.10 Post-Study Contacts

As indicated in Sections 6.5.4 and 6.5.5, planning for transition to non-study care and treatment should begin at the Week 38 Visit, and the transition should be implemented at the Week 50 Visit. Following the Week 50 Visit, study staff will complete a final study contact with each mother to confirm her transition and, in particular, confirm her access to non-study ARVs. Mothers will also be asked to report their non-study ARV regimen, their adherence to non-study ARVs, any potential intolerance or side effects associated with their non-study ARVs, and any other problems with accessing or taking their non-study ARVs. This contact should take place within four weeks after the Week 50 Visit and should be documented in each mother's study chart. These contacts are not expected to be entered into eCRFs. However, eCRF data collection is required after the Week 50 Visit in the following scenarios:

- If a mother is pregnant at the Week 50 Visit: Refer to Section 8.6; in this scenario, the pregnancy outcome must be ascertained and the relevant eCRFs entered after the Week 50 Visit to record the pregnancy outcome. Relevant eCRFs will also be entered to capture any ARV changes during the pregnancy (after the Week 50 Visit).

- If confirmation of maternal virologic failure is pending after the Week 50 Visit: Refer to Section 6.7; in this scenario, the confirmatory HIV-1 RNA PCR assay must be performed and the relevant eCRFs entered to record the result of the assay.

- If confirmation of infant HIV infection is pending after the Week 50 Visit: Refer to Section 6.8; in this scenario, the confirmatory HIV NAT must be performed and the relevant eCRFs entered to record the result of the test.

6.11 Maternal Medical and Medication History

Collection of medical and medication history information is required at each scheduled maternal visit. A baseline history is established at Screening and Entry, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on maternal self-report but available medical records should be obtained when possible to supplement self-reported information.

Documented medical conditions will be assessed for severity as described in Section 7.3.3, and new conditions occurring during follow-up will also be assessed for relationship to study drug as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; see Section 5.8 for more information on concomitant medications.

Table 3 specifies the baseline and interval medical and medications history elements that must be source documented for mothers, as well as associated eCRF entry requirements.

Table 3
Documentation Requirements for Maternal Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs
Maternal Baseline Medical and Medication History Elements	
Date of birth and other socio-demographics	Yes (all)
HIV diagnosis, WHO clinical staging, and treatment history (including all ARV use prior to enrollment)	Yes (all)
Reproductive and obstetrical history: • Dates and outcomes of all prior pregnancies • Date of last menstrual period prior to the current pregnancy • Complications in the current pregnancy • Other targeted conditions potentially associated with adverse pregnancy outcomes in the current pregnancy	Yes (all)
History of allergy and/or hypersensitivity (including to ARVs)	Yes (all)
History of bone fracture (traumatic and non-traumatic)	Yes (all)
History of depression and/or suicidality	Yes (all)
History of tobacco smoking and alcohol use	Yes (all)
Medical conditions (signs, symptoms, illnesses, and other diagnoses) occurring during the 28 days prior to enrollment and/or ongoing at enrollment	Yes (all)
Medications taken within the 28 days prior to enrollment and/or ongoing at enrollment	Yes (all)
Any other information needed to determine eligibility for the study	—

Table 3
Documentation Requirements for Maternal Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs
Maternal Interval Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last visit	Any newly identified adverse events that meet criteria in Section 7.2
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit (see Section 5.8.1 for more information on concomitant medications)	• All ARVs taken from time of enrollment through completion of follow-up (including timing of dosing at the Delivery and Week 6 Postpartum Visits) • Any new use of: – Cotrimoxazole – Isoniazid prophylaxis – Medications to treat active tuberculosis – Hormonal contraceptives • All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2 Note: eCRFs will also capture whether corticosteroids were taken for fetal lung maturity at any time during pregnancy.

In addition to the above, at the Delivery Visit, all of the following should be source documented and entered into eCRFs:

- Complications of pregnancy identified following enrollment and before delivery, regardless of severity grade
- Other targeted conditions potentially associated with adverse pregnancy outcomes identified following enrollment and before delivery, regardless of severity grade
- Date and time of onset of labor
- Type of labor (spontaneous or induced)
- Mode of delivery
- Complications of delivery
- Outcome of delivery

6.12 Maternal Physical Examinations

A physical examination is required at each scheduled maternal visit. Complete exams are required at the Screening and Entry Visits; targeted exams are required at all other visits.

Complete exams should include the following:

- Height measurement (at screening only)
- Weight measurement
- Blood pressure measurement
- Obstetric exam (at antepartum visits)
- Auscultation of chest (heart and lung exam)
- Examination of:
  - Skin
  - Head
  - Mouth
  - Neck
  - Abdomen
  - Extremities

Targeted exams should include the following:

- Weight measurement
- Blood pressure measurement
- Obstetric exam (at antepartum visits)
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician.

All exam findings should be source documented and the following should be entered into eCRFs: height (only at screening exam), weight, blood pressure, and fundal height (only at antepartum exams). Abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into adverse events eCRFs as specified in Section 7.2.

6.13 Fetal Ultrasound

A fetal ultrasound scan is required to permit more accurate calculation of gestational age at entry into the study and gestational age at delivery. Scans should be performed prior to study entry if possible, but may be performed within 14 days after study entry if necessary. When scans are performed prior to study entry, results must be used to estimate gestational age and assess for evidence of multiple gestation and fetal anomalies for purposes of eligibility determination. When scans are performed after study entry, any findings that indicate multiple gestation, fetal anomaly, or gestational age outside of the allowable range of 14-28 weeks will be recorded but will not be considered eligibility violations and will not result in withdrawal from the study.

Ultrasound scans may be performed at the study site or at off-site facilities. In the event that a scan is performed prior to the study screening period, and a result report meeting all requirements specified below is available, it is not necessary to perform another scan for study purposes.

A result report that minimally documents the following must be obtained for filing in participant study charts and entry into eCRFs; if more than one result report that meets these requirements is available, the earliest available results should be entered into eCRFs for estimation of gestational age:

- Date of scan
- Number of fetuses
- Estimated fetal weight if greater than 20 completed weeks gestation
- Biometry measures
  - If less than 14 weeks gestation:
    - Crown-rump length
  - If 14 or more weeks gestation:
    - Femur length
    - Abdominal circumference
    - Biparietal diameter and/or head circumference
- Ultrasound-based gestational age on the date of the scan or ultrasound-based estimated date of delivery

If any fetal anomalies are identified, these should also be documented in the result report.

6.14 Infant Medical and Medication History

Collection of medical and medication history information is required at each scheduled infant visit. A baseline history is established at the Delivery Visit and interval (since the last visit) histories are obtained at subsequent follow-up visits. Infant birth details should ideally be obtained from available medical records. Thereafter, history information may be obtained based on maternal report but available medical records should also be obtained when possible to supplement maternal report.

The infant baseline medical and medication history will consist of information recorded at birth as well as information obtained at the Delivery Visit. The Delivery Visit should take place as soon as possible after birth and within the targeted window of up to 14 days after birth; if the visit cannot be conducted within the targeted window, it may be conducted within the allowable window of up to 27 days after delivery. As such, information recorded at birth may differ from information obtained at the Delivery Visit.

Table 4 specifies the baseline and interval medical and medications history elements that must be source documented for infants, as well as associated eCRF entry requirements.

6.15 Infant Feeding History

An infant feeding history is required at each scheduled visit. At the Delivery Visit, feeding history since birth (including date and time of first breastfeeding, if applicable) will be collected. Thereafter, interval (since the last visit) histories will be collected. At each time point, data will be collected (source documented and entered into eCRFs) on feeding method, including whether the infant has been breastfed or formula fed, and date of last exposure to breast milk. Any therapeutic foods received will be recorded as concomitant medications (see Section 5.8.2).

Table 4
Documentation Requirements for Infant Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs
Infant Baseline Medical and Medication History Elements	
Date and time of birth	Yes (all)
Sex, estimated gestational age, length, weight, and head circumference at birth (obtain from medical records; measurements will also be performed by study staff at the infant Delivery Visit)	Yes (all)
Apgar scores at 1 and 5 minutes (obtain from medical records)	Yes (all)
Congenital anomalies and other medical conditions (signs, symptoms, illnesses, and other diagnoses) identified between birth and the Delivery Visit	Any conditions (adverse events) that meet criteria in Section 7.2 including all suspected congenital anomalies
Medications taken between birth and the Delivery Visit	• All ARVs • Any use of: – Cotrimoxazole – Isoniazid prophylaxis – Medications to treat active tuberculosis • All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2
Infant Interval Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last visit	Any newly identified adverse events that meet criteria in Section 7.2
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit (see Section 5.8.2 for more information concomitant medications)	• All ARVs • Any new use of: – Cotrimoxazole – Isoniazid prophylaxis – Medications to treat active tuberculosis • All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2

6.16 Infant Physical Examinations

A physical examination is required at each scheduled infant visit. A complete exam is required at the Delivery Visit; targeted exams are required at all other scheduled visits.

Complete exams should include the following:

- Newborn step-wise surface examination of:
  - Physical appearance
  - Length
  - Weight
  - Skin
  - Head (including fontanels and circumference)
  - Face (including mouth)
  - Neck
  - Chest
  - Abdomen and anus
  - Hips and genitalia
  - Arms, legs, fingers, and toes
  - Spine
- Auscultation of chest
- Neurologic assessment

The newborn step-wise surface examination will be performed consistent with WHO guidelines (available on the study-specific website: http://impaactnetwork.org/studies/IMPAACT2010.asp). The purpose of this examination is to establish each infant's physical condition at the Delivery Visit and to complete a systematic and standardized assessment for congenital anomalies. All elements of the surface examination should be performed for purposes of assessing for congenital anomalies in all infants, with the exception of the intra-oral, cardiac, and genitourinary systems (which will be included in the general examination but will not be routinely assessed for presence of congenital anomalies). If any potential congenital anomalies are identified on examination of any body system, these should be photographed by the examining clinician and a site pediatrician should ideally examine the infant as soon as possible.

Targeted exams should include the following:

- Length measurement
- Weight measurement
- Head circumference measurement
- Assessment of fontanel closure
- Auscultation of chest
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician. Also at all visits, the measurements listed above will be used to determine weight-for-length z-scores, which will be assessed in relation to WHO growth standards; measurements may also be charted on standard infant growth charts.

All exam findings should be source documented and the following should be entered into eCRFs: length, weight, head circumference, fontanel closure. Abnormal findings — including any suspected congenital anomaly in any body system — will be entered into adverse events eCRFs as specified in Section 7.2; photographs of abnormal findings may be securely uploaded to the DMC upon request to permit review and evaluation of findings by the CMC.

Note: Suspected congenital anomalies identified in body systems that are not part of the systematic surface examination (i.e., the intra-oral, cardiac, and genitourinary systems) or that may not be included in analyses of major congenital anomalies (e.g., polydactyly), should still be source documented and entered into eCRFs.

6.17 Maternal and Infant DXA Scans

At selected sites, mothers will undergo DXA scans of the lumbar spine and hip at Week 50 postpartum and infants will undergo DXA scans of the whole body and lumbar spine at Week 26 postpartum. Scans will be performed according to standardized procedures described in the study-specific MOP. Scan images will be transferred electronically for centralized reading and results will be transmitted electronically from the central readers to the DMC. The centralized readings of all scans will be made available to the study sites after the last scan has been read centrally. However, in the event that an infant experiences a bone fracture subsequent to his or her scan, the result of his or her scan will be provided to the site as soon as available.

6.18 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures.

6.18.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be posted on the study-specific webpage at: http://impaactnetwork.org/studies/IMPAACT2010.asp.

In accordance with US National Institutes of Health (NIH) recommendations, adult (maternal) blood collection will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period; pediatric (infant) blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period.

In the event that maternal blood collection must be limited, available specimens should be prioritized for use in the following order: (1) confirmatory HIV testing (if needed at Screening Visit), (2) HIV-1 RNA, (3) chemistry, (4) hepatitis B surface antigen (at Entry Visit only), (5) hematology, (6) CD4+ cell count, and (7) plasma, cell pellet, and serum storage for purposes other than HIV-1 RNA.

In the event that infant blood collection must be limited, available specimens should be prioritized for use in the following order: (1) HIV NAT, (2) chemistry, (3) hematology, and (4) serum storage.

6.18.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.18, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC. Any specimens stored at the Screening Visit for mothers who do not subsequently enroll in the study will be destroyed.

At each study site, all maternal plasma HIV-1 RNA assays must be performed in real time in a VQA-certified laboratory using the testing platform specified in the LPC. For mothers who experience virologic failure, antiretroviral resistance testing will be performed in real time at designated VQA-certified laboratories. Blood collected for resistance testing at Confirmation of Virologic Failure Visits will be processed locally, with plasma retained at the site laboratory pending HIV-1 RNA testing to confirm virologic failure. If failure is confirmed, aliquots of plasma stored for resistance testing at the Screening Visit and the Confirmation of Virologic Failure Visit will be shipped to a designated VQA-certified testing laboratory (residual plasma aliquots will be stored at the site laboratory); if failure is not confirmed, all plasma aliquots will remain stored at the site laboratory.

Infant HIV NAT must be performed in a VQA-certified laboratory (for non-US sites) or a CLIA-certified laboratory (for US sites). Whenever these tests are performed, any plasma remaining after the assay is completed should be stored.

Most specimens collected and stored at site laboratories per the Schedule of Evaluations are expected to be requested for centralized testing after all participants have completed follow-up (through Week 50 postpartum). However, an interim shipment is planned when all enrolled mothers have delivered. At this time, all specimens stored for centralized HIV-1 RNA testing will be requested for shipment to the designated testing laboratory. These specimens will then be tested as needed to evaluate outcomes through the delivery time point. Interim shipments may also be required for urine samples stored for evaluation of markers of renal toxicity. Alternative shipping arrangements may be specified by the Protocol Team as needed; detailed shipping instructions will be provided in the LPC.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Mothers will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies. Mothers may choose to provide or to decline informed consent for future research use of residual specimens — for themselves and for their infants — with no impact on other aspects of participation in the study. If mothers initially provide informed consent for future research use of residual specimens but subsequently change their mind and withdraw that consent, all remaining residual samples will be destroyed.

6.18.3 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the US Centers for Disease Control and Prevention, NIH, and other applicable agencies. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures. The safety monitoring roles of the study-specific Safety Review Group (SRG) and DSMB are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.2 and 9.5.3.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

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

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Protocol Co-Chairs, selected Protocol Investigators, Medical Officers, Statisticians, Data Managers, and Clinical Trial Specialists. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, management of AEs, and management of antiretroviral regimens.

7.1.3 Safety Review Group (SRG)

An SRG comprised of the Protocol Medical Officers, Protocol Statisticians, Protocol Data Managers, and other designated individuals with expertise in adult HIV medicine, obstetrics, and pediatrics who are independent of the Protocol Team will monitor participant safety through routine review of study data reports as described in Section 9.5.2.

7.1.4 Data and Safety Monitoring Board (DSMB)

An independent DSMB will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.3 for more information on the role of the DSMB in monitoring of this study.

7.2 Safety-Related Data Collection

Note: This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Sections 7.3.3 and 7.3.2, respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all mothers and infants, beginning at the time of enrollment, regardless of subsequent administration of or exposure to study drug. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified prior to enrollment will be considered pre-existing conditions. Refer to Section 4.4 for more information on defining the effective point of enrollment in the study.

Pre-existing conditions and adverse events will be entered into eCRFs as specified in Sections 7.2.1 (for mothers) and 7.2.2 (for infants).

7.2.1 Safety-Related Data Collection for Mothers

Pre-Existing Conditions

All pre-existing conditions identified among mothers during the 28 days prior to study entry will be entered into maternal medical history eCRFs.

Adverse Events

The following adverse events — inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses except as specified in the IMPAACT Do Not Report List — will be entered into maternal adverse events eCRFs:

- All grade 3 or higher adverse events
- All grade 2 or higher rashes
- All grade 2 or higher psychiatric events
- All events involving suicidal ideation or attempt
- All suspected or confirmed diagnoses of clinical hepatitis
- All suspected or confirmed diagnoses of immune reconstitution inflammatory syndrome (IRIS)
- All adverse events that lead to any change of ART regimen (i.e., any hold, discontinuation, switch/replacement, dose or frequency modification)
- All serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE Manual

In addition to the above specifications for entry into adverse events eCRFs, further detailed eCRFs will be entered for hepatic events resulting in discontinuation of DTG or EFV; suicide-related events that meet criteria for reporting as EAEs (see Section 7.3.2); and serious hypersensitivity reactions to ABC that occur among mothers who switch from TDF or TAF to ABC.

Laboratory Test Results

In addition to the recording specified above, the following laboratory test results will be entered into the relevant maternal laboratory eCRFs, regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes:

- All creatinine and creatinine clearance results
- All grade 1 or higher LFT results
- All grade 3 or higher hemoglobin, white blood cell count, absolute neutrophil count, and platelet count results
- All results that lead to a change of ART regimen (i.e., any hold, discontinuation, switch/replacement, dose or frequency modification)
- All results that are serious as defined in Version 2.0 of the DAIDS EAE Manual
- All results that are relevant to events that meet criteria for reporting as EAEs (see Section 7.3.2)

7.2.2 Safety-Related Data Collection for Infants

Pre-Existing Conditions

Because infants will be exposed to study drug *in utero*, all abnormal conditions identified during and after birth will be considered adverse events. No pre-existing conditions will be entered into eCRFs for infants.

Adverse Events

The following adverse events — inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses except as specified in the IMPAACT Do Not Report List — will be entered into infant adverse events eCRFs:

- All grade 3 or higher adverse events
- All suspected congenital anomalies
- All SAEs as defined in Version 2.0 of the DAIDS EAE Manual

Laboratory Test Results

In addition to the recording specified above, the following laboratory test results will be entered into the relevant infant laboratory eCRFs, regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes:

- All creatinine results
- All grade 2 or higher ALT results
- All grade 3 or higher hemoglobin, white blood cell count, absolute neutrophil count, and platelet count results
- All results that are serious as defined in Version 2.0 of the DAIDS EAE Manual

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

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

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at: http://rsc.tech-res.com/safetyandpharmacovigilance.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 EAE Reporting Requirements for this Study

As indicated in Table 5, below, both the SAE (serious adverse event) and SUSAR (suspected unexpected serious adverse reaction) reporting categories, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The SUSAR category is used for participants in Arm 3, who will be exposed to an approved regimen at approved doses for an approved indication.

Table 5
Expedited Adverse Event Reporting Requirements for IMPAACT 2010

	Study Entry through Week 14 Postpartum		After Week 14 Postpartum through Study Exit		Study Drugs for which Expedited Reporting is Required
	Mothers	Infants	Mothers	Infants	
Arm 1	SAEs	SAEs	SAEs	SUSARs	DTG, FTC, TAF
Arm 2	SAEs	SAEs	SAEs	SUSARs	DTG, FTC, TDF
Arm 3	SUSARs	SUSARs	SUSARs	SUSARs	EFV, FTC, TDF

For mothers in Arm 1 or Arm 2, the EAE reporting categories listed above will be remain unchanged regardless of ART regimen changes. For mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen, the EAE reporting category will also be switched to the SAE reporting category, from the date of the switch through study exit.

In addition to the above, the following must also be reported in an expedited manner (i.e., as EAEs) for mothers in Arm 1 or Arm 2 and for mothers in Arm 3 who switch to a DTG-containing or TAF-containing regimen:

- Pregnancy complications that result in medically indicated and/or elective termination of the pregnancy
- Spontaneous abortions and fetal deaths

In addition to the above, the following must also be reported in an expedited manner (i.e., as EAEs) for mothers in all arms:

- Hepatic toxicities that result in discontinuation of DTG or EFV
- Serious ABC hypersensitivity reactions in mothers switching from TDF or TAF to ABC

7.3.3 Grading Severity of Events (applies to EAEs and all other adverse events)

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables. In addition, the following protocol-specific grading scheme for axillary measured fever will be used in this study:

Grade 1 37.4 to <38.0°C
Grade 2 38.0 to <38.7°C
Grade 3 38.7 to <39.4°C
Grade 4 ≥39.4°C

Note: The DAIDS AE Grading Table parameter for unintentional weight loss excludes postpartum weight loss. Therefore, maternal weight loss will not be graded in this study.

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specified period of follow-up, beginning at the time of randomization and ending on the date of the final follow-up visit.

After the above-specified period, only SUSARs will be reported if study staff become aware of such events on a passive basis (e.g., from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Maternal and Infant Adverse Events

All maternal and infant adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 10. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study drug, assessed according to the following categories and definitions:

Related There is a reasonable possibility that the adverse event may be related to study drug.

Not related There is not a reasonable possibility that the adverse event may be related to study drug.

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual (referenced in Section 7.3.1). Note that adverse events assessed as secondary to immune reconstitution should not be considered related to study drug (refer to Section 8.8 for further information on management of IRIS).

For mothers, relationship should be assessed for each study drug received (ingested).

For infants, relationship should be assessed for study drug received by the mother to which the infant may have been exposed *in utero* or through breastfeeding.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Grade 3 or higher laboratory tests should be repeated as soon as possible (within three business days) and all grade 3 or higher adverse events should be re-evaluated at least weekly until improvement to grade 2 or lower. Additional evaluations may be performed at the discretion of the site investigator to determine the etiology of an event and/or further assess its severity or relationship to study drug. Clinical management of all adverse events should be consistent with the best medical judgment of the site investigator and local clinical practice standards. Adverse events that are ongoing at the time of the final study visit, particularly those of Grade 3 or higher severity, should generally be followed to resolution or stabilization by the site investigator; if this is not possible, the site investigator should actively facilitate referral to local non-study sources of appropriate medical care and treatment.

Please refer to Section 8.2 for further guidance on management of maternal adverse events; infant management is addressed in Section 8.9. When management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within three business days of site awareness of the event.

8.2 Management of Maternal Adverse Events

Maternal adverse events will be managed based on their severity and assessed relationship to study drug, as described in the remainder of this section. Please refer to the management tables in Appendix II for detailed guidance on management of maternal rash (Table II.2), asymptomatic ALT or AST elevation (Table II.3), clinical hepatitis (Table II.4), increased creatinine and decreased creatinine clearance (Table II.5), psychiatric events (Table II.6), and allergic reaction (Table II.7). All other adverse events should be managed as shown in Table II.1. For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6. Refer to Table II.8 for further guidance when switching from TAF or TDF to ZDV or ABC.

8.3 Monitoring and Management of Maternal HIV Viral Load

Monitoring

Maternal HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedule of Evaluations. All maternal HIV-1 RNA assays must be performed in a VQA-certified laboratory using the testing platform specified in the LPC. Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concerns. As noted in Section 5.7, viral load results should be provided to participants and may be used to guide adherence counseling.

Definition of Virologic Failure

Virologic failure is defined as two successive plasma HIV-1 RNA test results ≥200 copies/mL, with specimen collection for the first test occurring at or after 24 weeks counted from the date of randomization. For mothers who switch ARVs within the first 24 weeks on study, the counting of weeks for purposes of defining virologic failure is generally not expected to be altered by the switch (i.e., the counting of 24 weeks would generally not be re-started at the time of the switch). However, treatment interruption for a period of 14 days or longer may require alternative management. The CMC should be consulted regarding any mother who interrupts treatment for 14 or more days for any reason.

Confirmation of Virologic Failure

Any mother with a plasma HIV-1 RNA level ≥200 copies/mL at or after 24 weeks on study should be recalled to the clinic for confirmatory testing as soon as possible and within 28 days of the date of specimen collection for the initial test. As indicated in Section 6.7, specimen collection for antiretroviral resistance testing will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing. All procedures should be performed regardless of reported adherence to study drug or any other factors that may affect HIV-1 RNA results.

Management of Confirmed Virologic Failure

The CMC should be consulted regarding management of all participants with confirmed virologic failure.

For mothers with confirmed virologic failure, upon receipt of the confirmatory HIV-1 RNA test result, specimens collected for antiretroviral resistance testing at the Screening Visit and the

Confirmation of Virologic Failure Visit should be shipped to a designated VQA-certified testing laboratory. Resistance test results will be provided in real time to help guide ART regimen management, as described below.

If the virologic failure is assessed as likely due to non-adherence, the current ART regimen may be continued, with enhanced adherence support per site SOPs (see Section 5.7) and continued virologic monitoring. Likewise, if the failure is assessed as due to intercurrent illness or other factors not associated with the current regimen, the current regimen may be continued. Otherwise, the regimen should generally be modified in consultation with the CMC. Recommendations for alternative regimens should take into consideration the participant's preferences and medical history, current regimen, current local standard guidelines for first- and second-line regimens, and resistance test results. For any mother whose regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6.

8.4 Management of Mothers who Develop Active Tuberculosis

Mothers who develop active tuberculosis and need rifampin-containing treatment during follow-up may have their study drug regimen modified consistent with the relevant Package Inserts and guidelines for co-administration of ARVs and TB treatment medications. Such modifications will include increasing the frequency of DTG dosing from 50 mg once daily to 50 mg twice daily. In addition, TAF should be switched to TDF. The CMC should be informed of each TB diagnosis and consulted on study drug regimen management on a case-by-case basis. After the period of rifampin treatment is completed, the original ART regimen should be resumed.

For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6.

8.5 Management of Mothers who are Co-Infected with Hepatitis B

Hepatitis B surface antigen testing will be performed at study entry so that hepatitis B infection status can be taken into account when evaluating maternal adverse events and managing study drug regimens. Hepatitis B testing is not required after study entry per the Schedule of Evaluations but may be performed at any time during follow-up if clinically indicated.

Hepatitis B co-infected mothers who initiate or discontinue ARVs that are active against hepatitis B may be at risk of immune reconstitution or rebound hepatitis viremia (respectively) and subsequent transaminitis. These mothers should be closely monitored for any symptoms of hepatitis; should any such symptoms occur, the CMC should be consulted regarding further management. Periodic monitoring of liver function tests and markers of hepatitis B virus replication should also be considered. Further guidance on management of elevated ALT and AST values and symptomatic hepatitis is provided in Tables II.3 and II.4.

For infants of mothers who are co-infected with hepatitis B, every effort should be made to facilitate access to the best available local standard management for hepatitis B exposure, including (but not limited to) the hepatitis B vaccine series, ideally beginning at birth.

8.6 Contraception and Management of Mothers who Become Pregnant on Study

Mothers should be provided with contraception counseling as needed during their participation in the study. Counseling should be provided per site SOPs, which should reflect WHO guidelines for HIV-infected women as well as local standards of care. Counseling should begin during pregnancy and continue postpartum as needed for each mother, and should reflect the ARVs that mothers are currently taking and the potential interactions between these ARVs and available contraceptive methods. Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants and should provide referrals to non-study sources of methods that cannot be provided at the study site.

Pregnancy testing is not required per the study Schedule of Evaluations. Nonetheless, testing may be performed when clinically indicated at any time during maternal follow-up.

Mothers who become pregnant will be maintained in follow-up and may remain on their current ART regimen during the new pregnancy. When the new pregnancy is identified, mothers will be provided information and counseling on their current regimen and what is known about the safety of the ARVs that comprise the regimen during pregnancy. Mothers who wish to change regimens based on this counseling will be permitted to do so, and site clinicians may consult with the CMC regarding any mothers for whom a regimen change may be clinically indicated or otherwise considered in the best interest of the mother or fetus. For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6. Mothers who choose to receive study drug during a subsequent pregnancy must provide separate informed consent to do so (refer to Section 12.3 and Appendix V).

All pregnancies and pregnancy outcomes should be ascertained and entered into eCRFs. For mothers who are pregnant at the time of study exit, additional post-study contacts should be completed to ascertain their pregnancy outcomes as well as any ART regimen changes after study exit (see Section 6.10). These data may be ascertained based on maternal report but medical records should be obtained whenever possible to supplement maternal reports.

Study sites are strongly encouraged to prospectively register participants with subsequent pregnancies in the Antiretroviral Pregnancy Registry (APR) prior to pregnancy outcome by calling the following number in the US: +1-800-258-4263. Outside of the US, please see the APR website (www.apregistry.com) for additional toll-free numbers.

8.7 Management of Maternal Nervous System and Psychiatric Symptoms

As described in Section 1.8, use of EFV is commonly associated with nervous system symptoms (e.g., dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia) that usually begin on the first or second day of therapy and resolve within 2-4 weeks on therapy. To minimize these possible effects, mothers receiving EFV in this study will be encouraged to take EFV at bedtime; mothers will also be informed of the potential for exacerbation of these symptoms associated with use of alcohol and psychoactive drugs.

Insomnia, headache, and anxiety have been reported with DTG. Participants who experience insomnia with evening dosing of DTG may have resolution of insomnia after switching to morning dosing (123).

Mothers who experience nervous system symptoms should generally be managed consistent with the guidance provided in Table II.1. For any mothers who experience persistent symptoms that cannot be tolerated, the CMC should be consulted regarding a change of study drug regimen.

Serious psychiatric adverse events, including severe depression and suicidal ideation or attempts, have also been observed with use of EFV (and rarely with DTG). Patients with a history of psychiatric disorder are a highest risk for these events; for this reason, mothers with a history of suicidality or psychiatric illness that requires treatment with psychoactive medication will be excluded from this study.

Mothers who enroll in the study will be assessed for sleep disturbances, anxiety, and depression through collection of medical history information at each scheduled visit as well as through administration of the Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder 7-Item Scale (GAD-7), and Edinburgh Postnatal Depression Scale (EPDS). Further information on administering these standardized questionnaires is provided in the study-specific MOP.

The PSQI, GAD-7, and EPDS are not intended to be — and should not be — used for diagnostic purposes or to make decisions regarding study drug changes. However, responses to these questionnaires may prompt further evaluation for neuropsychiatric problems. For participants with questionnaire responses indicating possible neuropsychiatric symptoms of concern, a designated study staff member will continue discussion with the participant to determine whether she may require additional support, evaluation, and/or treatment, following site SOPs.

The DAIDS AE Grading Table provides guidance on grading the severity of insomnia, psychiatric disorders (including anxiety and depression) and suicidal ideation or attempt. Study-specific guidance for management of these conditions is provided in Table II.6. As indicated this table, any participant identified with a grade 1 or grade 2 condition accompanied by suicidal ideation, or any grade 3 or 4 condition, should be referred to appropriate mental health services.

8.8 Management of Immune Reconstitution Inflammatory Syndrome (IRIS)

Inflammatory syndromes with manifestations of opportunistic or other infections have been reported shortly after initiation of ART (usually within three months). While these syndromes may appear as a recurrence or worsening of disease, they more likely reflect improvement in the body's ability to control infection as the immune system recovers on ART. IRIS can have various manifestations, including lymph node inflammation associated with *Mycobacterium avium intracellulare*, eye inflammation associated with *cytomegalovirus*, worsening of tuberculosis, cryptococcosis, or toxoplasmosis symptoms, and elevated liver enzymes in people with hepatitis B or C co-infection. There have also been case reports of temporary worsening of *Pneumocystis* pneumonia, progressive multifocal lymphadenopathy, herpes simplex and varicella zoster (shingles), warts due to human papillomavirus, and other skin conditions. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment and sometimes can be an atypical presentation.

As noted in Section 8.1, adverse events assessed as secondary to immune reconstitution should not be considered related to study drug; the rationale for this is that although IRIS is related to ART initiation, assessment of relationship of IRIS to a specific ART regimen is not meaningful for a given event. In addition, the DAIDS EAE Manual specifies that IRIS events should not be reported as EAEs, as IRIS is considered an anticipated event for antiretroviral therapies.

When IRIS is suspected, the following management guidelines should be followed in consultation with the CMC:

- Continue ART
- Confirm diagnosis of the infection
- Continue or initiate specific therapy for the infection
- Evaluate the participant clinically to exclude a new infectious process if the participant was already receiving therapy for the infection

Anti-inflammatory agents — initially nonsteroidal anti-inflammatory medications or corticosteroids if needed — may be initiated at the discretion of the site investigator in consultation with the CMC.

8.9 Infant Management

Infants enrolled in this study should receive ARV prophylaxis and other standard interventions such as cotrimoxazole, isoniazid preventive therapy, and childhood immunizations consistent with local standards of care from non-study sources. Likewise, infants diagnosed with HIV infection should receive ART consistent with local standards of care from non-study sources.

In the event that mothers need to interrupt ART (e.g., due to an adverse event), information and counseling will be provided regarding locally-available options for reducing the risk of perinatal HIV transmission. Such options may include infant ARV prophylaxis during breastfeeding and replacement feeding if determined to be safe and accessible and if the mother's ART interruption is likely to be prolonged.

Infant adverse events will be managed consistent with the best medical judgment of the site investigator and local clinical practice standards. It is not expected that maternal study drug regimens will routinely be modified in response to infant adverse events; site investigators may modify use of infant ARVs and other concomitant medications in response to infant adverse events. Consultation with the CMC is available but not required for most infant adverse events. However, should an infant experience a grade 3 or higher adverse event that is assessed by the site investigator as related the mother's current study drug regimen, the CMC should be consulted.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase III, three-arm, randomized, open-label study to compare the virologic efficacy and safety of three antiretroviral regimens — DTG+FTC/TAF, DTG+FTC/TDF, and EFV/FTC/TDF — for HIV-1-infected pregnant women and their infants. Mother-infant pairs will be randomized at 14-28 weeks gestation in a 1:1:1 ratio to receive either DTG+FTC/TAF (Arm 1),

DTG+FTC/TDF (Arm 2), or EFV/FTC/TDF (Arm 3). The primary objectives are to compare the DTG-containing arms (Arms 1 and 2) to the EFV-containing arm (Arm 3) with respect to maternal viral suppression at delivery; to compute all pairwise regimen comparisons for a composite adverse pregnancy outcome (spontaneous abortion, fetal death, preterm delivery, or small for gestational age); and to compute all pairwise regimen comparisons for maternal and infant grade 3 or higher adverse events through 50 weeks postpartum. All mothers and infants are planned to be followed through 50 weeks postpartum. The total sample size is 639 mother-infant pairs (approximately 213 per arm) and accrual is expected to be completed within 12 months after the first pair is enrolled. The sample size will be re-evaluated as further described in Section 9.4.2, with the possibility of adjustment prior to the closure of participant accrual.

The primary virologic efficacy analysis will combine the two DTG-containing randomized arms for comparison to EFV/FTC/TDF. The DTG-containing arms will be combined because viral load at delivery is not expected to vary between these arms. This combined analysis also weighs feasibility against the need to provide information on the possibility of effect modification of DTG in the presence of TDF or TAF. Powering the study for all three pairwise comparisons would be ideal scientifically; however, this would require an infeasible sample size.

Viral suppression at delivery was chosen as the primary efficacy endpoint because of the importance of maintaining high viral suppression to minimize perinatal HIV transmission. A conclusion for superiority in viral suppression of a DTG-containing regimen relative to EFV/FTC/TDF might hasten the adoption of a DTG-containing regimen for use during pregnancy and postpartum. However, a conclusion of non-inferiority might allow for an increase in the options available to pregnant and postpartum women. Because of these two important possible conclusions at the end of the study, the primary analysis will be an analysis of non-inferiority while a superiority comparison is specified as an important secondary analysis. Testing both superiority and non-inferiority does not constitute multiple testing (124); however, non-inferiority must be established before a conclusion of superiority can be made.

A conclusion of non-inferiority will be predicated on the following considerations:

- The 95% CI for the difference excludes the non-inferiority margin.
- There is a high degree of consistency with the protocol plans. For example, the levels of protocol deviations and loss to follow-up will need to be similar to those in previous studies in which superiority has been shown (e.g., PROMISE, PROMOTE).
- The EFV-containing arm shows its usual efficacy.
- The ITT and the per-protocol analyses show similar results.

All three pairwise regimen comparisons will be conducted for the adverse pregnancy and maternal adverse event primary objectives. The DTG-containing arms (Arm 1 and Arm 2) will not be combined for these primary analyses because little is known about safety in pregnancy through one year postpartum between these two arms.

An open-label study design was selected because the number of pills per day and instructions for administration vary between treatment arms. Potential sources of bias with an open-label study include increased attribution and reporting of specific toxicities in a treatment arm. Site investigators may be more likely to change antiretroviral therapy if a treatment arm is perceived as suboptimal. Efforts will be made to minimize these biases by establishing standard criteria and guidelines for toxicity and ARV regimen management (Section 8), safety-related data recording and reporting (Section 7), and inadequate virologic response (Section 8.3).

9.2 Outcome Measures

Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2.

The primary and secondary outcome measures listed in Sections 9.2.1 and 9.2.2 below will be addressed in the study's primary statistical analysis plan, which will define the content of the primary analysis report. This report will form the basis for the primary study publication and results reporting to ClinicalTrials.gov. Other outcomes of interest for secondary objectives (intended for subsequent publications) are listed as other outcome measures. Outcomes of interest for exploratory objectives are listed in Section 9.2.3.

9.2.1	**Primary Outcome Measures**
9.2.1.1	Efficacy • HIV-1 RNA <200 copies/mL at delivery (up to 14 days postpartum), using real-time test results obtained at site laboratories
9.2.1.2	Safety • Composite outcome of spontaneous abortion (occurring at <20 weeks gestation), fetal death (occurring at ≥20 weeks gestation), preterm delivery (<37 completed weeks), or small for gestational age (<10th percentile) • Maternal grade 3 or higher adverse events, including events resulting in death due to any cause, through 50 weeks postpartum (refer to Section 7.3.3 for severity grading) • Infant grade 3 or higher adverse events, including events resulting in death due to any cause, through 50 weeks postpartum (refer to Section 7.3.3 for severity grading)
9.2.2	**Secondary Outcome Measures**
9.2.2.1	• HIV-1 RNA <200 copies/mL at delivery (up to 14 days postpartum) using real-time test results obtained at site laboratories
9.2.2.2	• HIV-1 RNA <50 copies/mL at delivery (up to 14 days postpartum) using batched test results obtained from central laboratory • HIV-1 RNA <200 copies/mL at 50 weeks postpartum using real-time test results obtained from site laboratories • Time to first HIV-1 RNA <200 copies/mL through delivery (up to 14 days postpartum) using real-time results obtained from site laboratories
9.2.2.3	• HIV-1 RNA <200 copies/mL at delivery (up to 14 days postpartum) using real-time test results obtained from site laboratories and FDA snapshot algorithm • HIV-1 RNA <200 copies/mL at 50 weeks postpartum using real-time results obtained from site laboratories and FDA snapshot algorithm
9.2.2.4	• Composite outcome of spontaneous abortion (occurring at <20 weeks gestation), fetal death (occurring at ≥20 weeks gestation), preterm delivery (<37 completed weeks), or small for gestational age (<10th percentile) • Maternal grade 3 or higher adverse events, including events resulting in death due to any cause, through 50 weeks postpartum (refer to Section 7.3.3 for severity grading) • Infant grade 3 or higher adverse events, including events resulting in death due to any cause, through 50 weeks postpartum (refer to Section 7.3.3 for severity grading)

9.2.2.5	• Composite outcome of spontaneous abortion (occurring at <20 weeks gestation), fetal death (occurring at ≥20 weeks gestation), preterm delivery (<37 completed weeks), or small for gestational age (<10th percentile) or major congenital anomaly* • Ranked composite infant safety outcome (defined in Section 9.6.2) through 50 weeks postpartum • Infant HIV infection at delivery and through 50 weeks postpartum • Infant death due to any cause through 50 weeks postpartum • Maternal serum creatinine and creatinine clearance rate (Cockcroft-Gault formula) • Infant serum creatinine and creatinine clearance rate (Schwartz formula) • HIV-1 antiretroviral drug resistance mutations at the time of maternal virologic failure (and at screening for mothers with resistance detected at the time of virologic failure to determine if the resistance was present prior to enrollment or occurred post-enrollment) using the Stanford algorithm • HIV-1 antiretroviral drug resistance mutations at the time HIV diagnosis for HIV-infected infants
9.2.2.6	• Preterm delivery (<37 completed weeks) • Small for gestational age (<10th percentile)
	Other Outcome Measures
	The other outcome measures below correspond to secondary objective 2.2.5: • Maternal urine protein:creatinine ratio, urine beta 2 microglobulin: creatinine ratio, and urine retinol binding protein:creatinine ratio • Maternal lumbar spine and hip BMD Z-scores based on DXA scan at 50 weeks postpartum • Infant whole body and lumbar spine BMC Z-scores based on DXA scan at 26 weeks postpartum
9.2.3	**Exploratory Outcome Measures**
9.2.3.1	• Maternal postpartum depression as indicated by EPDS score at 6 weeks and 50 weeks postpartum • Composite of the following outcomes of subsequent pregnancy: spontaneous abortion (occurring at <20 weeks gestation), fetal death (occurring at ≥20 weeks gestation), preterm delivery (<37 completed weeks), small for gestational age (<10th percentile), or major congenital anomaly*
9.2.3.2	• Immunologic and hormonal predictors of adverse pregnancy outcomes and postpartum maternal health outcomes (potential predictors will be further defined by the Protocol Team after the study is completed, based on available scientific information and state-of-the-art assays at that time; these outcomes may include but are not limited to: IDO, K/T ratio, IL-6, D-dimer, hsCRP, sCD14/sCD163, TNFRI/II, progesterone, prolactin)
9.2.3.3	• Composite outcome of spontaneous abortion (occurring at <20 weeks gestation), fetal death (occurring at ≥20 weeks gestation), preterm delivery (<37 completed weeks), or small for gestational age (<10th percentile) • Preterm delivery (<37 completed weeks)
9.2.3.4	• Antiretroviral drug concentrations in maternal hair at delivery • Maternal and infant grade 3 or higher adverse events through delivery and from delivery through 6 weeks postpartum (refer to Section 7.3.3 for severity grading)

9.2.3.5	• Antiretroviral drug concentrations in maternal and infant hair, and ratio thereof as a measure of transfer from mother-to-infant, at delivery • Antiretroviral drug concentrations in maternal plasma, breast milk, and infant plasma at 6 weeks postpartum
9.2.3.6	• Antiretroviral drug concentrations in maternal hair at delivery • Self-reported adherence to maternal ART regimens through 50 weeks postpartum • Self-reported barriers and facilitators of adherence to maternal ART regimens at 50 weeks postpartum

*Major congenital anomaly will be defined for this study consistent with the definition of malformation provided by Holmes and Westgate, i.e., a structural abnormality with surgical, medical, or cosmetic importance (125). The following will not be considered major congenital anomalies: genetic disorders, chromosome abnormalities, minor anomalies, birth marks, positional deformities, prematurity related findings, prenatal ultrasound-only findings (i.e., findings only identified by ultrasound and not by the examining pediatrician), and polydactyly (postaxial, type B). Findings consistent with the definition of malformation will be included in analyses as major congenital anomalies. All suspected congenital anomalies will be entered into eCRFs and a small group of study investigators (blinded to randomized study arm), including an expert on birth defects, will review all suspected anomalies in near real time to determine whether they meet the study-specific definition of major congenital anomaly.

9.3 Enrollment/Randomization

A dynamic permuted block system will be used to randomize mother-infant pairs in approximately equal numbers to DTG+FTC/TAF (Arm 1) or DTG+FTC/TDF (Arm 2) or EFV/FTC/TDF (Arm 3). To ensure balance in the three arms, the randomization will be stratified by gestational age at enrollment (14-18 weeks or 19-23 weeks or 24-28 weeks) and by country. There will be no limit on the number of pairs in each stratum. The rationale for stratifying by gestational age is that mothers who enter the study later in gestation will be less likely to achieve the desired viral load decrease but will be exposed to study drug for a shorter period of time compared with mothers who enroll earlier in gestation.

9.4 Sample Size and Accrual

The sample size of 639 mother-infant pairs was set using the primary virologic efficacy objective and adjusting for two interim analyses assumed (O'Brien-Fleming like error spending function (126)) to maintain a two-sided Type I error rate (α) of 0.05. No adjustment for interim analyses was made for the primary safety comparisons: composite adverse pregnancy safety objective, maternal adverse event safety objective, or infant adverse event safety objective. For the sample size calculations, it was assumed that 10% of the data for the primary outcomes would be missing due to loss to follow-up, insufficient specimens, invalid results, or other reasons for being non-evaluable. Therefore, with a sample size of 639 pairs, it was assumed that there would be 575 (90%) evaluable pairs. SAS 9.4 proc seqdesign was used for the power calculations. The tables below display power analyses for efficacy (Table 8 and Table 9) and safety outcomes (Table 10, Table 11, and Table 12).

Because there is some uncertainty in assumptions underlying the sample size calculation (as is very often the case), the study design includes checks on assumptions at each DSMB review, and a formal re-evaluation of sample size once at least 192 women have HIV-1 RNA data at delivery (approximately 33% of the expected information). The re-evaluation will be undertaken earlier if accrual is expected to be completed before the next scheduled DSMB meeting. DSMB reviews are described in more detail in Section 9.5.3, below.

The sample size of 639 pairs was chosen to provide 80% power for a 10% non-inferiority margin for virologic efficacy (<200 copies/mL) at delivery when comparing the combined DTG-containing arms to the EFV-containing arm. The sample size was adjusted for two interim analyses (O'Brien-Fleming like error spending function (126)), with interim analyses at 33% and 66% of the maximal information to maintain a two-sided Type I error rate (α) of 0.05. The variance of the estimated difference was computed under the alternative hypothesis that the combined DTG-containing arms and the EFV-containing arm are equivalent. The percent suppressed at delivery was assumed to be 80% for the combined DTG-containing arms and 80% for the EFV-containing arm. A non-inferiority margin of 10% was selected because a difference smaller than 10% is not thought to be of clinical importance, is expected to have similar perinatal transmission risk, and 10% is expected to retain much of the efficacy of the EFV-containing arm. Further considerations on the choice of the 10% margin are discussed below.

Eighty percent suppression was chosen to power the study as this is the lowest expected viral suppression percent at delivery, and this assumption will lead to a conservative sample size that will maintain at least 80% power for non-inferiority if viral suppression percentages are higher than 80%. The PROMOTE study showed that women who initiated an EFV based regimen at 12-28 weeks of gestation can achieve a delivery suppression percentage of 97.6% at 400 copies/mL (127). In the Phase IIb SPRING-1 trial of 205 treatment-naive adults (14% women), participants were randomized to start DTG (10 mg, 25 mg, or 50 mg) or EFV (20). Week 16 suppression percentages (for <50 copies/mL) were 93% for all doses of DTG and 60% for EFV. The PROMOTE study used a higher viral suppression cutoff (<400 copies/mL at an approximate average of 19 weeks of EFV exposure) than will be used in IMPAACT 2010, while the SPRING-1 trial used a lower cutoff (<50 copies/mL at 16 weeks of EFV exposure). The average result across these two studies for EFV-containing regimens is 79% suppressed, similar to the 80% assumed for the EFV-containing arm in IMPAACT 2010.

9.4.1 Justification of the Non-Inferiority Margin

The non-inferiority margin was set to 10%. This section highlights how a 10% margin is expected to retain much of the efficacy of the EFV-containing regimen based on the Historical Evidence of Sensitivity to Drug Effects (HESDE).

To statistically justify the non-inferiority margin it is common to set the margin as a percentage of the efficacy for the active comparator (EFV-containing arm) (128). The data that the efficacy for the active comparator are based on is called HESDE, which is defined in the FDA guidance entitled, *Non-Inferiority Clinical Trials to Establish Effectiveness:*

> "HESDE means that prior studies, which were appropriately designed and conducted trials in the past and that used a specific active treatment (generally the one that is to be used in the new NI study or, in some cases, one or more pharmacologically closely related drugs), regularly showed this treatment to be superior to placebo (or some other treatment). Consistent findings in past studies allow for a reliable estimate of the drug's effect compared to placebo."

Five trials were considered to estimate the efficacy of the EFV-containing arm (M1): PACTG 076, which demonstrated that ZDV was superior to placebo for perinatal transmission (129); PACTG 185, from which estimates of viral suppression at delivery for women receiving ZDV are available (94); the PROMISE trial, in which two triple ART regimens (ZDV/3TC+LPV/r and FTC/TDF+LPV/r) were found to be superior to ZDV+sdNVP+FTC/TDF tail for prevention of perinatal transmission (9); the SPRING Phase IIb study, which demonstrated that DTG was superior to EFV; and the PROMOTE study, in which an EFV-based regimen was found to be superior to LPV/r-based regimens for virologic suppression at delivery. These studies imply that ZDV/3TC+LPV/r and FTC/TDF+LPV/r are superior to placebo for prevention of perinatal transmission. However, the superiority of the EFV-based regimen over LPV/r-based regimens for viral suppression implies that an EFV-based regimen is highly likely to be superior to placebo for perinatal transmission. With the exception of the SPRING Phase IIb study, all of the studies were conducted in HIV-positive, pregnant women. IMPAACT 2010 will be conducted at many of the same sites as PROMISE, so the conduct of IMPAACT 2010 is expected to be similar to PROMISE. The gestational age at entry for IMPAACT 2010 is most similar to the PROMOTE study. Unlike PROMISE, IMPAACT 2010 and PROMOTE do not include a CD4 threshold in the study entry criteria. Summary data for these trials are shown in Table 6.

Table 6
Historical Evidence of Sensitivity to Drug Effects

Study	Gestational Age at Randomization	Control Group	Experimental Group	Percent Suppressed		Perinatal Transmission	
				Control	Experimental	Control	Experimental
PACTG 076[1] (N=409)	14-34 weeks (median=26)	Placebo	ZDV	Not available	Not available	25.5%	8.3%
PACTG 185[1] (N=451)	20-30 weeks (median=26)	ZDV + immune globulin without HIV-1 antibody	ZDV + immune globulin with HIV-1 antibody	24% (presented across arms)		4.8%	4.7%
PROMISE Period 1 & 2[1] (N=3,084)	>14 weeks (median=25)	ZDV alone	ZDV/3TC + LPV/r	16%	68%	1.8%	0.5%
PROMOTE[1] (N=389)	12-28 weeks (median=21)	LPV/r-based ART	EFV-based ART	86%	97.7%	0.56%	0.00%
SPRING IIb[2] (N=205)	NA (16 week response rate)	EFV only	DTG only	60%	87%	NA	NA

[1]Study in HIV-positive, pregnant women; [2]Study in treatment naïve adults
Note: PACTG 185 used a lower viral load limit of 500 copies/mL; both PROMOTE and PROMISE used a lower viral load limit of 400 copies/mL.
Note: The gestational age at entry will be 14-28 weeks for IMPAACT 2010.

One possible way to estimate the efficacy for the active comparator is to use the imputed placebo approach in which data from historical trials are combined (128). The imputed placebo approach estimates the suppression rate of placebo that would have occurred if placebo was present in a trial compared to the EFV-containing arm. The ZDV arms displayed in Table 6 were used to stand in for placebo, a conservative and necessary approach. This approach is conservative (will give smaller values for M1) because ZDV alone can reduce viral load. This approach is necessary because viral load at delivery is not available from PACTG 076. For example, an estimated M1 with PROMISE as the target trial is given by:

$$\widehat{M1} = \left(\frac{\widehat{pEFV_{PROMOTE}}}{pLPV + \widehat{RTV_{PROMOTE}}}\right) * pLPV + \widehat{RTV_{PROMISE}} - \widehat{pZDV_{Promise}}$$
$$= \left(\frac{.977}{.86}\right) * .68 - .16 = .62.$$

This formula effectively discounts the EFV PROMOTE estimate by the ratio of the PROMOTE and PROMISE LPV/r arms.

Table 7
95% CI for M1: The Estimated IMPAACT 2010 EFV-Containing Arm Effect Relative to Placebo

Target Trial	Data Used	95% CI for M1
Average of PACTG 185 and PROMISE	All data in Table 6	(46%, 57%)
PROMISE	PROMISE and PROMOTE	(54%, 66%)
Average of PROMOTE and SPRING IIb	All data in Table 6	(64%, 73%)
PROMOTE	PROMISE and PROMOTE	(77%, 84%)
ZDV in PACTG 185, EFV in SPRING IIb, and PROMOTE	PACTG 185 (ZDV), SPRING IIb (EFV), PROMOTE (EFV)	(47%, 63%)

To account for uncertainty in the estimate of M1, the bootstrap was used to compute 95% CIs. The lower bound of the bootstrap 95% CI with PROMISE as the target trial is 54%, a conservative estimate of M1. Furthermore, five scenarios were considered. The results for these scenarios are displayed in Table 7. The smallest lower limit of the 95% CI is 46%. This estimate used the ZDV suppression probabilities from PROMISE and PACTG 185, and the EFV suppression percentages from PROMOTE and SPRING IIb.

Clinical Justification

Ten percent was chosen by the Protocol Team as an acceptable level of difference because a difference of 10% with high levels of suppression is not expected to confer a large difference in perinatal transmission. In the PROMOTE study (Table 6), the suppression difference was 11.7% but the difference in perinatal transmission was 0.56%. Similarly, the difference in suppression for PROMISE was 52% but the difference in perinatal transmission was 1.3%. Importantly, the perinatal transmission probability was lower, in all arms of PROMOTE and PROMISE, than the World Health Organization's targets of 5% in breastfeeding populations and 2% in non-breastfeeding populations (130). This implies that a difference smaller than 10% is unlikely to confer large differences in perinatal transmission.

Percent of Efficacy Retained

Assuming that M1 is 0.46, a 10% margin will preserve at least 64% ((.46-.10)/.55) of the efficacy of an EFV-based regimen. This is a conservative estimate of M1, using the lowest lower bound of the 95% confidence interval for M1 (Table 7). Preserving this percentage of efficacy was considered acceptable to the Protocol Team.

Constancy Assumption

The constancy assumption is expected to hold because there have been no advancements of standard clinical care in the field of HIV treatment that would affect viral load in the absence of receipt of ART. Similarly, the effect of ART on viral load is expected to remain the same. Table 6 provides indirect evidence of a constant treatment effect across studies by comparing PACTG 185 to PROMISE for the ZDV arm. Both studies had a median gestational age of 26 at randomization. PACTG 185 was conducted between October 1993 and March 1997, while PROMISE was conducted between April 2011 and October 2014. Even still, the suppression rates for ZDV are similar, and differences are likely due to different participant populations: PROMISE enrolled healthy women, while PACTG 185 enrolled a relatively sicker participant population.

Assay Sensitivity

According to the FDA guidance, assay sensitivity means that had the non-inferiority study included a placebo arm, a control drug-placebo difference of at least M1 would have been present. IMPAACT 2010 will have assay sensitivity due to the following reasons:

1) Many of the IMPAACT 2010 sites are the same sites from the PROMISE study.
2) The difference observed in PROMISE (52%) was larger than the conservative estimate of M1.
3) The PROMOTE EFV -based ART regimen was shown to be superior to the LPV/RTV -based ART regimen that was used in PROMISE.
4) IMPAACT 2010 will have adequate power for a 10% difference, much smaller than the estimated value for M1 (see Table 8).

Power

The power for a conclusion of non-inferiority with a sample size of 639 is 80% with a non-inferiority margin of 10%, assuming that the EFV-containing arm and the DTG-containing arms have an 80% suppression percentage, and 90% evaluable (Table 8). To account for the possibility that the percentage of viral suppression at delivery might deviate from 80% in the EFV-containing arm, Table 8 also includes scenarios in which the suppression percentage varies from 60% to 90%. If the true suppression percentage is 85% in both the DTG-containing and the EFV-containing arms then the power is 88%, while a suppression percentage of 90% in both the DTG-containing and the EFV-containing arms results in 96% power. Suppression percentages of 95% and 85% provide high power, and these percentages could have reasonably been selected to size the study. If the percent suppressed in the EFV-containing arm is lower than expected, the power is reduced: 60% versus 60% results in 63% power and 70% versus 70% results in 69% power. In addition, a small increase in the true rate of suppression for the combined DTG-containing arms results in a significant increase in power: 83% suppressed results in 96% power assuming an 80% true percentage of suppression in the EFV-containing arm. Assuming 85% evaluable, the power is reduced by 1-3%. With a sample size of 639 pairs, the half-lengths of the 95% CI for the difference in percentages range from 5% to 9%.

Table 8
Viral Suppression (HIV-1 RNA <200) Primary Non-Inferiority Efficacy Analysis Comparing the DTG-containing Arms Versus the EFV-containing Arm

Percent Suppressed		N		Assuming 90% Evaluable		Assuming 85% Evaluable	
DTG-containing arms	EFV-containing arm	DTG-containing arms	EFV-containing arm	95% CI Half-Length*	Power**	95% CI Half-Length*	Power**
60%	60%	426	213	8.5%	63%	8.7%	60%
70%	70%	426	213	8.0%	69%	8.2%	66%
80%	80%	426	213	6.9%	80%	7.1%	78%
81%	80%	426	213	6.9%	87%	7.1%	85%
83%	80%	426	213	6.8%	96%	7.0%	95%
85%	85%	426	213	6.2%	88%	6.4%	86%
90%	90%	426	213	5.2%	96%	5.4%	95%

*Half-length was computed for the difference in percentages.
**Power for a non-inferiority design (10% margin) testing a two sample difference in binomial proportions comparing the combined DTG-containing arms relative to the EFV-containing arm. The power was adjusted to account for two interim analyses with an O'Brien-Fleming like error spending function and 85%-90% evaluable at delivery.

This study was powered for non-inferiority, not superiority. However, superiority is an important secondary analysis. Under the assumptions stated above, there will be 86% power to detect a 10% difference in the percent suppressed between the combined DTG-containing arms relative to the EFV-containing arm (Table 9). To account for the possibility that the percent of viral suppression at delivery might deviate from 80% in the EFV-containing arm, Table 9 includes scenarios in which the suppression percentage varies from 60% to 90%. If the percent suppressed is higher than 80% in the EFV-containing arm the power ranges from 85% to 94%. If the percent suppressed in the EFV-containing arm is lower than expected, the power is reduced: 80% versus 70% results in 72% power and 70% versus 60% results in 65% power. Power will also be reduced if more than the assumed 10% are not evaluable. Assuming 15% non-evaluability, the power is reduced by 2-3%. With a sample size of 639 pairs, the half-lengths of the 95% CI for the difference in percentages range from 5% to 9%.

Table 9
Viral Suppression (HIV-1 RNA <200) Secondary Superiority Efficacy Analysis Comparing the DTG-containing Arms Versus the EFV-containing Arm

Percent Suppressed		N		Assuming 90% Evaluable		Assuming 85% Evaluable	
DTG-containing arms	EFV-containing arm	DTG-containing arms	EFV-containing arm	95% CI Half-Length*	Power**	95% CI Half-Length*	Power**
70%	60%	426	213	8.3%	65%	8.6%	62%
80%	70%	426	213	7.6%	72%	7.8%	70%
90%	80%	426	213	6.4%	86%	6.6%	84%
94%	85%	426	213	5.6%	85%	5.8%	83%
97%	90%	426	213	4.6%	86%	4.7%	84%
91%	80%	426	213	6.3%	93%	6.5%	92%
95%	85%	426	213	5.5%	93%	5.7%	92%
98%	90%	426	213	4.5%	94%	4.6%	93%

*Half-length was computed for the difference in percentages.
**Power for a non-inferiority design (10% margin) testing a two sample difference in binomial proportions comparing the combined DTG-containing arms relative to the EFV-containing arm. The power was adjusted to account for two interim analyses with an O'Brien-Fleming like error spending function and 90% evaluable at delivery.

Table 10 contains a power analysis for the primary adverse pregnancy outcome. All pairwise comparisons will be conducted for this analysis; hence, power was calculated using a sample size of 213 in each comparison group. The composite adverse pregnancy outcome event percentage was assumed to be 27% for the EFV-containing arm (31). The upper and lower alternative was calculated to give 80% and 90% power. With 213 in each comparison group, 41% versus 27% and 15% versus 27% results in 80% power; 43% versus 27% and 14% versus 27% results in 90% power. The half-lengths of the 95% CI for the difference in percentages range from 8% to 10%.

Table 10
Power Analysis for Primary Composite Adverse Pregnancy Outcome Objective (All Pairwise Comparisons)

Percent with a Composite Outcome		N		Assuming 90% Evaluable		Assuming 85% Evaluable	
Comparison Group 1	Comparison Group 2	Comparison Group 1	Comparison Group 2	95% CI Half-Length	Power*	95% CI Half-Length	Power*
41%	27%	213	213	9.4%	80%	9.6%	78%
43%	27%	213	213	9.4%	90%	9.7%	88%
15%	27%	213	213	8.1%	80%	8.3%	78%
14%	27%	213	213	8.0%	90%	8.2%	88%

*Power for two sided alpha 0.05 test difference in binomial proportions. Power was NOT adjusted interim analyses. Ninety percent and 85% evaluable was assumed. This table can also be used to judge power for each pairwise comparison.

This study is not powered to detect differences in infant mortality (67% power for a difference of 4.4% versus 0.6%, as was observed in the PROMISE trial).

Table 11 contains a power analysis for the primary maternal safety objective. All pairwise comparisons will be conducted for this analysis; hence, power was calculated using a sample size of 213 mothers in each comparison group. The outcome event percentage was assumed to be 15% for the EFV-containing arm (127). The upper and lower alternative was calculated to give 80% and 90% power. With 213 mothers in each comparison group, 27% versus 15% and 6% versus 15% results in 80% power; 29% versus 15% and 5% versus 15% results in 90% power. The half-lengths of the 95% CI for the difference in percentages range from 6% to 8%.

Table 11
Power Analysis for Primary Composite Maternal Adverse Event Objective
(All Pairwise Comparisons)

Percent with a Composite Outcome		N		Assuming 90% Evaluable		Assuming 85% Evaluable	
Comparison Group 1	Comparison Group 2	Comparison Group 1	Comparison Group 2	95% CI Half-Length	Power*	95% CI Half-Length	Power*
27%	15%	213	213	8.1%	80%	8.3%	78%
29%	15%	213	213	8.2%	90%	8.4%	89%
6%	15%	213	213	6.1%	80%	6.3%	78%
5%	15%	213	213	5.9%	90%	6.0%	88%

*Power for two sided alpha 0.05 test difference in binomial proportions. Power was NOT adjusted interim analyses. Ninety percent and 85% evaluable was assumed. This table can also be used to judge power for each pairwise comparison.

Table 12 contains a power analysis for the primary infant safety objective. All pairwise comparisons will be conducted for the analysis; hence, power was calculated using a sample size of 213 infants in each comparison group. The outcome event percentage was assumed to be 25% for the EFV-containing arm (127). The upper and lower alternative was calculated to give 80% to 90% power. With 213 infants in each comparison group, 38% versus 25% and 14% versus 25% results in 80% power; 40% versus 25% and 12% versus 25% results in 90% power. The half-lengths of the 95% CI for the difference in percentages range from 8% to 10%.

Table 12
Power Analysis for Primary Composite Infant Adverse Event Objective
(All Pairwise Comparisons)

Percent with a Composite Outcome		N		Assuming 90% Evaluable		Assuming 85% Evaluable	
Comparison Group 1	Comparison Group 2	Comparison Group 1	Comparison Group 2	95% CI Half-Length	Power*	95% CI Half-Length	Power*
38%	25%	213	213	9.2%	80%	9.5%	78%
40%	25%	213	213	9.3%	90%	9.5%	89%
14%	25%	213	213	7.9%	80%	8.1%	78%
12%	25%	213	213	7.7%	90%	7.9%	88%

*Power for two sided alpha 0.05 test difference in binomial proportions. Power was NOT adjusted interim analyses. Ninety percent and 85% evaluable was assumed. This table can also be used to judge power for each pairwise comparison.

DXA scans will be performed measured in a subset of approximately 213 (71 per arm) mothers and infants. Two hundred and thirteen DXA measurements will provide 80% power to detect at least one half a standard deviation difference which the team assessed as clinically relevant (difference of approximately 0.40 g for spine bone mineral content and 2.75 g for whole body bone mineral content for infants (7) and 0.07 g lumbar spine for mothers).

9.4.2 Re-Evaluation of Sample Size

The main purpose of the sample size re-evaluation is to use the observed data to inform the following parameters used in the sample size calculations: the percent of participants with evaluable data and the percent of mothers with HIV-1 RNA <200 copies/mL at delivery. This is to evaluate whether a sample size increase is needed to achieve the desired statistical power for the primary efficacy objective of the study. The sample size re-evaluation will take place at one interim analysis, once sufficient information is available to estimate the proportion of mothers with HIV-1 RNA <200 copies/mL at delivery. To maintain power for the primary safety analyses, the maximal sample size should not be decreased.

The re-evaluation will be undertaken by a statistician who is blinded to the randomized treatment arms. The statistician will be given study datasets without access to the randomized treatment arms. The re-evaluated sample size will be computed for the DSMB at the interim analysis in which at least 192 women have delivery HIV-1 RNA data available (approximately 33% of the expected information) or at the scheduled DSMB review before accrual is completed, whichever comes first. If accrual of 639 mother-infant pairs is expected to be completed before the next scheduled DSMB meeting, accrual may be paused when 639 pairs have been enrolled but accrual would not formally close until the DSMB has reviewed the sample size adjustment. The DSMB will review the sample size re-evaluation based on a pre-specified algorithm and make recommendations concerning sample size.

Further guidelines for the DSMB in considering sample size re-evaluation include the following:

- The sample size should not increase because the percent of non-evaluable women at delivery is higher than 15%. The primary rationale for this guideline is that the percent could potentially be so high relative to the anticipated percent suppressed that the results of the study may be difficult to interpret. Thus, the main point of considering the percent evaluable is because a rate lower than 15% may be relevant in offsetting any increase in sample size needed due a lower than expected suppression percentage at delivery.

- The DSMB will be provided with estimated primary outcome rates by arm at each interim efficacy analysis. A concern, however, with sample size re-evaluation is that it may affect the Type I error rate and introduce bias in estimates of the difference in outcomes between arms (and associated CIs). This is generally avoided if the interim information used to re-evaluate the sample size is pooled over randomized treatment arms (131).

- A sample size re-evaluation algorithm will be followed. To re-power the study, the amount of information will be fixed to the amount used to calculate the sample size of 639 pairs. The maximal amount of information for this study is:

$$\text{I}=(.8*(1-.8)/(.9*639*\tfrac{2}{3})+.8*(1-.8)/(.9*639*\tfrac{1}{3}))\text{^}-1\ \approx 797.2.$$

Maximal information was computed from the inverse of the variance of the estimate of the difference in binomial proportions calculated under the alternative hypothesis. At the time of the sample size re-evaluation, the observed pooled binomial proportion ($\hat{P}$) will be used to compute the re-evaluated sample size. If we let ε be the proportion evaluable, after solving the information formula for N, the formula to re-compute the total sample size is:

$$N = \frac{\mathrm{I}}{\varepsilon} * \left[\frac{9}{2}\hat{P}(1-\hat{P})\right].$$

Following this procedure (132) will aid in maintaining 80% power for a non-inferiority margin of 10% assuming that the comparison groups have the same but arbitrary suppression probabilities.

9.4.3 Accrual

Accrual of 639 mother-infant pairs is expected to be completed within approximately 12 months after the first pair is enrolled. Monthly accrual rates are expected to be low initially, as sites obtain approvals and are activated to initiate the study. Once all sites are activated, accrual rates of up to 90-100 pairs per month are expected.

If the sample size re-evaluation described in Section 9.4.2 results in a recommendation to increase the sample size, the accrual period may be extended beyond 12 months.

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard procedures described in the IMPAACT Manual of Procedures. Included in these standard procedures is monthly review of participant accrual and retention by the IMPAACT Management Oversight Group. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 10 and 11 provide more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety, and virologic efficacy across sites is provided below.

9.5.1 Monitoring by the Protocol Team

All reports prepared for Protocol Team review will provide data pooled across the three randomized study arms.

Study Progress and Quality of Study Conduct

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones and quality of study conduct.

The Protocol Team will closely monitor participant accrual based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections. The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. For any site that is delayed in completing the

study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

The Protocol Team will monitor participant retention in a manner similar to participant accrual.

On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., data completeness, data and specimen completeness) based on reports generated by the SDMC and will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation. This routine monitoring will include real-time assessment of the completeness and timeliness of performing fetal ultrasound scans as specified in Sections 6.1 and 6.2. In the event of any missed or delayed ultrasound scan, the CMC will communicate with the site investigator and coordinator (e.g., via conference call) to discuss the problem(s) encountered and operational strategies to address these. If ultrasound scans are missed or delayed for more than approximately 10% of participants at a given site, the CMC will consider whether to pause accrual at that site until sufficient corrective actions have been taken to assure that the problems have been fully resolved (as judged by the CMC). The CMC will also monitor the timeliness of maternal and infant Delivery Visits at each site in a similar manner. Sites that do not consistently complete these visits within the targeted window will be required to implement appropriate corrective action plans; consideration may also be given to pausing accrual at such sites while corrective action is being taken.

9.5.2 Monitoring by the SRG

The SRG will monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will provide tabulations of the maternal and infant adverse events specified for entry into eCRFs in Section 7.2 pooled across the three randomized study arms. The SRG will review these reports via conference call or other meeting at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs reported to the DAIDS Safety Office that are not yet reflected in the data reports. The SRG will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. If the SRG identifies a potential safety concern, the Protocol Statisticians or Medical Officers will notify the DSMB and request further DSMB review and recommendations; among the recommendations requested will be whether the CMC should be informed of the SRG and/or DSMB review findings.

9.5.3 Monitoring by the DSMB

The study will be monitored by a NIAID-convened Data and Safety Monitoring Board (DSMB), which will perform its monitoring functions consistent with the NIAID Policy on Data and Safety Board Operations, available at: https://www.niaid.nih.gov/research/data-and-safety-monitoring-boards.

Interim analyses of study progress and conduct as well as participant safety will be reviewed at least every six months starting within 12 months after the first mother-infant pair is randomized. Two interim efficacy analyses will be performed when approximately 33% and 66% of the anticipated information on viral suppression at delivery have been observed, unless otherwise requested by the DSMB. Assuming participant accrual as described in Section 9.4.3 and that the average gestational age at entry is 24 weeks, it is projected that 33% of the total information will be available 10 months after the first mother-infant pair is enrolled in the study.

The DSMB will be provided with masked by-arm study data reports. Based on any of its reviews, the DSMB may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The DSMB may also provide operational recommendations to address any study implementation challenges that may be identified.

Statistical Stopping Guidelines for Evaluating Efficacy

Efficacy decision boundary guidelines will be based on the group sequential Lan-DeMets O'Brien-Fleming like error spending approach. The Z test statistic for the difference in proportions when comparing the DTG-containing arms to the EFV-containing arm will be compared to the z-value decision boundary guideline computed from the Lan-DeMets O'Brien-Fleming like error spending approach. The z-value decision boundary guideline is approximately ±3.7 at 33% of information and ±2.5 at 66% of information. As the decision boundary guidelines change depending on the amount of information at the interim analysis, these boundaries are only given for illustrative purposes. If the Z test statistic is larger in magnitude than the z-value decision boundary guideline, in either direction, then early termination of the study may be considered. A conclusion for non-inferiority of the combined DTG-containing arms relative to the EFV-containing arm at an interim analysis in the absence of superiority would not warrant stopping for efficacy. Because a conclusion for superiority will be predicated on the existence of non-inferiority, the ability for the study to conclude non-inferiority should also be considered by the DSMB.

Assessment of Futility for the Efficacy Comparisons

IMPAACT 2010 should not be stopped at an interim analysis for futility if it appears unlikely that that a conclusion of superiority or non-inferiority can be made at the maximal sample size. There are two reasons why futility of the primary efficacy comparisons should not be considered at interim analyses: 1) the study will be quite advanced in its conduct by the time a reasonable number of participants have outcome information for the futility analyses, and 2) it will be important to collect as much safety data as possible for the 3 primary safety objectives.

Timing of Data Release Should the Study Continue to the Maximal Sample Size

The primary outcomes can be measured at two different study times. Efficacy and pregnancy outcomes are measured at the delivery visit, whereas maternal and infant adverse events are measured through Week 50. Due to this difference, and so that the study results can have maximum impact, the primary virologic efficacy and maternal safety results (through delivery), including the adverse pregnancy outcomes endpoint, may be analyzed and presented while postpartum and infant follow-up are ongoing.

9.6 Analyses

Further details of the proposed analyses will be described in a statistical analysis plan that will be developed before the first enrollment in the study.

All of the primary and secondary analyses will be performed with the principle of ITT. For the analyses testing the null hypothesis of no difference, the ITT analysis is the primary analysis.

There are two secondary non-inferiority objectives (see Section 2.2.6) and one primary non-inferiority analysis objective (see Section 2.1.1). Non-inferiority analyses typically require additional considerations relative to an analysis of superiority, including the congruence between an ITT analysis and a per-protocol analysis. Thus, the non-inferiority analyses, ITT and per-protocol, should be given equal weight in the non-inferiority analyses. Further requirements for a conclusion of non-inferiority are described in Section 9.1.

Per-protocol analyses will censor or exclude participants' data who do not remain on the randomized regimen up to the time of the measured outcome. Any change, defined as the first switch, first addition, or first removal of any of the ARVs in the randomized regimen will be considered a change from the randomized regimen, with the exception of switches made due to a requirement for other concomitant medications.

The unit of analysis for infant and pregnancy outcomes will be the mother-infant pair. Analysis summaries will use the most extreme (worst) infant or pregnancy outcome for each pregnancy. For example, if one infant of a multiple birth becomes HIV-infected but the other does not, this will count as one event in the analyses. If both infants become infected, this will count as one event for the mother-infant pair in the analysis, not two. This is a conservative approach and addresses the fact that data on infants from multiple births may be related.

Summaries and regimen comparisons will not be adjusted for the two stratification factors. By-arm regimen comparisons of the primary outcomes for each stratum of gestational age at study entry will be included in the final study report. P-values for these treatment comparisons will be provided if there is a statistically significant interaction between the treatment arm and gestational age at study entry.

There are ten primary comparisons to be made, including one efficacy comparison and nine safety comparisons. All ten comparisons are described in Section 9.6.1. There will be no adjustments for multiple comparisons. Type I error rates (α) will be controlled at the comparison level where a statistical difference will be declared if the p-value is less than 0.05. The p-value for the primary efficacy comparison will be adjusted for the repeated interim analyses, and the safety analyses will use an unadjusted nominal p-value. The safety analyses will not be adjusted for multiple comparisons or interim analyses to minimize the chance of a Type II error (β). The trial-wise Type I error will be larger than 5%.

9.6.1 Primary Outcome Analyses

Efficacy: Viral Suppression

Analyses will compare the DTG-containing arms to the EFV-containing arm.

Viral suppression will be summarized using a difference in binomial proportions with a success defined as HIV-1 RNA <200 copies/mL at delivery. The denominator for this analysis will include women who have an HIV-1 RNA measurement within the delivery visit window (+14 days). A two-sided, two-sample test for the difference in proportions will be used for this analysis. CIs and p-values for the difference in proportions will be adjusted for the interim analyses to maintain a two-sided Type 1 error rate of 0.05 using the time ordered calculations. Ninety-five percent repeated confidence intervals (RCIs) will be computed at interim analyses to aid the determination of non-inferiority. A p-value less than 0.05 testing the equality of proportions will be considered statistically significant and a p-value testing the equality of the proportions will be provided only if non-inferiority is established. Similarly, a 95% CI (or RCI at

interim analyses) that excludes a difference of 10% in favor of the EFV-containing regimen will be considered statistically significant for the non-inferiority analysis. Sensitivity analyses will be carried out using multiple imputation for women missing the HIV-1 RNA measurement within the delivery visit window.

Safety: Spontaneous Abortion, Fetal Death, Preterm Delivery, and Small for Gestational Age

Analyses will compare DTG+FTC/TDF (Arm 2) to DTG+FTC/TAF (Arm 1), DTG+FTC/TDF (Arm 2) to EFV/FTC/TDF (Arm 3), and DTG+FTC/TAF (Arm 1) to EFV/FTC/TDF (Arm 3).

The analyses of the composite adverse pregnancy outcomes will be summarized as differences in proportions. A two-sided, two-sample test for the equality of the difference in proportions will be used for the by arm comparisons. A nominal (not adjusted for interim analyses) p-value less than 0.05 will be considered statistically significant. The Type I error rate for each comparison will be 5%. Two important separate sensitivity analyses will be conducted: 1) by including mothers who are lost to follow-up before experiencing any one of these pregnancy outcomes as failures to account for the possibility of informative missingness, and 2) by stratifying by the presence of a major congenital anomaly. The analysis stratifying by the presence of a major congenital anomaly will be conducted to investigate effect modification if there is a by-arm imbalance in major congenital anomalies. Conclusions based on the analysis stratified by the presence of a major congenital anomaly should be interpreted with care as some major congenital anomalies may have occurred after randomization.

Safety: Maternal Grade 3 or Higher Adverse Events

Analyses will compare DTG+FTC/TDF (Arm 2) to DTG+FTC/TAF (Arm 1), DTG+FTC/TDF (Arm 2) to EFV/FTC/TDF (Arm 3), and DTG+FTC/TAF (Arm 1) to EFV/FTC/TDF (Arm 3).

The primary maternal safety analysis will use a Kaplan-Meier estimate of the event probability through 50 weeks postpartum. The proportion experiencing an event for each group will be computed from the Kaplan-Meier survival curve and Greenwood's formula will be used to compute the variance of the difference. A Z score will be computed by taking the difference in the estimated probabilities and dividing this difference by the square root of the sum of variances as estimated by Greenwood's formula. Since the time from randomization to a pregnancy outcome will vary among the mothers, the Week 50 event probability estimate will be taken from the average time from randomization to the mother's pregnancy outcome plus 50 weeks. The Z score will then be compared to the standard normal curve to compute a p-value. A nominal (not adjusted for interim analyses) p-value less than 0.05 will be considered statistically significant. The Type 1 error rate for each comparison will be 0.05. Important sensitivity analyses will be conducted by including mothers who drop out of the study early as failures to account for the possibility of informative missingness.

Safety: Infant Grade 3 or Higher Adverse Events

Analyses will compare DTG+FTC/TDF (Arm 2) to DTG+FTC/TAF (Arm 1), DTG+FTC/TDF (Arm 2) to EFV/FTC/TDF (Arm 3), and DTG+FTC/TAF (Arm 1) to EFV/FTC/TDF (Arm 3).

The primary infant safety analysis will use a Kaplan-Meier estimate of the event probability through Week 50. The proportion experiencing an event for each group will be computed from the Kaplan-Meier survival curve and Greenwood's formula will be used to compute the variance of the difference. A Z score will be computed by taking the difference in the estimated probabilities and dividing this difference by the square root of the sum of variances as estimated by Greenwood's formula. The Z score will then be compared to the standard normal curve to compute a p-value. A nominal (not adjusted for interim analyses) p-value less than 0.05 will be considered statistically significant. The Type 1 error rate for each comparison will be 0.05. Important sensitivity analyses will be conducted by including infants who drop out of the study early as failures to account for the possibility of informative missingness.

9.6.2 Secondary and Other Outcome Analyses

Section 2.2 lists how the three arms will be used for the secondary regimen comparisons.

Analyses to test the equality of differences in event probabilities at delivery will be performed using a similar approach as for the primary analyses. This includes estimates of the probability of mothers with HIV-1 RNA <50 copies/mL at delivery, the probability of HIV-1 RNA <200 copies/mL at delivery and through 50 weeks postpartum as defined by the FDA snapshot algorithm, the probability of mothers with adverse pregnancy outcomes, HIV drug resistance mutations acquired post-randomization as defined by the Stanford algorithm, and the probability of infant HIV infection at delivery. A two-sided, two-sample test for the equality of the difference in proportions will be used for the by-arm comparisons. A nominal (not adjusted for interim analyses) p-value less than 0.05 will be considered statistically significant. The Type I error rate for each of these analyses will be 5%.

A non-inferiority analysis of preterm delivery and small for gestational age will be conducted as a secondary analysis. The non-inferiority analysis will be conducted because the Protocol Team believes that is important to set a predefined decision rule for a conclusion of non-inferiority before the data are observed. A non-inferiority margin of 10% will be used. This margin reflects the judgment of the Protocol Team. The non-inferiority analysis will be conducted to test if DTG+FTC/TDF is non-inferior to EFV/FTC/TDV, if DTG+FTC/TAF is non-inferior to EFV/FTC/TDF, and if DTG+FTC/TAF is non-inferior to DTG+FTC/TDF. For the non-inferiority analyses, a p-value will not be computed; instead, statistical significance for non-inferiority will be determined by the appropriate limit of a 95% CI rejecting the non-inferiority margin. This procedure for the non-inferiority analyses controls a one-sided Type I error rate of 0.025. Further guidance on the requirements for a conclusion of non-inferiority is discussed in Section 9.1.

Week 50 postpartum cumulative event probabilities will be estimated using the Kaplan-Meier method. This analysis will estimate the probability of a confirmed infant HIV infection through 50 weeks postpartum and the probability of infant mortality through 50 weeks postpartum. Greenwood's formula will be used to compute the standard error of the difference between the estimated probabilities.

Time to viral suppression (first HIV-1 RNA <200 copies/mL) through delivery will be compared using a log-rank test, and will be displayed graphically using the Kaplan-Meier estimate of the survival curve. An important sensitivity analysis will be conducted by considering deaths and loss to follow-up as a competing risk.

Continuous outcomes, which include infant DXA outcomes and markers of maternal and infant renal toxicity, will be analyzed by using two sample t-tests and multivariable linear regression.

Infants and pregnancy outcomes will be classified into the worst group using the following hierarchy:

1. Infant death
2. Spontaneous abortion (<20 weeks gestation) or fetal death (≥20 weeks gestation)
3. Infant HIV infection
4. Extremely and very early preterm (<32 completed weeks)
5. Major congenital anomaly
6. Preterm delivery (<37 completed weeks)
7. Small for gestational age (<10th percentile)
8. Hospitalization
9. Grade 3 or 4 adverse event
10. None of the above

Proportions of participants in each classified group will summarized and all three pairwise regimen comparisons will be compared using ordinal logistic regression.

9.6.3 Exploratory Outcome Analyses

A detailed analysis plan will be written before the exploratory analyses are conducted.

The DTG-containing arms will be compared to the EFV-containing arm for the maternal postpartum depression score using a two-sample t-test to test the equality of means.

The composite outcome of the subsequent pregnancies will be tested using Fisher's exact test with the mid-p option. Three Fisher's exact tests will be conducted, one for each pairwise regimen comparison.

Generalized linear models and Cox regression models will be used to investigate immunologic and hormonal predictors of adverse pregnancy outcomes and postpartum maternal health outcomes while adjusting for potential confounders.

The adjusted relative risk of a primary composite pregnancy outcome and, separately, preterm delivery (<37 completed weeks) will be estimated using multivariable log-linear models comparing mothers who experienced any grade 3 or 4 clinical adverse event (i.e., excluding isolated abnormal laboratory test results), pregnancy complication, or targeted condition that may be associated with adverse pregnancy outcome to mothers who did not experience any of these events. Clinical adverse events, pregnancy complications, and targeted conditions that overlap with the outcome for the adjusted analysis will be excluded.

Generalized linear models will be used to test antiretroviral drug concentrations in maternal and infant hair, drug concentrations in maternal breast milk, drug concentrations in infant plasma, and self-reported barriers and facilitators of adherence while adjusting for potential confounders.

Analyses that associate adverse events with antiretroviral drug concentrations will be conducted using two disjoint time periods for the adverse event outcomes: 1) adverse events that occurred up to and including the delivery visit, and 2) adverse events that occurred after the delivery visit and up to and including the week 6 postpartum visit while adjusting for the events observed at delivery. These two time periods were selected because hair will only be collected at the delivery visit.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Management Responsibilities

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

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled mother-infant pairs, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 10.2).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFs, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at: https://www.frontierscience.org.

10.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures.

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

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

All study records must be accessible for inspection, monitoring, and/or auditing during and after the conduct of the study by authorized representatives of the study sponsors and their contracted monitors, IMPAACT, Gilead Sciences, Mylan, ViiV Healthcare Ltd, the FDA, site drug regulatory authorities, site IRBs/ECs, OHRP, and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

10.3 Quality Control and Quality Assurance

Study sites must ensure that essential documents and participant research records are subject to continuous quality control and quality assurance procedures consistent with the DAIDS policy on Requirements for Clinical Quality Management Plans, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures.

11 CLINICAL SITE MONITORING

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

12 HUMAN SUBJECTS PROTECTIONS

12.1 Institutional Review Board/Ethics Committee Review and Approval

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

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 13.2).

12.2 Vulnerable Participants

The NIH is mandated by law to ensure that pregnant women and children be included in clinical research when appropriate (133, 134). This study responds to that mandate and will provide clinical research data to inform HIV treatment guidelines for pregnant women. Nonetheless, the pregnant women, fetuses, and children who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to maternal, fetal, and infant participants as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children).

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

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 13.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site.

Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child (as determined locally). IRBs/ECs must document their risk determination, and study sites should adapt the signature pages of their site-specific ICFs as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with all IRB/EC requirements and the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures.

12.3 Informed Consent

Refer to Section 4.4 and the study-specific MOP for further information on informed consent procedures for this study.

Written informed consent for maternal and infant study participation will be obtained before any study-specific procedures are performed (see Appendix III). The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will emphasize the randomized nature of the study and the differences in care and treatment that mothers and infants may experience as part of the study relative to current local standards of care.

Mothers will be asked to provide written informed consent for storage and future research testing (including genetic testing) of biological specimens remaining after protocol-specified testing has been completed (see Appendix IV). This consent is optional; mothers may decline storage and all future testing of residual samples, or may decline genetic testing only, with no impact on other aspects of study participation. While the mother's consent is optional, conduct of an informed consent process to determine the mother's consent decision is not. This consent process must be conducted, but need not be conducted prior to study entry. It may be conducted at any time during study participation but ideally as soon as possible and within three months after study entry.

Mothers who become pregnant during postpartum follow-up will be provided with information and counseling on their current study drug regimen and what is known about the potential risks of the ARVs that comprise the regimen during pregnancy. Mothers who wish to change regimens based on this counseling will be permitted to do so, and all mothers who choose to receive one or more study drugs during the pregnancy will provide written informed consent to do so (see Appendix V).

As indicated above, it is generally expected that mothers will provide informed consent for their own and their infant's participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 12.2; all IRB/EC requirements must be followed.

Should the consenting mother of an enrolled infant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study-specific infant evaluations should be performed until informed consent for continued study participation is obtained from the infant's authorized guardian, as defined locally. Study sites may continue to provide care for the infant as needed and appropriate (outside of the study), consistent with local standards of care, but no study-specific procedures (outside of the standard of care) may be performed. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the infant must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 12.2), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled infant, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

12.4 Potential Benefits

There may be no direct benefit to mothers and infants who take part in this study. However, information learned in this study may be of benefit to participants and others in the future, particularly information that may lead to optimized treatment guidelines for HIV-infected pregnant women and their infants. Mothers may also appreciate the opportunity for themselves and their infants to contribute to HIV-related research.

12.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with the study drugs.

Most study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, or swelling. There is a very small chance of infection where the needle is inserted. There is also a very small chance of cutting the skin when hair is collected with scissors. It may be uncomfortable to express breast milk.

DXA scans involve exposure to radiation. Assuming that three attempts may be required to complete scans of the lumbar spine and hip, mothers who undergo DXA scans will be exposed to a maximum of 2.04 mrem (0.22 mrem for each scan of the spine, 0.46 mrem for each scan of the hip). This is comparable to the dose of radiation received from naturally occurring sources over a 2-3 day period at sea level (approximately 0.8 mrem per day). Assuming that three attempts may be required to complete scans of the whole body and lumbar spine, infants who undergo DXA scans will be exposed to a maximum of 4.08 mrem (0.89 mrem for each scan of the whole body, 0.47 mrem for each scan of the spine). This is comparable to the dose of radiation received from naturally occurring sources over a 5-day period at sea level. For both mothers and infants, the exposure to radiation associated with the DXA scans is well below limits set forth by the FDA in 21 CFR 361.1(b)(3).

Please refer to Sections 1.2-1.8 and the Package Inserts for the study drugs for a complete description of the potential risks associated with use of these drugs.

Please refer to Section 12.7 for further information on privacy and confidentiality. Despite all efforts to maintain confidentiality, involvement in the study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts. Mothers may become worried, stressed, or anxious in relation to the results of the infant HIV test performed for the study. Trained study staff will be available to assist mothers who may experience these issues and problems.

12.6 Reimbursement/Compensation

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

12.7 Privacy and Confidentiality

All study procedures will be conducted in private and every effort will be made to protect participant privacy and confidentiality to the extent possible. Participant information will not be released without written permission to do so except as necessary for review, monitoring, and/or auditing as described in Section 10.2. If any photographs of physical exam findings are taken, standard precautions will be followed to protect participant privacy and confidentiality.

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

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

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

12.8 Communicable Disease Reporting

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

12.9 Management of Incidental Findings

Site clinicians will provide mothers with clinically meaningful maternal and infant physical exam findings and laboratory test results. When applicable, site clinicians will also provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

12.10 Management of New Information Pertinent to Study Participation

Study staff will provide mothers with any new information learned over the course of the study that may affect their willingness to continue receiving study drug and/or remain in follow-up.

12.11 Post-Study Access to Study Drug

It is expected that DTG will be registered in all of the study site countries by the end of the study. In the event that DTG is not available locally as women on a DTG-based regimen complete their study participation, women will be switched to the best available standard of care regimen. While it may be preferable for women to continue a DTG-based regimen if they have been tolerating the regimen well and are virologically suppressed, adverse consequences are not anticipated when switching to an alternate first-line regimen (e.g., to an EFV- or a PI-based regimen).

TAF may be registered in many participating sites by the time the study is completed. If TAF is not available locally, women can be switched from TAF to TDF when coming off-study. TDF is currently available in all participating study site countries and adverse consequences are not anticipated when switching from TAF to TDF.

13 ADMINISTRATIVE PROCEDURES

13.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). Gilead Sciences, Mylan, and ViiV Healthcare Ltd will provide study drugs for this study but are not involved in sponsorship or regulatory oversight of the study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study drugs prior to and during the conduct of the study, in accordance with its sponsor obligations. As the convening authority of the DSMB, NIAID is the single entity with authority and responsibility to act upon the recommendations of the DSMB.

NIAID and NICHD provide funding to the clinical research sites at which this study will be conducted. Each institute contracts with independent clinical site monitors who will perform monitoring visits as described in Section 11. As part of these visits, monitors will inspect study-related documentation to ensure compliance with all applicable US and local regulatory requirements.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by their local IRBs/ECs and any other applicable regulatory entity. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

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

For any future protocol amendments, upon receiving final IRB/EC and any other applicable regulatory entity approvals, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available on the RSC website at: http://rsc.tech-res.com/clinical-research-sites/protocol-registration.

13.3 Study Implementation

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

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational Procedures specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 10.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

13.4 Protocol Deviation Reporting

Per the policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available at the website referenced in Section 10.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

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

13.5 Critical Event Reporting

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

13.6 ClinicalTrials.gov

This protocol is subject to the United States Food and Drug Administration Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

14 PUBLICATIONS

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

15 REFERENCES

1. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2013. 2013.
2. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. Second Edition. June 2016.
3. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: What's New. 2015.
4. Sonderup MW, Maughan D, Gogela N, Setshedi M, Wainwright H, Meintjes G, et al. Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa. AIDS. 2016;30(9):1483-5.
5. Mollan KR, Smurzynski M, Eron JJ, Daar ES, Campbell TB, Sax PE, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Annals of internal medicine. 2014;161(1):1-10.
6. Sibiude J, Mandelbrot L, Blanche S, Le Chenadec J, Boullag-Bonnet N, Faye A, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). PLoS medicine. 2014;11(4):e1001635.
7. Siberry G, Tierney C, Stranix-Chibanda L, Marr C, Shepherd JA, Browning R, et al. Impact of Maternal Tenofovir Use on HIV-Exposed Newborn Bone Mineral. Conference on Retroviruses and Opportunistic Infections Boston, MA2016.
8. Siberry GK, Jacobson DL, Kalkwarf HJ, Wu JW, DiMeglio LA, Yogev R, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(6):996-1003.
9. Fowler MG, Qin M, Fiscus SA, Currier J, Makanani B, Martinson F, et al. PROMISE: efficacy and safety of 2 strategies to prevent perinatal HIV transmission [Abstract 31LB]. Conference on Retroviruses and Opportunistic Infections; Seattle, WA2015.
10. Prabhu VR, Wong C, Jenkins S, Nizami S, Catlin K, Domanico P, editors. New ARVs could represent over USD 3 billion in cost savings through 2025. Conference on Retroviruses and Opportunistic Infections; 2016; Boston, MA.
11. Ripin D, Prabhu VR. A cost-savings analysis of a candidate universal antiretroviral regimen. Current opinion in HIV and AIDS. 2017;12(4):403-7.
12. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. The New England journal of medicine. 2013;369(19):1807-18.
13. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States [cited 2016 August 23]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.

14. UNITAID, UNAIDS and CHAI Launch Initiatives Seeking Expanded Access to New HIV Treatments 2015 [cited 2016 February 16]. Available from: http://unitaid.org/en/statements/1503-three-new-agreements-announced-with-the-potential-to-expand-access-to-innovative-hiv-treatment-in-low-and-middle-income-countries.
15. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.
16. Walensky RP, Horn TH, Paltiel AD. The Epi-TAF for Tenofovir Disoproxil Fumarate? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015.
17. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. The lancet HIV. 2015;2(4):e127-36.
18. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;383(9936):2222-31.
19. Orrell C, Hagins Dm, Belonosova E, Porteiro N, Walmsley S, Falco V, et al., editors. Superior efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed dose combination (FDC) compared with ritonavir (RTV) boosted atazanavir (ATV) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in treatmentnai naive women with HIV-1 infection (ARIA Study). International AIDS Conference; 2016; Durban, South Africa: International AIDS Society.
20. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. The Lancet Infectious diseases. 2012;12(2):111-8.
21. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. The Lancet Infectious diseases. 2013;13(11):927-35.
22. Fettiplace A, Stainsby C, Winston A, Givens N, Puccini S, Vannappagari V, et al. Psychiatric Symptoms in Patients Receiving Dolutegravir. Journal of acquired immune deficiency syndromes (1999). 2017;74(4):423-31.
23. de Boer MG, van den Berk GE, van Holten N, Oryszcyn JE, Dorama W, Moha DA, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS. 2016;30(18):2831-4.
24. Quercia R, Roberts J, Murungi A, Curtis L, Payvandy N, Koteff J, et al., editors. Psychiatric adverse events from the DTG ART-naive phase 3 clinical trials. JOURNAL OF THE INTERNATIONAL AIDS SOCIETY; 2016: INT AIDS SOCIETY AVENUE DE FRANCE 23, GENEVA, 1202, SWITZERLAND.
25. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2017. Wilmington, NC: Registry Coordinating Center2017.
26. Mulligan N, Best BM, Capparelli E, Stek A, Barr E, Smith E, et al., editors. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. Conference on Retroviruses and Opportunistic Infections 2016; Boston, MA.
27. Mirochnick M. Personal communication. 2016.

28. Zash R, Jacobson DL, Mayondi G, Diseko M, Makhema J, Mmalane M, et al. Dolutegravir / tenofovir / emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz / tenofovir / emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. International AIDS Conference; 23-26 July 20172017.
29. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis. 2011;57(5):773-80.
30. Huang JS, Hughes MD, Riddler SA, Haubrich RH. Bone mineral density effects of randomized regimen and nucleoside reverse transcriptase inhibitor selection from ACTG A5142. HIV clinical trials. 2013;14(5):224-34.
31. Zash R, Souda S, Chen JY, Binda K, Dryden-Peterson S, Lockman S, et al. Reassuring Birth Outcomes With Tenofovir/Emtricitabine/Efavirenz Used for Prevention of Mother-to-Child Transmission of HIV in Botswana. Journal of acquired immune deficiency syndromes (1999). 2016;71(4):428-36.
32. Ruane PJ, DeJesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. Journal of acquired immune deficiency syndromes (1999). 2013;63(4):449-55.
33. Mills A, Crofoot G, Jr., McDonald C, Shalit P, Flamm JA, Gathe J, Jr., et al. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate in the First Protease Inhibitor-Based Single-Tablet Regimen for Initial HIV-1 Therapy: A Randomized Phase 2 Study. Journal of acquired immune deficiency syndromes (1999). 2015;69(4):439-45.
34. Agarwal K, Fung SK, Nguyen TT, Cheng W, Sicard E, Ryder SD, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. Journal of hepatology. 2015;62(3):533-40.
35. Gilead Announces Top-Line Results From Two Phase 3 Studies Evaluating Tenofovir Alafenamide (TAF) for Patients With Chronic Hepatitis B Infection Foster City, CA: Business Wire; 2016 [updated 5 January 2016]. Available from: http://www.businesswire.com/news/home/20160105005560/en/.
36. Custodio J. Personal communication, Gilead Sciences. 2016.
37. Hodder S, Squires K, Kityo C, Hagins D, Avihingsanon A, Plotnikova Y, et al. Efficacy and safety of switching to EVG/COBI/FTC/TAF in virologically suppressed women. Conference on Retroviruses and Opportunistic Infections (CROI); February 13-16, 2017; Seattle, WA2017.
38. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. The New England journal of medicine. 1988;319(4):189-94.
39. Gilead Sciences. Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) [package insert] 2016. Available from: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf.
40. Scwarcberg J. Personal communication, Gilead Sciences. 2015.
41. Neumanova Z, Cerveny L, Ceckova M, Staud F. Interactions of tenofovir and tenofovir disoproxil fumarate with drug efflux transporters ABCB1, ABCG2, and ABCC2; role in transport across the placenta. AIDS. 2014;28(1):9-17.
42. Cahn P, Rolon MJ, Figueroa MI, Gun A, Patterson P, Sued O. Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. J Int AIDS Soc. 2017;20(1):1-7.
43. Taiwo BO, Zheng L, Nyaku AN, Stefanescu A, Sax PE, Haas D, et al., editors. ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. International AIDS Conference; 2017 23-26 July 2017; Paris, France.

44. Saag MS, Cahn P, Raffi F, Wolff M, Pearce D, Molina JM, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. Jama. 2004;292(2):180-9.
45. Benson CA, van der HC, Lamarca A, Haas DW, McDonald CK, Steinhart CR, et al. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. AIDS. 2004;18(17):2269-76.
46. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2016. Wilmington, NC: Registry Coordinating Center2016.
47. Szczech GM, Wang LH, Walsh JP, Rousseau FS. Reproductive toxicology profile of emtricitabine in mice and rabbits. ReprodToxicol. 2003;17(1):95-108.
48. Benaboud S, Pruvost A, Coffie PA, Ekouevi DK, Urien S, Arrive E, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrobial agents and chemotherapy. 2011;55(3):1315-7.
49. Gilead Sciences. Emtriva (emtricitabine) [package insert] 2012. Available from: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/emtriva/emtriva_pi.pdf.
50. Sellier P, Clevenbergh P, Mazeron MC, Cazals-Hatem D, Evans J, Cervoni J, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. Scand J Infect Dis. 2004;36(6-7):533-5.
51. Neau D, Schvoerer E, Robert D, Dubois F, Dutronc H, Fleury HJ, et al. Hepatitis B exacerbation with a precore mutant virus following withdrawal of lamivudine in a human immunodeficiency virus-infected patient. J Infect. 2000;41(2):192-4.
52. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. Jama. 2004;292(2):191-201.
53. Arribas JR, Pozniak AL, Gallant JE, DeJesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. Journal of acquired immune deficiency syndromes (1999). 2008;47(1):74-8.
54. Schooley RT, Ruane P, Myers RA, Beall G, Lampiris H, Berger D, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. AIDS. 2002;16(9):1257-63.
55. Squires K, Pozniak AL, Pierone G, Jr., Steinhart CR, Berger D, Bellos NC, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. Annals of internal medicine. 2003;139(5 Pt 1):313-20.
56. Margot NA, Isaacson E, McGowan I, Cheng A, Miller MD. Extended treatment with tenofovir disoproxil fumarate in treatment-experienced HIV-1-infected patients: genotypic, phenotypic, and rebound analyses. Journal of acquired immune deficiency syndromes (1999). 2003;33(1):15-21.
57. Mulenga L, Musonda P, Mwango A, Vinikoor MJ, Davies MA, Mweemba A, et al. Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2014;58(10):1473-80.
58. Habert A, Linde R, Reittner A, et.al. Safety and Efficacy of Tenofovir in Pregnant women. 15th Conference on Retroviruses and Opportunistic Infections, Program Abstract Book, Boston MA February 3-6, 2008. 2008.
59. Burchett S, Best B, Mirochnick M, et.al. Tenofovir pharmacokinetics during pregnancy, at delivery, and postpartum. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, CA. 2007.

60. Bonora S, de Requena DG, Chiesa E, al. e. Transplacental passage of tenofovir and other ARVs at delivery. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, CA. 2007.
61. Hirt D, Urien S, Rey, et.al. Population Pharmacokinetics of Tenofovir in HIV-infected Pregnant Women and their Neonates: TemAA ANRS 12109. 15th Conference on Retroviruses and Opportunistic Infections, Program Abstract Book, Boston MA February 3-6, 2008. 2008.
62. Hirt D, Urien S, Ekouevi DK, Rey E, Arrive E, Blanche S, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). Clinical pharmacology and therapeutics. 2009;85(2):182-9.
63. Palombi L, Pirillo MF, Marchei E, Jere H, Sagno JB, Luhanga R, et al. Concentrations of tenofovir, lamivudine and efavirenz in mothers and children enrolled under the Option B-Plus approach in Malawi. J Antimicrob Chemother. 2016;71(4):1027-30.
64. Tarantal AF, Castillo AB, Ekert JE, Bischofberger N, Martin RB. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (Macaca mulatta). Journal of acquired immune deficiency syndromes (1999). 2002;29(3):207-20.
65. Van Rompay KK, Durand-Gasselin L, Brignolo LL, Ray AS, Abel K, Cihlar T, et al. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects. Antimicrobial agents and chemotherapy. 2008;52(9):3144-60.
66. Nuesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, et al. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS. 2008;22(1):152-4.
67. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. Jama. 2014;312(4):362-71.
68. Bunge K, Balkus J, Noguchi L, Pan J, Piper J, Kabwigu S, et al. Pregnancy incidence and outcomes in women receiving tenofovir-based PrEP in the VOICE trial. International AIDS Society; Vancouver, Canada2015.
69. Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL, et al. Class-sparing regimens for initial treatment of HIV-1 infection. The New England journal of medicine. 2008;358(20):2095-106.
70. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Annals of internal medicine. 2011;154(7):445-56.
71. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet. 2004;363(9417):1253-63.
72. Cohen CJ, Molina JM, Cassetti I, Chetchotisakd P, Lazzarin A, Orkin C, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomised trials. AIDS. 2013;6:939-50.
73. DeJesus E, Rockstroh JK, Lennox JL, Saag MS, Lazzarin A, Zhao J, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. HIV clinical trials. 2012;13(4):228-32.
74. Rockstroh JK, DeJesus E, Lennox JL, Yazdanpanah Y, Saag MS, Wan H, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. Journal of acquired immune deficiency syndromes (1999). 2013;63(1):77-85.

75. Smith C, Ryom L, Monforte A, Reiss P, Mocroft A, El-Sadr W, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. J Int AIDS Soc. 2014;17(4 Suppl 3):19512.
76. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. J Int AIDS Soc. 2014;17:19214.
77. Bristol-Myers Squibb Company. Sustiva (efavirenz) [package insert] Princeton, NJ2015. Available from: http://packageinserts.bms.com/pi/pi_sustiva.pdf.
78. Abdelhady AM, Shugg T, Thong N, Lu JB, Kreutz Y, Jaynes HA, et al. Efavirenz Inhibits the Human Ether-A-Go-Go Related Current (hERG) and Induces QT Interval Prolongation in CYP2B6*6*6 Allele Carriers. Journal of cardiovascular electrophysiology. 2016.
79. Hill A, Ford N, Boffito M, Pozniak A, Cressey TR. Does pregnancy affect the pharmacokinetics of efavirenz? AIDS. 2014;28(10):1542-3.
80. Cressey TR, Stek A, Capparelli E, Bowonwatanuwong C, Prommas S, Sirivatanapa P, et al. Efavirenz pharmacokinetics during the third trimester of pregnancy and postpartum. Journal of acquired immune deficiency syndromes (1999). 2012;59(3):245-52.
81. Schneider S, Peltier A, Gras A, Arendt V, Karasi-Omes C, Mujawamariwa A, et al. Efavirenz in human breast milk, mothers', and newborns' plasma. Journal of acquired immune deficiency syndromes (1999). 2008;48(4):450-4.
82. Gandhi M, Mwesigwa J, Aweeka F, Plenty A, Charlebois E, Ruel TD, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. Journal of acquired immune deficiency syndromes (1999). 2013;63(5):578-84.
83. Ford N, Mofenson L, Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS. 2014;28 Suppl 2:S123-31.
84. Mofenson LM, Watts DH. Safety of pediatric HIV elimination: the growing population of HIV- and antiretroviral-exposed but uninfected infants. PLoS medicine. 2014;11(4):e1001636.
85. Williams PL, Crain MJ, Yildirim C, Hazra R, Van Dyke RB, Rich K, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. JAMA Pediatr. 2015;169(1):48-55.
86. Floridia M, Mastroiacovo P, Tamburrini E, Tibaldi C, Todros T, Crepaldi A, et al. Birth defects in a national cohort of pregnant women with HIV infection in Italy, 2001-2011. BJOG : an international journal of obstetrics and gynaecology. 2013;120(12):1466-75.
87. Knapp KM, Brogly SB, Muenz DG, Spiegel HM, Conway DH, Scott GB, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. The Pediatric infectious disease journal. 2012;31(2):164-70.
88. Brogly SB, Abzug MJ, Watts DH, Cunningham CK, Williams PL, Oleske J, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. The Pediatric infectious disease journal. 2010;29(8):721-7.
89. Ford N, Calmy A. Efavirenz is not a known teratogen. The Pediatric infectious disease journal. 2012;31(9):999; author reply 1000.
90. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016.
91. de Ruiter A, Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Med. 2014;15 Suppl 4:1-77.

92. de Oliveira HM, Damiani AP, Dias Rde O, Romao PR, Andrade VM. Effect of antiretroviral drugs on the DNA damage in mice. Environmental toxicology and pharmacology. 2014;37(1):390-5.
93. Nightingale SL. FDA Expanded Access Programs for Experimental Medicines. Jama. 2015;314(12):1296.
94. Mofenson LM, Lambert JS, Stiehm ER, Bethel J, Meyer WA, III, Whitehouse J, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. New England Journal of Medicine. 1999;341(6):385-93.
95. Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and Infants Transmission Study Group. NEnglJ Med. 1999;341(6):394-402.
96. Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50(4):585-96.
97. Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogwu A, Lockman S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. The Journal of infectious diseases. 2012;206(11):1695-705.
98. Lopez M, Figueras F, Hernandez S, Lonca M, Garcia R, Palacio M, et al. Association of HIV infection with spontaneous and iatrogenic preterm delivery: effect of HAART. Aids. 2012;26(1):37-43.
99. Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. The Journal of infectious diseases. 2011;204(4):506-14.
100. Perry M, Taylor GP, Sabin CA, Conway K, Flanagan S, Dwyer E, et al. Lopinavir and atazanavir in pregnancy: comparable infant outcomes, virological efficacies and preterm delivery rates. HIV Med. 2016;17(1):28-35.
101. Koss CA, Natureeba P, Plenty A, Luwedde F, Mwesigwa J, Ades V, et al. Risk factors for preterm birth among HIV-infected pregnant Ugandan women randomized to lopinavir/ritonavir- or efavirenz-based antiretroviral therapy. Journal of acquired immune deficiency syndromes (1999). 2014;67(2):128-35.
102. Crum-Cianflone NF, Huppler HK, Roediger M, Ganesan A, Patel S, Landrum ML, et al. A randomized clinical trial comparing revaccination with pneumococcal conjugate vaccine to polysaccharide vaccine among HIV-infected adults. J InfectDis. 2010;202(7):1114-25.
103. van den Berk G, Oryszczyn J, Blok W, van der Meche N, Regez R, Moha DA, et al., editors. Unexpectedly high rate of intolerance for dolutegravir in real-life setting. Conference on Retroviruses and Opportunistic Infections; 2016; Boston, MA
104. Powis KM, Smeaton L, Hughes MD, Tumbare EA, Souda S, Jao J, et al. In-utero triple antiretroviral exposure associated with decreased growth among HIV-exposed uninfected infants in Botswana. Aids. 2016;30(2):211-20.
105. Hofer CB, Keiser O, Zwahlen M, Lustosa CS, Frota AC, de Oliveira RH, et al. In Utero Exposure to Antiretroviral Drugs: Effect on Birth Weight and Growth Among HIV-exposed Uninfected Children in Brazil. The Pediatric infectious disease journal. 2016;35(1):71-7.

106. Alimenti A, Forbes JC, Oberlander TF, Money DM, Grunau RE, Papsdorf MP, et al. A prospective controlled study of neurodevelopment in HIV-uninfected children exposed to combination antiretroviral drugs in pregnancy. Pediatrics. 2006;118(4):e1139-45.
107. Sirois PA, Huo Y, Williams PL, Malee K, Garvie PA, Kammerer B, et al. Safety of perinatal exposure to antiretroviral medications: developmental outcomes in infants. The Pediatric infectious disease journal. 2013;32(6):648-55.
108. Bae WH, Wester C, Smeaton LM, Shapiro RL, Lockman S, Onyait K, et al. Hematologic and hepatic toxicities associated with antenatal and postnatal exposure to maternal highly active antiretroviral therapy among infants. Aids. 2008;22(13):1633-40.
109. Dryden-Peterson S, Shapiro RL, Hughes MD, Powis K, Ogwu A, Moffat C, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. Journal of acquired immune deficiency syndromes (1999). 2011;56(5):428-36.
110. Ziske J, Kunz A, Sewangi J, Lau I, Dugange F, Hauser A, et al. Hematological changes in women and infants exposed to an AZT-containing regimen for prevention of mother-to-child-transmission of HIV in Tanzania. PloS one. 2013;8(2):e55633.
111. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. The New England journal of medicine. 2003;348(24):2379-85.
112. Papp E, Mohammadi H, Loutfy MR, Yudin MH, Murphy KE, Walmsley SL, et al. HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. The Journal of infectious diseases. 2015;211(1):10-8.
113. Papp E, Balogun K, Banko N, Mohammadi H, Loutfy M, Yudin MH, et al. Low Prolactin and High 20-alpha-Hydroxysteroid Dehydrogenase Levels Contribute to Lower Progesterone Levels in HIV-Infected Pregnant Women Exposed to Protease Inhibitor-Based Combination Antiretroviral Therapy. The Journal of infectious diseases. 2016;213(10):1532-40.
114. Zaba B, Calvert C, Marston M, Isingo R, Nakiyingi-Miiro J, Lutalo T, et al. Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community-based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA). Lancet. 2013;381(9879):1763-71.
115. Calvert C, Ronsmans C. The contribution of HIV to pregnancy-related mortality: a systematic review and meta-analysis. Aids. 2013;27(10):1631-9.
116. Phillips T, McNairy M, Zerbe A, Myer L, Abrams EJ. Postpartum transfer of care among HIV-infected women initiating antiretroviral therapy during pregnancy. Journal of acquired immune deficiency syndromes (1999). 2015.
117. Okawa S, Chirwa M, Ishikawa N, Kapyata H, Msiska CY, Syakantu G, et al. Longitudinal adherence to antiretroviral drugs for preventing mother-to-child transmission of HIV in Zambia. BMC pregnancy and childbirth. 2015;15:258.
118. Ngarina M, Kilewo C, Karlsson K, Aboud S, Karlsson A, Marrone G, et al. Virologic and immunologic failure, drug resistance and mortality during the first 24 months postpartum among HIV-infected women initiated on antiretroviral therapy for life in the Mitra plus Study, Dar es Salaam, Tanzania. BMC infectious diseases. 2015;15:175.
119. Kim MH, Zhou A, Mazenga A, Ahmed S, Markham C, Zomba G, et al. Why Did I Stop? Barriers and Facilitators to Uptake and Adherence to ART in Option B+ HIV Care in Lilongwe, Malawi. PloS one. 2016;11(2):e0149527.
120. Beumer J, Bosman I, Maes R. Hair as a biological specimen for therapeutic drug monitoring. In J Clin Pract. 2001;55:353-7.
121. Koss CA, Natureeba P, Mwesigwa J, Cohan D, Nzarubara B, Bacchetti P, et al. Hair concentrations of antiretrovirals predict viral suppression in HIV-infected pregnant and breastfeeding Ugandan women. AIDS. 2015;29(7):825-30.

122. Wilson IB, Lee Y, Michaud J, Fowler FJ, Jr., Rogers WH. Validation of a New Three-Item Self-Report Measure for Medication Adherence. AIDS and behavior. 2016.
123. Capetti AF, Di Giambenedetto S, Latini A, Sterrantino G, De Benedetto I, Cossu MV, et al. Morning dosing for dolutegravir-related insomnia and sleep disorders. HIV Med. 2017.
124. Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. British journal of clinical pharmacology. 2001;52(3):223-8.
125. Holmes LB, Westgate MN. Inclusion and exclusion criteria for malformations in newborn infants exposed to potential teratogens. Birth defects research Part A, Clinical and molecular teratology. 2011;91(9):807-12.
126. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med. 1994;13(13-14):1341-52; discussion 53-6.
127. Cohan D, Natureeba P, Koss CA, Plenty A, Luwedde F, Mwesigwa J, et al. Efficacy and safety of lopinavir/ritonavir versus efavirenz-based antiretroviral therapy in HIV-infected pregnant Ugandan women. AIDS. 2015;29(2):183-91.
128. Fleming TR. Current issues in non-inferiority trials. Statistics in medicine. 2008;27(3):317-32.
129. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. NEnglJMed. 1994;331(18):1173-80.
130. World Health Organization. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphilis. 2014.
131. Food and Drug Administration. Guidance for industry: adaptive design clinical trials for drugs and biologics. Washington DC, USA: Food and Drug Administration; 2010.
132. Mehta CR, Tsiatis AA. Flexible sample size considerations using information-based interim monitoring. Drug Information Journal. 2001;35(4):1095-112.
133. National Institutes of Health. Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research. Federal Register. 1994 March 18. Report No.
134. National Institutes of Health. NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. 1998 March 6. Report No.

Appendix I Schedule of Evaluations
Antepartum

Study Visit	Screen	Entry	Weeks During Pregnancy				Post ARV Switch[2]	Early D/C[3]
			Week 4	Week 8	Week 12	Q4 Weeks[1]		
Visit Window	up to -14 d	Day 0	±2 wks	±2 wks	±2 wks	±2 wks		
MATERNAL EVALUATIONS								
Informed consent	X							
Maternal medical history	X	X	X	X	X	X	X	X
ARV adherence questionnaire[4]			X	X	X	X	X	X
Sleep and anxiety questionnaires		X		X			X	
Depression questionnaire							X	
Physical examination	X	X	X	X	X	X	X	X
Fetal ultrasound	prior to or within 14 days after entry							
Confirmatory pregnancy testing[5]	X							
Confirmatory HIV testing	0-6 mL							
Hepatitis B surface antigen		3 mL						
AST, ALT, creatinine, CrCl	4 mL		4 mL		4 mL	4 mL Wk 24	4 mL	4 mL
Complete blood count	3 mL							
CD4+ cell count		3 mL						
HIV-1 RNA (store residual plasma)[6]		6 mL	6 mL	6 mL	6 mL	6 mL Wk 24[6]	6 mL	6 mL
Stored plasma	6 mL							
Stored plasma and cell pellets		10 mL		10 mL				
Stored urine		15 mL						15 mL
Total blood volume	13-20 mL	22 mL	10 mL	16 mL	10 mL	0-10 mL	10 mL	10 mL

[1]Refer to Section 6.3.4. After antepartum study Week 12, mothers will complete scheduled follow-up visits every four weeks (Q4) prior to delivery. Depending on the date of delivery, these visits may take place at antepartum study Weeks 16, 20, 24, and 28.
[2]Refer to Section 6.6.
[3]Refer to Section 6.9.
[4]Routine questionnaire at all indicated visits; barriers and facilitators questionnaires at Antepartum Week 8.
[5]Refer to Section 6.1. If available medical records document a positive pregnancy test result, or if pregnancy is confirmed by ultrasound scan prior to entry, no pregnancy testing is required. Otherwise, a blood (1 mL) or urine (5 mL) pregnancy test should be performed, with results available for final eligibility determination prior to entry. The total blood volume shown in the Screen column above accommodates collection of 1 mL of blood if needed.
[6]It is generally not expected that mothers will meet the criteria for confirmation of virologic failure (≥200 copies/mL at or after at least 24 weeks on study) during antepartum follow-up; however, if these criteria are met prior to delivery, the Confirmation of Virologic Failure evaluations shown on the next page and further described in Section 6.7 should be performed.

Appendix I Schedule of Evaluations
Delivery and Postpartum

	Delivery	Weeks Postpartum					Post	Confirmation	
Study Visit	up to 14/27 d*	6	14	26	38	50	ARV	of Virologic	Early
Visit Window	*New Day 0*	±2 wks	±6 wks	±6 wks	±6 wks	±6 wks	Switch[1]	Failure[2]	D/C[3]
MATERNAL EVALUATIONS									
Maternal medical history	X	X	X	X	X	X	X	X	X
ARV adherence questionnaire[4]	X	X	X	X	X	X	X	X	X
Sleep and anxiety questionnaires					X		X		
Depression questionnaire		X				X	X		
Physical examination	X	X	X	X	X	X	X	[X]	X
AST, ALT, creatinine, CrCl	4 mL		4 mL	4 mL		4 mL	4 mL		4 mL
Complete blood count				3 mL		3 mL			
CD4+ cell count				3 mL		3 mL			
HIV-1 RNA (store residual plasma)	6 mL		6 mL	6 mL	6 mL	6 mL	6 mL	6 mL	6 mL
ARV resistance testing (store residual plasma)								6 mL	
Stored plasma	6 mL	6 mL							
Stored plasma and cell pellets	10 mL					10 mL			
Stored serum[5]	0-4 mL[5]								
Stored breast milk		20 mL if BF							
Stored urine						15 mL			15 mL
Stored hair	X								
DXA scan (at selected sites)[6]						X[6]			
Total blood volume	26-30 mL	6 mL	10 mL	16 mL	6 mL	26-27 mL	10 mL	12 mL	10 mL
INFANT EVALUATIONS									
Infant medical and feeding history	X	X	X	X	X	X			X
Physical examination	X	X	X	X	X	X			X
HIV NAT (store remnant samples)[7,8]	3 mL	4 mL[8]	3 mL	3 mL if BF	3 mL if BF	3 mL			3 mL
ALT and creatinine[9]	1 mL			1 mL if BF					
Complete blood count[9]	1 mL			1 mL if BF					
Stored serum[5]	0-1 mL[5]								
Stored hair	X								
DXA scan (at selected sites)				X					
Total blood volume	5-6 mL	4 mL	3 mL	0-5 mL	0-3 mL	3 mL			3 mL

Appendix I Delivery and Postpartum Footnotes:

*The Delivery Visit should be conducted as soon as possible after delivery and within a targeted window of 14 days after delivery. If the visit cannot be conducted within the targeted window, it may be conducted within an allowable window of 27 days after delivery. The timeliness of visit completion at each site will be closely monitored and corrective actions taken when needed, as described in Sections 6.4 and 9.5.1.
[1]Refer to Section 6.6.
[2]Refer to Sections 6.7 and 8.3.
[3]Refer to Section 6.9.
[4]Routine questionnaire at all indicated visits; barriers and facilitators questionnaires at Postpartum Week 38.
[5]At Delivery, collect maternal and infant blood for serum storage only if the mother is at risk for Zika virus infection (due to local transmission, travel, or other exposure) and maternal Zika virus infection during the current pregnancy is suspected.
[6]Maternal DXA scan must be preceded by a pregnancy test. A blood (1 mL) or urine (5 mL) pregnancy test may be performed on the day of the scan (preferably) or within 14 days prior to the scan. The total blood volume shown in the Week 50 column above accommodates collection of 1 mL of blood if needed.
[7]For infants ever exposed to breast milk, perform HIV NAT at Delivery and Weeks 6, 14, 26, 38, and 50. For infants never exposed to breast milk, perform HIV NAT at Delivery and Weeks 6, 14, and 50. Also refer to Section 6.8. Any infant with an initial positive HIV NAT result should be recalled to the clinic as soon as possible for confirmatory testing.
[8]At Week 6, 4 mL is required to provide sufficient plasma for HIV NAT and testing of ARV drug levels.
[9]At Week 26, perform testing (ALT, creatinine, complete blood count) for infants ever exposed to breast milk.

Appendix II
Maternal Toxicity Management Guidelines

Refer to Section 8 for comprehensive information on participant management and Section 8.1 for an overview of guidance applicable to all adverse events.

Maternal adverse events will be managed based on their severity and assessed relationship to study drug, as specified in the tables provided in this appendix. Table II.1 provides general guidelines. Tables II.2 through II.8 provide specific guidelines for the following types of events:

Table II.2	Rash
Table II.3	Asymptomatic ALT or AST elevation
Table II.4	Clinical hepatitis
Table II.5	Increased creatinine and decreased creatinine clearance
Table II.6	Psychiatric events
Table II.7	Allergic reaction
Table II.8	Switching from TDF or TAF to ZDV or ABC

Each of the above-listed types of events should be managed according to the corresponding table; all other events should be managed according to Table II.1.

When management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within three business days of site awareness of the event.

As a general principle, unless stated otherwise, it is preferable to avoid stopping an entire ARV regimen during pregnancy or while breastfeeding (to reduce the chance of viremia and therefore of HIV transmission to the infant), and instead to substitute a new ARV for the drug that is suspected of causing toxicity. In the event that mothers need to interrupt ART (e.g., due to an adverse event), information and counseling will be provided regarding locally-available options for reducing the risk of perinatal HIV transmission. Such options may include infant ARV prophylaxis during breastfeeding and replacement feeding if determined to be safe and accessible and if the mother's ART interruption is likely to be prolonged.

If DTG or EFV are held due to suspected hypersensitivity, elevated LFTs, and/or clinical hepatitis, then DTG or EFV should be permanently discontinued and the participant should not be re-challenged with the same drug, as detailed further below. For any mother whose study drug regimen is modified such that DTG or EFV is replaced with another ARV, an additional study visit should be conducted approximately four weeks after the switch as described in Section 6.6.

For any mother who experiences an adverse event that results in holding or permanently discontinuing use of EFV, FTC/TDF should be given for seven days after stopping EFV to minimize the risk of resistance, unless the reason for hold or discontinuation involves possible FTC/TDF toxicity.

Table II.1
General Guidelines for Maternal Toxicity Management
The guidance provided in this table applies to adverse events other than those for which event-specific guidance is provided in Tables II.2-II.7.

Grade 1 or Grade 2	**Regardless of assessed relationship to study drug**, the current study drug regimen may be continued; consultation with the CMC is available but not required.
Grade 3	**If assessed as not related to study drug**, the current study drug regimen may be continued. Re-evaluation should continue at least weekly until improvement to grade 2 or lower, then resume the frequency of evaluation specified in the SoE unless more frequent monitoring is clinically indicated.
	If assessed as related to study drug, the suspect study drug should be replaced or the entire regimen held unless the site investigator assesses that continuation of the current regimen is in the best interest of the participant. The CMC must be informed of the grade 3 event and consulted on the site investigator's proposed clinical and ARV management plan, with any change of any ARV in the regimen approved by the CMC. Re-evaluate at least weekly until improvement to grade 2 or lower, then resume the frequency of evaluation specified in the SoE unless more frequent monitoring is clinically indicated. The suspect study drug (or entire regimen) may be resumed when the event has improved to grade 2 or lower. Following resumption, if the event recurs at grade 3 or higher, the suspect study drug should be permanently discontinued.
Grade 4	**If assessed as not related to study drug**, the current study drug regimen may be continued. The CMC must be informed of the grade 4 event and the site investigator's proposed clinical and ARV management plan. Re-evaluation should continue at least weekly until improvement to grade 2 or lower.
	If assessed as related to study drug, the entire study drug regimen should be held. The CMC must be informed of the grade 4 event and the site investigator's proposed clinical and ARV management plan. The participant should be re-evaluated at least weekly until improvement to grade 2 or lower, at which time study drug may be resumed. When resuming study drug, the suspect study drug should be replaced, with any change of any ARV in the regimen approved by the CMC. On a case-by-case basis, the CMC may also approve resumption of the prior regimen with close monitoring for potential recurrence; in this case, should the event recur at grade 3 or higher, the suspect study drug should be permanently discontinued.

Management of Maternal Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Rash generally occurs within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and usually resolves within two to three weeks (even with continuation of DTG). The index case of hypersensitivity with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and erythema multiforme, have been reported for DTG in clinical trials.

Mild to moderate rash is also occurs frequently after initiation of EFV-containing ART. In controlled clinical trials, 26% (266/1008) of adults treated with EFV 600 mg experienced new skin rash (versus 17% of patients treated with non-EFV regimens). Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating EFV (median time to onset of rash in adults was 11 days). Rash resolves within one month (median 16 days) in most patients continuing EFV. Severe or life-threatening rash occurred in 0.9% (9/1008) of patients treated with EFV (with grade 4 rash occurring in 0.1%). (77)

Table II.2
Management of Maternal Rash

All grades	**Assess for signs and symptoms of clinical hepatitis, as listed in Table II.4, and of hypersensitivity, as listed in Table II.7. Reinforce participant awareness of these signs and symptoms.** Instruct participant to contact the site clinician should any such signs or symptoms occur and follow appropriate guidance tables. **Assess for alternative causes of the rash** and manage alternative causes, consistent with local standards of care (e.g., discontinue suspected concomitant medications if possible).
Grade 1 or Grade 2	• If the rash is not generalized, or there is a definitive alternative explanation for the rash (other than study drug), the current study drug regimen may be continued with no additional evaluations required. • If the rash is generalized and there is no definitive alternative explanation for the rash, perform liver function tests (LFTs)* within three business days. – If the participant has no suspected hypersensitivity reaction or signs/symptoms of clinical hepatitis, study drug may be continued pending receipt of LFT results. If LFT results are grade 1 or lower, the current study drug regimen may be continued with close monitoring and instruction to return to the study site in the event of new symptoms or worsening rash. – If the participant has suspected hypersensitivity reaction or clinical hepatitis or any grade 2 or higher LFT result, all ARVs should be held and the CMC should be consulted on change of regimen. DTG or EFV should be permanently discontinued.

Table II.2
Management of Maternal Rash

Grade 3	• Hold all ARVs. • Perform LFTs* and CBC with differential within three business days. If the participant has suspected hypersensitivity reaction or clinical hepatitis or any grade 2 or higher LFT result, EFV or DTG should be permanently discontinued. • If there is an alternative explanation for the rash (and no signs/symptoms of hypersensitivity or hepatitis), the current study drug regimen may be resumed with close follow-up at the discretion of the investigator, in consultation with the CMC. The timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC. • Follow the participant closely until the rash resolves to grade 2 or lower.
Grade 4	• Hold all ARVs and permanently discontinue DTG or EFV. • The timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC. • Follow the participant closely until the rash resolves to grade 2 or lower.
*Signs and symptoms of potential hypersensitivity reaction are provided in Table II.7. Signs and symptoms of clinical hepatitis are provided in Table II.4. LFTs should minimally include ALT and AST; additional tests may be ordered at the discretion the site investigator and/or at the recommendation of the CMC.	

Table II.3
Management of Maternal Asymptomatic ALT/AST Elevations
If participant becomes symptomatic, follow management for symptomatic hepatitis.

All grades	**Assess for signs and symptoms of clinical hepatitis, as listed in Table II.4, and of hypersensitivity, as listed in Table II.7. Reinforce participant awareness of these signs and symptoms.** Instruct participant to contact the site clinician should any such signs or symptoms occur and follow appropriate guidance tables. **Assess for alternative causes of the ALT/AST elevation** and manage alternative causes consistent with local standards of clinical practice (e.g., diagnose and treat concomitant illness*, discontinue suspect concomitant medications if possible).
Grade 1	**Regardless of assessed relationship to study drug,** the current study drug regimen may be continued; consultation with the CMC is available but not required. Repeat ALT/AST within 14 business days. If repeat ALT/AST result is grade 1 or lower, resume the frequency of monitoring specified in the SoE. If repeat ALT/AST result is grade 2 or higher, follow management for the relevant grade.
Grade 2	• If the participant has suspected clinical hepatitis (Table II.4) or hypersensitivity (Table II.7), all ARVs should be held and the CMC informed within three business days. DTG or EFV should be permanently discontinued. • If the participant does not have suspected clinical hepatitis or hypersensitivity, then repeat ALT/AST within three to four business days (at most within one week) and also check total and direct bilirubin**. If repeat ALT/AST result is grade 1, 3, or 4, follow management for the relevant grade. If repeat ALT/AST result is grade 2, inform the CMC and: – If total bilirubin ≥2 x ULN and direct bilirubin >35% of total bilirubin, all ARVs should be held. DTG or EFV should be permanently discontinued. – If total bilirubin <2 x ULN and the participant remains asymptomatic, ARVs may be continued at the discretion of the site investigator. In these instances, the participant should be re-evaluated after one to two weeks (clinically and with ALT/AST). If repeat ALT/AST is grade 2 or lower, resume the frequency of evaluation specified in the SoE. If repeat ALT/AST is grade 3 or higher, follow management for the relevant grade. • If study drugs are held, the timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC.

Table II.3
Management of Maternal Asymptomatic ALT/AST Elevations
If participant becomes symptomatic, follow management for symptomatic hepatitis.

Grade 3	• If the participant has suspected clinical hepatitis (Table II.4) or hypersensitivity (Table II.7), all ARVs should be held and the CMC informed within three business days. DTG or EFV should be permanently discontinued. • If the participant does not have suspected clinical hepatitis or hypersensitivity, then repeat ALT/AST within three business days and also check total and direct bilirubin**. If repeat ALT/AST result is grade 1, 2, or 4, follow management for the relevant grade. If repeat ALT/AST result is grade 3, inform the CMC and: – If total bilirubin ≥2 x ULN and direct bilirubin >35% of total bilirubin, all ARVs should be held. DTG or EFV should be permanently discontinued. – If total bilirubin <2 x ULN and the participant remains asymptomatic, ARVs may be continued at the discretion of the site investigator. In these instances, the participant should be re-evaluated approximately weekly (clinically and with ALT/AST) until improvement to grade 2 or lower (then resume the frequency of evaluation specified in the SoE). If improvement to grade 2 or lower does not occur within 14 days of the initial elevated result, the CMC should be consulted about potentially discontinuing DTG or EFV. • If study drugs are held, the timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC.
Grade 4	• If the participant has suspected clinical hepatitis (Table II.4) or hypersensitivity (Table II.7), all ARVs should be held and the CMC informed within three business days. DTG or EFV should be permanently discontinued. • If the participant does not have suspected clinical hepatitis or hypersensitivity, then repeat ALT/AST within three business days and also check total and direct bilirubin**. If repeat ALT/AST result is grade 1, 2, or 3, follow management for the relevant grade. If repeat ALT/AST result is grade 4, all ARVs should be held and DTG or EFV should be permanently discontinued; inform the CMC. • The participant should be re-evaluated approximately weekly until improvement to grade 2 or lower (then resume the frequency of evaluation specified in the SoE). • The timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC.

*Careful assessments should be done to assess/rule out pregnancy-related causes (e.g., HELLP), the use of alcohol, non-study drug-related drug toxicity, viral hepatitis, or other potential causes of LFT elevations. Consider the following additional tests as clinically indicated to further evaluate the liver event:

– Viral hepatitis serologies (e.g., hepatitis A IgM antibody; HBsAg and hepatitis B core antibody [IgM]; hepatitis C RNA; hepatitis E IgM antibody; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody or, if unavailable, obtain heterophile antibody or monospot testing)
– Syphilis screening
– Complete blood count with differential to assess eosinophilia
– Liver imaging (e.g., ultrasound or computerized tomography)

**Events of a pure drug-induced liver injury (DILI) leading to jaundice, without a liver transplant, have a case fatality rate of 10-50%. Increased ALT or total bilirubin are relatively common (particular in HIV/AIDS) but the combination of ALT >3 x ULN and total bilirubin >2 x ULN is rare and raises concerns for DILI.

Table II.4
Management of Maternal Clinical Hepatitis

- See also Section 8.6 for management of mothers who are co-infected with Hepatitis B.
- Signs and symptoms of clinical hepatitis include unexplained anorexia, nausea or vomiting, right upper quadrant tenderness (i.e., liver tenderness or hepatomegaly), acholic stools, bilirubinuria, scleral icterus, and jaundice. Malaise and new or worsening fatigue are common in pregnancy but should also be assessed in relation to potential acute hepatotoxicity. All mothers should be instructed contact the site clinician should they experience any of these signs or symptoms.
- **For mothers with signs or symptoms of clinical hepatitis**, immediately test ALT and AST as well as total and direct bilirubin (and PT/INR if available) and inform the CMC. All ARVs should be held for grade 2 or higher ALT/AST if accompanied by signs/symptoms of clinical hepatitis. DTG or EFV should be permanently discontinued.
- Participants should be evaluated approximately weekly or more frequently, until signs/symptoms are grade 2 or lower*.
- The timing of resumption of antiretroviral treatment and the choice of regimen to be initiated should be determined in consultation with the CMC.

*Careful assessments should be done to assess/rule out pregnancy-related causes (e.g., HELLP), the use of alcohol, non-study drug-related drug toxicity, viral hepatitis, or other potential causes of LFT elevations. Consider the following additional tests as clinically indicated to further evaluate the liver event:

- Fractionated bilirubin
- Viral hepatitis serologies (e.g., hepatitis A IgM antibody; HBsAg and hepatitis B core antibody [IgM]; hepatitis C RNA; hepatitis E IgM antibody; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody or, if unavailable, obtain heterophile antibody or monospot testing)
- Syphilis screening
- Complete blood count with differential to assess eosinophilia
- Liver imaging (e.g., ultrasound or computerized tomography)

**Events of a pure drug-induced liver injury (DILI) leading to jaundice, without a liver transplant, have a case fatality rate of 10-50%. Increased ALT or total bilirubin are relatively common (particular in HIV/AIDS) but the combination of ALT >3 x ULN and total bilirubin >2 x ULN is rare and raises the concerns for DILI.

Management of Maternal Increased Creatinine and Decreased Creatinine Clearance

DTG can inhibit the tubular secretion of creatinine and can therefore be associated with a slight increase in serum creatinine and apparent decrease in the estimated glomerular filtration rate (GFR, generally by 10% or less). This type of change occurs within the first four weeks of treatment with DTG (remaining stable thereafter) and is not associated with renal damage nor with true decline in renal function. At the same time, pregnancy can affect creatinine: normal creatinine ranges are slightly higher in non-pregnant adults (0.5-0.9 mg/dL) compared with during the first trimester (0.4-0.7 mg/dL), second trimester (0.4-0.8 mg/dL), or third trimester (0.4-0.9 mg/dL) of pregnancy (and estimated GFR is higher during pregnancy). TDF and TAF can cause renal insufficiency.

Table II.5
Management of Maternal Increased Creatinine and Decreased Creatinine Clearance

All grades	Assess participant for other potential causes of decreased renal function. Make appropriate renal dosing adjustments of all ARVs (and other concomitant medications if possible), consistent with Package Inserts. Management, below, should be based on the worst result (CrCl or creatinine).
Estimated CrCl ≥90 mL/min OR Grade 1 creatinine	Monitor as per SoE.
Estimated CrCl <90 to 50 mL/min OR Grade 2 creatinine	Monitor creatinine at least every two weeks until establish that creatinine and estimated CrCl are stable to improving.
Estimated CrCl <50 mL/min OR Grade 3 or higher creatinine	**If the participant is on TDF or TAF, consult the CMC and:** • Repeat creatinine and estimated CrCl within three business days. • Evaluate for potential causes of decreased renal function. TDF or TAF should be substituted with another ARV (e.g., ZDV or ABC) while the etiology of the decreased renal function is investigated. • If est. CrCl <50 mL/min or grade 3 or higher creatinine are confirmed, then TDF or TAF should be held (or switched to another ARV). • In women known to be co-infected with hepatitis B virus who develop renal toxicity on TDF, TAF may be substituted for TDF in consultation with the CMC and with close follow-up • Re-evaluate approximately weekly until improvement in creatinine and estimated creatinine clearance to grade 2 or lower (est. CrCl ≥60 mL/min). – If improvement of estimated creatinine clearance to grade 2 or lower (est. CrCl ≥60 mL/min) and if TDF or TAF was held but an alternate etiology was identified, consideration can be given to resuming TDF or TAF in consultation with the CMC, with close monitoring of renal function. – If no alternate etiology can be identified, TDF or TAF should be permanently discontinued. • Close monitoring should include approximately weekly evaluation for one month followed by monthly re-evaluation for three months.
	If the participant is not on TDF or TAF: Evaluate for potential causes of decreased renal function and consult the CMC on study drug regimen and frequency of re-evaluation.

Management of Maternal Psychiatric Events

Prior psychiatric history or postnatal depression may be risk factors for psychiatric events (which have also been observed with use of EFV and DTG).

Table II.6
Management of Maternal Psychiatric Events
(Insomnia, Psychiatric Disorders, Suicidal Ideation or Attempt)

Grade 1 without suicidal ideation	**Mild sleep disturbance and/or symptoms of psychiatric disorder with no or minimal interference with usual social and functional activities. May include preoccupation with thoughts of death but no suicidal ideation or intent:** The current study drug regimen may be continued (with referral to non-study sources of mental health services at the discretion of the site investigator). Consultation with the CMC is available but not required.
Grade 2 without suicidal ideation	**Moderate sleep disturbance and/or symptoms of psychiatric disorder causing greater than minimal interference with usual social and functional activities without suicidal ideation:** The current study drug regimen may be continued (with referral to non-study sources of mental health services at the discretion of the site investigator). Consultation with the CMC is available but not required.
Grade 1 or Grade 2 with suicidal ideation	**Mild or moderate sleep disturbance and/or symptoms of psychiatric disorder causing greater than minimal interference with usual social and functional activities with suicidal ideation:** Consult the CMC about the frequency of ongoing monitoring, timing of study drug resumption, and the choice of study drug regimen: • If the event is assessed as related to EFV, EFV should generally be switched to an alternative ARV (e.g., to DTG or a PI). • If the event is assessed as related to DTG, consideration may be given to replacing DTG (e.g., with a PI). The participant should be referred to non-study sources of mental health services.
Grade 3	Consult the CMC about the frequency of ongoing monitoring, timing of study drug resumption, and the choice of study drug regimen: • If the event is limited to sleep disturbance only, consideration may be given to continuing the current study drug regimen in consultation with CMC. For all other grade 3 psychiatric events, if assessed as related to study drug (any agent), the entire study drug regimen should be held. • If the event is assessed as related to EFV or DTG, these drugs should be permanently discontinued. The participant should be referred to non-study sources of mental health services.
Grade 4	Hold the entire study drug regimen. Consult the CMC about the frequency of ongoing monitoring, timing of study drug resumption, and the choice of study drug regimen. If the event is assessed as related to EFV or DTG, these drugs should be permanently discontinued. The participant should be referred to non-study sources of mental health services as soon as possible.

Table II.7
Management of Maternal Allergic Reactions

Signs and symptoms of potential hypersensitivity reaction may include rash, fever, general malaise, fatigue, muscle or joint aches, facial edema, eosinophilia, angioedema, and difficulty breathing. Malaise and new or worsening fatigue are common in pregnancy but should also be assessed in relation to potential hypersensitivity reaction. All mothers should be instructed to contact the site clinician should they experience any of these signs or symptoms. **For participants receiving ABC, refer to Table II.8.**	
Grade 1 or Grade 2	• Study drug may be continued at the discretion of the site investigator. The participant should be advised to contact site staff immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed. • If the participant has suspected clinical hepatitis (Table II.4) or Grade 2 or higher ALT/AST, all ARVs should be held. DTG or EFV should be permanently discontinued. Inform the CMC.
Grade 3 or Grade 4	If the grade 3 or 4 allergic reaction is assessed as related to DTG or EFV, DTG or EFV should be should permanently discontinued. Consult the CMC on the frequency of ongoing monitoring, timing of study drug resumption, and choice of regimen.

Table II.8
Management of Participants Switching from TDF or TAF to ZDV or ABC

To ZDV from TDF or TAF	ZDV should be initiated with caution in participants with known anemia (hemoglobin concentration <7.5 g/dL) or neutropenia (absolute neutrophil count <750/mm^3), and alternative causes for anemia and/or neutropenia should be sought and treated prior to starting ZDV if possible (or a drug other than ZDV should be selected).
To ABC from TDF or TAF	• Where HLA-B*5701 screening is considered standard of care, it is recommended that site investigators screen for presence of the HLA-B*5701 allele in any participant starting if their HLA-B*5701 status is unknown (even if the participant has previously tolerated ABC). ABC should not be used in participants known to carry HLA-B*5701. • Where HLA-B*5701 screening is not considered standard of care, site investigators must obtain a complete history of: any previous exposure to ABC-containing products; and any events surrounding the discontinuation of this previous exposure, and evaluate for the possibility of a clinically suspected hypersensitivity reaction. If the possibility of a clinically suspected ABC HSR cannot be ruled out then treatment with any ABC-containing product should not be started, due to the risk for a potential life threatening and sometimes fatal re-challenge reaction. Where participants have previously tolerated treatment with ABC, restarting ABC should be done in a setting where medical assistance is readily available, and the site staff and participant should be vigilant for signs/symptoms of possible ABC hypersensitivity reaction. • **In the event of clinically suspected ABC hypersensitivity reaction, treatment with ABC must be promptly and permanently discontinued, regardless of the participant's HLA-B*5701 status.** Such events should then be managed appropriately as outlined in the local prescribing information.
Note: In some countries (e.g., the USA), the use of ABC in participants known to carry HLA-B*5701 is contraindicated; investigators must initiate treatment with ABC in accordance with relevant recommendations and any restrictions included in the local product labeling.	

Appendix III
Sample Informed Consent Form

IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens for HIV-1-Infected Pregnant Women and their Infants

Version 2.0, [date]

Introduction

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

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

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

About the Study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[insert site name]* are doing this study to test anti-HIV medicines (ARVs) for pregnant women who have HIV. HIV is the virus that causes AIDS.

You are being asked to join this study with your baby because you are pregnant and have HIV. The study will include about 640 mothers and babies from Botswana, Brazil, Haiti, India, Malawi, South Africa, Thailand, Uganda, the United States, Tanzania, and Zimbabwe. Each mother and baby will be in the study during pregnancy and for about 1 year after the baby is born.

The person in charge of the study at *[insert site name]* is *[insert name of IoR]*. The United States National Institutes of Health is paying for the study.

1. The study is testing different combinations of ARVs in pregnant women and their babies.

People with HIV usually take a combination of 3 or more ARVs. This study will test 3 different combinations of ARVs. The ARVs that will be tested are: *[sites may substitute locally appropriate drug names here and throughout this form]*

- Dolutegravir (DTG)
- Tenofovir alafenamide (TAF)
- Tenofovir disoproxil fumarate (TDF)
- Efavirenz (EFV)
- Emtricitabine (FTC)

All of these ARVs are approved in the United States and Europe. *[Sites to modify as needed:* EFV, TDF, and FTC are approved in *[site country].* DTG and TAF are not currently approved in *[site country]]*.

EFV, TDF, and FTC have been used widely throughout the world. DTG and TAF are newer ARVs that have not yet been used as widely. DTG and TAF are as safe and effective for controlling HIV as other ARVs. As a result, use of DTG and TAF is becoming more common. However, there is little information available as of now on use of DTG and TAF in pregnant women.

This study will test combinations of DTG, TAF, and the other ARVs listed above in pregnant women. The study will look at the safety of the ARVs and whether they cause any bad effects for mothers and babies. The study will also look at how well the ARVs control the amount of HIV in mothers' blood.

More information about the study and the ARVs is given in the rest of this form. The combinations of ARVs that will be tested are given in #8 (see below).

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

If you decide to join the study with your baby, we will first do some tests to find out if you qualify. More information about the tests is given in #4 (see below). If you qualify, you and your baby will be entered in the study. If you do not qualify, you and your baby cannot be entered in the study.

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

Deciding to join the study with your baby is voluntary (your choice). You are free to join or not join. If you join, you can change your mind and leave the study. Your decisions will have no effect on the medical care that you and your baby would normally receive. Your access to services, and the benefits and rights you normally have, will not be affected.

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

No matter what you decide about the study, it is important for you to take ARVs. Taking ARVs is the best known way to maintain your health and avoid passing HIV to your baby.

Finding Out if You and Your Baby Qualify

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

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

- Review your medical records.
- Ask about your health and the medicines you take.
- Ask about ARVs you have taken in the past.
- Talk with you about the study requirements and if you are able to meet the requirements.
- Give you a physical examination. This will include an obstetric exam *[here and below, sites may use locally appropriate terminology to refer to this exam]* that will check on how long you have been pregnant and whether you may be pregnant with more than one baby.

- Draw your blood (up to 20 mL or about 4 teaspoons) for tests. The tests will:
  - Check your blood cells.
  - Check how well your liver and kidneys are working.
  - Confirm that you have HIV. There are certain HIV tests that are required for this study. If the required tests are not in your medical records, we will do the tests that are needed.

  Some blood will not be tested right away. It will be saved for later testing for resistance to ARVs. This test shows whether different ARVs may work against the HIV in your blood.

We may also do a test to confirm that you are pregnant. If there is no pregnancy test in your medical records, we will use some of your blood or collect urine for a pregnancy test.

These procedures will take about 2 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

5. We will do an ultrasound scan.

The study requires an ultrasound scan of your baby *[sites may use locally appropriate terminology to refer to the scan]*. The scan uses sound waves to check the size of your baby, which shows how long you have been pregnant. Ultrasound scans are commonly done among pregnant women. If you have already had this type of scan done (outside the study), we may be able to use that scan for the study. If not, we will do the scan as part of the study.

To do the scan, gel is placed on your belly. Then a small device is moved back and forth on your belly to send and receive sound waves. The scan will show a picture of your baby. Depending on how long you have been pregnant, you might be able to see the baby's hands, arms, or legs. However, you should not worry if you cannot see the baby in the picture. The person who does the scan will explain what can be seen in the picture.

[Sites to modify first three sentences as needed:] The scan will be done at *[insert clinic name and/or location]*. It will take less than 30 minutes. We will arrange for you to have the scan at a scheduled time. The scan should ideally be done before entering the study. If this is not possible, we will arrange for you to have the scan within 2 weeks after entering the study. There is no cost to you for transport or having the scan done.

6. We will tell you if you and your baby qualify.

We will give you the results of all procedures and explain the results to you. While waiting for the results, it is important for you to keep taking any ARVs that you been given (outside of the study).

If you or your baby have any medical problems, or you do <u>not</u> qualify for the study for any reason, we will tell you this. You will <u>not</u> be entered in the study.

If you and your baby do qualify for the study, and you agree to join, you will be entered in the study.

If you do not qualify for the study, or you decide not to join, we will tell you where you can go for ARVs and other care you and your baby may need. *[Sites may insert locally appropriate information as needed:]* There are programs available for pregnant women with HIV and their babies. You have the option to receive services from these programs as an alternative to being in this study. If you do not join the study, the blood drawn at your first visit will not be kept for later testing (it will be destroyed).

Entering the Study

7. If you and your baby qualify, you will enter the study within 2 weeks of your first visit.

On the day you enter the study, we will:

- Ask about your health, ARVs, and other medicines.
- Give you a physical examination, including an obstetric exam.
- Draw your blood (22 mL or about 4-5 teaspoons) for tests. These tests will check:
  - If you have hepatitis B. Hepatitis B is a disease of the liver.
  - The amount of HIV in your blood. This is called your HIV viral load. Your HIV viral load should decrease over time as you take ARVs.
  - Your CD4 cells. These cells help your body fight infections. HIV attacks CD4 cells. The number of CD4 cells should increase over time as you take ARVs.

  Some blood will be saved for later testing. The later tests will look at factors in the blood that may predict pregnancy outcomes. For example, the tests may look for factors that predict why some women deliver their babies too early.
- Collect urine (15 mL or about 3 teaspoons) to save for later testing. The later testing will check on your kidneys.

If you have not already had an ultrasound scan of your baby, we will arrange for you to have the scan within 2 weeks after entering the study (see #5 above).

At this visit, you will be told which combination of ARVs you will take during the study. We will give you the ARVs and show you how to take them. You will need to take either 1 or 2 tablets once a day every day. It is very important that you take the ARVs as instructed. We will take as much time as needed for you to understand the instructions and come up with plans to help you take the ARVs as instructed.

These procedures will take about 4 hours.

Being in the Study

8. Mothers and babies will be placed in different groups that receive different ARVs.

Mothers and babies will be placed in 1 of 3 groups. The ARVs given to mothers in the study will depend on the group they are in. The combinations are shown below using abbreviations for the ARV names (see #1 for full names). Some of the ARVs in the groups are the same, some are different.

EFV + TDF + FTC	The ARVs in this group are most commonly given to pregnant women worldwide.
DTG + TDF + FTC	The ARVs in this group differ from the first group because DTG is given instead of EFV.
DTG + TAF + FTC	The ARVs in this group differ from the first group because DTG is given instead of EFV and TAF is given instead of TDF.

To test each combination of ARVs, the mothers and babies in each group will be compared to the mothers and babies in the other groups.

Each mother and baby is placed in a group at random, [like flipping a coin; *sites may insert a different example if preferred]*. Each mother and baby has a 1-in-3 or 33% chance of being placed in each group. We have no say in which group each mother and baby are placed. Mothers also cannot choose. Mothers must be willing to take the combination of ARVs assigned to their group. Mothers who are not willing to take the assigned combination of ARVs should not join the study.

9. Mothers will have visits every 4 weeks while pregnant.

The number of visits during pregnancy will depend on when each mother enters the study and when her baby is born. Most mothers will have about 5 visits while pregnant. Some may have 1-2 visits; others may have up to 7 visits.

Each visit will take about 1-2 hours. At these visits we will:

- Review your medical records.
- Ask about your health, ARVs, and other medicines.
- Give you a physical examination, including an obstetric exam.
- Draw your blood (up to 16 mL or about 3 teaspoons) for tests. At different visits, the tests will check:
  - How well your liver and kidneys are working.
  - Your HIV viral load.

  Some blood will be saved for later tests of factors that may predict pregnancy outcomes.
- Give you supplies of ARVs as needed.

10. Mothers and babies will have a visit soon after delivery. Then they will have 5 more visits over 1 year.

We will stay in contact with you as you get close to your delivery date. We will ask you to contact us when your labor begins. We will arrange for your first mother-baby visit as soon as possible after delivery. It is important for this visit to take place close to the baby's birth. At the latest, the visit must be within 14 days of the baby's birth. This visit will take up to 4 hours.

After your first mother-baby visit, you and your baby will have a visit when your baby is about 6 weeks of age. After that, visits will be scheduled when your baby is about 3, 6, 9, and 12 months of age. Each visit will take about 2 hours.

Different procedures will be done at these visits for mothers and babies. Some procedures will be done for both mothers and babies. Other procedures will be done only for mothers or only for babies.

For mothers and babies, at these visits we will:

- Review your and your baby's medical records.
- Ask about your and your baby's health, ARVs, and other medicines.
- Ask about how you are feeding your baby.
- Give you and your baby a physical examination. If any abnormalities are seen when your baby is examined, we may take a photo of the abnormality. The photo will help the doctors working on the study look at the abnormality and decide if it is important for your baby's health. We will tell you the doctors' opinion within about 3 months. *[Here and in #24, sites may modify text regarding photographs if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.]*

- Collect hair from you and your baby (only at the first mother-baby visit). We will cut about 100 strands of hair from the back of your and your baby's head to be saved for later testing. The later testing will look at the amount of ARVs that can be found in the hair.

[To be included at DXA sites only:] Mothers and babies will also have DXA scans of their bones. DXA stands for a kind of x-ray called dual energy x-ray absorptiometry. DXA scans check how hard and strong the bones are. When having the scan, mothers lie on a table while a machine passes over their body. Babies are held on a table while the machine passes over their body. The machine does not touch the body and the scan does not hurt. The scan may take up to 15 minutes. Babies scans will be done at 6 months of age. Mothers scans will be done when their babies are about 12 months of age. Mothers must have a pregnancy test to confirm they are not pregnant before having the scan. The results of the scans will not be available while the study is ongoing. We will tell you how to contact us if you would like to receive your and your baby's results after the study is done.

For mothers, we also will:

- Draw blood for tests. The amount of blood drawn will range from 6 to 30 mL (about 1-6 teaspoons) at different visits. At different visits, the tests will check:
  - Your blood cells.
  - How well your liver and kidneys are working.
  - Your HIV viral load.
  - Your CD4 cells.

  Some blood will be saved for later testing. These later tests may look at your HIV viral load and factors that may predict pregnancy outcomes. The tests may also look for a virus called Zika. Zika may cause problems during pregnancy and birth defects in babies.
- Collect breast milk. If you are breastfeeding when your baby is 6 weeks of age, you will express 20 mL (about 5 teaspoons) of milk for later testing. The later tests will look at the amount of ARVs that can be found in the milk.
- Collect urine (15 mL or about 3 teaspoons) to be saved for later testing. This will be done when your baby is 12 months of age. The later testing will check on your kidneys.
- Give you supplies of ARVs as needed.

For babies, we also will:
[Sites may modify the text in this section consistent with current guidelines for infant feeding. In particular, sites at which breastfeeding is not recommended may modify the wording related to breastfeeding consistent with local, regional, and/or national standards.]

- Draw blood (up to 6 mL or about 1 teaspoon) for tests. The tests done at each visit will depend on whether the baby is breastfeeding.
  - All babies will have an HIV test at the first mother-baby visit and at 6 weeks, 3 months, and 12 months of age. Babies who are breastfeeding will also have HIV tests at 6 and 9 months of age.
  - At the first mother-baby visit, all babies will have tests of their blood cells, liver, and kidneys. For babies who are breastfeeding, these tests will also be done at 6 months of age.

  Some blood will be saved for later testing. The later tests will look at the amount of ARVs in the blood. The tests may also look for Zika virus.

If any test done for the study shows that your baby has HIV, we will ask you to bring your baby to the clinic as soon as possible for another test. We will collect about 3 mL (less than 1 teaspoon) of blood for HIV testing and for later testing for resistance. Whether your baby has HIV or not, you and your baby will stay in the study as originally planned. The study cannot provide care and treatment for babies who have HIV, but we will tell you where you can go for the care and treatment your baby may need.

11. We will ask questions about how you have been sleeping and feeling.

At some visits, we will ask questions about how well you have been sleeping and how you have been feeling (for example, if you have felt happy or sad or scared). Sometimes mothers feel abnormally sad after having their babies. This is called postpartum depression. If the questions show that you have been sadder than normal, we will talk with you about this. We will also talk with you about problems with sleep or feeling anxious. If you have these types of feelings or problems, we will tell you about other services outside the study that might help you.

12. Mothers will have extra visits if their ARVs are changed or if their HIV is not controlled.

Mothers may have their ARVs changed at any time in the study. If DTG or EFV is changed to another ARV, mothers will have an extra visit about 4 weeks after the change. More information about why ARVs may be changed is given in #16 (see below).

Mothers will have viral load tests at most visits. After being in the study for about 6 months, a mother's viral load should be very low. If tests show that the viral load is higher than expected, mothers will have an extra visit.

These extra visits will take about 1 hour. At these visits we will:

- Review your medical records.
- Ask about your health, ARVs, and other medicines.
- Give you a physical examination.
- Draw your blood (up to 12 mL or about 2-3 teaspoons) for tests. The tests will check your HIV viral load. If you changed ARVs, the tests will also check how well your liver and kidneys are working. If your HIV is not controlled, the tests will check for resistance. Some blood will be saved for later testing.
- Give you additional supplies of ARVs as needed.

13. Mothers and babies may have extra visits if they are sick.

Mothers and babies may have extra visits if they are sick or need more tests to check on their health. Additional blood or urine may be collected at these visits if needed. Please contact us if you or your baby become sick.

14. Mothers who become pregnant again may have extra procedures.

Mothers could become pregnant again while in the study. We will talk with you about family planning. If you wish to become pregnant again, or think you may be pregnant, please tell us right away. We will test your blood or urine to find out if you are pregnant.

If you become pregnant again, you and your older baby will stay in the study as originally planned (until your older baby is about 12 months of age). If you are pregnant at your last study visit, we will contact you after that to find out the outcome of your pregnancy.

The study cannot provide medical care related to a new pregnancy or delivery of a new baby. If you have another baby, that baby will not be in the study. Therefore, it is important to receive medical care for a new pregnancy outside the study. We will tell you where you can go for the care you need. *[Sites may modify or add to the preceding sentence to provide site-specific details on provision and/or referral for care.]*

We will talk with you about your choices for taking ARVs during a new pregnancy. We will ask you to sign a separate consent form to record your choices.

15. Tests will be done at different laboratories.

We will do most tests of your and your baby's blood at our laboratory. We will give you the results of these tests at the next scheduled visit, or sooner if necessary. We will explain the results to you. If the results show that you or your baby may need medical care or treatment that cannot be provided by the study, we will tell you where you can go for this care.

Other tests will be done at laboratories in the United States and other countries. This includes:

- Some tests of your HIV viral load
- Some tests of your kidney
- Tests for resistance to ARVs
- Tests for factors that may predict pregnancy outcomes
- Tests of the amount of ARVs that can be found in blood, breast milk, and hair
- Tests for Zika virus

The results of most of these tests will not be available while the study is ongoing. If any of the results may be important for your or your baby's health, we will tell you about them. Otherwise, the results will not be given to you.

16. We may change or stop your ARVs.

At all of your visits, we will check whether the ARVs you are taking may be causing bad effects. If so, the ARVs may be changed or stopped. The ARVs may be changed if you have certain illnesses or need to take other medicines that cannot be taken with ARVs. We will always discuss ARV changes with you. Please tell us about any problems you may have with taking your ARVs.

We may stop all the ARVs you are receiving from the study if:

- You are not able to come to study visits.
- You are not able to take the ARVs.
- Taking the ARVs may be harmful to you.
- You ask to stop taking the ARVs.

If we stop all your ARVs, we will talk with you about options for receiving ARVs from outside the study. You and your baby will stay in the study as originally planned.

17. We may take you and your baby off the study early.

Each mother and baby is expected to stay in the study until the baby is about 12 months old. However, we may take you and your baby off the study if:

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

18. Please tell us if you want to leave the study.

You and your baby are free to leave the study at any time for any reason. The care that you and your baby would normally receive will not be affected, but it is important that we know your decision. We will ask you and your baby to come to the clinic for one last visit. At this visit, we will do the same types of procedures listed in #10 (see above). We will answer any questions you may have and tell you how to contact us in the future, if you wish.

19. We will contact you after your last visit.

After your last study visit, the study cannot keep giving you ARVs. We will talk with you about this and help make sure you can get ARVs from outside the study after your last visit. We will also contact you within the month after your last visit to confirm that you are getting ARVs from outside the study.

Risks of the Study

20. There is little risk from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to you and your baby. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection. You or your baby could be cut when hair is collected with scissors. Expressing breast milk could be uncomfortable. There is no risk from ultrasound.

Your baby will be tested for HIV while in this study. You may become worried or anxious about your baby's test results. We will explain all tests to you and provide counseling to help with feelings you may have about the tests and your baby's results.

[To be included at DXA sites only:] For mothers and babies who have DXA scans, there is a small risk from x-rays, also known as radiation. Radiation is energy in the form of waves. All people are exposed to a low level of natural radiation from the sun. This is called background radiation. High levels of radiation can cause cancer. However, the level of radiation from a DXA scan is much lower than the level that causes cancer. The level from DXA scans for this study is also about the same as the background radiation every person normally has over 5 days. The study staff have been trained to do DXA scans using the smallest amount of radiation possible.

21. There are risks from ARVs.

All ARVs can cause side effects. This includes any ARVs that you would receive outside the study. Some side effects are minor; others can be severe. Some side effects are common, others are rare. Some people who take ARVs have some of the side effects. Other people have no side effects.

Some of the most common and most serious side effects of ARVs are listed below. Until you join the study, we will not know what specific ARVs you will take. Therefore, this form gives information about all the ARVs that may be given in the study (see #1 and #8 above).

This form does not list all possible side effects for all ARVs. If you join the study, we will tell you more specific information about the ARVs that you will be taking. At each study visit, we will check on whether the ARVs you are taking may be causing side effects. If you have questions or concerns about side effects at any time, please tell us.

22. Some side effects can be severe.

First, you should know about the possible severe side effects of ARVs. These effects are rare, but they can cause serious health problems and can result in death. Please contact us if you have any of these symptoms or if you feel sick at any time.

- Severe rash. This can be caused by EFV and DTG. Please contact us or go to the nearest hospital immediately if you have a rash and any of the following symptoms:
  - Fever
  - Feel very ill or without energy
  - Muscle or joint aches
  - Blisters or sores in mouth
  - Blisters or peeling of the skin
  - Redness or swelling of the eyes
  - Swelling of the mouth or face
  - Problems breathing

- Liver problems. The liver is an organ near the stomach. If you get liver problems, you might have yellowing of the skin or whites of the eyes; dark or tea-colored urine; pale colored stools; upset stomach or vomiting; loss of appetite; pain, aching or tenderness of the right side below the ribs; or itchy skin. This can be caused by EFV and DTG. The risk of these problems may be higher during pregnancy and the 3 months after giving birth while taking EFV.

- Pancreas problems. The pancreas is an organ near the stomach. If your pancreas becomes inflamed, you may have stomach pain, upset stomach or vomiting, or more fats in the blood. This can be caused by EFV.

- Kidney problems. The kidneys are organs near the middle of your back (one on each side). Doctors usually find out about kidney problems from tests of the blood. This can be caused by TDF, TAF, and DTG.

- Severe depression, including thoughts or acts of hurting or killing oneself. People with a history of psychiatric problems may be at greater risk for these serious psychiatric problems. This can be caused by EFV and DTG. Please contact us or go to the nearest hospital immediately if you have any thoughts of hurting yourself.

- Other severe mental problems, including aggressive behavior or psychosis-like symptoms, such as abnormal thinking, paranoia, and delusions. This can be caused by EFV.

23. Other side effects are more common.

You should also know about the more common side effects of ARVs, which are not usually severe. These are listed below.

Overall Body Effects • Changes in the placement of body fat (increasing around the stomach, neck, or breast or decreasing in the arms, legs, or cheeks) • Overall weakness or tiredness • Allergic reaction • Numbing, tingling, or pain in the hands and feet • Fever	**Effects on Your Blood** • More fats in the blood that may increase the risk of heart problems • More acid in the blood that may be related to liver problems • Other changes in blood tests that may show problems with the muscles, liver, kidneys, or pancreas. The blood tests may show how well these organs are working, or they may look for substances made by the organs, or they may look for fats in the blood.
Effects on Your Muscles and Bones • Aches and pains • Loss of muscle • Bone thinning or softening (which could increase the chance of breaking a bone)	**Effects on Your Head** • Headache • Yellowing of the eyes • Runny nose • Swelling of the face, lips, or tongue
Effects on Your Skin • Itching • Rash • Darkening of the palms and soles of feet	**Effects on Your Mind or Mental Function** • Drowsiness • Trouble sleeping • Abnormal dreams • Dizziness • Confusion • Difficulty concentrating • Hallucinations • Feeling of strangeness and losing touch with reality • Exaggerated feeling of well-being • Agitation or anxiety • Feeling of deep sadness or unworthiness (depression)
Effects on Your Stomach • Pain or upset stomach • Loose or watery stools • Nausea • Vomiting • Gas	
Effects on Your Chest • Cough • Shortness of breath • Changes seen in tests of heart rhythm	

24. There are other possible risks from ARVs.

Possible effects on pregnancy, unborn babies, and breastfeeding babies

Taking ARVs is the best known way for a mother who has HIV to maintain her health and avoid passing HIV to her baby during pregnancy and breastfeeding. However, HIV and ARVs may cause some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some ARVs are more likely to cause these effects than others.

[Sites to modify as needed to reflect local standards: The combination of ARVs with EFV is recommended (outside of the study) for women with HIV.*]* This combination with EFV also seems to be safe in pregnancy, especially when taken after the first 3 months of pregnancy. EFV may cause harm to

the baby when taken in the first 3 months of pregnancy. We do not yet know if DTG or TAF are safe in pregnancy. Some studies done in animals showed that the ARVs were safe in animals.

In this study, ARVs are given after the first 3 months of pregnancy. The ARVs are continued through pregnancy and after delivery. After delivery, mothers who become pregnant again may be taking ARVs during the first 3 months of their new pregnancy. If you become pregnant again, we will talk with you about your choices for taking ARVs during your new pregnancy (see also #14 above).

Babies who breastfeed may receive the ARVs taken by their mothers through breast milk. We do not know how much of the ARVs go into breast milk or what effects this may have on babies.

We are doing this study to learn more about safety of the ARVs given in the study for pregnant women and their babies. We will also learn how much of the ARVs are passed to babies and what effects this may have.

Immune reconstitution syndrome

In some people with advanced HIV infection, signs and symptoms from other infections or certain diseases can occur soon after starting ARVs. Some of these symptoms may be life threatening. If you start having new symptoms, or if any existing symptoms get worse after starting ARVs, please tell us immediately.

Hepatitis B

Some ARVs are active against hepatitis B. For women who have hepatitis B, and take ARVs that are active against hepatitis B, stopping the ARVs could cause the hepatitis B to worsen. If this happens, most women get better quickly without treatment, but in rare cases this has resulted in death.

Risk of resistance

If ARVs are not taken as instructed, this can cause resistance. Resistance means that an ARV may no longer work against HIV. To avoid resistance, it is important to take ARVs instructed and avoid missing doses.

25. There could be risks of disclosure of your or your baby's information.

We will make every effort to keep your and your baby's information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, your and your baby's names will be written on some records.

[Sites may modify this paragraph if IRBs/ECs mandate a separate form for obtaining informed consent for photographs.] If we take photos of abnormalities seen when your baby is examined, we will not photograph your baby's face unless the abnormality is on the face. In that case, we will make every effort to hide details that could identify your baby. Photos will be labeled only with a code number (not with your or your baby's name). Photos will be kept securely with other information collected for the study. Photos also may be shared with other doctors working on the study. The other doctors may be here at *[site name]* or in other countries. These doctors will not be given your or your baby's name, and they will be required to keep the photos private and confidential. When the study is completed, the photos will be destroyed.

Despite our best efforts to keep your and your baby's information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, you or your baby could be treated badly or unfairly. You could feel stress or embarrassment.

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

Benefits of the Study

26. There may be no benefit from being in the study.

By joining the study, you and your baby will be part of the search for new treatments for pregnant women with HIV. However, being in the study may not benefit you or your baby in any way.

You and your baby will have regular visits here and frequent checks on your health. It is possible that the procedures done may help you and your baby stay healthy. If these procedures show that you or your baby may need medical care that cannot be provided through the study, we will tell you where you can go for the care you or your baby may need.

Other information about the study

27. There are no costs to you for being in the study.

There are no costs to you for study visits or procedures or the ARVs that are given by the study.

[Insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given *(specify amount).]*

28. Study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The companies that make the ARVs given in the study: Gilead Sciences, Mylan, and ViiV Healthcare Ltd

The study staff and these groups are required to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your name or your baby's name or identify you or your baby personally.

A description of this study will be available on ClinicalTrials.gov as required by United States law. This website will not include information that can identify you or your baby. At most, the website will include a summary of the results of the study. You can search this website at any time.

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

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

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

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat you or your baby or tell you where you can get the treatment you or your baby need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *[site name or]* the United States National Institutes of Health.

Who to Contact

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

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

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

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

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

Signatures

If you decide to join this study with your baby, sign or make your mark below.

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

We will tell you any new information from this study or other studies that may affect your willingness for you and your baby to stay in the study. You can ask questions or request more information at any time.

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

[Insert signature blocks as required by site IRB/EC policies.]

Name of Mother (print)	Signature of Mother	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

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

IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants

Version 2.0, [date]

You have decided to join the study named above with your baby. As part of the study, you will have blood, urine, and hair collected. You may have breast milk collected if you breastfeed your baby. Your baby will have blood and hair collected. After these samples are tested for the study, some samples may be left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

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

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

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

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

[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

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

A repository is a secure facility that is used to store samples. The IMPAACT Network has a repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

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

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

If you agree, the extra samples could also be used for research that looks at your or your baby's genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your and your baby's samples would only be used to look at genes related to HIV, how the body responds to ARVs, pregnancy, and the immune system.

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

The research done with extra samples is not expected to give any information relevant to your or your baby's health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your or your baby's study records.

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

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

There may be some risks from tests of your or your baby's genes. If others found out the results of these tests, they could treat you or your baby badly or unfairly. However, this is almost impossible because the results will not be given to the study staff or to you, and will not be in your or your baby's study records.

5. There may be no benefit to you or your baby.

By allowing your extra samples to be used for research, you and your baby will be part of the search for new information that may benefit people with HIV in the future. However, the research done with the extra samples is not expected to directly benefit you or your baby in any way.

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

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

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

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other US, local, and international regulatory entities

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

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

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

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

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

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

Signatures

Before deciding whether to allow your and your baby's extra samples to be used for research, make sure you have read this form, or had it read to you. Make sure all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

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

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination if the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing].

For YOUR extra samples, write your initials or make your mark next to your choice.

_____ I allow my extra samples to be used for research on HIV, pregnancy, the immune system, ARVs, and other diseases. I also allow my samples to be used for tests of my genes.

_____ I allow my extra samples to be used for research on HIV, pregnancy, the immune system, ARVs and other diseases. I do not allow my samples to be used for tests of my genes.

_____ I do not allow my extra samples to be used for any research.

For YOUR BABY's extra samples, write your initials or make your mark next to your choice.

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

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

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

_____	_____	_____
Name of Mother (print)	Signature of Mother	Date
_____	_____	_____
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
_____	_____	_____
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix V
Sample Informed Consent Form for Use of Study Drug during Subsequent Pregnancy

IMPAACT 2010
Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants

Version 2.0, [date]

You are taking anti-HIV medicines (ARVs) from the study named above. Because you are pregnant again, it is important for you to choose whether to keep taking ARVs from the study.

This form gives information about taking ARVs while you are pregnant. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decision on taking ARVs from the study at the end of the form.

1. It is your decision whether to take ARVs from the study while you are pregnant.

When you first joined the study, you were assigned to receive a combination of ARVs. You were given information about these ARVs, and you agreed to take these ARVs while pregnant. Now that you are pregnant again, you have a choice of whether to keep taking ARVs from the study.

You are free to say yes or no, and to change your mind at any time. Your decision will not affect your or your baby's participation in the study. No matter what you decide, you and your baby will still stay in the study as originally planned.

2. We will discuss your choice of ARVs with you.

We will talk with you about the ARV you are currently taking and how these compare to the ARVs that are usually given to pregnant women. If you are doing well on the ARVs you are currently taking, we may recommend that you keep taking the same ARVs during your new pregnancy. If we have any concerns, or if you have any concerns, we will discuss changing your ARVs. If you wish to consider changing your ARVs, we will tell you about the ARVs that are available from the study and the ARVs that are available outside the study.

No matter what you decide, it is important that you take ARVs during your new pregnancy. Taking ARVs is the best known way to maintain your health and avoid passing HIV to your baby.

3. The risks and benefits of taking ARVs from the study in your new pregnancy are the same as in your previous pregnancy.

If you are past the first three months in your new pregnancy, there is no change in the possible risks and benefits of taking ARVs from the study now compared to when you first joined the study. If you are in the first three months, it is possible that the risks and benefits could be different. We do not yet know much about this at this time.

We will review what is known about the risks and benefits with you. If any new information about the risks and benefits becomes available later, we will give you that information and again discuss your choice of ARVs. You can ask questions or request more information at any time.

4. There is no cost to you for taking ARVs from the study.

If you choose to keep taking ARVs from the study, you will receive the ARVs here at the study clinic free of charge.

If you choose to take ARVs from outside the study, there may be costs to you *[or your health insurance]*, depending on whether the ARVs are available free of charge outside the study. *[Sites may modify the preceding sentence as needed to reflect the local context.]*

5. Your ARVs could be changed or stopped.

No matter what you decide about taking ARVs from the study, you will keep having the same clinic visits, examinations, and tests to check on your health while you are in the study. If we find that the ARVs could be causing problems, we will make recommendations to change or stop the ARVs if needed. This is no different from what would be done in the study if you were not pregnant again.

6. The study cannot provide medical care for your new pregnancy.

The study cannot provide medical care related to your new pregnancy or delivery of a new baby. If you have another baby, that baby will not be in the study. Therefore, it is important for you to receive medical care related to your pregnancy outside the study. We will tell you where you can go for this care. *[Sites may modify or add to the preceding sentence to provide site-specific details on provision and/or referral for care.]*

7. If you get sick or injured, contact us right away.

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

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat you or your baby or tell you where you can get the treatment you or your baby need. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *[site name or]* the United States National Institutes of Health.

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

- If you have questions about the study or your choice of ARVs:
  [insert name and telephone number of investigator or other study staff].

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

- If you have any health or other problems that may be related to your study participation:
  [insert name and telephone number of investigator or other study staff].

- If you want to leave the study:
  [insert name and telephone number of investigator or other study staff].

Signatures

Before deciding whether to take ARVs from the study during your new pregnancy, make sure you have read this form, or had it read to you. Make sure all of your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

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

[Insert initial and signature blocks as required by site IRB/EC policies.]

Write your initials or make your mark next to your choice. Then sign or make your mark below.

_____ I choose to take ARVs from the study during my new pregnancy.

_____ I choose to <u>not</u> take ARVs from the study during my new pregnancy.

_____	_____	_____
Name of Mother (print)	Signature of Mother	Date
_____	_____	_____
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
_____	_____	_____
Name of Witness (as appropriate; print)	Signature of Witness	Date