IMPAACT 2023

A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1

A 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

Pharmaceutical Support Provided by:
ViiV Healthcare

DAIDS Study ID #38637
IND #110847 Held By NIAID

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Version 2.0
23 March 2022

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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 Council for Harmonisation Guideline for Good Clinical Practice (ICH 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
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area Under the Curve
C_{24}	Plasma concentration observed at end of 24-hour dosing interval
C_{max}	Maximum drug concentration
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CL/F	Clearance
CLIA	Clinical Laboratory Improvement Amendments
CMC	Clinical Management Committee
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRMS	Clinical Research Management System
CRPMC	Clinical Research Products Management Center
CYP3A4	Cytochrome P450 3A4
DAIDS	Division of AIDS
DAERS	DAIDS Adverse Experience Reporting System
DBS	Dried Blood Spot
DHHS	US Department of Health and Human Services
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
DT	Dispersible Tablet
DTG	Dolutegravir
EAE	Expedited Adverse Event
EC	Ethics Committee
eCRF	Electronic Case Report Form
EIA	Enzyme Immunoassay
FDA	US Food and Drug Administration
GCLP	Good Clinical Laboratory Practices
GM	Geometric Mean
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INSTI	Integrase Strand Transfer Inhibitor
IoR	Investigator of Record

IQR	Interquartile Range
IRB	Institutional Review Board
KM	Kaplan-Meier
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
MOP	Manual of Procedures
NAT	Nucleic Acid Test
NFV	Nelfinavir
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PID	Participant Identification Number
PK	Pharmacokinetic
PRO	DAIDS Protocol Registration Office
RAL	Raltegravir
RNA	Ribonucleic Acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORE	DAIDS Site Clinical Operations and Research Essentials
SDMC	IMPAACT Statistical and Data Management Center
SES	Study Enrollment System
SID	Study Identification Number
sIRB	Single IRB
SMC	Study Monitoring Committee
SPDSMP	Study Progress, Data, and Safety Monitoring Plan
SoE	Schedule of Evaluations
SOP	Standard Operating Procedure
UGT	UDP glucuronosyltransferase
UGT1A1	UDP Glucuronosyltransferase Family 1 Member A1
US	United States
VQA	Virology Quality Assurance
WB	Western Blot
WBC	White Blood Cells
WHO	World Health Organization
ZDV	Zidovudine

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SCHEMA

Purpose: To propose an appropriate dolutegravir (DTG) dosing regimen for infants born to mothers living with HIV-1.

Design: Phase I, multi-site, open-label, non-comparative dose-finding study to evaluate safety, tolerability, and pharmacokinetics (PK).

Study Population and Sample Size: Infants born to mothers living with HIV-1 and receiving a single or combination antiretroviral (ARV) drug(s) per local standard of care. Mothers will also be enrolled in the study but will not receive study drug (DTG).

Cohort 1: A minimum of 12 and up to 36 mother-infant pairs (across strata) will be enrolled to achieve six evaluable infants in each stratum receiving the DTG dose regimen selected as the starting dose regimen for Cohort 2. Strata 1A and 1B will be enrolled concurrently. Stratum 1C will only be enrolled if Strata 1A and 1B PK and safety data support administration of the DTG 5 mg dispersible tablets (DT) in all eligible neonates or in neonates with a minimum weight.

Strata 1A and 1C (DTG-naïve):	Infants with no *in utero* exposure to maternal DTG (no exposure to DTG during the two weeks prior to delivery).
Stratum 1B (DTG-exposed):	Infants with *in utero* exposure to maternal DTG (mothers who receive at least one dose of DTG within 72 hours prior to delivery).

Cohort 2: A minimum of 24 (12 in each stratum) and up to 72 mother-infant pairs (across both strata) will be enrolled to achieve 12 evaluable infants in each stratum receiving the final proposed chronic DTG dose regimen. At least eight breastfeeding and eight formula-feeding infants will be enrolled in Cohort 2 across both strata.

Stratum 2A (DTG-naïve):	Infants with no *in utero* exposure to maternal DTG (no exposure to DTG during the two weeks prior to delivery).
Stratum 2B (DTG-exposed):	Infants with *in utero* exposure to maternal DTG (mothers who receive at least one dose of DTG within 72 hours prior to delivery).

Study Drug: DTG 5 mg/mL liquid suspension and DTG 5 mg DT

Cohort 1: Two single doses of DTG administered at two time points. The initial dose for Strata 1A and 1B will be 0.5 mg/kg; dose adjustments for Strata 1A and 1B may occur based on experience within the cohort. Dosing in Stratum 1C (if enrolled) will be determined based on data from Strata 1A and 1B.

Stratum 1A: DTG 5 mg/mL liquid suspension. First dose will be administered at 0-5 days of life at Entry. Second dose will be administered 7-10 days after the first dose.

Stratum 1B: DTG 5 mg/mL liquid suspension. First dose will be administered at 2-5 days of life at Entry. Second dose will be administered 7-10 days after the first dose.

Stratum 1C: DTG 5 mg DT. First dose will be administered at 0-5 days of life at Entry. Second dose will be administered 7-10 days after the first dose.

Cohort 2: DTG dosing will be initiated within the first five days of life at Entry and continue through the Week 4 or Week 6 visit based on the duration of local standard ARV prophylaxis (4-6 weeks). The DTG formulation, timing of first dose, and starting dose regimen for each stratum will be selected based on data from Cohort 1. Dose adjustments may occur based on experience within the cohort.

Study Duration: Approximately 28 months total. Accrual is expected to require approximately 24 months. Infants will be followed through 16 weeks of life and mothers will be off study after completion of the Entry visit.

Primary Objectives

- To evaluate the safety and tolerability of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.
- To evaluate the pharmacokinetics of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.
- To propose an appropriate DTG dose regimen during the first four weeks of life for HIV-1-exposed infants.

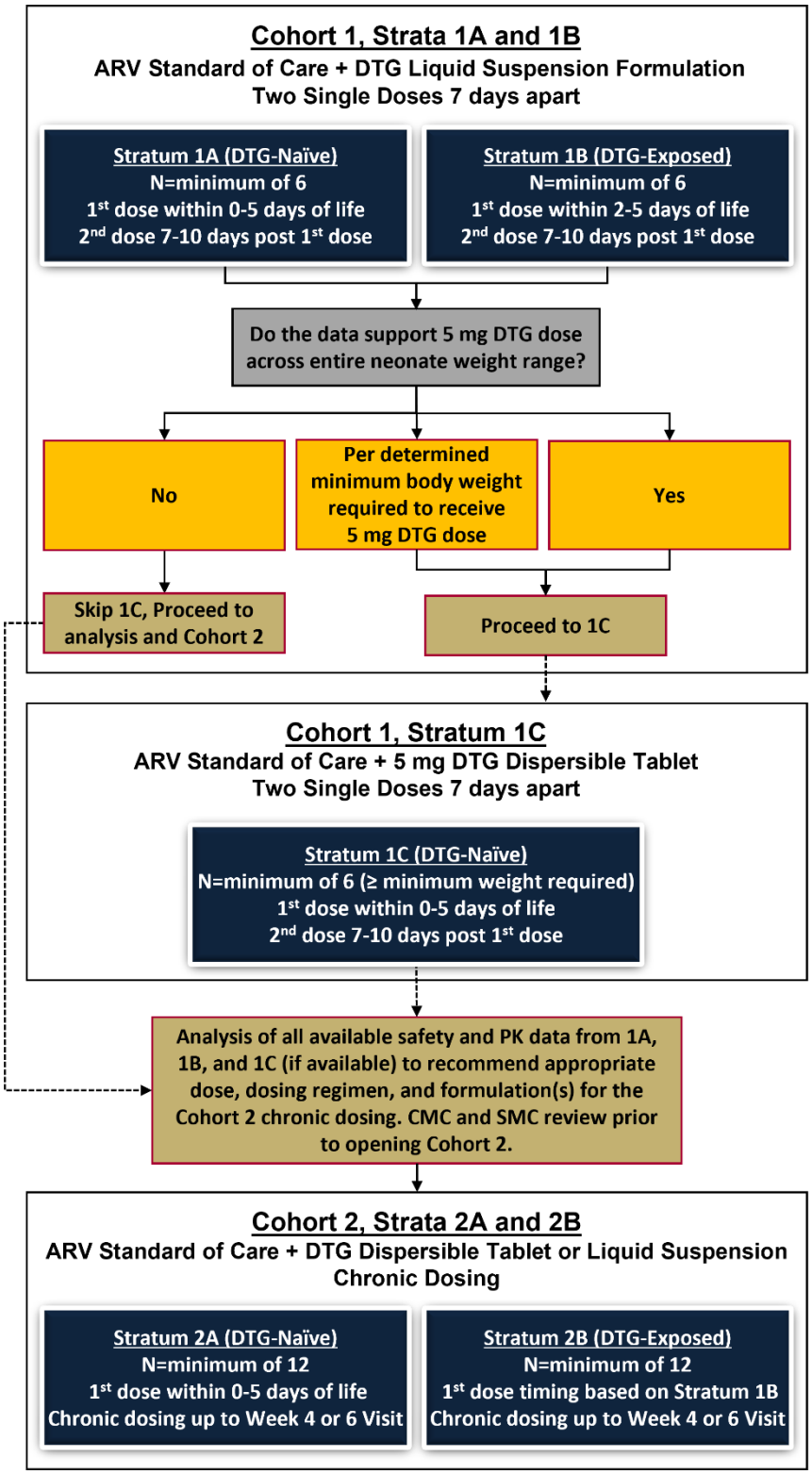
Secondary Objective

- To evaluate the safety of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first 16 weeks of life.

Other Objective

- To investigate the relationship between infant DTG elimination and UGT1A1 genotypes.

Figure 1
Overview of Study Design



1 INTRODUCTION

1.1 Background

Dolutegravir (DTG) has promise for use in neonates for both prophylaxis and early treatment of human immunodeficiency virus (HIV) (1). Postnatal prophylaxis with multiple antiretroviral (ARV) agents is currently recommended for neonates at high risk for acquiring HIV-1, and DTG could play a role as a valuable new ARV for inclusion in neonatal prophylaxis regimens (2). ARVs may also be used in neonates for therapy of HIV, either as presumptive therapy for neonates at highest risk of HIV pending return of their initial HIV test results or as part of treatment regimens for neonates with documented diagnosis of HIV from positive initial HIV tests. Provision of HIV therapy soon after birth to neonates living with HIV may prevent seeding of neonatal viral reservoirs, preserve neonatal immune function, and potentially allow future treatment interruptions or functional cure. Early effective ARV treatment is recommended for those infants at highest risk for HIV-1 (2).

DTG could play an important role as an integrase inhibitor component of neonatal HIV-1 treatment regimens (2). Despite the need for ARV treatment of neonates, there are few ARVs with formulations appropriate for use in neonates and limited neonatal safety and dosing information for most ARVs. Of the nucleoside reverse transcriptase inhibitors, only zidovudine (ZDV), lamivudine (3TC), emtricitabine, and stavudine are approved for use in neonates less than 14 days of life. While nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor, is not approved by the US Food and Drug Administration (FDA) for neonates less than 15 days of life, it is widely used in neonates for both prophylaxis and treatment. Both the US Department of Health and Human Services (DHHS) and World Health Organization (WHO) guidelines recommend NVP in neonates with estimated gestational age ≥ 34 weeks. Of the protease inhibitors, only nelfinavir (NFV) has pharmacokinetic (PK) data available for neonates. These data demonstrate highly variable plasma concentrations, and the optimal dosing regimen remains uncertain (3, 4). The powder formulation of NFV that was studied in neonates is no longer commercially available, and NFV is not approved in children less than two years old. Lopinavir/ritonavir is available as a pediatric solution; however, its dosing is uncertain in the first weeks of life, and its use is not recommended in neonates less than two weeks old and ≤ 42 weeks postmenstrual age, as several cases of life-threatening toxicities (including brady-arrhythmias and cardiac dysfunction) have been reported (5, 6). In November 2020, maraviroc became the first entry inhibitor to receive FDA approval for treatment of HIV-1 in full-term neonates weighing at least 2 kg. The three-drug ARV regimen with the greatest experience in neonates is ZDV/3TC/NVP, and alternative agents for use in this population are urgently needed.

Use of integrase inhibitors as part of neonatal HIV prophylaxis may further reduce transmission risk, as these agents block integration of viral deoxyribonucleic acid (DNA) into the host cell—a critical step in the HIV lifecycle required for productive infection to occur. Integrase inhibitors could also play a part in HIV prophylaxis in infants born to mothers with HIV-1 resistant to ARVs from other classes. In November 2017, raltegravir (RAL) oral granules for suspension became the first integrase inhibitor to receive FDA approval for use in full-term neonates exposed to HIV-1. However, RAL has a low barrier to the development of resistance; has a complicated neonatal dosing regimen, with three dosing changes in the first four weeks of life; and the procedures for reconstitution of RAL granules into a liquid suspension may be difficult for some families to perform (1).

DTG was the third approved integrase strand transfer inhibitor (INSTI) and has a higher genetic barrier to resistance than RAL. DTG has potential for use both as a prophylaxis to prevent HIV-1 transmission in neonates and as part of early intensive treatment of neonates with HIV-1. DTG is primarily metabolized by the UDP Glucuronosyltransferase Family 1 Member A1 (UGT1A1) enzyme, which is also responsible for glucuronidation of bilirubin. UDP glucuronosyltransferase (UGT) enzyme activity is low at birth and increases rapidly over the first weeks to months of life. In neonates whose mothers received DTG during pregnancy, infant washout elimination after birth of trans-placentally acquired DTG had a median half-life of 32.8 hours, which is severalfold longer than that of older children and adults (7). DTG safety and PK must be described in neonates to develop a dosing regimen that will allow DTG to be used safely and effectively in the first weeks of life.

1.2 Prior Research

1.2.1 Dolutegravir Film-Coated Tablets Pharmacokinetics and Safety in Adolescents and Children Living with HIV-1

In 2013, the FDA approved DTG 50 mg film-coated tablets for use in combination with other ARVs for the treatment of HIV-1 in adults and children at least 12 years of age and weighing at least 40 kg. In 2016, the FDA extended approval of DTG for children down to 30 kg, and the European Commission approved dosing down to 15 kg the following year (8). These approvals were based on the results of IMPAACT P1093, an open-label trial of DTG in adolescents, children, and infants living with HIV-1 evaluating the PK, safety, and appropriate dosing for all age groups from four weeks to less than 18 years of age (9-11).

In June 2020, the FDA expanded the indication of the 50 mg film-coated tablet to include children weighing at least 20 kg (12). The DTG film-coated tablets are available as 10 mg, 25 mg, and 50 mg. For children weighing 14 to less than 20 kg and able to swallow pills, 40 mg (4 x 10 mg tablets) is the recommended dose using the film-coated tablets. These approvals were based on the collective analyses of IMPAACT P1093 and ODYSSEY trials (12).

1.2.2 Pharmacokinetics and Safety of Dolutegravir Administered as Dispersible Tablets for Suspension in Infants and Young Children

Along with the expanded indication of the 50 mg tablet in June 2020, the FDA also approved DTG Dispersible Tablets (DT) for Oral Suspension (Tivicay® PD 5 mg) for infants and children at least four weeks of age and weighing at least 3 kg. These approvals were based on collective analyses from IMPAACT P1093 and ODYSSEY trials. The FDA-approved weight-band dosing regimen for the DTG 5 mg DT for oral suspension, the number of participants included in the weight band, and the PK parameter geometric mean (%CV) are presented in Table 1 (12).

Table 1
Summary of Pharmacokinetic Parameters in Pediatric Participants Living with HIV-1 (Pooled Analyses for IMPAACT P1093 and ODYSSEY[a] Trials)

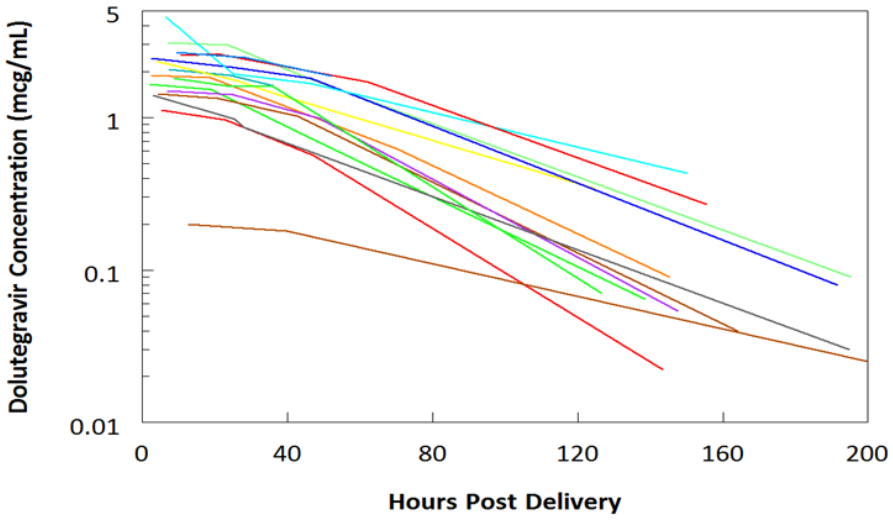
Weight Band	Dose of TIVICAY® or TIVICAY® PD[b]	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C_{max} (mcg/mL)	AUC_{0-24h} (mcg·h/mL)	C_{24h} (ng/mL)
3 kg to <6 kg	TIVICAY® PD 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	TIVICAY® PD 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to <14 kg	TIVICAY® PD 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)
14 kg to <20 kg	TIVICAY® PD 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	TIVICAY® PD 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	TIVICAY® 50 mg once daily	49	4.92 (40)	54.98 (43)	778 (62)

[a] Data from two weight-band-based pharmacokinetic sub-studies in the ODYSSEY trial.
[b] The bioavailability of TIVICAY® tablets for oral suspension is ~1.6-fold that of TIVICAY® tablets.

1.2.3 Dolutegravir Pharmacokinetics and Safety in Neonates

Washout PK of DTG in infants born to mothers living with HIV-1 who received DTG during pregnancy was studied in IMPAACT P1026s. The median (interquartile range (IQR)) for the ratio of cord blood to maternal plasma DTG concentration was 1.25 (1.07-1.40), demonstrating that DTG readily crosses the placenta (7). The population studied in IMPAACT P1026s included 22 infants with median (range) gestational age at birth (weeks) of 38.9 (34.9-42.3) and included four preterm infants and four low birth weight infants (< 2500 grams). The median (IQR) infant DTG maximum plasma concentration (C_{max}) after birth was 1.64 mcg/mL (1.31-2.38) and the median (IQR) half-life was 32.8 hours (25.9-35.9) (7); refer to Figure 2.

Figure 2
Individual infant dolutegravir concentrations versus time postdelivery



Clinical abnormalities were noted at birth in seven infants, and in all but two infants these findings were considered unrelated to DTG exposure due to the timing of initiation of DTG during pregnancy. Renal abnormalities were found on ultrasound in two infants: an isolated renal cyst in one infant and a multi-cystic dysplastic kidney in another infant also diagnosed with cystic fibrosis. Both of these infants were born to mothers who began DTG during the first trimester, and these abnormalities were considered possibly related to DTG exposure by the protocol team (7).

There are limited data on the transfer of DTG into breast milk. In the DolPHIN study, DTG plasma and breast milk concentrations were measured in mothers living with HIV-1 who were on DTG therapy prior to delivery and postpartum. The DTG infant daily dose from breast milk immediately postpartum was estimated to be 2.2 mcg/kg/day which is significantly less than the mg/kg doses planned in this study (13). Based on population PK modeling, a breastfeeding infant whose mother is receiving DTG is estimated to have a DTG plasma exposure approximately 12% of maternal plasma exposure (14).

Dolutegravir is primarily metabolized by UGT1A1, the same enzyme that is responsible for the elimination of bilirubin and RAL. UGT enzyme activity is low at birth and dramatically increases over the first weeks of life. The approved neonatal RAL dosing regimen requires an 8-fold increase in dose, from 1.5 mg/kg once a day immediately after birth to 6 mg/kg twice a day at four weeks of age, to maintain consistent RAL plasma concentrations in the face of the increase in UGT1A1 metabolism after birth (15). Neonatal washout elimination of DTG acquired across the placenta is prolonged, but the pattern of increase in DTG elimination during the first weeks of life is unknown. The current approved dose for DTG in a 4-week-old is a single DTG 5 mg DT. The DTG DT cannot be used to provide accurate doses smaller than 5 mg, either by splitting a tablet or by taking only a portion of the mixture of a full tablet dispersed in liquid.

Dolutegravir binds more avidly to albumin binding sites than bilirubin so that when DTG plasma concentrations are extremely high, DTG will displace unconjugated bilirubin from albumin. Plasma unconjugated bilirubin not bound to albumin can cross the blood-brain barrier, leading to bilirubin-induced neurologic dysfunction. The effect of DTG on neonatal bilirubin binding is unlikely to be clinically significant unless concentrations many times higher than typical peak

concentrations are reached, but it is critical that a neonatal DTG dosing regimen is devised to avoid accumulation of such elevated plasma DTG concentrations (16). For this reason, a conservative approach will be taken in this study, specifically to initially study the DTG PK and safety of two single doses of a DTG liquid suspension in the first 4-6 weeks of life. The PK data from these infants will be used in PK modeling and simulations to evaluate likely plasma exposures after administration of the DTG 5 mg DT to neonates. If the simulations suggest that the DTG 5 mg DT can be safely used in neonates, then subsequent infants will be enrolled who will receive the DTG 5 mg DT. If the simulations suggest that use of the DTG 5 mg DT in neonates results in accumulation of elevated plasma DTG concentrations, then subsequent infants will be enrolled receiving the DTG liquid suspension that can accurately provide doses smaller than 5 mg.

1.3 Dolutegravir Use in Pregnancy

Dolutegravir is widely used as part of ARV regimens in pregnant women living with HIV. In the DHHS *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV-1 Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*, DTG is now a preferred ARV drug throughout pregnancy and an alternative ARV drug for women who are trying to conceive (11). Therefore, it is anticipated that a significant number of infants will have *in utero* exposure to maternal DTG, and it is important to stratify according to DTG-exposure in this study. The DHHS guidelines are available at: https://aidsinfo.nih.gov/guidelines.

1.4 Rationale

New ARVs are needed for use in neonates for both prophylaxis against transmission of HIV and treatment of newborns living with HIV. Dolutegravir is a more potent ARV with a high barrier to resistance that is widely used across the age spectrum outside of newborns. The DTG DT formulation is simpler to prepare and administer than RAL oral granules, but the DTG DT cannot be used to accurately deliver less than a 5 mg dose. A DTG liquid suspension has been developed to facilitate the PK study for IMPAACT 2023 as it provides maximum dosing flexibility. Before DTG can be used in neonates, its safety and PK in this vulnerable population must be delineated so a safe and effective dose can be proposed.

The goal of this study is to provide the PK and initial safety data necessary to establish a proposed neonatal DTG dose with either the DTG DT formulation or the DTG liquid suspension. PK and safety data from Cohort 1 will inform the dose, dosing regimen, and also the formulation suitable for chronic dosing in Cohort 2. It is also possible that the DTG DT may only be suitable down to a certain weight. Commercialization of either study product will depend on the data from the study. The liquid formulation has been designed in such a way that it could be commercialized if deemed necessary and available for use in neonates if the DT cannot be used in this population. Depending on the results of the study, either the DT or the liquid formulation, or possibly both, would have an indication for the treatment of HIV-1 in neonates in combination with other ARV agents.

Dolutegravir will be added to the standard of care regimen that newborns receive for prevention or treatment of HIV. While HIV-1-exposed infants at low risk for transmission often receive only four weeks of prophylaxis, those at higher risk may receive combination ARV treatment as empiric treatment for up to six weeks (17). The provision of an additional ARV agent to standard of care newborn prophylaxis and treatment regimens has been accepted as an appropriate way to study ARV PK and safety in neonates by institutional review boards (IRBs), ethics committees (ECs) and regulatory agencies who reviewed P1110 (RAL in neonates) and IMPAACT 2007

(maraviroc in neonates), the most recently completed IMPAACT studies examining neonatal ARV PK and safety. The design for this study is modeled from IMPAACT 2007 and P1110. Raltegravir, maraviroc, and DTG bind more avidly to albumin than bilirubin, posing the risk of bilirubin-induced neurologic dysfunction at elevated plasma concentrations. The P1110 and IMPAACT 2007 studies enrolled small initial cohorts receiving two separate single doses followed by PK sampling to safely provide the neonatal PK data needed for PK modeling and simulations to determine chronic dosing regimens likely to achieve adequate plasma drug concentrations while avoiding elevated concentrations that could result in clinically significant amounts of bilirubin displacement from albumin. The PK sampling schedules in this study were devised based on the experience with neonatal PK sampling in P1110 and IMPAACT 2007, as well as anticipated pharmacology of DTG after birth. The 16-week duration of follow up was selected based on experience with these studies and represents 10 to 12 weeks of follow-up post-completion of DTG dosing, consistent with standard of care ARV prophylaxis. Based on recommendations in the US Pediatric HIV treatment guidelines, the definitive exclusion of HIV diagnosis in non-breastfed infants is based on two or more negative virologic tests, with one obtained at age ≥ one month and one at age ≥ 16 weeks (2). A follow-up period to confirm HIV status through approximately four months of age will ensure appropriate safety monitoring of study participants consistent with current US HIV treatment guidelines.

Cohort 1 infants in this study will receive a single DTG dose at Entry and a second single DTG dose at the 7 Days Post Initial Dose visit. Infants in Cohort 1 will be enrolled in up to three strata. Infants in the first two strata (Strata 1A and 1B) will receive two single doses of 0.5 mg/kg of the DTG liquid formulation. The approved dose of DTG at four weeks of age is 5 mg, and the 0.5 mg/kg dose for Strata 1A and 1B was chosen based on extrapolation from neonatal PK data for ZDV and RAL, two other ARVs eliminated primarily by glucuronidation via UGT. Stratum 1A infants will be DTG-naïve (no maternal DTG use within two weeks prior to delivery) and will receive DTG starting within 0-5 days of life. Stratum 1B infants will be DTG-exposed (maternal DTG use within 72 hours prior to delivery) and will receive DTG starting within 2-5 days of life, to allow washout elimination after birth to reduce the infant plasma concentration of DTG acquired across the placenta to a level with no risk of accumulation to potentially harmful plasma concentrations after administration of an infant dose. The smallest dose that can be administered with the DTG DT formulation is 5 mg. If the PK data from Strata 1A and 1B suggest that a 5 mg DT dose can be safely administered to neonates, then a third group of infants who are DTG-naïve receiving two single DTG 5 mg DT doses will be enrolled in Stratum 1C.

Infants and their mothers will be enrolled in this study as a pair. Following completion of the Entry visit, mothers will exit the study. Maternal HIV viral load will be evaluated at study entry to assess risk of perinatal transmission of HIV to infants. This information may also be used by site clinicians to determine the appropriate ARV regimen and duration (four vs. six weeks) for infants. A complete medical and medication history for mothers will also be collected to assess study eligibility of infants.

The PK data from Cohort 1 infants will then be used to select the DTG formulation, dose size, and dose frequency for chronic dosing to be evaluated in Cohort 2 infants. Cohort 2 infants will receive 5 mg doses with the DTG DT formulation if the PK modeling and simulations from Cohort 1 data suggest that this formulation can be safely used as chronic doses without risk of accumulation of DTG plasma concentrations to potentially harmful concentrations. If the Cohort 1 PK analyses suggest that a smaller dose size is needed, then Cohort 2 infants will receive the DTG liquid formulation, which can be used to deliver accurately measured doses below 5 mg. Cohort 2 infants will be enrolled into two strata, DTG-naïve and DTG-exposed, based on maternal DTG use prior to delivery. The data from the two Cohort 2 strata will provide the PK

data needed to make a dosing recommendation for when after birth chronic DTG dosing can safely be initiated in DTG-exposed newborns. A description of the planned PK analyses for both cohorts is provided in Section 10. All Cohort 2 infants enrolled in this study will receive DTG from Entry through at least the Week 4 visit and up to the Week 6 visit in addition to their standard of care ARV prophylaxis.

1.5 Hypothesis

DTG is well tolerated in neonates and young infants and can be safely administered to achieve adequate drug exposure for prevention or treatment of HIV-1.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

2.1.1 To evaluate the safety and tolerability of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.

2.1.2 To evaluate the pharmacokinetics of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first four to six weeks of life.

2.1.3 To propose an appropriate DTG dose regimen during the first four weeks of life for HIV-1-exposed infants.

2.2 Secondary Objective

The secondary objective of this study is:

2.2.1 To evaluate the safety of DTG administered to HIV-1-exposed infants with standard ARV prophylaxis in the first 16 weeks of life.

2.3 Other Objective

The other objective of this study is:

2.3.1 To investigate the relationship between infant DTG elimination and UGT1A1 genotypes.

3 STUDY DESIGN

This is a Phase I, multi-centered, open-label, non-comparative dose-finding study to evaluate the safety, tolerability, and PK of DTG when added to standard ARV prophylaxis in infants born to mothers living with HIV-1. Refer to Figure 1 for an overview of the study design; Sections 4.1 and 4.2 for the study eligibility criteria; and Section 4.4 for a description of the study recruitment, screening, and enrollment process. Mother-infant pairs are expected to be enrolled at study sites in Brazil, South Africa, Thailand, and the United States.

A minimum of 36 mother-infant pairs will be enrolled in the study to achieve a target of 36 evaluable infants receiving the proposed dose of DTG for the relevant stratum. As dose adjustments for a stratum may be warranted or infants may need to be replaced due to evaluability concerns, a total of up to 108 mother-infant pairs may be enrolled in the study to ensure the target of 36 evaluable infants receiving the proposed dose of DTG is met. Infants who meet the maternal DTG exposure requirements for the relevant stratum indicated in inclusion criterion 4.1.3 will be enrolled. Infants with maternal DTG exposure more than 72 hours and less than or equal to two weeks prior to delivery will not be enrolled in the study.

A minimum of 12 and up to 36 mother-infant pairs (across strata) will be enrolled in Cohort 1 to achieve a target of six evaluable infants in each stratum receiving the DTG dose that provides PK and safety data to determine the starting DTG dose for each stratum in Cohort 2. A minimum of 24 (12 in each stratum) and up to 72 mother-infant pairs (across both strata) will be enrolled in Cohort 2 to achieve a target of 12 evaluable infants in both Strata 2A and 2B receiving the final proposed chronic dose of DTG. Breastfeeding and formula-feeding infants are eligible for both Cohorts 1 and 2. At least eight breastfeeding and eight formula-feeding infants will be enrolled in Cohort 2 across both strata.

The term evaluable in this study refers to infants who will be included in the dose-finding evaluation described in Section 9.5.1. To be considered **evaluable**, an infant must be both safety-evaluable and PK-evaluable for the DTG dose (i.e., drug formulation, strength, and frequency of administration) being evaluated. Safety-evaluable and PK-evaluable for the dose-finding evaluation are defined as follows:

- **Safety-evaluable for the dose-finding evaluation**: An infant must have received the DTG dose being evaluated for the relevant stratum from Entry through the Week 4 visit or prior to the Week 4 visit experienced an adverse event (AE) assessed as related to study drug or AE that results in permanent discontinuation of study drug. Safety-unevaluable infants will be replaced per Section 9.4.

- **PK-evaluable for the dose-finding evaluation**: An infant must have received the DTG dose being evaluated for the relevant stratum and have PK data available from applicable intensive PK sampling specified in Section 6. Infants with missing intensive PK samples or PK samples below the limit of assay quantitation will be assessed for evaluability by the IMPAACT 2023 Clinical Management Committee (CMC) on a case-by-case basis. Every effort should be made to collect all scheduled PK sampling time points. PK-unevaluable infants will be replaced per Section 9.4.

Infants will be enrolled in two sequential dosing cohorts: Cohort 1 and Cohort 2, as described in Sections 3.1 and 3.2, respectively. Cohort 1 will be enrolled first, with Strata 1A and 1B being opened concurrently, to evaluate the PK and safety of two single DTG liquid suspension doses for the relevant stratum. If the PK and safety data from Strata 1A and 1B support administration of a DTG 5 mg dose, then a third stratum in Cohort 1, Stratum 1C, will be enrolled, to evaluate the DTG 5 mg DT (refer to Section 10). Intensive PK sampling will be performed following administration of DTG at the Entry visit (Strata 1A and 1C: within 0–5 days of life; Stratum 1B: within 2–5 days of life) and at the 7 Days Post Initial Dose visit (Strata 1A, 1B, and 1C). PK samples will be shipped for testing after the 7 Days Post Initial Dose visit, with CMC review of the PK and safety data as available.

Following enrollment of six infants receiving the DTG liquid suspension in both Stratum 1A and Stratum 1B, accrual will be paused as the CMC reviews the PK and safety data to assess the DTG

dose for the relevant stratum. The CMC may subsequently resume accrual in a stratum as needed to obtain the minimum evaluable infants (i.e., six infants in each stratum) required for the dose evaluation. As indicated above, Stratum 1C will be opened if Strata 1A and 1B PK and safety data support administration of a DTG 5 mg dose (as DT) across all eligible neonates (i.e., ≥ 2 kg) or in neonates with a minimum weight based on PK modeling and simulations of Strata 1A and 1B. If Stratum 1C is opened to accrual, the team will assess the DTG dose and DT in this stratum based on review of PK and safety data for the first six evaluable infants enrolled. Cohort 1 PK and safety data will be evaluated following PK and Safety Guidelines in Section 10.4 and Section 9.5.2, respectively, for determining the appropriate DTG dose, with options of adjusting the current dose, proceeding with enrollment in the appropriate Cohort 2 stratum, or assessing next steps for the study, including study discontinuation.

Accrual into Cohort 2, Strata 2A and 2B, will be initiated when the DTG dose and formulation to be administered for each stratum are established based on the PK and safety data from all Cohort 1 strata (Strata 1A and 1B, and 1C if applicable) and available data from other studies. If Stratum 1C is not opened to enrollment, Strata 2A and 2B may be opened independently (i.e., at different time points) based on PK and safety data from the corresponding stratum in Cohort 1. The IMPAACT Study Monitoring Committee (SMC) will review the applicable Cohort 1 PK and safety data prior to each Cohort 2 stratum being opened to enrollment. Infants in Cohort 2 will have intensive PK sampling at the 7 Days Post Initial Dose (+ 3 days) and Week 4 (23–33 days of life) visits. PK samples will be shipped in real-time, with CMC review of PK and safety data as available.

Following enrollment of at least six evaluable infants in Cohort 2 across both strata, the CMC will review the PK and safety data to assess the DTG dose. Up to two additional evaluable infants may be enrolled while the CMC evaluates the interim PK and safety data (i.e., up to eight evaluable infants).

Following accrual of 12 infants in a Cohort 2 stratum receiving the DTG dose under evaluation, accrual in the stratum will be paused as the CMC assesses the dosing regimen for the relevant stratum based on the PK and Safety Guidelines in Section 10.4 and Section 9.5.2, respectively. The CMC may subsequently resume accrual in a stratum as needed to obtain the minimum evaluable infants (i.e., 12 infants in each stratum) required for the dose evaluation. If PK targets are met and Safety Guidelines (Section 9.5.2) are passed, then the appropriate dosing of DTG has been established; otherwise, the CMC will adjust the DTG dose and repeat the process above or assess next steps for the study, including study discontinuation. Available PK targets established for infants, children, and adults will be used to assess PK results.

All infants will be followed through the Week 16 visit (112–140 days of life) to assess long-term safety, among other objectives in Section 2.

3.1 Cohort 1

Infants exposed to HIV-1 will be stratified by *in utero* exposure to maternal DTG, as indicated below, with concurrent enrollment of Strata 1A and 1B and subsequent enrollment of Stratum 1C if allowable as described above.

Strata 1A and 1C* (DTG-naïve):	Infants with no *in utero* exposure to maternal DTG (no exposure to DTG during the two weeks prior to delivery)

Stratum 1B (DTG-exposed):	Infants with *in utero* exposure to maternal DTG (mothers who receive at least one dose of DTG within 72 hours prior to delivery)

*If PK and safety data from Strata 1A and 1B do not support the use of a DTG 5 mg dose then Stratum 1C will not be enrolled (refer to Section 10).

Mother-infant pairs will be enrolled within five days of the infant's birth. Infants will receive two single doses of DTG within the first weeks of life. At Entry, infants in Strata 1A and 1C will receive the first single DTG dose within 0–5 days of life, and infants in Stratum 1B will receive the first single DTG dose within 2–5 days of life. Infants in Strata 1A, 1B, and 1C will receive the second single DTG dose at the 7 Days Post Initial Dose visit (+ 3 days). Intensive PK sampling will be performed at each of these visits.

Infants will be followed through the Week 16 visit (112–140 days of life), with clinical and laboratory evaluations performed as shown in the Schedule of Evaluations (SoE) in Appendix IB. Mothers will have evaluations performed at Screening and Entry visits only as shown in Appendix IA.

3.2 Cohort 2

Accrual into each stratum will be opened following the Cohort 1 dose evaluation and once the chronic dosing regimen for a Cohort 2 stratum is determined, as described in Section 9.5.1. Infants exposed to HIV-1 will be stratified by *in utero* exposure to maternal DTG, as indicated below.

Stratum 2A (DTG-naïve):	Infants with no *in utero* exposure to maternal DTG (no exposure to DTG during the two weeks prior to delivery)
Stratum 2B (DTG-exposed):	Infants with *in utero* exposure to maternal DTG (mothers who receive at least one dose of DTG within 72 hours prior to delivery)

Mother-infant pairs will be enrolled within five days of the infant's birth. Infants will receive chronic DTG dosing based on PK modeling and simulations of PK data and assessment of safety data from Cohort 1. Infants will receive their first dose of DTG at Entry (0–5 days of life), with the time of the initial DTG dose for Stratum 2B infants based on experience in Stratum 1B. All infants in Strata 2A and 2B will continue chronic DTG dosing through the Week 4 visit (23–33 days of life) and up to the Week 6 visit (37–47 days of life) depending on local standard duration of ARV prophylaxis. Intensive PK sampling will be performed at the 7 Days Post Initial Dose and Week 4 visits. Population PK sampling will be performed at the 2 Days Post Initial Dose visit for all Cohort 2 infants, and at the Week 6 visit only for infants who are taking DTG through the Week 6 visit per local standard of care for ARV prophylaxis.

Infants will be followed through the Week 16 visit (112–140 days of life), with clinical and laboratory evaluations performed as shown in the SoE in Appendix IC. Mothers will have evaluations performed at Screening and Entry visits only as shown in Appendix IA.

4 STUDY POPULATION

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

Note: Some of the eligibility criteria specified in Sections 4.1 and 4.2 refer to eligibility determination based on the mother's report and available medical records. For these criteria, it is expected that relevant information will be requested from the mother and that available medical records will be reviewed for information relevant to these criteria. Unless otherwise specified, both maternal report and medical records are not required. For example, it is not expected that a mother will be able to recall all information recorded in medical records, and medical records are not required to substantiate maternal report. However, all available medical records must be reviewed and the totality of information from both sources must be considered when making eligibility determinations.

4.1 Inclusion Criteria

Potential participants must meet all criteria specified below to be included in this study. In these criteria, "at entry" is used to refer to the day of enrollment in the study.

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

Note: All sites must follow all applicable IRB/EC policies and procedures; for US sites, this includes single IRB (sIRB) policies and procedures.

4.1.2 Mother has confirmed HIV-1 infection based on positive test results from two samples collected from two separate blood collection tubes per Sample #1 and Sample #2 requirements. Test results may be obtained from medical records or from testing performed during the study screening period:

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., CLIA, GCLP, or VQA) and related to regulatory authority (e.g., FDA) approvals do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must be tested in a laboratory that operates according to CLIA or equivalent (for US sites) or GCLP (for non-US sites) guidelines and participates in an appropriate external quality assurance program. If nucleic acid testing is used, at least one test must be performed in the site's CLIA-certified or equivalent (for US sites) or VQA-certified (for non-US sites) laboratory.
- All study-specific samples tested to determine HIV-1 status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site

by the IMPAACT Laboratory Center (for NIAID-funded sites) or Westat (for NICHD-funded sites). All test methods should be FDA-approved, if available.

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

- Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes, which may include use of a combination antigen-antibody based rapid test.
- One enzyme immunoassay (EIA) or Western blot (WB) or immunofluorescence assay or chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV ribonucleic acid (RNA) PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

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

- Rapid antibody-based 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. Combination antigen-antibody based rapid tests may be used.
- One EIA or WB 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 HIV total nucleic acid test

If the second test does not confirm an initial positive result, the CMC should be consulted for guidance on next steps to confirm the potential participant's HIV-1 status. Pending confirmatory testing, prophylaxis and treatment should be managed consistent with local standards of care.

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

For Cohort 1, Strata 1A and 1C, and Cohort 2, Stratum 2A

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

For Cohort 1, Stratum 1B, and Cohort 2, Stratum 2B

4.1.3.2 Infant born to a mother who received at least one dose of DTG less than or equal to 72 hours prior to delivery.

Note: Formula-feeding and breastfeeding infants are eligible for each stratum.

4.1.4 Infant was singleton with a gestational age at birth of at least 37 weeks.

Note: Singleton versus multiple birth may be determined based on maternal report if medical records documentation is not available. If gestational age at birth is not documented in available medical records, site investigators may assess gestational age at the earliest possible opportunity during the screening period and use this assessment for purposes of eligibility determination.

4.1.5 At birth, infant's weight was as follows:

For Cohort 1, Strata 1A and 1B, and Cohort 2, Strata 2A and 2B
4.1.5.1 At least 2 kg

For Cohort 1, Stratum 1C
4.1.5.2 **a)** At least 2 kg
b) At least 3 kg

Note: Stratum 1C will only be enrolled if PK and safety data from Strata 1A and 1B support administration of a DTG 5 mg DT dose in neonates. Sites will be notified if Stratum 1C opens to enrollment and of the minimum infant's weight above (i.e., 4.1.5.2a or 4.1.5.2b) to be used for study eligibility per the dose regimen communication process in Section 5.9.

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

4.1.6 At screening, infant has the following laboratory test results, based on severity grading specified in Section 7.3.3:

4.1.6.1 ALT (normal)
4.1.6.2 AST (normal or Grade 1)
4.1.6.3 Total bilirubin (normal or Grade 1)
4.1.6.4 Hemoglobin (normal, Grade 1, or Grade 2)
4.1.6.5 White blood cells (normal, Grade 1, or Grade 2)
4.1.6.6 Platelets (normal, Grade 1, or Grade 2)
4.1.6.7 Creatinine (normal, Grade 1, or Grade 2)

Note: Laboratory tests may be repeated during the screening period, with the latest results used for eligibility determination.

4.1.7 At entry, infant is less than or equal to five days of life.

4.1.8 At entry, infant has initiated standard of care ARV prophylaxis (i.e., received at least one dose of ARV regimen prior to entry).

4.1.9 At entry, infant is generally healthy as determined by the site investigator based on review of all available medical history information and physical examination findings.

4.2 Exclusion Criteria

Mother-infant pairs must be excluded from the study if any of the conditions specified below are identified during the screening period. The screening period begins when informed consent is obtained and ends immediately prior to enrollment. For criteria involving a potential participant's medical history, it is expected that each exclusionary condition will be assessed at screening and subsequently reviewed and confirmed on the day of study entry, prior to enrollment.

4.2.1 Known maternal-fetal blood group incompatibility as evidenced by the presence of an unexpected clinically significant maternal red blood cell antibody that is known to cause hemolytic disease of the fetus and newborn.

4.2.2 Infant or breastfeeding mother is receiving any disallowed medication listed in Section 5.8.1.

4.2.3 At entry, infant with a documented positive HIV nucleic acid test result (NAT).

Note: HIV NAT results are not required prior to entry, but any positive results obtained prior to entry are exclusionary.

4.2.4 Infants with prior exchange transfusion or with elevated bilirubin that would require exchange transfusion.

Note: Any indication in the infant's medical records that a transfusion has occurred or is required should be considered exclusionary. In the absence of such medical records documentation, the site investigator should assess this criterion based on their clinical judgement and all information available during the study screening period.

4.2.5 Mother or infant has any 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 study visit burden, blood draw volumes, and interpretation of outcome data across studies. Co-enrollment in observational studies does not require protocol team approval. Co-enrollment in interventional studies must be approved in advance by the protocol teams of both studies. Requests for such approval should be emailed to the IMPAACT 2023 CMC.

4.4 Recruitment, Screening, and Enrollment Process

Although mother-infant pairs will not be enrolled in this study until after delivery, recruitment will typically begin with provision of information about the study to pregnant women living with HIV-1 attending antenatal care clinics. The study-specific informed consent process will typically be conducted during the second or third trimester of pregnancy; however, the process may be conducted, in whole or in part, after delivery.

It is generally expected that the informed consent process will take place over the course of more than one session, and women will be invited to bring their partners or other persons of their choosing to these sessions, if they wish. The informed consent process will include detailed review of the study informed consent form (ICF), time to address any questions or concerns, and an assessment of understanding before proceeding to the informed consent decision. The informed consent process will be fully documented, consistent with the Division of AIDS (DAIDS) requirements referenced in Section 11.2. Refer to Section 13.3 for further information on informed consent procedures for this study.

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

Study staff will remain in contact with potentially eligible women as they approach their expected dates of delivery, with instructions provided to inform study staff upon onset of labor. Study staff will arrange to see each woman as soon as possible after delivery to discuss the study again and confirm continued consent for study participation. For infants born to mothers who provided informed consent prior to delivery, screening—including review of medical records and other available medical history information, physical examination, and specimen collection for laboratory testing—may be performed prior to confirmation of continued consent. Final eligibility determination at the Entry visit and next steps toward enrollment will only proceed after confirmation of continued consent. Screening procedures may be performed on the day of enrollment; however, the mother's HIV test results and the infant's laboratory results, as specified in Section 4.1.6, must be available for final eligibility determination prior to study enrollment.

Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment and the cohorts open for enrollment. Mother-infant pairs who are found to meet the study eligibility criteria will be enrolled, and infants will receive their first dose of DTG within five days of life at the Entry visit.

The IMPAACT Data Management Center (DMC) Study Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, participant identification numbers (PIDs) will be assigned to the mother and infant. For pairs found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number (SID) and prescribing information for the cohort in which the infant has been enrolled. For pairs who are found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs). Refer to Section 9.5 for more information on monitoring participant accrual in this study.

4.5 Participant Retention

Once a mother-infant pair is enrolled in this study, study staff will make every effort to retain them for the protocol-specified duration of follow-up, thereby minimizing potential biases and loss of statistical power 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 or Termination from the Study

Regardless of the participant retention procedures referenced above, mothers may voluntarily withdraw themselves and/or their infants from the study prior to scheduled completion of study follow-up. Participants may also be terminated from the study early by the site investigator under the following circumstances:

- Infant is not administered an initial dose of DTG within the timeframe specified for their assigned dose regimen
- Participant relocates away from the study site (with no options for transfer to another site) or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled by the sponsors or government or regulatory authorities
- Site participation in the study is canceled by the sponsors, government, or regulatory authorities, the sIRB (for US sites), or site IRBs/ECs (for non-US sites)

For any infant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort to complete final evaluations as described in Section 6.10. If the circumstances that led to an infant's withdrawal or termination change (e.g., the family returns to the study site area after having relocated previously), the site investigator or designee should contact the CMC to discuss options for resuming follow-up.

5 STUDY DRUG

Site pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. For this study, the term study drug refers to DTG 5 mg/mL liquid, lipid-based suspension and DTG 5 mg DT. Appropriately-sized dosing cups and/or syringes will be supplied with each study drug. Refer to the Investigator's Brochure (IB) for further information about these study drug formulations.

5.1 Study Drug Regimen

Both mothers and infants will be enrolled in the study; however, only infants will receive the study drug. Infants will be enrolled into two cohorts and stratified by infant *in utero* exposure to maternal DTG, as described in Section 3, and will receive study drug as indicated below. Strata 1A and 1B within Cohort 1 will be enrolled concurrently. Stratum 1C will be enrolled only if the data from Strata 1A and 1B support administration of a DTG 5 mg dose (i.e., DT). Enrollment of each stratum in Cohort 2 will be opened upon dose selection based on Cohort 1 data.

5.1.1 Cohort 1 (Single Doses)

Two single doses of DTG will be administered in this cohort. The first dose will be administered at the study Entry visit. The second dose will be administered at the 7 Days Post Initial Dose visit. Starting doses are provided in Table 2.

Table 2
Cohort 1 Dosing Regimen

Cohort 1 Stratum	Cohort 1 Initial Study Drug Regimen	
Stratum 1A	First Dose	DTG 0.5 mg/kg liquid suspension administered orally at Entry visit (0-5 days of life)
	Second Dose	DTG 0.5 mg/kg liquid suspension administered orally at 7 Days Post Initial Dose visit (+ 3 days) visit
Stratum 1B	First Dose	DTG 0.5 mg/kg liquid suspension administered orally at Entry visit (2-5 days of life)
	Second Dose	DTG 0.5 mg/kg liquid suspension administered orally at 7 Days Post Initial Dose visit (+ 3 days)
Stratum 1C *To be enrolled only if data from Strata 1A and 1B support DTG 5 mg DT dosing*	First Dose	DTG 5 mg DT administered orally at Entry visit (0-5 days of life)
	Second Dose	DTG 5 mg DT administered orally at 7 Days Post Initial Dose visit (+ 3 days)

For Cohort 1, Strata 1A and 1B, the infant's birth weight should be used to determine the appropriate dose of the DTG liquid suspension administered at both the Entry visit and the 7 Days Post Initial Dose visit (i.e., same dose should be given at both visits even if the infant gains or loses weight between visits). For Cohort 1, Stratum 1C (if enrolled), a 5 mg dose of the DTG DT will be administered at both the Entry visit and the 7 Days Post Initial Dose visit.

Dose adjustments for each stratum may occur as needed based on experience within the cohort. If, after the starting dose for each stratum is evaluated, a dose adjustment is determined to be required for Cohort 1, Stratum 1A or Stratum 1B, an adjusted dose will be selected from the tables in Appendix II and will be communicated to sites per Section 5.9. Site Pharmacists must receive a new prescription from an authorized prescriber for each dose and/or frequency adjustment.

5.1.2 Cohort 2 (Chronic Dosing)

Dosing for each stratum in Cohort 2 will be chronic dosing and be initiated as shown in Table 3. The starting DTG dose, timing of first dose, formulation, and frequency for each stratum will be selected based on PK and safety data from Cohort 1 and communicated to sites per Section 5.9.

Table 3
Cohort 2 Dosing Regimen

Cohort 2 Stratum	Cohort 2 Study Drug Regimen	
Stratum 2A	Chronic Dosing	Chronic dosing of DTG administered orally, initiated at Entry visit (0-5 days of life) and continuing up to Week 4 or 6 visit*
Stratum 2B	Chronic Dosing	Chronic dosing of DTG administered orally, initiated at Entry visit (time of initial dose based on experience in Stratum 1B) and continuing up to Week 4 or 6 visit*

**The duration that infants receive study drug may vary based on local standard of care for ARV prophylaxis at each site.*

If the DTG 5 mg/mL liquid suspension is selected for chronic dosing, for the first DTG dose administered at Entry, the infant's birth weight should be used to determine the appropriate dose. For all subsequent DTG 5 mg/mL liquid suspension doses, the infant's weight measured at the most recent study visit (protocol-specified and any interim visits as needed per site investigator's discretion) should be used to determine the appropriate dose. If the DTG 5 mg DT is selected for chronic dosing, all Cohort 2 infants will receive the 5 mg dose, regardless of the infant's weight.

At visits with intensive PK sampling, if a DTG dose change is indicated based on the infant's weight measured at the visit, the dose change should be implemented after the intensive PK sampling is completed. The dose of DTG given at the visit should be the same dose the infant was receiving immediately prior to the visit. Thereafter, the next DTG dose given (i.e., after the PK sampling is completed) should be the changed dose based on the infant's current weight.

Dose adjustments for each stratum may occur as needed based on experience within the cohort. If, after the starting dose for each stratum is evaluated, a dose adjustment is determined to be required for Cohort 2, Stratum 2A or Stratum 2B, an adjusted dose will be selected from the tables in Appendices II, III, IV, or V, and will be communicated to sites per Section 5.9. Site Pharmacists must receive a new prescription from an authorized prescriber for each dose and/or frequency adjustment.

5.2 Study Drug Formulation and Storage

5.2.1 DTG Liquid Suspension

The DTG 5 mg/mL liquid suspension is provided in an amber bottle. The liquid contains some sedimentation which, when shaken, becomes a white to off-white opaque suspension. The liquid suspension is packaged in bottles filled to 50 mL with a child-resistant closure. Store and dispense from the original package, protect from moisture, and keep the bottle upright and tightly closed. In the study site pharmacy, store up to 30°C (86°F).

Once a bottle of DTG liquid suspension is opened, the shelf life is 42 days when stored upright in the original container, with the cap tightly closed, up to 30°C (86°F).

5.2.2 DTG Dispersible Tablets

The DTG 5 mg DT is white, round, biconvex, and debossed 'SV H7S' on one side and '5' on the opposite side. Store and dispense in the original package, protect from moisture,

and keep the bottle tightly closed. Do not remove desiccant. In the study site pharmacy, store up to 30°C (86°F). Once a bottle of DTG DTs is opened, the shelf life is 60 days.

5.3 Study Drug Dispensing, Preparation, and Administration

Cohort 1

The pharmacist will dispense study drug for infants to study staff for administration at the Entry visit and the 7 Days Post Initial Dose visit. Administration by study staff will occur in the context of PK sampling as described in Sections 6 and 10. If the participant vomits most or all of the dose within the first 30 minutes after administration, the dose should not be repeated, and the PK sampling should not be completed. The infant should not receive any further doses of study drug but should continue on study per Section 6.11. An additional infant should be enrolled for PK evaluation.

Cohort 2

The pharmacist will dispense study drug for infants to study staff for administration or to the infant's caregiver/guardian to be administered in the home setting. The first dose of DTG at Entry will be administered by study staff. The DTG doses at the 7 Days Post Initial Dose and Week 4 visits will be administered by study staff or the caregiver/guardian and directly observed at the site as described in Sections 6 and 10. The infant's caregiver/guardian will be instructed not to administer the DTG dose in the home on the day of intensive PK sampling visits, and to bring the study drug to the site for intensive PK sampling visits for observed administration by study staff. The caregiver/guardian will administer all other DTG doses.

The pharmacist will dispense a sufficient quantity of study drug at the Entry visit to last, at a minimum, through the infant's next scheduled visit. The first DTG dose should be administered to the participant from the dispensed study product supply. At Entry, the study staff will instruct the infant's caregiver/guardian how to properly prepare and administer doses to the infant, using study-supplied dosing cups and/or syringes. Subsequent doses after the Entry visit can be prepared and administered by caregivers/guardians as part of the teaching process. Competency of the infant's caregiver/guardian to properly prepare and administer the doses to the participant must be documented in the participant's chart by study staff prior to discharge from the hospital.

If the infant vomits most or all of the DTG dose within the first 30 minutes after administration, the dose should be repeated. If the infant vomits within 30 minutes after administration on an intensive PK sampling day, the dose should be repeated, but the PK sampling should be rescheduled within 1-2 days when the infant can receive another study drug dose.

After an infant begins the study drug regimen on DTG liquid suspension or DTG DT, the infant may not switch to the alternate DTG formulation.

5.3.1 DTG Liquid Suspension Preparation and Administration

DTG Liquid Suspension Preparation

With first use of the DTG liquid suspension bottle, the provided adaptor must be inserted firmly into the neck of the bottle. Upon insertion, the adaptor should come to a hard stop. Once the adaptor is inserted, firmly screw the cap back on.

DTG liquid suspension will be prepared as follows:

1) With cap firmly screwed on, shake the bottle until any solids have fully remixed into the liquid. This will take approximately 10 seconds. Allow air bubbles to settle out for about 30 seconds.
2) Pull back the plunger of the supplied 1 mL syringe to the required dose volume.
3) Unscrew the bottle cap and firmly push the syringe tip into the adaptor as far as it will go. Push the plunger down fully to inject air into the bottle.
4) Invert the bottle and syringe. Slowly pull the plunger back to the required volume. Return the bottle to upright and remove the syringe.
5) Wipe away any medicine from the top of the adaptor with a clean cloth. Screw the bottle cap back on firmly.

DTG Liquid Suspension Administration

To administer the dose, place the tip of the syringe against the inside of the infant's cheek. Gently push down the plunger to give the dose slowly. The syringe should be cleaned after use so that it may be re-used for subsequent doses.

5.3.2 DTG Dispersible Tablet Preparation and Administration

DTG Dispersible Tablet Preparation

DTG DTs will be prepared as follows:

1) Pour 5 mL of clean drinking water into the supplied dosing cup.
2) Add one DTG dispersible tablet to the water.
3) Swirl the cup gently for 1 to 2 minutes to disperse the tablet. The medicine will become cloudy. If there are any lumps of tablet remaining, swirl the cup until they are gone.
4) If any medicine is spilled, clean up the spill and prepare a new dose.
5) Place the tip of the supplied 10 mL syringe into the prepared medicine and draw up all of the medicine into the syringe by pulling up on the plunger.
6) The prepared medicine must be administered to the infant within 30 minutes.

DTG Dispersible Tablet Administration

To administer the dose, place the tip of the prepared syringe against the inside of the infant's cheek. Gently push down the plunger to give the dose slowly. Add another 5 mL of drinking water to the cup and swirl. Draw up the remaining medicine into the syringe and give it all to the infant. Repeat if any medicine remains to make sure the infant gets the full dose. The syringe and dosing cup should be cleaned after use so that they may be re-used for subsequent doses.

At each intensive PK visit, the DTG dose must be administered and/or observed by study staff, and the exact DTG dose time, dose amount, and draw time of each PK sample must be entered into appropriate eCRFs.

5.4 Study Drug Supply

DTG 5 mg/mL liquid suspension will be manufactured and supplied by ViiV Healthcare Ltd. Bottle adaptors and oral syringes (1 mL) will also be supplied by ViiV Healthcare Ltd.

DTG 5 mg DTs will be manufactured and supplied by ViiV Healthcare Ltd. Dosing cups (30 mL) and oral syringes (10 mL) will also be provided by ViiV Healthcare Ltd. As DTs will be supplied

together with oral syringes and dosing cups, the syringes and cups are considered medical devices, and the three components together are considered a combination product that is subject to post-marketing safety reporting requirements. See Section 7.4 for further guidance on compliance with these requirements.

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

5.5 Study Drug Accountability

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

5.6 Final Disposition of Study Drug

Any unused study drug and supplies 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 caregivers/guardians of Cohort 2 infants throughout the study as needed. Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills-building, and support needs of each infant's caregiver/guardian administering DTG to the infant. Information on correct use of study drug should be provided, particularly at the time of enrollment and in the early stages of follow-up, as well as at the time of any dose changes. Counseling should also address any identified challenges related to consistent use of study drug over time, with the aim of supporting each infant's caregiver/guardian in identifying strategies to address such challenges. Study staff will confirm adherence of the three consecutive DTG doses prior to the date of PK sampling for Cohort 2 PK visits as specified in Section 6.

5.8 Concomitant Medications

Caregivers/guardians will be asked to inform study staff of all concomitant medications received by infants. The term concomitant medication used in this study refers to medications other than study drug as defined in Section 5. This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; antacids; vitamins and other nutritional supplements; and alternative, complementary, and traditional medications and preparations. Due to the potential for drug-drug interactions between concomitant medications and DTG, site investigators should evaluate for such interactions at all study visits, particularly when new concomitant medications are reported or are being considered for a participant.

See Sections 6.14 and 6.15 for more information on source documentation and eCRF requirements for concomitant medications identified as part of the medical and medication histories obtained at study visits.

For infants taking iron supplements or multivitamins containing iron, the supplements or multivitamins should be administered at least six hours before or six hours after DTG dosing to avoid potential drug interaction.

As needed, mothers will be counseled on the importance of adherence to ARV regimens both for their own health and for prevention of HIV-1 transmission to their infants.

5.8.1 Disallowed Medications for Infants and Breastfeeding Mothers

Any infant exposed to the following disallowed medications (either directly or through breastfeeding) while taking study drug should permanently discontinue DTG and remain in follow-up for safety:

Metabolic inducers leading to decreased plasma DTG concentrations:
- Phenytoin
- Phenobarbital
- Rifampin
- Carbamazepine

Infant exclusionary ARVs:
- RAL
- INSTIs (e.g., elvitegravir, bictegravir, cabotegravir)
- Didanosine

Other infant medications/supplements:
- Calcium supplements

Contraindicated medications in breastfeeding mothers:
- Tipranavir/ritonavir
- St. John's wort
- Dofetilide
- Fampridine (not available in the USA)
- Dalfampridine

In the event that a need for one or more of the above-listed medications is identified, the site investigator or designee should notify the CMC as soon as possible and within three days of awareness. Contact the CMC for any other questions or concerns about potential drug-drug interactions that are not listed above.

5.9 Site Dose Regimen Communications

Following interim analysis of PK and safety data, if the CMC determines that sites should continue the current dosing regimen (i.e., no change is made), a Memorandum of Operational Instruction approved by the CMC will be distributed to sites to communicate this. If the CMC determines that a dose size and/or regimen adjustment is needed during the study, then the selected dosing table or regimen option in protocol Appendices II, III, IV, and/or V will also be

communicated to sites in a Memorandum of Operational Instruction approved by the CMC. Each site must confirm receipt of the memorandum distributed by the protocol team prior to implementation of the dose regimen change. The site Investigator of Record is responsible for ensuring the memorandum is distributed to relevant study staff and that the site pharmacist is aware of any dose regimen changes. If the appropriate dose and/or regimen option is not included in the protocol, then an updated dosing table or regimen option will be provided through a protocol amendment.

If the CMC determines that Stratum 1C will be opened to enrollment based on the PK and safety data from Strata 1A and 1B, the protocol team will distribute a Memorandum of Operational Instruction to sites to notify them that Stratum 1C is open to enrollment and specify the minimum infant's weight to use from inclusion criterion 4.1.5 (i.e., 4.1.5.2a or 4.1.5.2b) for eligibility determination.

6 STUDY VISITS AND PROCEDURES

Overviews of the study visit and evaluation schedules for mothers and infants are provided in Appendices IA (mothers), IB (Cohort 1 infants), and IC (Cohort 2 infants). Blood draw volumes for each visit are also detailed in these appendices. Presented in this section is additional information on visit-specific study procedures.

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

All visits should be conducted as close as possible to specified target visit dates and within the specified visit windows. Procedures specified to be performed at a given study visit should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed), visits may be split, with procedures performed on more than one day within the visit window.

All visits and procedures must be documented in accordance with DAIDS requirements for source documentation; refer to Section 11 for more information on documentation requirements and completion of eCRFs. Refer to Section 7.3 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

Note: For sites that may experience operational disruptions due to COVID-19, guidance for study implementation during periods of disruption is provided in Appendix VI.

6.1 Maternal Screening Visit

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

Maternal Screening Visit Procedures *(during pregnancy or within 0 – 5 days after delivery)*	
Administrative and Regulatory	• Obtain written informed consent • Assign PIDs to mother and infant • Obtain screening number from SES
Clinical	• Obtain available medical records and medical and medication history
Laboratory	*Only if needed per inclusion criterion 4.1.2*: • Collect blood for confirmatory HIV-1 testing

6.2 Infant Screening Visit (Cohorts 1 and 2)

Infant screening procedures must be completed within five days of the infant's date of birth. Written informed consent must be obtained before any study-specific screening procedures are performed. For infants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

The results of laboratory tests performed as part of clinical care may be abstracted from infant medical records and used for purposes of eligibility determination if the tests meet the requirements specified in Section 6.18 and were conducted within the visit window (i.e., within 0-5 days of birth). Operationally, specimen collection for required evaluations should be managed by the site investigator to minimize needle sticks, when possible.

The result of the HIV NAT performed at this visit is not required prior to study entry; however, infants with any positive HIV NAT result available prior to study entry are not eligible for this study and should not be enrolled. If the result of the HIV NAT performed at the Screening visit is positive and is obtained after study enrollment, the infant should return to the clinic as soon as possible for confirmatory testing per Section 6.13.

Infant Screening Visit Procedures *(within 0 – 5 days of birth)*	
Administrative and Regulatory	• Assess eligibility based on currently available information
Clinical	• Obtain available medical records and medical and medication history information • Perform physical exam
Laboratory	Collect blood for: • HIV NAT • Complete blood count (CBC) including white blood cells (WBC) and differential • AST, ALT, total bilirubin, creatinine

6.3 Maternal and Infant Entry Visit (Cohorts 1 and 2)

The mother and her infant are enrolled as a pair, and therefore final eligibility determination for both the mother and infant must be completed prior to enrollment. Procedures that may provide information to confirm eligibility for the study (e.g., medical and medication history, physical examination), should be performed first, prior to final eligibility determination. If a mother-infant pair is found to be ineligible on the day of enrollment, then enrollment should not occur.

All infant screening and entry visit procedures should be performed within five days of birth. For infants who are screened and enrolled on the same day, the results of all required screening evaluations must be available for eligibility determination prior to enrollment. PK sampling and specimen collection for dried blood spot (DBS) storage should be performed after enrollment.

For Cohort 1, the Entry visit may be conducted over multiple days as a split visit. The administrative and regulatory procedures should be conducted on the first day of the split visit; procedures that may provide information relevant to eligibility for the study should be performed first, prior to final eligibility determination. For infants who remain hospitalized since birth, Entry visit procedures may be performed in-hospital. Otherwise, procedures are expected to be performed at the clinical research site or associated facility.

Entry visits should ideally be scheduled on a day when the first dose of study drug (DTG) can be administered to the infant, such that eligible infants are enrolled and administered their first DTG dose on the day of the Entry visit. For infants for whom the first dose of study drug must be administered on day 2, 3, 4, or 5 of life (e.g., Cohort 1, Stratum 1B), the Entry visit should be scheduled on one of these days in which the first DTG dose will be administered. If this is not possible (expected to be rare), the Entry visit may be conducted as a split visit starting on the day of birth (i.e., Day 0) or on day 1 of life. In this case, enrollment may occur prior to day 2 of life with the expectation that the mother-infant pair will return on day 2, 3, 4, or 5 of infant life for administration of the first DTG dose. Additional considerations for this scenario are as follows:

- The first dose of study drug must be administered by day 5 of life.
- Prior to administration of the first dose of study drug, the infant's medical and medication history should be reviewed and updated since the prior visit, and the site investigator should confirm that the infant continues to meet all study eligibility criteria. This assessment should be source documented in the infant's study chart. If the infant does not meet all eligibility criteria, or if other concerns are identified, the first dose of study drug should not be administered, and the CMC should be consulted as soon as possible.

For Cohort 1 infants, the intensive PK sampling must be initiated on the same day as administration of the first dose of DTG. Cohort 1 infants undergoing intensive PK sampling at Entry are generally expected to remain at the visit, with their mothers, at least through the 4-8 hours intensive PK sampling timepoint. Depending on site capacity and participant preferences, infants and their mothers may stay at the clinical research site or associated facility overnight. Alternatively, they may leave the site or associated facility after the 4-8 hours intensive PK sampling and return for the 11-13 hours, 22-26 hours, and/or 48-72 hours intensive PK sampling timepoints. For infants enrolled on day 2, 3, 4, or 5 of life, it is acknowledged that the later intensive PK sampling timepoints may occur after the fifth day of life.

Additional requirements for sequencing of procedures at the Entry visit are as follows:

- Final eligibility determination and confirmation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing of study drug must precede dispensing of study drug
- Ingestion of study drug must precede tolerability assessment

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

For Cohort 1 infants undergoing intensive PK sampling:

- Intensive PK sampling for DTG must be initiated on the same day as the first dose of DTG and conducted per the time points below. The DTG dose must be administered by study staff.
- If there is any clinical indication or concern that the infant has an intercurrent illness or infection, contact the CMC prior to administering the DTG dose.
- The exact DTG dose time, dose amount, and draw time of each PK sample must be entered into eCRFs.
- If the infant vomits most or all of the dose within 30 minutes after administration, the dose should not be repeated. The PK sampling should not be completed, and no further DTG doses should be administered. The infant should continue on study per Section 6.11.

At Entry and follow-up visits through study drug discontinuation, study staff should assess for potential medical device deficiencies and report any detected device deficiencies as outlined in Section 7.4.

For Cohort 1 infants, applicable reminders should be provided for the scheduled 7 Days Post Initial Dose visit date, including expectations for the intensive PK sampling.

For Cohort 2 infants, applicable reminders should be provided for the scheduled 2 Days Post Initial Dose visit, including expectations for the population PK sampling. Administration of study drug for the doses taken after the Entry visit and preceding the 2 Days Post Initial Dose visit should be confirmed prior to the visit; however, the 2 Days Post Initial Dose visit does not need to be rescheduled if adherence is not confirmed. Adherence support should be provided to help ensure appropriate dose administration on days preceding the visit date.

Maternal Entry Visit Procedures *(within 0 – 5 days of delivery)*	
Administrative and Regulatory	• Review elements of informed consent and confirm mother's continued consent for study participation* • 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 medication history since screening*
Laboratory	Collect blood for*:* • HIV-1 RNA

**Perform prior to enrollment*

Infant Entry Visit Procedures *(within 0 – 5 days of birth)*	
Administrative and Regulatory	• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the mother-infant pair, print and file a copy of the confirmation file
Clinical	• *If Entry visit is conducted on a different day than the Screening visit,* update infant medical and medication history since last visit and perform physical exam*

Study Drug	*Cohort 1*:
	• Prescribe and dispense study drug for in-clinic administration
	• Administer initial DTG dose within 1 hour after collection of pre-dose intensive PK sample:
	  ○ Strata 1A and 1C: within five days of life
	  ○ Stratum 1B: within 2–5 days of life
	• Provide information on potential study drug side effects
	• Complete tolerability assessment after administration of study drug
	
	Cohort 2:
	• Prescribe and dispense study drug for administration at the visit and in-home administration
	• Administer the first dose of study drug:
	  ○ Stratum 2A: within five days of life
	  ○ Stratum 2B: time of administration of DTG will be based on experience in Cohort 1 (*see Section 5*)
	• Provide instructions and adherence counseling for in-home administration
	• Provide information on potential study drug side effects
	• Complete tolerability assessment after administration of first dose of study drug
	• Provide instructions for documenting tolerability assessment during in-home administration of study drug

Laboratory	*Cohort 1*: collect blood for:
	• Intensive PK sampling (0.25 mL at each of the following time points):
	  ○ Prior to observed dose of study drug
	  ○ 1-2 hours (±15 minutes) after observed dose of study drug
	  ○ 4-8 hours (±15 minutes) after observed dose of study drug
	  ○ 11-13 hours (±15 minutes) after observed dose of study drug
	  ○ 22-26 hours (±15 minutes) after observed dose of study drug
	  ○ 48-72 hours (±15 minutes) after observed dose of study drug
	• Total bilirubin at 48-72 hours after observed dose of study drug
	
	For all infants, if informed consent for genetic testing is obtained, collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

**Perform prior to enrollment*

6.4 2 Days Post Initial Dose Visit (Cohort 2 only)

This visit is targeted to take place two days after an infant's initial DTG dose, with an allowable window of up to two days after the target visit date (i.e., 2 to 4 days after initial DTG dose).

Applicable reminders should be provided for the scheduled 7 Days Post Initial Dose visit date, including expectations for the intensive PK sampling. Administration of study drug for the three doses preceding the 7 Days Post Initial Dose visit should be confirmed prior to the visit. If adherence is not confirmed, the visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date. The caregiver/guardian should be instructed not to administer the DTG dose in the home on the day of the PK sampling at the 7 Days Post Initial Dose visit.

2 Days Post Initial Dose Visit Procedures *(2 days after administration of initial DTG dose + 2 days)*	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug	• Confirm adherence for the DTG doses preceding the visit • Complete tolerability assessment • Prescribe and dispense study drug for in-home administration as needed • Provide instructions for documenting tolerability assessment during in-home administration of study drug
Laboratory	Collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine • Population PK sampling (0.25 mL) *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.5 7 Days Post Initial Dose Visit (Cohorts 1 and 2)

This visit is targeted to take place seven days after an infant's initial DTG dose, with an allowable window of up to three days after the target visit date (i.e., 7 to 10 days after initial DTG dose).

For Cohort 1 and Cohort 2 infants undergoing intensive PK sampling:

- The DTG dose must be administered and/or observed by study staff per Section 5.3.
- If there is any clinical indication or concern that the infant has an intercurrent illness or infection, contact the CMC prior to administering the DTG dose.
- The exact DTG dose time, dose amount, and draw time of each PK sample must be entered into appropriate eCRFs.
- For Cohort 1, if the infant vomits most or all of the dose within 30 minutes after administration, the dose should not be repeated, and the PK sampling should not be completed. The infant should continue on study per Section 6.11.
- For Cohort 2, if the infant vomits most or all of the DTG dose within the first 30 minutes after administration, the dose should be repeated. The PK sampling should be rescheduled within 1-2 days when the infant can receive another study drug dose.
- For Cohort 1, the second dose of DTG should not be administered until the ALT and AST results for this visit have been reviewed; see Section 8.2.1 for toxicity management guidelines. The pre-dose PK sample can be collected at any time within 48 hours prior to DTG dosing.
- For Cohort 2 infants, the three consecutive DTG doses prior to the date of PK sampling must be confirmed prior to the PK visit date. If one of the three scheduled DTG doses prior to the PK sampling is missed, the sampling should be rescheduled (within the allowable visit window). See Section 10.2 for further guidance.

For Cohort 2 infants, applicable reminders should be provided for the scheduled Week 4 visit date, including expectations for the intensive PK sampling. Administration of study drug for the three consecutive doses preceding the Week 4 visit should be confirmed prior to the visit. If adherence is not confirmed, the visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date. The caregiver/guardian should be instructed not to administer the DTG dose in the home on the day of the PK sampling at the Week 4 visit.

7 Days Post Initial Dose Visit Procedures *(7 days after administration of initial DTG dose + 3 days)*	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug	*Cohorts 1 and 2*: • Prescribe and dispense study drug for in-clinic administration as needed • Study drug administration following pre-dose PK sampling (see Cohort 1 note below) • Complete tolerability assessment after administration of study drug *Cohort 2:* • Confirm adherence to the three consecutive DTG doses preceding the visit • Prescribe and dispense study drug for in-home administration as needed • Provide instructions for documenting tolerability assessment during in-home administration of study drug
Laboratory	*For all infants*, collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine (*For Cohort 1, ALT and AST results must be reviewed prior to administering the second DTG dose*) *Cohort 1:* Collect blood (0.25 mL) for intensive PK sampling at each of the following time points: • Prior to observed dose of study drug (at any time within 48 hours prior to DTG dosing) • 1-2 hours (±15 minutes) after observed dose of study drug • 22-26 hours (±15 minutes) after observed dose of study drug *Cohort 2:* Collect blood (0.25 mL) for intensive PK sampling at each of the following time points: • Prior to observed dose of study drug • 1-2 hours (±15 minutes) after observed dose of study drug • 6-10 hours (±15 minutes) after observed dose of study drug • 22-26 hours (±15 minutes) after observed dose of study drug (*collect PK sample prior to administration of next DTG dose if every 24-hour dosing interval used*) • Prior to administration of the next dose (*a sample at this time point should only be collected for Cohort 2 infants with DTG dose regimen administered more than every 24 hours, e.g., every 48 or 72 hours*) *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at <u>one</u> visit from Entry through Week 16 visit)

6.6 Week 4 Visit (Cohorts 1 and 2)

The Week 4 visit is targeted to take place on Day 28, counted from the date of birth as Day 0, with an allowable window of ± five days (i.e., Day 23–33 of life).

For Cohort 2 infants undergoing intensive PK sampling:

- The DTG dose must be administered and/or observed by study staff.
- If there is any clinical indication or concern that the infant has an intercurrent illness or infection, contact the CMC prior to administering the DTG dose.
- The exact DTG dose time, dose amount, and draw time of each PK sample must be entered into appropriate eCRFs.
- If the infant vomits most or all of the DTG dose within the first 30 minutes after administration, the dose should be repeated. The PK sampling should be rescheduled within 1-2 days when the infant can receive another study drug dose.
- The three consecutive DTG doses prior to the date of PK sampling must be confirmed prior to the PK visit date. If one of the three scheduled DTG doses prior to the PK sampling is missed, the sampling should be rescheduled (within the allowable visit window). See Section 10.2 for further guidance.

For Cohort 2 infants planned to take DTG through the Week 6 visit, applicable reminders should be provided for the scheduled Week 6 visit date, including expectations for the population PK sampling. Administration of study drug for the three doses preceding the Week 6 visit should be confirmed prior to the visit; however, the Week 6 visit does not need to be rescheduled if adherence is not confirmed. Adherence support should be provided to help ensure appropriate dose administration on days preceding the visit date.

Week 4 Visit Procedures (Day 23 to Day 33 of life)	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug	*Cohort 2*: • Confirm adherence to the three consecutive DTG doses preceding the visit • Study drug administration following pre-dose PK sampling • Complete tolerability assessment after study drug administration *Cohort 2 infants discontinuing DTG at the Week 4 visit per local standard of care for ARV prophylaxis*: • Collect any remaining study drug and supplies *Cohort 2 infants continuing DTG through the Week 6 visit per local standard of care for ARV prophylaxis*: • Prescribe and dispense study drug for in-home administration as needed • Provide instructions for documenting tolerability assessment during in-home administration of study drug

Laboratory	*For all infants,* collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine *Cohort 2:* Collect blood (0.25 mL) for intensive PK sampling at each of the following time points: • Prior to observed dose of study drug • 1-2 hours (±15 minutes) after observed dose of study drug • 6-10 hours (±15 minutes) after observed dose of study drug • 22-26 hours (±15 minutes) after observed dose of study drug (*collect PK sample prior to administration of next DTG dose if every 24-hour dosing interval used*) • Prior to administration of the next dose (*a sample at this time point should only be collected for Cohort 2 infants with DTG dose regimen administered more than every 24 hours, e.g., every 48 or 72 hours*) *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.7 Week 6 Visit (Cohorts 1 and 2)

The Week 6 visit is targeted to take place on Day 42, counted from the date of birth as Day 0, with an allowable window of ± five days (i.e., Day 37 to 47 of life).

If the result of an HIV NAT test performed at this visit is positive, the infant should return to the clinic as soon as possible for confirmatory testing per Section 6.13.

Week 6 Visit Procedures (Day 37 to Day 47 of life)	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug	*For Cohort 2 infants discontinuing DTG at the Week 6 visit*: • Confirm adherence to the three DTG doses preceding the visit • Confirm date of final study drug administration • Collect any remaining study drug and supplies • Complete tolerability assessment
Laboratory	*For all infants*, collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine *For all Cohort 1 infants and only Cohort 2 infants that discontinued DTG at the Week 4 visit,* collect blood for: • HIV NAT *For Cohort 2 infants taking DTG through the Week 6 visit,* collect blood (0.25 mL) for: • Population PK sampling *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.8 Week 8 Visit (Cohort 2 only)

For Cohort 2 only, a Week 8 visit is targeted to take place on Day 56, counted from the date of birth as Day 0, with an allowable window of ± five days (i.e., Day 51 to Day 61 of life).

If the result of an HIV NAT test performed at this visit is positive, the infant should return to the clinic as soon as possible for confirmatory testing per Section 6.13.

Week 8 Visit Procedures (Day 51 to Day 61 of life)	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	*For all infants*, collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine *For Cohort 2 infants that discontinued DTG at the Week 6 visit,* collect blood for: • HIV NAT *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.9 Week 12 Visit (Cohort 2 only)

For Cohort 2 only, a Week 12 visit is targeted to take place on Day 84, counted from the date of birth as Day 0, with an allowable window of ± seven days (i.e., Day 77 to Day 91 of life).

Week 12 Visit Procedures (Day 77 to Day 91 of life)	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	Collect blood for*:* • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.10 Week 16 or Early Study Discontinuation Visit (Cohorts 1 and 2)

The Week 16 visit is targeted to take place on Day 112 of life, counted from the date of birth as Day 0, with an allowable window up to Day 140 of life. If possible, the procedures below should be performed for any infant who prematurely discontinues study participation prior to completion of follow-up at Week 16.

At this visit, mothers and/or guardians will be informed of how to contact study staff with any post-study questions, and arrangements should be made to provide the infant's mother and/or guardian with clinically meaningful test results from the final evaluations. If the result of the HIV NAT performed at this visit is positive, the infant will be recalled to the clinic as soon as possible for confirmatory testing and referrals per Section 6.13. For all infants, referrals will be provided as needed to ensure transition to non-study sources of routine child health care.

Week 16 (Day 112 to Day 140 of life) or Early Study Discontinuation Visit Procedures	
Clinical	• Obtain interval medical and medication history • Perform physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Laboratory	*For all infants*, collect blood for*:* • HIV NAT • CBC including WBC and differential • AST, ALT, total bilirubin, creatinine *For all infants, if informed consent for genetic testing is obtained,* collect blood for DBS storage for PK genotyping (collect only at one visit from Entry through Week 16 visit)

6.11 Procedures for Infants who Prematurely Discontinue Study Drug

Infants who prematurely discontinue study drug and remain on study will continue follow-up visits and procedures per the relevant SoE through the Week 16 visit, except that no further PK sampling will be performed. Refer to Section 8.5 for further details on criteria for premature discontinuation of study drug.

6.12 Procedures for Infants who Prematurely Discontinue Study Participation

Refer to Section 4.6 for criteria for premature withdrawal or termination from the study. For any infant who discontinues study participation prior to completion of follow-up at the Week 16 visit, every effort should be made to complete a final series of study evaluations if possible. In general, the visit procedures in Section 6.10 should be performed, and arrangements should be made to provide the infant's mother and/or guardian with clinically meaningful test results from the final evaluations. The mother and/or guardian should also be provided information and referrals, as applicable, to non-study sources of care and treatment for the infant.

6.13 Procedures for Infants with Positive HIV NAT Results

After enrollment, any infant with a positive HIV NAT test result should be recalled to the site as soon as possible for confirmatory HIV NAT testing. Administration of DTG should be held pending receipt of the confirmatory test result; other ARVs should be managed consistent with local standards of care.

At the time of specimen collection for the confirmatory HIV NAT test, a sample for ARV resistance testing should also be collected per Appendices IB and IC and the Laboratory Processing Chart (LPC). If the HIV NAT test does not confirm the initial HIV positive result, the CMC should be consulted for guidance on next steps to confirm the infant's HIV status.

If HIV-1 diagnosis is confirmed, DTG will be permanently discontinued, and the specimen collected for ARV resistance testing will be shipped for testing. As the appropriate dose of DTG in neonates is not yet known and treatment of HIV is indicated, a complete regimen that includes ARVs with neonatal dosing recommendations should be prescribed.

The infant will remain in follow-up with visits and procedures performed per the relevant SoE through the Week 16 visit, except that no further HIV testing and no further PK sampling will be performed. The infant will be actively referred to non-study sources of HIV care and treatment, and ARV resistance test results will be provided to non-study care providers to guide ARV regimen selection. Study sites may also perform additional laboratory testing as needed to facilitate rapid initiation of ARV treatment.

6.14 Maternal Medical and Medication History

At Screening and Entry visits, the following should be source documented and entered into eCRFs:

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

6.15 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 Screening and Entry visits, and interval histories (since the last visit) 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 caregiver/guardian report; available medical records should also be obtained when possible to supplement caregiver/guardian report.

ARVs taken by each infant's mother to which the infant may have been exposed *in utero* and all ARVs taken by enrolled infants will be source documented and recorded on eCRFs as part of the ARV exposure history obtained at each visit. For breastfeeding infants, while receiving DTG, all ARVs taken by the infant's mother (to which the infant may have been exposed through breast milk) will be source documented and recorded on eCRFs.

In addition, while an infant is receiving DTG, all other concomitant medications received by infants and medications taken by breastfeeding mothers to which a breastfeeding infant may have been exposed through breast milk must be source documented and recorded on eCRFs.

Documented medical conditions will be assessed for severity as described in Section 7.3.3, and new conditions occurring after the first dose of study drug (DTG) will also be assessed for relationship to study drug as described in Section 8. Relevant dates will be recorded for all conditions and medications; see Section 5.8 for more information on concomitant medications.

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

Table 4
Documentation Requirements for Infant Medical and Medication Histories

Assess for and Source Document	Enter into eCRFs or SES
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 Screening visit)	Yes (all)
Apgar scores at 1 and 5 minutes (obtain from medical records, if available)	Yes (all)
Medical conditions, including congenital anomalies, identified between birth and time of the first dose of DTG	Yes (all)
All medications taken since birth	Yes (all)
Infant feeding method(s) since birth	Yes
Any other information needed to determine eligibility for the study	No
Infant Interval Medical and Medication History Elements	
Any change of guardianship	Yes
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new medical conditions (after the first dose of study drug) since the last visit	Any newly identified AEs that meet criteria in Section 7.2
Occurrence of any device deficiency (after the first dose of the study drug) since the last visit	Any newly identified AEs linked to a device deficiency in infants who meet criteria in Section 7.4
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	All ARVs and other concomitant medications taken while the infant is receiving DTG, including exposure through breast milk if breastfeeding
Any change in infant feeding method(s)	Yes

6.16 Infant Physical Examinations

A physical examination is required at each scheduled infant visit and should include the following:

- Weight measurement (every visit)
- Temperature (every visit)
- Pulse (every visit)
- Respiration (every visit)
- Auscultation of chest (every visit)
- Examination of skin, head, mouth, neck, abdomen, extremities (every visit)
- Length measurement (at Entry and Week 16 or Early Study Discontinuation visits)
- Head circumference (at Entry and Week 16 or Early Study Discontinuation visits)

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

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

All exam findings should be source documented and entered into appropriate eCRFs. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into AE eCRFs as specified in Section 7.2.

6.17 Cohort 1 and Cohort 2 Study Drug Tolerability

Study drug tolerability will be assessed at study visits as indicated in Appendix IB and Appendix IC and may include caregiver/guardian report on the overall ease of swallowing and/or problems the infant has in taking study drug. Prior to the participant leaving the clinic, any potential AEs reported or identified based on tolerability assessments should be clinically assessed. For Cohort 2 infants, study staff will provide instructions to caregivers/guardians for documenting tolerability problems and associated frequency during in-home administration of study drug to assist in completing the tolerability assessment at study visits. Further guidance and considerations for completing tolerability assessments and the timing of these assessments relative to other visit procedures are provided in the study-specific Manual of Procedures (MOP).

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 SoEs and per guidance provided in the LPC, which will be available on the study-specific website at: https://impaactnetwork.org/studies/IMPAACT2023

Consistent with US National Institutes of Health (NIH) Guidelines for Limits of Blood Drawn for Research Purposes at the NIH Clinical Center, in this study 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 over any eight-week period. In the event that infant blood collection must be limited, available specimens will be prioritized for use in the following order: (i) CBC; (ii) AST, ALT, total bilirubin, creatinine; (iii) HIV NAT; (iv) PK (intensive and population); and (v) DBS 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 SoEs and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC.

HIV-1 RNA assays must be performed in a laboratory that is CLIA-certified or equivalent (for US sites) or VQA-certified (for non-US sites) for the assay performed. For infants with confirmed HIV diagnosis, specimens collected for ARV resistance testing will be shipped to a designated VQA-certified testing laboratory.

Specimens collected for PK evaluations will be processed and stored at site laboratories prior to shipping to the designated testing laboratory as follows:

- **Cohort 1**: Intensive PK samples from the Entry and 7 Days Post Initial Dose visits will be shipped together after the 7 Days Post Initial Dose visit.

- **Cohort 2**: Intensive PK samples collected at the 7 Days Post Initial Dose and Week 4 visits will be shipped after each visit. Population PK samples collected at the 2 Days Post Initial Dose and Week 6 visits will be stored and shipped with intensive PK samples and/or in batch monthly.

Alternative specimen shipping arrangements may be specified by the protocol team as needed. Refer to the LPC for detailed shipping instructions.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Informed consent will be requested for future research use of these specimens, if permitted by IRBs/ECs and other applicable review bodies. Mothers may choose to provide or to decline this consent with no impact on other aspects of study participation.

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, 7.2, and 7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the CMC and the SMC are briefly referenced in Section 7.1 and described in greater detail in Sections 9.5.3 and 9.5.4.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the CMC if unexpected concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete EAE reporting as indicated in Section 7.3.

Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to all applicable IRBs/ECs and other applicable review bodies, per the procedures of each applicable review body.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Chair and Vice Chairs, Medical Officers, Statisticians, Data Managers, Pharmacologists, Pharmacists, Clinical Research Managers, Laboratory Specialists, Laboratory Technologists, Laboratory Data Managers, ViiV and GlaxoSmithKline (GSK) representatives, and one international Protocol Investigator. 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 and management of AEs; study drug administration; and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.3.

7.1.3 Study Monitoring Committee (SMC)

An independent SMC will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.4 for more information on the role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

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

The definition of the term AE provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), dated January 2010, will be used in this study. This definition will be applied to all infant participants, beginning after administration of the first dose of DTG. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified between the time of infant birth and the time of the first dose of DTG 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 AEs will be entered into eCRFs as specified below.

7.2.1 Safety-Related Data Collection for Infants

Pre-Existing Conditions

All pre-existing conditions (i.e., all Grade 1 or higher) identified between the time of infant birth and the time of the first dose of DTG will be entered into medical history eCRFs. Among other details, the severity of all such conditions will be entered into eCRFs.

Adverse Events

All AEs (i.e., all Grade 1 or higher) identified after the first dose of DTG, inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses, will be entered into AE eCRFs.

Note: Suspected, probable, and confirmed diagnoses of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be reported consistent with WHO case definitions for COVID-19 disease, which are available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-SurveillanceGuidance-2022.1

Laboratory Test Results

All safety-related laboratory test results will be entered into laboratory eCRFs, regardless of severity grade and regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes.

7.2.2 Data Collection for Mothers

Pre-Existing Conditions

All pre-existing conditions identified among mothers during pregnancy and from 30 days prior to study entry through study discontinuation (i.e., after the Entry visit is completed) will be entered into maternal medical history eCRFs at the maternal Screening and Entry visits.

7.3 Expedited Adverse Event (EAE) Reporting

Note: This section applies only to infant participants in this study.

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at:
https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

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:
https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting

For questions about DAERS, please contact NIAID Clinical Research Management System (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

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, dated January 2010, will be used for this study. The study agent for which expedited reporting is required is Dolutegravir (DTG).

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

The DAIDS 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:
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

In addition, grading of axillary measured fever in this study will follow Table 5.

Table 5
Infant Axillary Measured Fever Grading

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

Normal physiologic changes in renal function associated with the adaptation of the neonate to the extrauterine environment make evaluation of renal function challenging during the neonatal period (18). Infant plasma creatinine immediately after birth reflects maternal plasma creatinine; increases over the first few days of life, associated with contraction of the infant vascular space; and then decreases around four-fold over the next 3-4 weeks of life, associated with a physiologic increase in neonatal renal function (19). In addition, DTG has been shown in adults to decrease tubular creatinine secretion, elevating creatine clearance estimates while not changing the actual glomerular filtration rate (12, 20). As a result of these physiologic and drug-related changes, the DAIDS AE Grading Table grading for plasma creatinine and for creatinine clearance, which includes change from baseline, may be misleading when applied to neonates, as the effect of DTG on neonatal renal creatinine secretion is unknown. For this reason, creatinine clearance should not be graded for this study; plasma creatinine grading will follow Table 6 below.

Table 6
Creatinine Grading

Grade 1	Grade 2	Grade 3	Grade 4
1.1 to less than or equal to 1.3 x ULN	greater than 1.3 to less than or equal to 1.8 x ULN	greater than 1.8 to less than 3.5 x ULN	greater than or equal to 3.5 x ULN

7.3.4 EAE Reporting Period

The EAE reporting period for this study for each enrolled infant begins at the time of administering the first dose of study drug and continues through the protocol-specified end of follow-up.

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

7.4 Medical Device Reporting

DTG DTs are provided with an oral syringe and dosing cup for administration of the DT and are considered a combination product with a device component that is subject to post-marketing safety reporting requirements (see Section 5.4). Site investigators are responsible for detection and documentation of events meeting the definition of a device deficiency that occur during this study.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, as defined by GSK. This definition is based on European Medical Device Regulation 2017/745 for clinical device research and is in accordance with the International Organization for Standardization 14155 definition. Device deficiencies can

include malfunctions, use errors, and/or deficiencies in information supplied by the manufacturer. Device deficiencies may result in an SAE of an infant participant, including death or serious deterioration in health, or these serious events for a non-participant or "associated person"; a non-serious AE; or might have led to an AE or SAE if appropriate action had not been taken or intervention had not occurred.

If a device deficiency is detected for an enrolled infant or associated person, the site investigator must complete a GSK device deficiency form. A completed form for enrolled infants, or a completed form for associated persons with no protected health information included on the form, should be submitted by the site investigator to the CMC and GSK/ViiV via email in a timely manner, ideally within three business days of site awareness of the device deficiency. Instructions for form completion and submission are provided in the study-specific MOP. A copy of the completed device deficiency form for participants that is submitted to GSK/ViiV should be maintained on site in study records. See Section 11.1 for data management responsibilities of this form.

Any infant AEs resulting from a device deficiency should be entered into AE eCRFs as outlined in Section 7.2; infant SAEs resulting from a device deficiency should be reported in DAERS as outlined in Section 7.3. Further guidance on reporting events resulting from a device deficiency for associated persons (e.g., caregivers/guardians, study staff) is provided in the study-specific MOP.

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

All AEs identified in this study will be source documented in participant research records, consistent with the requirements referenced in Section 11. 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 by the site investigator according to the following categories and definitions:

Related There is a reasonable possibility that the AE may be related to DTG

Not related There is not a reasonable possibility that the AE may be related to DTG

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. As described in greater detail below, AEs identified in participants will be managed based on their severity and assessed relationship to study drug (DTG).

All AEs must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event and guidance in Sections 8.2, 8.3, and 8.4. Additional evaluations beyond those listed in Appendices IB and IC may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study drug. Clinical management of all AEs should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Grade 3 or higher laboratory tests should be repeated as soon as possible and within three business days. All Grade 3 or higher AEs should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

When management of an AE 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, unless otherwise directed below. The CMC should be notified of any interruption of study drug as soon as possible.

The remainder of this section provides further guidance on management of AEs. General toxicity management guidance is provided in Section 8.2. Further guidance for bilirubin and hypersensitivity reaction events is provided in Sections 8.3 and 8.4, respectively. Criteria for premature permanent discontinuation of study drug are provided in Section 8.5.

8.2 General Toxicity Management

The following general guidelines (by grade) apply to management of AEs and DTG in response to AEs, except bilirubin and hypersensitivity reaction events (see Sections 8.3 and 8.4, respectively). Any infants who prematurely discontinue administration of DTG will remain in follow-up per Section 6.11 and the relevant SoE in Appendices IB and IC with the exception that no further PK sampling will be done.

8.2.1 Cohort 1 Infants

AEs for infants in Cohort 1 should be managed per the guidelines below in Table 7. Any life-threatening AE should be reported to the CMC within three business days of site awareness. Evaluations for non-study drug explanations for clinical and laboratory abnormalities should be performed as determined by the site investigator.

Table 7
General Guidelines for Management of Infants in Cohort 1

Grade 1	**ALT** Repeat test as soon as possible and within three business days. Consult the CMC if the result is confirmed Grade 1. If Grade 1 ALT is confirmed prior to administration of the second DTG single dose, the second DTG single dose may be administered with close monitoring as determined by the site investigator. **All other laboratory and clinical events** If Grade 1 event occurs prior to administration of the second DTG single dose, the second DTG single dose may be administered. Continue routine monitoring per the SoE unless more frequent monitoring is clinically indicated as determined by the site investigator.
Grade 2	**ALT** Repeat test as soon as possible and within three business days and consult the CMC if confirmed Grade 2. If the initial Grade 2 ALT occurs prior to administration of the second DTG single dose, hold the second DTG single dose while awaiting the repeat test result. If the repeat test result is confirmed

	Grade 2, the second DTG single dose can only be administered with approval from the CMC after exclusion of signs of elevated bilirubin or symptomatic hepatitis. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. **AST** Repeat test as soon as possible and within three business days and consult the CMC if confirmed Grade 2. If Grade 2 AST is confirmed prior to administration of the second DTG single dose, the second DTG single dose may be administered with close monitoring as determined by the site investigator. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. **All other laboratory and clinical events** If Grade 2 event occurs prior to administration of the second DTG single dose, the second DTG single dose may be administered. Continue routine monitoring per the SoE unless more frequent monitoring is clinically indicated as determined by the site investigator.
Grade 3	**ALT or AST** Repeat test as soon as possible and within three business days. Consult the CMC as soon as possible and while awaiting repeat test results. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • If the initial Grade 3 ALT or AST occurs prior to administration of the second DTG single dose, hold the second DTG single dose while awaiting the repeat test result. • If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. • If the repeat test result is confirmed Grade 3, the second DTG single dose should not be administered. The infant should be followed for safety per Section 6.11. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC. **All other laboratory and clinical events** Upon initial identification of a Grade 3 AE, notify the CMC as soon as possible and within three business days. If the initial Grade 3 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • If Grade 3 event occurs prior to administration of the second DTG single dose, the second DTG single dose may be administered with close monitoring as determined by the site investigator. • If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result.

	For Grade 3 clinical events and confirmed Grade 3 laboratory events: Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.
Grade 4	**ALT** Upon initial identification of a Grade 4 ALT, hold DTG and repeat test as soon as possible and within three business days. Consult the CMC as soon as possible and within one business day while awaiting repeat test results. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. • If the repeat test result is confirmed Grade 4, DTG should be permanently discontinued. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC. **All other laboratory and clinical events** Upon initial identification of a Grade 4 AE, hold the second DTG single dose and notify the CMC as soon as possible and within one business day. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. If the initial Grade 4 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. For Grade 4 clinical events and confirmed Grade 4 laboratory events: • If the event is assessed as **not related** to study drug and occurs prior to administration of the second DTG single dose, the second DTG single dose may only be administered with approval from the CMC. • If the event is assessed as **related** to study drug, the second DTG single dose should not be administered and DTG should be permanently discontinued. Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

8.2.2 Cohort 2 Infants

AEs for infants in Cohort 2 should be managed per the guidelines below in Table 8. Any life-threatening AE should be reported to the CMC within three business days of site awareness. Evaluations for non-study drug explanations for clinical and laboratory abnormalities should be performed as determined by the site investigator.

Table 8
General Guidelines for Management of Infants in Cohort 2

Grade 1	**ALT** Repeat test as soon as possible and within three business days. Consult the CMC if the result is confirmed Grade 1. If Grade 1 ALT is confirmed, continue DTG with close monitoring as determined by the site investigator. **All other laboratory and clinical events** Continue DTG and routine monitoring per the SoE unless more frequent monitoring is clinically indicated as determined by the site investigator.
Grade 2	**ALT** Upon initial identification of a Grade 2 ALT, hold DTG and repeat test as soon as possible and within three business days. Consult the CMC while awaiting the repeat test result. If the repeat test result is confirmed Grade 2, DTG may only be resumed with approval from the CMC after exclusion of signs of elevated bilirubin or symptomatic hepatitis. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. **AST** Repeat test as soon as possible and within three business days and consult the CMC if confirmed Grade 2. If Grade 2 AST is confirmed, continue DTG with close monitoring as determined by the site investigator. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. **All other laboratory and clinical events** Continue DTG with close monitoring as determined by the site investigator.
Grade 3	**ALT or AST** Upon initial identification of a Grade 3 ALT or AST, hold DTG and repeat test as soon as possible and within three business days. Consult the CMC as soon as possible and while awaiting repeat test results. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. • If the repeat test result is confirmed Grade 3, DTG may only be resumed with approval from the CMC. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

	All other laboratory and clinical events Upon initial identification of a Grade 3 AE, hold DTG and notify the CMC as soon as possible and within three business days. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken as soon as possible and within three business days. If the initial Grade 3 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. For Grade 3 clinical events and confirmed Grade 3 laboratory events: • DTG may only be resumed with approval from the CMC for Grade 3 clinical events and if the repeat test result is confirmed Grade 3 for laboratory events. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.
Grade 4	**ALT** Upon initial identification of a Grade 4 ALT, hold DTG and repeat test as soon as possible and within three business days. Consult the CMC as soon as possible and within one business day while awaiting repeat test results. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. • If the repeat test result is confirmed Grade 4, DTG should be permanently discontinued. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC. **All other laboratory and clinical events** Upon initial identification of a Grade 4 AE, hold DTG and notify the CMC as soon as possible and within one business day. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. If the initial Grade 4 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. For Grade 4 clinical events and confirmed Grade 4 laboratory events: • If the event is assessed as **not related** to study drug, DTG may only be resumed with approval from the CMC. • If the event is assessed as **related** to study drug, DTG should be permanently discontinued. Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

8.2.3 Mothers

Maternal participants will not be exposed to study drug and will exit the study after completion of the Entry visit. Clinical management of all clinical events recorded as pre-existing conditions that occur after enrollment and prior to completion of the Entry visit should be managed per the best medical judgment of the site investigator and local clinical practice standards.

8.3 Management of Bilirubin

Due to the potential for interactions between DTG and bilirubin affecting DTG PK and bilirubin elimination and toxicity (see Section 1), special management procedures for bilirubin will be used. Bilirubin concentrations and interventions to lower bilirubin (such as phototherapy and exchange transfusion) will be entered into eCRFs. Bilirubin will be graded according to the DAIDS AE Grading Table in Section 7.3.3. Hyperbilirubinemia will be managed by site investigators according to local standards of care.

If total bilirubin is >16.0 mg/dL or an exchange transfusion is performed, DTG should be permanently discontinued, and participants should continue to be followed on study for safety per Section 8.5. Participants who receive phototherapy may continue to receive DTG as long as total bilirubin concentration remains ≤16.0 mg/dL.

The CMC should be notified as soon as possible and within three business days for Grade 3 or higher bilirubin, if DTG is held for hyperbilirubinemia, or if an infant received an exchange transfusion.

8.4 Management of Hypersensitivity Reactions

Hypersensitivity AEs for infants in Cohorts 1 and 2 should be managed as indicated below and graded according to the DAIDS AE Grading Table in Section 7.3.3.

8.4.1 Allergic Reaction

Allergic reaction events for infants in Cohorts 1 and 2 should be managed per Table 9. For all allergic reaction events, caregivers/guardians should be advised to contact the site immediately if symptoms worsen or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Table 9
Guidelines for Management of Allergic Reactions in Infants

Grade 1 or 2	• Continue DTG with close monitoring as determined by the site investigator.
Grade 3 or 4	• If the event is assessed as **related** to study drug, DTG should be permanently discontinued. • If the event is assessed as **not related** to study drug, hold DTG and consult the CMC. • For all Grade 3 or 4 events, notify the CMC as soon as possible and within one business day. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

8.4.2 Rash

Mild to moderate rash is a potential adverse reaction for DTG-containing ARV therapy. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy, and tend to resolve within three weeks. The index case of a hypersensitivity reaction 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, toxic epidermal necrolysis, and erythema multiforme, have been reported for DTG in clinical trials. Rash events for infants in Cohorts 1 and 2 should be managed per Table 10.

Table 10
Guidelines for Management of Rash in Infants

Grade 1	• If the rash is **isolated**, continue DTG with close monitoring as determined by the site investigator. • Caregivers/guardians should be advised to contact the site immediately if rash worsens, further systemic signs or symptoms develop, or mucosal involvement develops.
Grade 2	• If the rash is **isolated**, continue DTG with close monitoring as determined by the site investigator. • If the rash is **associated with an elevated ALT**, DTG should be permanently discontinued as well as other concomitant medications suspected by the site investigator as potentially causal. • Caregivers/guardians should be advised to contact the site immediately if rash does not resolve within two weeks, worsens, further systemic signs or symptoms develop, or mucosal involvement develops.
Grade 3 or Grade 4	• DTG should be permanently discontinued as well as other concomitant medications suspected by the site investigator as potentially causal. • Notify the CMC as soon as possible and within one business day. The CMC should be notified of the assessment of relationship to study drug and immediate management action taken. • Participants should be re-evaluated at least weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

8.5 Criteria for Premature Permanent Discontinuation of Study Drug

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

- The infant is confirmed to be living with HIV-1 per Section 6.13, or
- The infant experiences an AE that requires permanent study drug discontinuation as specified in Sections 8.2, 8.3, and 8.4, or
- The infant requires a disallowed medication listed in Section 5.8.1, or
- The site investigator determines that further administration of DTG would be detrimental to the infant's health or well-being, or
- New data become available that indicate DTG should be discontinued as determined by the CMC.

Participants that prematurely permanently discontinue study drug should continue to be followed on study per Section 6 and the SoEs, with the exception that no further PK sampling will be performed (see Section 6.11).

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I, multi-center, open-label, non-comparative dose-finding study to evaluate the safety, tolerability, and PK of DTG in infants born to mothers living with HIV-1. The primary goal of the study is to propose a dose of DTG that is safe and meets PK targets when administered to infants through the first four weeks of life in addition to the infant's standard HIV-1 ARV prophylaxis.

The infant and mother will be enrolled, with the mother taken off study after completing the Entry visit and the infant followed through the Week 16 visit (Days 112-140 of life). Singleton full-term infants (≥ 37 weeks gestation at birth) will be screened and enrolled in the study within the first five days of life. Infants will be enrolled in two sequential dosing cohorts: Cohort 1 (two single DTG doses) and Cohort 2 (chronic DTG dosing through Week 4 or 6 visit per local standard of care for ARV prophylaxis). Cohort 1 is intended to generate the PK and safety data that will inform DTG dose selection for Cohort 2.

To account for possible impact of infant's *in utero* exposure to maternal DTG and how this may affect the infant's initial DTG dosing (i.e., timing and/or strength), at enrollment infants will be stratified based on the infant's *in utero* exposure to maternal DTG (i.e., DTG-naïve and DTG-exposed). Based on the study definition of *in utero* DTG-naïve and DTG-exposed infants in inclusion criterion 4.1.3, mother-infant pairs in which the mother received at least one dose of DTG more than 72 hours and less than or equal to two weeks prior to delivery will not be enrolled in the study. Refer to Section 3 for definitions of PK and safety-evaluable infants for the dose-finding evaluations, the cohort strata, and description of the study design.

Safety data will include infant clinical data and laboratory test results and information on any infant deaths. Laboratory test results will include evaluations specified in the protocol and results from the infant's clinical care considered by the sites as relevant. Refer to Section 6 and Appendices IB and IC for an outline and schedule of infant safety assessments. Further information on the collection of safety data, definition of pre-existing conditions and AEs, and

grading of AEs is in Section 7, and AE attribution to the study drug is defined in Section 8. The team will review the safety data and assess study drug safety during the dose-finding evaluation phase (Section 9.5.1) and when study follow-up is completed (Section 9.6).

Tolerability data will include infant DTG tolerability assessments, safety data, and medication history. Refer to Section 6 and Appendices IB and IC for further information on these evaluations.

PK outcome measures, PK sampling schedule, and analyses are described in Section 10. All other statistical and data analysis considerations are described in the remainder of this section.

The primary analysis will be performed when complete data through the subsequent study visit after permanent treatment discontinuation are available.

9.2 Outcome Measures

The outcome measures listed in Table 11 will be further described in the study's Primary Statistical Analysis Plan (Primary SAP).

The following specifications are used for the safety outcome measures:

- To be considered safety-evaluable for the final analysis, an infant must have received at least one dose of the study drug and have safety evaluation(s) after the initial DTG dosing.
- AE attribution to study drug will be based on site assessment. If the SMC is consulted, the SMC's opinion will be used.
- "Day 0" is the day of birth.
- Life-threatening AE as defined in Version 2.0 of the DAIDS EAE Manual (see Section 7.3).

All infants who received at least one dose of the study drug (DTG) will be included in the analyses for the tolerability outcome measure.

Table 11
Outcome Measures

9.2.1	**Primary Outcome Measures**
9.2.1.1	The proportion of infants classified as "study drug-related" safety failures. An infant is classified as a "study drug-related" safety failure for the primary safety study objective if any of the following occurred after the initial study drug dosing through two weeks after permanent discontinuation of the study drug (i.e., two weeks after off treatment date): • Grade 3 or 4 AE assessed as related to study drug, or • Death (Grade 5 AE) assessed as related to the study drug, or • Life-threatening AE assessed as related to study drug, or • AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug.
9.2.1.2	The proportion of infants classified as safety failures. An infant is classified as a safety failure for the primary safety study objective if any of the following occurred after the initial study drug dosing through two weeks after permanent discontinuation of the study drug (i.e., two weeks after off treatment date): • Grade 3 or 4 AE, or • Death (Grade 5 AE)
9.2.1.3	The proportion of infants who are not able to tolerate the study drug. An infant is considered not able to tolerate the study drug if the infant experiences problems taking the study drug as defined in Section 6 or experiences any AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug. Tolerability will be assessed after the initial study drug dosing through study drug discontinuation (i.e., up to Week 6 visit).
	PK primary outcome measures are defined in Section 10.3
9.2.2	**Secondary Outcome Measures**
9.2.2.1	The proportion of infants classified as "study drug-related" safety failures. An infant is classified as a "study drug-related" safety failure for the secondary study safety objective if any of the following occurred after the initial study drug dosing through Week 16: • Grade 3 or 4 AE assessed as related to study drug, or • Death (Grade 5 AE) assessed as related to the study drug, or • Life-threatening AE assessed as related to study drug, or • AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug.
9.2.2.2	The proportion of infants classified as safety failures. An infant is classified as a safety failure for the secondary study safety objective if any of the following occurred after the initial study drug dosing through Week 16: • Grade 3 or 4 AE, or • Death (Grade 5 AE)
9.2.3	**Other Outcome Measures**
	The other PK outcome measure is defined in Section 10.3

9.3 Randomization

This study does not involve any randomization, and mother-infant pairs will be enrolled into the cohort that is open to study accrual. Upon study entry, the mother-infant pair will be stratified based on the infant's *in utero* exposure to maternal DTG.

Breastfeeding and formula-feeding infants may enroll in the study. The breastfeeding status of the infants will be determined at study entry with mixed-feeding infants classified as breastfeeding.

9.4 Sample Size and Accrual

9.4.1 Sample Size

A minimum of 36 and up to 108 mother-infant pairs will be enrolled in the study to achieve a target of 36 evaluable infants receiving the proposed dose of DTG for the relevant stratum. The accrual targets are specified in the Schema. The minimum target sample sizes were determined based on requirements for PK modeling and simulation as described in Section 10.6.4. The per cohort maximum accrual targets allow for replacement of infants who are not evaluable for dose-finding evaluations, stratum dose changes, and loss to follow-up.

Infants not evaluable for dose-finding evaluations will be replaced unless the maximum accrual of 36 infants in Cohort 1 (across strata) or the maximum accrual of 72 infants in Cohort 2 (across strata) is already achieved. It is possible to enroll the maximum participants in a cohort and not achieve the required evaluable infants for dose-finding evaluation (i.e., six infants in each Cohort 1 stratum and 12 infants in each Cohort 2 stratum); however, the maximum sample size of 108 infants for the study was determined to accommodate replacement for dose-finding evaluations, stratum dose changes, and loss to follow-up.

Table 12 shows the 90% Confidence Interval (CI) estimates around potential proportions of infants who are safety failures at possible sample sizes for the safety analysis. The 90% CI estimates on proportion of infants who are safety failures (described in Section 9.2) will be relatively wide for a sample size of six Cohort 1 infants who might contribute data to the Cohort 1 per stratum safety analysis but relatively narrower for a sample size of 24 Cohort 2 infants who might contribute data to the Cohort 2 across strata safety analysis. Note that infants excluded from the dose-finding safety evaluations may be included in the final safety analysis.

Table 12
90% Confidence Intervals around Potential Proportions of Infants Classified as Safety Failures[a]

Number of Infants	Observed Number of Safety Failures	Proportion of Safety Failures (90% CI)
6	0	0.00 (0.00, 0.39)
	1	0.17 (0.01, 0.58)
	2	0.33 (0.06, 0.73)
	3	0.50 (0.15, 0.85)
	4	0.67 (0.27, 0.94)
12	0	0.00 (0.00, 0.22)
	1	0.08 (0.00, 0.34)
	2	0.17 (0.03, 0.44)
	4	0.33 (0.12, 0.61)
	6	0.50 (0.25, 0.75)
	8	0.67 (0.39, 0.88)
24	0	0.00 (0.00, 0.12)
	1	0.04 (0.00, 0.18)
	2	0.08 (0.02, 0.24)
	6	0.25 (0.11, 0.43)
	12	0.50 (0.32, 0.68)
	15	0.62 (0.44, 0.79)
	18	0.75 (0.57, 0.89)
36	0	0.00 (0.00, 0.08)
	3	0.08 (0.02, 0.20)
	5	0.14 (0.06, 0.27)
	10	0.28 (0.16, 0.43)
	15	0.42 (0.28, 0.57)
	18	0.50 (0.35, 0.65)
	25	0.69 (0.55, 0.82)
72	0	0.00 (0.00, 0.04)
	5	0.07 (0.03, 0.14)
	10	0.14 (0.08, 0.22)
	20	0.28 (0.19, 0.38)
	36	0.50 (0.40, 0.60)
	40	0.56 (0.45, 0.66)
	50	0.69 (0.59, 0.78)

[a] Clopper-Pearson exact confidence interval estimates using PROC FREQ in SAS Version 9.4.

9.4.2 Accrual

To achieve the targeted sample size described in Section 3, accrual is expected to require 24 months.

Cohort 1 will be opened first to accrual, with Strata 1A and 1B being opened concurrently, to evaluate the PK and safety of two single DTG liquid suspension doses for the relevant stratum. Stratum 1C will only be opened to accrual if PK and safety data from Strata 1A and 1B infants support administration of DTG 5 mg DT across all neonates, or only in neonates with a minimum birth weight (see Section 10). Cohort 2, Strata 2A and 2B, will be opened to accrual when the DTG dose and formulation to be administered for each stratum are established based on the PK and safety data from all Cohort 1 strata (Strata 1A and 1B, and 1C if applicable) and available data from other studies.

9.5 Monitoring

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

9.5.1 Dose-Finding Phase

During the dose-finding phase of the study, the CMC will review the safety and PK data with the aim of determining the proposed dose for each stratum/cohort while protecting infant safety. The composition of the CMC is defined in Section 7.1.2.

The PK and safety data will be reviewed during routine monitoring:
(i) Safety data will be reviewed at least monthly, and the CMC will take action as needed as described in Section 9.5.3, and
(ii) PK data will be reviewed as soon as results become available according to specifications in Section 10.

In addition to the routine monitoring of PK and safety data, there are scheduled PK and safety evaluations to assess a cohort stratum dose done at: (i) full accrual to a Cohort 1 stratum (minimum of six evaluable infants); (ii) accrual of first six evaluable infants in a Cohort 2 stratum; and (iii) full accrual of a Cohort 2 stratum (minimum of 12 evaluable infants). During these dose-finding PK and safety evaluations, the dose will be evaluated to determine if the Cohort 1 stratum dose meets the Safety Guidelines (Section 9.5.2); there is sufficient PK data from Cohort 1 to determine Cohort 2 dosing; and the Cohort 2 dose meets the Safety Guidelines and the PK targets (Section 10.4).

Based on the CMC review of safety and PK data during the routine monitoring and at the scheduled dose-finding PK and safety evaluations, the CMC may decide to adjust the dose for a stratum or the cohort. There will be no individual dose adjustments.

Cohort 1 Dose-Finding PK and Safety Evaluation at Full Stratum Accrual

Strata 1A and 1B will be opened concurrently. Stratum 1C will only be opened to accrual if PK modeling and safety data from Strata 1A and 1B infants support administration of a DTG 5 mg DT in neonates, or only in neonates with a minimum birth weight (see Section 3).

An initial group of six evaluable infants will be enrolled in each Cohort 1 stratum for dose-finding evaluations, and their safety and PK data will be evaluated independently as follows:

At completion of the safety visit associated with the second DTG dosing of the initial group of six evaluable infants on the dose, if the safety-evaluable infants for dose-finding evaluations meet the Safety Guidelines, and if there are sufficient PK data to allow PK modeling and simulations for dose selection of a Cohort 2 stratum dose, then the starting dose for the Cohort 2 stratum will be established, and the CMC will propose to the SMC that the Cohort 2 stratum be opened for accrual. Otherwise, the CMC will evaluate the findings and determine which of the following is appropriate: (i) on the basis of the current data, propose a dose for a Cohort 2 stratum; (ii) enroll additional participants at the current dose and evaluate the expanded data; (iii) adjust the dose and evaluate the new dose; or (iv) close the study. The CMC will consult with the SMC prior to opening accrual in a Cohort 2 stratum with a proposed dose and/or if a stratum does not meet the Safety Guidelines.

If the dose is changed, six new evaluable infants will be enrolled at the adjusted dose, and the safety and PK evaluation will be repeated for the adjusted dose (i.e., second dosing regimen) following the algorithm described above. If the second dosing regimen needs to be adjusted, a third group of six evaluable infants receiving a second dose adjustment would be enrolled. The goal is to enroll at least six evaluable infants at a dose in each stratum in Cohort 1 to assess if a dose meets the Safety Guidelines and provide sufficient PK data to allow modeling and simulations for dose selection for the Cohort 2 stratum.

Accrual will be paused in the relevant stratum while awaiting completion of the required PK and safety interim analysis for the target n=6 evaluable infants in each stratum. The CMC may resume accrual if any of the infants is assessed as unevaluable for the dose-evaluation and needs to be replaced.

Cohort 2 Dose-Finding PK and Safety Evaluations at Accrual of First Six Evaluable Infants and at Full Stratum Accrual

Enrollment will begin in each Cohort 2 stratum (Stratum 2A and Stratum 2B) as soon as the stratum starting dose is established based on Cohort 1 PK and safety data. Each stratum dosing regimen will be evaluated independently as follows based on data on initial six evaluable infants and then on n=12 minimum evaluable infants:

The same algorithm described for Cohort 1 will apply to each stratum in Cohort 2 (Stratum 2A and Stratum 2B) with PK and safety evaluation done at enrollment of the first six evaluable infants and using the data of the initial set of safety-evaluable infants for dose-finding purposes, except that the dose-finding algorithm applied to each stratum will be based on PK and safety data through the Weeks 4-6 visits. If a stratum meets both Safety Guidelines and PK targets at a given dose, then additional evaluable infants for the dose-finding evaluation will be accrued and administered this dose to complete a full stratum of n=12 minimum evaluable infants. Safety and PK will then be assessed on the full stratum based on PK and safety data through the Weeks 4-6 visits. If Safety Guidelines and PK targets are met, then the dose is established for the stratum.

Otherwise, the dose may be adjusted, a new group of six evaluable infants will be enrolled at the adjusted dose, and the evaluation procedures described above will be repeated. This will proceed until a full stratum of n=12 minimum evaluable infants administered a given dose meet both the Safety Guidelines and the PK targets. The CMC will consult with the SMC when the Safety Guidelines are failed at a scheduled dose-finding assessment.

Enrollment of up to two additional mother-infant pairs will be allowed before the PK and safety dose-finding evaluation on the first six evaluable infants in the stratum has been completed (i.e., up to eight evaluable infants may be enrolled before enrollment is paused). Accrual will be paused in the relevant stratum while awaiting completion of the required PK and safety evaluations for the target n=12 evaluable infants. The CMC may resume accrual if any of the infants is assessed as unevaluable for the dose-evaluation and needs to be replaced.

9.5.2 Safety Guidelines

On behalf of the Protocol Team, the CMC will conduct dose-finding evaluations and will review the safety and PK data at full accrual of a Cohort 1 stratum (minimum of six evaluable infants), accrual of first six evaluable infants in a Cohort 2 stratum, and at full accrual of a Cohort 2 stratum (minimum of 12 evaluable infants). During these reviews, the CMC will assess whether the Safety Guidelines are passed and if PK data confirm that a dose is appropriate for the cohort stratum or if there is a need to change the dose for the stratum/cohort. Upon review of the PK and safety data, the CMC will take appropriate actions as described in Section 9.5.1.

The safety evaluation of a cohort stratum dose will be done using the data on all safety-evaluable infants for dose-finding evaluations who are on the dose being evaluated. It will be done when all infants to be included in the dose safety evaluation have completed the safety visit associated with the last study drug dosing, and the safety data for this visit are in the study database. The dose safety evaluation will be based on all available safety data at the time of data review.

The Safety Guidelines will consider the severity and seriousness of AEs and the attribution of AEs to study drug. AE attribution to study drug will be based on the site's assessment. If the SMC is consulted on AE assessment to study drug, the SMC's opinion will be used. The Safety Guidelines are considered to not be met if:

- at least one infant experienced a fatal or life-threatening (see Section 7.3) AE assessed as related to study drug; or
- more than 25% of the infants (e.g., two or more of six infants; four or more of 12 infants) experience a Grade 3 or higher AE assessed as related to study drug or experience any grade AE assessed as related to study drug that results in permanent discontinuation of study drug.

If none of these conditions are met, then the dose being evaluated has passed the Safety Guidelines.

In addition to the assessment of the Safety Guidelines, the CMC will also be provided with the following:

- For all safety-evaluable infants on the dose being evaluated, the following will be provided:
  - A listing of Grade 3 or higher AEs and AEs which result in permanent discontinuation of study drug. The list will indicate which AEs were assessed as related to study drug and which AEs resulted in permanent study drug discontinuation; and

    - A listing of reasons for temporary and permanent discontinuation of the study drug; and
    - A listing of all AEs which the SMC was asked to review. The listings will include information about the AEs and the site investigator's assessment of and the SMC's opinion on AE attribution to the study drug.
- A listing of infants who were started on the dose being evaluated but were safety- or PK-unevaluable for the dose-finding evaluation.

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

The extent to which the Safety Guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur if the study drug were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Table 13 range from conditions under which a given dose level would cause a high incidence of severe and life-threatening AEs to conditions under which severe AEs would be relatively rare and would not be life-threatening. For each of these hypothetical situations, we assume that a sample of six infants is drawn from the participant population and that the Safety Guidelines, summarized above, are followed.

Table 13 and Table 14 use a multinomial response model to assess the probability of failing the Safety Guidelines under each of these hypothetical situations. The calculations are performed as follows: Each of the six or twelve infants represents a trial, which may have 1 of 3 mutually exclusive outcomes: (i) death or life-threatening AE assessed as related to study drug; (ii) a Grade 3 or 4 non-life-threatening AE assessed as related to study drug; and (iii) a relatively benign outcome, satisfying neither the criteria in (i) nor (ii).

Table 13
Probability of Cohort 1 or 2 Six Infants Failing Safety Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Grade 3 or 4 Non-Life-Threatening Drug-Related AE	Life-Threatening or Fatal Drug-Related AE	
0.50	0.00	0.89
0.50	0.05	0.94
0.50	0.25	1.00
0.25	0.00	0.47
0.25	0.05	0.63
0.25	0.25	0.94
0.05	0.00	0.03
0.05	0.05	0.29
0.05	0.25	0.83
0.00	0.05	0.26
0.00	0.25	0.82

Table 14
Probability of Cohort 2 Twelve Infants Failing Safety Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Grade 3 or 4 Non-Life-Threatening Drug-Related AE	Life-Threatening or Fatal Drug-Related AE	
0.50	0.00	0.93
0.50	0.05	0.97
0.50	0.25	1.00
0.25	0.00	0.35
0.25	0.05	0.67
0.25	0.25	0.99
0.05	0.00	0.00
0.05	0.05	0.46
0.05	0.25	0.97
0.00	0.05	0.46
0.00	0.25	0.97

Table 13 presents results under which the set of trials would fail the Safety Guidelines for six safety-evaluable infants. For each of the hypothetical situations, it is assumed that a sample of six infants is drawn from the population and that the Safety Guidelines, summarized above, are followed. The probability of failing the Safety Guidelines represents the sum of the probabilities of these sets of results, and "1 minus the probability of failing the Safety Guidelines" represents the probability of passing the guidelines. The "True Toxicity Rates" presented in the table, along with the true rate of having neither of the two types of AEs represented by the true toxicity rates (which is "1 minus the sum of the true toxicity rates"), provide the probabilities for the outcomes that are used in the multinomial calculations for each of the hypothetical situations.

As an example of how to read Table 13, the second row shows that there is a 94% chance of failing the Safety Guidelines at doses in which the true rate of drug-related life-threatening AEs is 5% and the true rate of drug-related non-life-threatening AEs is 50%. Under the conditions specified in row two of the table, assuming that further exposure to a dose that has these true rates of AEs would be undesirable, the 6% chance of NOT failing the Safety Guidelines would represent the probability of error. As a further example, the table also shows that there is a 3% chance of failing when the true rate of a drug-related Grade 3 or 4 non-life-threatening AE is only 5% and the true rate of drug-related life-threatening or fatal AE is zero. Assuming that the potential benefits associated with further exposure to this dose would outweigh the risks associated with this relatively low rate of toxicity, failing the Safety Guidelines under these conditions would be an error.

Note that during routine monitoring, the CMC may pause accrual across all cohort strata if a fatal or life-threatening AE occurring in a given stratum is assessed as related to study drug. Thus, the probability of pausing accrual into a cohort stratum (pending a safety review) is somewhat higher than that of failing the Safety Guidelines within a given cohort stratum (as presented in Table 13), because accrual into a given cohort stratum may be paused due to events occurring within the cohort.

9.5.3 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

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

The Protocol Team will closely monitor participant accrual and retention based on reports that will be generated at least monthly by the IMPAACT Statistical and Data Management Center (SDMC). The team will also monitor site actual accrual relative to site-specific accrual 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. Accrual performance will be reported by the DMC, by site and across sites, and the team will review and discuss study progress at least monthly. The team will communicate with any site that is delayed in completing the study activation process, or that falls short of its accrual projections, to identify the barriers the site has encountered and the operational strategies and action plans to address these.

During the routine monitoring of safety and PK data, the CMC will determine the evaluability status of the infants on behalf of the Protocol Team, and the SDMC will record the decision in the

database. Relevant study treatment information (e.g., study treatment status, on/off study treatment dates) will be provided to the CMC to facilitate assessment of the infants' evaluability status. The team will monitor accrual and communicate to sites when sample size targets are reached.

The Protocol Team will also review participant retention and other key indicators of the quality of study conduct (e.g., protocol deviations, data quality, and 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.

Infant Safety

On behalf of the Protocol Team, the CMC will closely monitor infant safety through routine review of safety data reports generated by the SDMC. These reports will be based on safety-related data collection in enrolled infants described in Section 7.2 and will provide listings and/or tabulations of AEs and laboratory test results. The CMC will review these reports at least monthly. At the time of each review, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS RSC Safety Office that are not yet reflected in the data reports.

The CMC will continually evaluate the pattern and frequency of reported AEs and assess for any individual AE occurrences or trends of concern. The CMC will monitor for the occurrences of AEs meeting criteria to pause participant accrual and/or convene an *ad hoc* SMC review, as described in Section 9.5.4.

The CMC will review the site's assessment of the relationship of AEs listed in toxicity summary reports. If the CMC has questions about the site investigator's assessment, the CMC will discuss the AE further with the investigator and ideally come to consensus with the investigator. If consensus cannot be achieved, the CMC will request adjudication by the SMC.

9.5.4 Monitoring by the SMC

An independent SMC will review the study regularly, following policies described in the IMPAACT Network MOP.

SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise, or as requested by the CMC. The SMC will monitor study progress, quality of study conduct, and participant safety. Additional SMC reviews focused on safety may also occur as indicated below (*Infant Safety).*

Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

Study Progress and Quality of Study Conduct

The SMC will monitor study progress and the quality of study conduct through review of the same types of data reports as the Protocol Team and CMC.

Infant Safety

The SMC will monitor participant safety through review of the same types of safety data reports as the CMC. *Ad hoc* SMC reviews may be triggered based on CMC review of PK and safety data during routine monitoring and at scheduled safety and PK dose-finding evaluations. For *ad hoc* or triggered safety reviews, more limited data may be provided, focusing on the events that triggered the reviews.

Ad hoc or triggered SMC reviews will occur as follows:

(1) In the event of **any AE that is life-threatening or results in death,** the site will consult with the CMC per Section 8.
- If after CMC review of an AE that results in death, the site investigator assessment or the CMC review indicate the AE as **related to study drug**, accrual and administration of study drug in the relevant cohort (all strata) will be paused and the SMC will be consulted.
- If after CMC review of an AE that is life-threatening, the site investigator assessment or the CMC review indicate the AE as **related to study drug**, accrual will be paused in the relevant cohort (all strata) and the SMC will be consulted. The CMC and/or SMC may also pause administration of study drug in the cohort (all strata).
- If the site investigator assessment and CMC review indicate the AE(s) as **not related to study drug**, participant accrual in the cohort (all strata) will continue. The SMC will be informed of the AE along with the CMC's review and decision-making.

(2) In the event of a Grade 3 or higher AE, or any grade AE which results in permanent discontinuation of the study drug, the site will consult with the CMC per Section 8.
- If at the scheduled assessment of the Safety Guidelines in Section 9.5.1, more than 25% of the safety-evaluable infants for the dose-finding evaluation experience a Grade 3 or higher AE assessed as related to study drug or any AE assessed as related to study drug that results in permanent discontinuation of study drug, participant accrual in the relevant cohort (all strata) will be paused and the SMC will be consulted.

(3) If a consensus between the site assessment and CMC review of AE attribution to the study drug cannot be achieved, the CMC will request adjudication by the SMC.

(4) The SMC will be consulted prior to opening each Cohort 2 stratum to accrual. The SMC will review all relevant safety and PK data along with the CMC recommendation on Cohort 2 dosing.

(5) Bilirubin will be managed by site investigators and/or other clinicians of infants according to local standards of care, see Section 8. If there are any safety concerns about increased bilirubin, participant accrual and administration of study drug in the cohort may be paused; the CMC will discuss how the study should proceed and will consult with the SMC.

(6) In the event of any unresolvable disagreement within the CMC on an issue that would impact decision-making, or if the CMC encounters any AE or AE trend of concern, an SMC review of the relevant data will be convened. The CMC may choose to pause participant accrual and/or administration of study drug, pending the outcome of the SMC review.

9.6 Analyses

The analyses listed below will be performed to address the study objectives. Exceptions are analyses for PK-related study objectives, which are described in Section 10. The report will also include a per infant line listing of all AEs reviewed by the SMC, showing the site investigator's assessment of and the SMC's opinion on AE attribution to the study drug.

Separate data summaries will be done for each cohort. When applicable, summary statistics for each stratum or a dosing within a cohort will be provided. Additional details on the planned analyses listed in this section will be included in the Primary SAP.

9.6.1 Primary Analyses

Primary Safety Analyses

To address the primary safety objective, the analyses will focus on DTG safety through two weeks after an infant is permanently off DTG (Outcome Measures 9.2.1.1 and 9.2.1.2). Point and 90% Clopper-Pearson CI estimates of the proportion of infants classified as safety failures will be generated.

Point estimates of the proportion of infants who meet each criterion for the safety failure and relevant infant listings of safety data will be provided. Analyses will be done for the following groups with additional group analyses added if needed.

- All infants whose starting dose for DTG has been the final dose proposed for their cohort stratum (i.e., group on the proposed dose).
- All infants who received at least one dose of DTG (i.e., all exposed group).

An infant who is taken off DTG due to HIV-1 diagnosis will be included in the analyses.

Primary Tolerability Analyses

Point and 90% Clopper-Pearson CI estimates of the proportion of infants who experience problems taking the study drug as defined in Section 6 or experience any AE assessed as related to study drug that leads to premature permanent discontinuation of the study drug (Outcome Measure 9.2.1.3) will be provided. Point estimates of the proportion of infants meeting each component of the composite tolerability endpoint and relevant safety listings will be provided. Analyses for the group on the final proposed dose and the exposed group as defined above will be done.

9.6.2 Secondary Analyses

Secondary Safety Analyses

To address the secondary safety objective, the analyses will focus on DTG safety through the Week 16 visit (i.e., Outcome Measures 9.2.2.1 and 9.2.2.2). Point and 90% Clopper-Pearson Confidence CI estimates of the proportion of infants classified as safety failures will be generated. The analyses will have similar specifications as the primary safety analyses described in Section 9.6.1.

Infants in Cohort 2 will receive DTG from Entry through the Week 4 or 6 visit depending on the duration of the infant's standard ARV prophylaxis, although some infants would have stopped DTG early for other reasons. To understand the Cohort 2 infants' exposure to DTG, summary statistics on infants' age at first and last DTG dosing and the duration of receipt of DTG will be provided. The infants' age at start/end and duration of the infants' ARV prophylaxis will also be summarized.

Additional analysis on Cohort 2 infants who received at least one dose of DTG:

As an additional analysis, and if the data allow for the analysis, a time-to-event analysis will be performed on time to safety failure using follow-up data through the Week 16 visit with follow-up censored at the date of the last safety assessment. Kaplan-Meier (KM) estimates of proportion of safety failures at Weeks 6, 8, and 16 will be generated.

9.6.3 Other Analyses

Association between Infant DTG Elimination and UGT1A1 Genotype

Infant genotype testing for UGT1A1 is optional. All infants with DTG clearance (CL/F) and UGT1A1 genotype data will be included in the analyses.

Summary statistics for DTG CL/F by UGT1A1 genotype groups will be generated. The median DTG CL/F of the UGT1A1 genotype groups will be compared using Wilcoxon Rank-Sum test or Kruskal-Wallis test at α=5%. The power of the test will depend upon the number of genotype groups being compared and the distributions of the variables to be analyzed and will be extremely limited if the sample size is small.

Maternal Data and Additional Infant Data

Maternal medical history, maternal ARVs during pregnancy and at the Entry visit, duration of infant DTG, infant's standard of care ARVs, and infant's receipt of breast milk may be relevant for the interpretation of safety and PK data. Listings and summary tables will be generated.

Regulatory Submission

For regulatory submission purposes, the analyses will follow specifications in the Primary SAP. Additional analyses and additional analyses specifications for regulatory submission tables, figures, and listings will be specified in a separate document.

9.7 Additional Considerations

Special statistical and data analysis considerations may be warranted in the event that the COVID-19 pandemic or other unanticipated occurrences (e.g., natural disasters) affect the conduct of this study and/or the integrity of study data. To the extent possible, any such considerations will be addressed in the study SAP. Alternatively, a separate analysis plan focused on these considerations—describing, for example, changes of analysis populations, visit windows, outcome measures, and analyses to assess impacts of and account for missing data—may be prepared. All analysis plans will take into consideration applicable regulatory guidance and industry best practices.

10 CLINICAL PHARMACOLOGY PLAN

The design and analysis plans for objectives 2.1.2 and 2.1.3 are described in this section. PK sample collection, processing, storage, and shipping instructions are provided in the LPC.

10.1 Pharmacology Overview and Objectives

- To evaluate the PK of DTG during the first four to six weeks of life when administered to HIV-1 exposed infants with standard ARV prophylaxis.
- To propose an appropriate dose of DTG during the first four weeks of life for HIV-1 exposed infants, when administered with standard ARV prophylaxis.

This study is designed to assess the PK and safety of DTG administered as either a liquid suspension or a DT in infants during the first four to six weeks of life. Infants will be stratified in Cohorts 1 and 2 by maternal use of DTG (refer to Section 3). Cohort 1 infants will receive two single doses of DTG. Infants in Stratum 1A (DTG-naïve) will receive DTG as a liquid suspension at two time points with intensive PK sampling around each dose. The first single dose, at Entry, will be within 0-5 days of life. Infants in Stratum 1B (DTG-exposed) will also receive DTG liquid suspension at two time points with intensive PK sampling around each dose. The first single dose, at Entry, will be within 2-5 days of life. Infants in both Stratum 1A and Stratum 1B will receive the second single dose at the 7 Days Post Initial Dose visit (+3 days).

Intensive PK results will be reviewed by the CMC as available. The protocol pharmacologists will determine whether PK parameters can be estimated from the specimens collected, and, as described in Section 3, these determinations will be used to determine whether participants are evaluable. If PK samples are determined to be consistently below the limit of assay quantitation for a given participant, adherence data will be reviewed by the CMC and the participant may need to be replaced. However, any information obtained that could be used for PK modeling and simulations will be utilized if possible, such as elimination half-life. All assessments related to PK evaluability by the CMC will be documented.

Emerging data from Cohort 1, Stratum 1A and Stratum 1B, will be evaluated using modeling and simulation-based approaches. If modeling and simulation supports the use of a 5 mg dose across all eligible neonates, or only in neonates with a minimum threshold body weight**,** then the third stratum (Stratum 1C) may be enrolled in Cohort 1. DTG-naïve infants—either all eligible participants or those meeting a specific weight threshold as indicated by analysis—will be enrolled accordingly in Stratum 1C and receive two single 5 mg doses of DTG administered as a DT at study entry within 0-5 days of life and at the 7 Days Post Initial Dose visit (+3 days) with intensive PK sampling around each of the doses. All available safety and PK data from Strata 1A, 1B, and 1C (if applicable) will be analyzed to determine the appropriate dose, dosing regimen, and formulation(s) for chronic dosing evaluation in Cohort 2. ***If PK modeling and simulations do not support the use of the DTG 5 mg dose or if safety concerns have been observed, then the study will not enroll in Stratum 1C and Cohort 2 will proceed using the DTG liquid suspension formulation.*** Any further dose regimen or formulation-related changes will be undertaken based on emerging safety and exposure data.

Cohort 2 infants will receive chronic dosing of DTG beginning within five days of life using an appropriate formulation, dose size, and dose frequency determined based on PK and safety data from the corresponding stratum in Cohort 1. Infants in Cohort 2 will have intensive PK sampling at 7 Days Post Initial Dose and Week 4 visits. Population PK samples will be collected for all

Cohort 2 infants at the 2 Days Post Initial Dose visit, and at the Week 6 visit only for Cohort 2 infants receiving DTG per local standard of care for ARV prophylaxis through the Week 6 visit. Refer to Section 3 for further details on the study design.

10.2 Pharmacology Sampling

Infants in Cohorts 1 and 2 will have intensive and population PK samples collected per the timepoints indicated at study visits in Section 6.

At PK visits, if there is any clinical indication or concern that the infant has an intercurrent illness or infection, contact the CMC prior to administering the DTG dose. At each intensive PK visit the DTG dose must be administered and/or observed by study staff. The exact DTG dose time, dose amount, draw time of each PK sample, and, if applicable, time of emesis within first four hours must be entered into appropriate eCRFs. Refer to Section 5 for further details on DTG administration.

Intensive and population PK results are not expected to be routinely provided to site investigators or mothers and/or guardians. However, if CMC review of the results, together with other relevant study data (e.g., adherence data, clinical data, HIV-1 test results), identifies any potential concerns or clinical management issues, the team will contact the site investigator to discuss the results and any potential management actions that may be considered. Likewise, site investigators may contact the team to request PK results on a case-by-case basis if they determine that such results may assist with participant management.

10.3 Pharmacology Outcome Measures

The study PK outcome measures are listed in Table 15.

Table 15
PK Outcome Measures

10.3.1	**Primary PK Outcome Measures**
10.3.1.1	Cohort 1: C_{last} and area under the curve (AUC) for DTG.
10.3.1.2	Cohort 2: C_{trough} and $AUC_{0\text{-}tau}$ for DTG.
10.3.2	**Other PK Outcome Measures**
10.3.2.1	Other PK outcome variables will include the association of UGT1A1 gene sequence variants with DTG CL/F.

10.4 Pharmacokinetic Guidelines for Dose Adjustment

The study will implement a dose-finding algorithm based on the review of the single-dose PK and safety data from Cohort 1: Stratum 1A (DTG-naïve, liquid suspension), Stratum 1B (DTG-exposed, liquid suspension), and if enrolled, Stratum 1C (DTG-naïve, DT). Cohort 1 will enroll six participants determined to be PK-evaluable in each stratum and provide PK data that will be used to characterize DTG exposure in neonates. Appropriate analyses will be performed (e.g., Population PK and simulations) with Cohort 1 data to determine initial formulation and doses for Cohort 2. Cohort 2 dosing regimens that will optimize the potential to meet the DTG exposure targets while minimizing the risk of over-exposure will be selected for each stratum. Cohort 2 DTG-naïve infants will be enrolled in Stratum 2A and DTG-exposed infants will be enrolled in Stratum 2B; at least eight breastfeeding and eight formula-feeding infants will be enrolled across both strata. No restrictions will be made on time of dosing in relation to food intake.

The doses for Cohort 2 will be selected to achieve target exposures as defined by C_{trough} (Primary PK endpoint) and $AUC_{0\text{-}tau}$ (Secondary endpoint). The target C_{trough} population exposure (geometric mean, GM) of 995 ng/mL (697-2260 ng/mL) is selected to achieve comparable exposures as seen in adults and is based on PK data from phase III adult studies ING111762 and ING113086 where the PK of DTG was characterized without regard to food. The lower limit reflects the 70% of GM (697 ng/mL= 995 ng/mL * 0.7) and the upper limit (2260 ng/mL) is the upper 90th percentile of plasma concentration observed at end of 24-hour dosing interval (C_{24h}) concentrations from combined data in ING111521 and ING112276.

The Cohort 2 $AUC_{0\text{-}tau}$ target population exposure (GM) of 46 µg*h/mL (37 -134 µg*h/mL) reflects the exposures seen in adults based on combined data from ING111521 and ING112276 studies following 50 mg once daily dosing. The lower limit reflects the 80% of the target GM (46 µg.h/mL *0.8= 37 µg*h/mL) while upper limit (134 µg*h/mL) is the upper 95th percentile of AUC obtained at steady state following 50 mg BID dosing. Similar targets (C_{trough} and AUC) were used in a previous DTG pediatric study (IMPAACT P1093).

There is no known C_{max} target as there are limited PK and safety data in young children and no experience in the administration of DTG to neonates. In children four weeks to < 18 years of age enrolled on IMPAACT P1093 and the ODYSSEY study, the C_{max} PK parameter geometric mean (%CV), ranged from 3.8 (34%) to 7.16 (26%) mcg/mL. To avoid potential displacement of bilirubin from albumin and toxicity related to hyperbilirubinemia, five times the upper limit of the typical C_{max} observed in adults of 3.67 µg/mL will be used in this study as the C_{max} target (C_{max} < 18.35 µg/mL). As new information about DTG safety and PK becomes available, the C_{max} target may be lowered.

Infants in Cohort 1, Stratum 1A and Stratum 1B, will receive only the DTG liquid suspension formulation. If opened, infants in Cohort 1, Stratum 1C, will receive the DTG DT formulation. Infants in Cohort 2 strata will receive either the DTG liquid suspension or the DT depending upon results of Cohort 1.

Cohort 1, Stratum 1C (DTG-naïve, single dose DT) will be opened only if modeling and simulation of emerging data from Stratum 1A and Stratum 1B support the use of a 5 mg dose across all eligible neonates or neonates with minimum threshold bodyweight according to weight band dosing. Simulations will consider different dosing frequencies, including but not limited to once-daily dosing and every other day dosing. If PK modeling and simulations do not support the use of a DTG 5 mg dose across all eligible neonates (i.e., ≥ 2 kg) or in neonates with a minimum weight, then the study will proceed to Cohort 2 using the DTG liquid suspension formulation. Any further DTG dose regimen or formulation-related changes will be undertaken based on emerging safety and exposure data. This determination will be made according to the same PK targets above; that is, in order for Stratum 1C to be opened to enrollment, modeling and simulation must support that a dose of DTG 5 mg DT will achieve:

- Target C_{trough} population exposure (GM) of 995 ng/mL (697-2260 ng/mL)
- $AUC_{0\text{-}tau}$ target population exposure (GM) of 46 µg*h/mL (37-134 µg*h/mL)
- C_{max} < 18.35 µg/mL

A minimum of 24 and up to 72 mother-infant pairs will be enrolled in Cohort 2 to achieve a target of 24 evaluable infants (across both strata) receiving the final proposed DTG regimen.

In a prior clinical study (209354, NCT03921723) the relative bioavailability of the DTG liquid suspension and DT formulation intended to be used in IMPAACT 2023 was evaluated in adult volunteers. All exposure parameters (C_{max}, $AUC_{(0\text{-}tau)}$ and $AUC_{(0\text{-}inf)}$) for the liquid suspension were within the bioequivalence limits (80%-125%) compared to those from the DT formulation. There are no data on the absorption of the DT in neonates including the impact of formula feeding or breastfeeding on C_{max} and bioavailability. Therefore, the objective of Stratum 1C is to obtain preliminary PK data on the DT in neonates after developmental PK data for DTG have been obtained in Stratum 1A and Stratum 1B to assess the appropriateness of studying the DTG 5 mg DT in this population.

Emerging PK data from Strata 2A and 2B will be evaluated prior to full accrual of each strata as described in Section 3. If three or more of the 12 infants in Stratum 2A or 2B do not meet the DTG exposure target (Primary PK endpoint C_{trough} and secondary endpoint $AUC_{0\text{-}tau}$), the CMC will evaluate available data to make appropriate study-related recommendations. Simulations derived from PK modeling of Cohort 1 and available Cohort 2 data will be used to evaluate dosing regimens and inform any formulation, dose, and/or frequency adjustment decisions for each subsequent stratum in Cohort 2. Enrollment of additional groups of six infants receiving adjusted formulation, doses, and/or frequency will be allowed, and the above process will be repeated, unless the maximum sample size for the cohort has been reached.

10.5 Interim Analyses

The PK data may be analyzed for each individual infant enrolled in this study in real-time. Results from the interim analyses of emerging PK data will be reviewed by the CMC. A summary of the PK data will be prepared at the following times:

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

10.6 Pharmacology Study Design, Modeling, and Data Analysis

10.6.1 Initial Dose Selection

The initial single DTG dose selected for evaluation in Cohort 1 is based on available PK data from other studies for DTG and modeling and simulations. In pediatric participants in the 3 to <6 kg weight band (~ four months age), approximately 1 mg/kg dose as a DTG 5 mg fixed DT at steady state achieved exposure comparable to adults (Table 16). It is anticipated that neonates will require a much lower mg/kg dose in the first days of life based on experience with RAL in the IMPAACT P1110 study.

Table 16
Summary of DTG PK Parameters in Infants > four weeks and < six months of age living with HIV: IMPAACT P1093 Study

Weight Band (kg)	Dose	N	PK Parameter GM (%CV)		
			AUC_{0-24h} (µg*h/mL)	C_{max} (µg/mL)	C_{24h} (ng/mL)
3 to <6	5 mg DT	8	49.37 (49)	3.8 (34)	962 (98)

Based on preliminary modeling and simulations, exposure for neonatal participants following administration of a single proposed 0.5 mg/kg starting dose for Cohort 1 is summarized in Table 16. Doses used in these simulations were determined based on 5 mg/mL DTG formulation suspension in Miglyol with minimum syringe volume of 0.1 mL for accurate dose dispensing. PK parameters summarized in Table 17 are not at steady state and represent the administration of DTG on Day 1 after birth.

Table 17
Simulated PK Parameters Following Administration of DTG at 24 hours After Birth as 5 mg/mL Suspension in Miglyol in Term Neonates

WT	Volume of 5 mg/mL DTG (mL)	DOSE (mg)	PK Parameters (Day 1) Geomean (95%CI)		
			AUC_{0-24} (µg*h/mL)	C_{max} (µg/mL)	C_{24h} (ng/mL)
0.5 mg/kg Dose					
2 kg	0.2	1	11.94 (6.43-20.91)	0.803 (0.451-1.377	332 (101-805)
3 kg	0.3	1.5	14.44 (7.94-25.12)	0.956 (0.543-1.644)	414 (134-974)
4 kg	0.4	2	16.46 (9.09-28.54)	1.081 (0.614-1.863)	482 (163-1125)

10.6.2 Noncompartmental PK analysis

Cohort 1

Single dose PK parameters including primary endpoint C_{trough} and secondary endpoint area-under-the-concentration-time curve over the sampling time (AUC_{0-t}) for DTG from Cohort 1 infants will be determined data permitting, post each dose using noncompartmental methods. Additional other relevant PK parameters of interest may include maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), CL/F, apparent volume of distribution during the terminal phase (Vz/F), elimination rate constant (k), and terminal elimination half-life ($t_{1/2}$).

Cohort 2

Steady state PK parameters including primary endpoint C_{trough} and secondary endpoint area-under-the-concentration-time curve over the dose interval (AUC_{0-tau}) for DTG from Cohort 2 infants will be determined data permitting, at the 7 Days Post Initial Dose (+3 days) and Week 4

visits using noncompartmental methods. In Cohort 2, additional PK parameters of interest will include the plasma concentrations at the beginning (C_{0h}) and end of the dosing interval (C_{last}), and the minimum plasma concentration (C_{min}).

10.6.3 Population PK Analysis

DTG exposure will be characterized utilizing appropriate population PK approaches incorporating all available data (intensive and population PK data) generated in the study. Existing clinical data from other pediatric and adult clinical studies may be included in these analyses if warranted. The impact of relevant study, treatment, and participant-related factors such as co-medication (including NVP and efavirenz), formulation, method of feeding (e.g., formula vs. breastfeeding), and ontogeny will be evaluated as data permit to propose optimal dosing regimen(s) that achieve target DTG exposures comparable to those seen in adults.

10.6.4 PK Sample Size

This study is powered to target a 95% CI within 60% - 140% of the geometric mean estimate of DTG oral clearance in neonates with 80% power. The target sample size for this study is 36 evaluable infants (six evaluable infants in each Cohort 1 stratum and 12 evaluable infants in each Cohort 2 stratum). Based upon investigator experience, the target sample size is sufficient to estimate DTG PK parameters and to perform intended modeling and simulation. Data from this study will be integrated into existing pediatric and adult DTG population PK models in order to characterize the PK and dosing requirements of DTG in neonates and infants during the first four to six weeks of life.

10.7 Anticipated Outcomes

The goal of this study is to gain an understanding of DTG PK and safety in neonates in order to determine an appropriate DTG dosing regimen for use in neonates.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

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

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled mother-infant pairs, including 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 Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study 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.

The Protocol Team and/or study oversight bodies (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

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

GSK device deficiency forms will be made available to study sites and completed forms will be maintained by GSK/ViiV. See Section 7.4 for instructions on medical device reporting requirements. GSK/ViiV may also contact sites to request additional information on medical device deficiency forms submitted to GSK/ViiV, as needed. A copy of completed device deficiency forms submitted to GSK/ViiV for study participants should be maintained on site in study records.

11.2 Essential and Source Documents and Access to Source Data

Study sites must comply with DAIDS requirements for essential documents and source documentation as specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. 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 US Code of Federal Regulations (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; if no application is filed or 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; GSK/ViiV Healthcare; the FDA; site drug regulatory authorities; site IRBs/ECs; the sIRB (for US sites); Office for Human Research Protections; 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.

11.3 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 SCORE Manual.

12 CLINICAL SITE MONITORING

Under contract to DAIDS or NICHD, site monitors will inspect study site facilities and review participant study records—including informed 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. 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 monitors.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by DAIDS or NICHD. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity (21). Site investigators will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, Medidata Rave Imaging Solution, Medidata Remote Source Review, site-controlled SharePoint or cloud-based portal, and direct access to electronic medical records. Other secure platforms that are 21 CFR Part 11 and HIPAA compliant may be utilized, as allowed by DAIDS Office of Clinical Site Oversight (OCSO) or NICHD.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Non-US sites are frequently overseen by more than one IRB/EC. US sites are overseen by an sIRB, with additional review by local IRBs if required per their agreements with the sIRB. Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs/ECs. All such policies and procedures must be followed, and complete documentation of all correspondence to and from all applicable 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 (also refer to Section 14.2).

13.2 Vulnerable Participants

It is NIH policy to ensure that pregnant women and children be included in clinical research when appropriate (22, 23). This study responds to that mandate and will provide clinical research data to inform DTG safety and dosing in full-term infants. The infants who take part in this study are considered vulnerable participants per US Code of Federal Regulations, and site IRBs/ECs must

consider the potential risks and benefits to infant participants as described in 45 CFR 46 Subpart B (for pregnant women, fetuses, and neonates) and 45 CFR 46 Subpart D (for children).

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

With respect to 45 CFR 46 Subpart D, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC further determines the parental informed consent requirements for the study at each site. Per 45 CFR 46.408 (b), the IRB/EC may find that the consent of one parent is sufficient for research to be conducted under 46.404 or 46.405. If the IRB/EC finds that the research is covered by 46.406 or 46.407, both parents must give their consent, unless one parent is deceased, unknown, incompetent, 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 DAIDS requirements for enrolling minors in clinical research as specified in the DAIDS SCORE Manual. In addition to the US regulations cited above, sites must also comply with all applicable local and national and international guidelines and regulations. In cases where multiple different sets of requirements apply, the most stringent requirements must be followed.

13.3 Informed Consent

Refer to Section 4.4 and the study-specific MOP for further information on informed consent procedures for this study. Refer to Appendices VII and VIII for the sample informed consent forms.

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

The informed consent process will include information exchange; detailed discussion; and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will include a description of what is currently known about the safety and efficacy of the study drug and the context of current local standards of care for HIV treatment. Mothers will be extensively counseled on the importance of adherence to their standard of care ARV regimen for prevention of perinatal transmission and adherence to the infant's ARV regimen.

As part of the informed consent process, mothers will be asked to provide written consent for protocol-specified genetic testing. Mothers will also be asked to provide written consent for storage and future research testing (including genetic testing) of biological specimens remaining after all protocol-specified testing has been completed. Both protocol-specified genetic testing and future research testing of biological specimens may be declined with no impact on other aspects of study participation.

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

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. No further study drug should be administered, and no study-specific visits or procedures may 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 guardian does not consent to continued study participation, the infant must be withdrawn from the study.

In accordance with the DAIDS requirements for enrolling minors in clinical research (as specified in the DAIDS SCORE Manual), 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.

13.4 Potential Benefits

There may or may not be a direct benefit to mothers or infants who take part in this study. Infants enrolled in Cohort 1 will receive only two single doses of DTG (in addition to standard of care ARVs), and infants enrolled in Cohort 2 will receive chronic doses of DTG through the Week 4 or Week 6 visit (i.e., up to 47 days of life). While there is no established direct benefit of administering DTG in neonates, DTG given in addition to proven ARV prophylaxis may provide some prophylactic benefit for HIV. Information learned in this study may be of benefit to participating infants and others in the future, particularly information that may lead to more preventive and treatment options for infants living with HIV. Mothers may also appreciate the opportunity for themselves and their infants to contribute to HIV-related research.

13.5 Potential Risks

The potential risks of participation in this study include risks associated with study procedures and risks associated with receipt of DTG.

Many study procedures are routine medical procedures that are associated with minimal to no risk in participants. Blood collection may cause pain, bruising, swelling, and (rarely) infection at the site where the needle is inserted.

Refer to Section 1 and the IB for DTG DT and liquid formulation for a description of the potential risks associated with the use of DTG.

DTG-based regimens have been shown to be highly effective treatment options for both treatment-naïve and treatment-experienced, INSTI-naïve children (down to four weeks old and weighing at least 3 kg), adolescents, and adults. DTG-based regimens have also demonstrated a high barrier to resistance in INSTI-naïve patients, and have shown excellent tolerability, as shown by the low rate of discontinuations due to AEs. The most common AEs across the adult clinical program have been diarrhea, nausea, insomnia, fatigue, and headache; these events occurred at similar rates across treatment groups, were not treatment limiting, and were generally mild in intensity.

Potential severe adverse reactions include hypersensitivity and hepatotoxicity. Combination ARV therapy has also been associated with immune reconstitution syndrome and lipodystrophy. Other reported AEs for DTG include rash, pruritis, abdominal pain, flatulence, anorexia, fever, myositis, abnormal dreams, depression, anxiety, dizziness, and excessive weight gain. There can also be laboratory abnormalities of liver enzymes, myositis, renal impairment, lipase, neutropenia, anemia, and dyslipidemias.

IMPAACT P1093 is an ongoing Phase I/II, multicenter, open-label, non-comparative intensive PK study of DTG in participants ≥ four weeks to <18 years of age administered DTG film-coated tablets, oral granules for suspension (formulation development discontinued), or DTs. A total of 181 participants enrolled in the study, with the last enrollment on 19 February 2020; the study is ongoing as of March 2022. At the interim analysis in April 2019, the most frequently observed AEs through 24 weeks of treatment were cough, pyrexia, diarrhea, rhinorrhea/nasal congestion, and nausea and vomiting (24). These were mostly Grade 1 or 2 severity. The majority of reported AEs were expected for this population since childhood infections are common. Through 24 weeks of treatment, 15/159 (9.4%) participants reported at least one SAE, and these came most frequently from the Infections and Infestations category. The most commonly reported SAEs were gastroenteritis (n = 4), pneumonia (n = 2), and immune reconstitution syndrome (n = 3) (24). Three participants experienced drug-related SAEs, all of which were cases of immune reconstitution syndrome. The safety profile reported in this study to date appears no different to those observed to the clinical trials in adults.

Some AEs have been reported in persons taking DTG that are not relevant to the neonatal population. Among these AEs are embryo-fetal toxicity and suicidality. Embryo-fetal toxicity may occur when used at the time of conception and early in pregnancy. Suicidality is reported primarily in adolescents and adults with pre-existing psychiatric diagnoses.

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

13.6 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 and/or other materials as per applicable IRB/EC policies and procedures.

13.7 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 11.2.

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms, photographs of observed reactions) 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 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 deemed issued for the IMPAACT Network by the 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.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities. Participants/guardians will be made aware of all applicable reporting requirements as part of the study informed consent process.

13.9 Management of Incidental Findings

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

13.10 Management of New Information Pertinent to Study Participation

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

13.11 Post-Trial Access to Study Drug

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

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the NIH. Study drug is provided by ViiV Healthcare; however, this organization is not involved in sponsorship or regulatory oversight of this study.

Within NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study products prior to and during the conduct of the study, in accordance with its sponsor obligations.

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

14.2 Protocol Registration

This study will be initiated under protocol Version 2.0. Prior to implementation of this protocol version, and any subsequent full version amendments, each site must have the protocol and the protocol ICFs approved, as appropriate, by applicable IRBs/ECs and any other applicable regulatory entities; for US sites, this includes the sIRB. 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 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 for protocol Version 2.0. 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 other applicable regulatory entity approvals, sites should implement the amendment immediately, unless instructed otherwise. 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 required documents have been received. 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. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO.

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: https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration

14.3 Study Implementation

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

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS SCORE Manual specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials. These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the requirements for source documentation specified in the DAIDS SCORE Manual, 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 applicable 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 Network MOP.

14.5 ClinicalTrials.gov

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The protocol team will comply with this policy as well as the requirements of 42 CFR 11.

15 PUBLICATIONS

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

16 REFERENCES

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APPENDICES

Appendix IA: Maternal Schedule of Evaluations

Study Visit	**Screening**	**Entry**
Visit Window	**During pregnancy through 0 – 5 days**	**0 – 5 days**
Informed Consent	X	
Confirmatory HIV-1 Testing (if needed)	X [0–6 mL]	
Medical and Medication History	X	X
HIV-1 RNA		6 mL
Total Maximum Blood Volume	**0–6 mL**	**6 mL**

Day 0 is defined as the date of delivery (infant date of birth).

Appendix IB: Cohort 1 (Strata 1A, 1B, and 1C) – Infant Schedule of Evaluations

Study Visit	Screening	Entry	7 Days Post Initial Dose	Week 4	Week 6	Week 16 or Early Study Discontinuation
Visit Window[1]	**0 – 5 days**	**0 – 5 days**	**+ 3 days**	**23 – 33 days**	**37 – 47 days**	**112 – 140 days**
Clinical Evaluations						
Medical and Medication History[2]	X	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X	X
Study Drug Dosing[3,4]		X	X			
Tolerability Assessment		X	X			
Laboratory Evaluations						
HIV Nucleic Acid Test	3 mL				3 mL	3 mL
CBC including WBC and differential	0.5 mL		0.5 mL	0.5 mL	0.5 mL	0.5 mL
AST, ALT, total bilirubin, creatinine[5]	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
DBS (optional PK genotyping)		0.5 mL at one visit				
HIV Confirmatory Testing and Genotypic Resistance Testing		*If the initial HIV NAT is positive, confirm as soon as possible with an HIV NAT test (3 mL) on a second sample drawn on a different day. Refer to Section 6.13 for further instructions. If the infant is confirmed with HIV-1 diagnosis, collect an additional 3 mL of blood for genotypic resistance testing. Note: The total blood volume for these visits may require an additional 6 mL of blood for these tests. Refer to Section 6.18 and the LPC for further instructions.*				
Intensive PK Sampling		1.5 mL	0.75 mL			
Total Maximum Blood Volume	**4.5 mL**	**2.5 – 3.0 mL**	**2.25 – 2.75 mL**	**1.5 – 2.0 mL**	**4.5 – 5.0 mL**	**4.5 – 5.0 mL**

1. Day 0 is defined as the infant's date of birth, and all follow-up visits are scheduled from this date except the 7 Days Post Initial Dose visit, which is scheduled seven days (+ 3 days) from the day the initial DTG dose is administered at Entry.
2. If the Entry visit is conducted on a different day than the Screening visit, a physical exam should be performed at the Entry visit, and the medical and medication history should be updated since the last visit (see Section 6.3).
3. Infants in Stratum 1B (DTG-exposed) should receive the first single dose of DTG within 2-5 days of life at Entry. See Section 5 for instructions on study drug administration.
4. The second dose of DTG should not be administered until the ALT and AST results have been reviewed at the 7 Days Post Initial Dose visit; see Section 6.5 for further guidance and Section 8 for toxicity management guidelines.
5. At the Entry visit, collect blood for total bilirubin only at 48-72 hours after the initial DTG dose is administered at the Entry visit.

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

Study Visit	Screening	Entry	2 Days Post Initial Dose	7 Days Post Initial Dose	Week 4	Week 6	Week 8	Week 12	Week 16 or Early Study Discontinuation
Visit Window[1]	**0 – 5 days**	**0-5 days**	**+2 days**	**+3 days**	**23 – 33 days**	**37 – 47 days**	**51 – 61 days**	**77 – 91 days**	**112 – 140 days**
Clinical Evaluations									
Medical and Medication History[2]	X	X	X	X	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X	X	X	X	X
Study Drug Dosing[3]		X	X	X	X	X			
Tolerability Assessment		X	X	X	X	X			
Laboratory Evaluations									
HIV Nucleic Acid Test[4]	3 mL					3 mL	3 mL		3 mL
CBC including WBC and differential	0.5 mL		0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
AST, ALT, total bilirubin, creatinine	1 mL		1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
DBS (optional PK genotyping)		0.5 mL at one visit							
HIV Confirmatory Testing and Genotypic Resistance Testing		*If the initial HIV NAT is positive, confirm as soon as possible with an HIV NAT test (3 mL) on a second sample drawn on a different day. Refer to Section 6.13 for further instructions. If the infant is confirmed with HIV-1 diagnosis, collect an additional 3 mL of blood for genotypic resistance testing. Note: The total blood volume for these visits may require an additional 6 mL of blood for these tests. Refer to Section 6.18 and the LPC for further instructions.*							
Intensive PK Sampling				1 – 1.25 mL	1 – 1.25 mL				
Population PK Sampling[5]			0.25 mL			0.25 mL			
Total Maximum Blood Volume	**4.5 mL**	**0 – 0.5 mL**	**1.75 – 2.25 mL**	**2.5 – 3.25 mL**	**2.5 – 3.25 mL**	**1.5 – 5.25 mL**	**1.5 – 5.0 mL**	**1.5 – 2.0 mL**	**4.5 – 5.0 mL**

1. Day 0 is defined as the infant's date of birth, and all follow-up visits are scheduled from this date except the 7 Days Post Initial Dose visit, which is scheduled seven days (+ 3 days) from the day the initial DTG dose is administered at Entry.
2. If the Entry visit is conducted on a different day than the Screening visit, a physical exam should be performed at the Entry visit, and the medical and medication history should be updated since the last visit (see Section 6.3).
3. See Section 5 for instructions on study drug administration.
4. An HIV NAT at the Week 6 visit should only be done for infants who discontinue DTG at the Week 4 visit. An HIV NAT at the Week 8 visit should only be done for infants who discontinue DTG at the Week 6 visit.
5. A population PK sample at the Week 6 visit should only be collected for infants taking DTG through the Week 6 visit per local standard of care for ARV prophylaxis.

Appendix II: Dolutegravir Weight Band Dosing Tables for DTG Liquid Suspension

Note: The selected table for any stratum dose adjustments for Cohort 1 (Stratum 1A and Stratum 1B) and the dose and frequency for Cohort 2 (Stratum 2A and Stratum 2B) will be communicated to study sites as per Section 5.9. If the CMC determines that a stratum dose or dosing schedule adjustment is required and the appropriate dose is not included in the tables below, an updated dosing table will be provided through a protocol amendment.

Table A: Dose of 0.25 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	0.25 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	0.5 mg	0.1 mL
3 to <4	1 mg	0.2 mL
4 to <5	1 mg	0.2 mL

Table B: Dose of 0.5 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	0.5 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	1.5 mg	0.3 mL
3 to <4	2 mg	0.4 mL
4 to <5	2.5 mg	0.5 mL

Table C: Dose of 0.75 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	0.75 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	2 mg	0.4 mL
3 to <4	2.5 mg	0.5 mL
4 to <5	3.5 mg	0.7 mL

Table D: Dose of 1 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	1 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	2.5 mg	0.5 mL
3 to <4	3.5 mg	0.7 mL
4 to <5	4.5 mg	0.9 mL

Table E: Dose of 1.5 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	1.5 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	4 mg	0.8 mL
3 to <4	5.5 mg	1.1 mL
4 to <5	7 mg	1.4 mL

Table F: Dose of 2 mg/kg using DTG 5 mg/mL Liquid Suspension

Weight Band (kg)	2 mg/kg	Volume (mL)
	Dose in (mg) to be Administered	Volume to Administer
2 to <3	5 mg	1 mL
3 to <4	7 mg	1.4 mL
4 to <5	9 mg	1.8 mL

Appendix III: Dolutegravir Weight Band Dosing Table for 5 mg Dispersible Tablet

Note: The DTG 5 mg DT may only be administered to infants in Cohort 1, Stratum 1C (if applicable), and Cohort 2, Strata 2A and 2B, who meet the dosing shown in the table below.

Weight Band (kg)	Dose (mg/kg)	Final Dose (mg)	Number of Tablets to Disperse	Volume to Administer (mL)
2 to <3	2	5 mg	1	5 mL
3 to <4	1.5			
4 to <5	1			

Appendix IV: Dolutegravir Weight Band Dosing Table for 5 mg Fixed Dose using DTG 5 mg/mL Liquid Suspension

Note: This table applies only for infants who initiate therapy on the DTG liquid suspension and an increase to 5 mg dose is indicated when the infant reaches 3-4 weeks of age as switching formulations during the conduct of the study is not allowed (i.e., may not switch to DTG 5 mg dispersible tablet).

Weight Band (kg)	Dose (mg/kg)	Dose to be administered in mg	Volume to Administer (mL)
2 to <3	2	5 mg	1 mL
3 to <4	1.5		
4 to <5	1		

Appendix V: Dolutegravir 5 mg Dispersible Tablet or Dolutegravir 5 mg/mL Liquid Suspension Dosing Frequency Table

Regimen Option Number	Neonate Week of Life					
	1	2	3	4	5	6
1	Q 24 hours					
2	Q 48 hours	Q 24 hours				
3	Q 48 hours		Q 24 hours			
4	Q 48 hours			Q 24 hours		
5	Q 48 hours				Q 24 hours	
6	Q 72 hours	Q 48 hours			Q 24 hours	
7	Q 72 hours	Q 48 hours		Q 24 hours		
8	Q 72 hours	Q 48 hours	Q 24 hours			
9	Q 72 hours		Q 48 hours		Q 24 hours	

Appendix VI: Operational Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19

To safeguard the health and well-being of study participants and study staff in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19), the guidance provided in this appendix may be implemented at sites experiencing disruptions due to COVID-19.

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the IMPAACT 2023 Protocol Team. Should a determination be made in the future that the guidance provided in this appendix is no longer applicable, sites will be formally notified and instructed to inform their IRBs/ECs and other applicable regulatory entities.

Visit Scheduling

- Sites are advised that potential participants who are screened for the study should only be enrolled if the site investigator has confidence that local conditions will allow for the following to be completed:
  - At a minimum, safety and PK evaluations through the Week 4 visit can be conducted in-person at the study site.
  - For intensive PK evaluations, the site investigator is confident that intensive PK samples can be collected, processed, and shipped consistent with Section 6 and relevant sections of the study-specific Manual of Procedures and Laboratory Processing Chart.
  - Study staff can administer dolutegravir (DTG) doses in-person prior to intensive PK sampling.
- Sites are advised to optimize the visit windows specified in Section 6 when scheduling study visits during periods of operational disruption. Sites that anticipate operational disruptions or closures are advised to conduct study visits early in the visit window before the disruption occurs. Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the visit window.
- Sites should utilize the protocol-specified visit windows to schedule study visits in-person, when possible, in full compliance with the protocol. Visits conducted outside of the protocol-specified windows are preferred to missed visits. Sites that anticipate a visit may need to be conducted prior to or after closing of the protocol-specified visit window, due to operational disruptions or closures, should contact the CMC for guidance on visit completion on a case-by-case basis.
- When visits must be delayed or missed, sites should make every effort to avoid gaps in DTG supply (see further guidance for study drug supply below).

Prioritization of Study Visit Procedures

- If it is not possible to conduct study visits in-person at the study site, visit procedures may be performed off-site or remotely (e.g., by telephone) as described below. Site investigators must ensure that standard operating procedures are in place for off-site and remote procedures.
- Sites may conduct study visits—in full or in part—off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, study staff should communicate with participants' caregivers/guardians to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality.
- Off-site visit procedures should be conducted by designated study staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR) or designee, with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to

immediately assess and/or manage adverse events (AEs) or social impacts that may occur during the visits. If AEs requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed.

- As indicated under Visit Scheduling, it is generally expected that study visits through the Week 4 visit will be conducted in-person at the study site. For subsequent visits, sites with limited capacity to conduct in-person visits should perform safety evaluations to the extent possible and should prioritize laboratory evaluations consistent with Section 6.18.1. If laboratory tests cannot be performed consistent with a site's Protocol Analyte List (non-US sites) or at a CAP/CLIA-certified laboratory, the tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing). When necessary, medical and medication histories may be obtained remotely.

Study Drug Supply

- As indicated above, Cohort 1 infants should not be enrolled if it is not possible for study staff to administer the two single doses of DTG at Entry and the 7 Days Post Initial Dose visits.
- For Cohort 2 infants, sites are advised to dispense study drug supplies in quantities sufficient through the Week 4 visit (and up to Week 6 for infants taking DTG through the Week 6 visit), except for DTG doses to be administered by study staff prior to intensive PK sampling.
- Sites are advised to maintain frequent communication with caregivers/guardians (e.g., by telephone) to inquire about each participant's health, use of study drug, and study drug supplies.
- Sites are encouraged to implement study drug dispensing and delivery options involving outdoor pick-up or drop-off. Sites are also advised that, when other options are not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants and their caregiver(s)/guardian(s). This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Guidelines* for additional details on this method.
- Sites are encouraged to provide adherence counseling and support remotely (e.g., by telephone).

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2023.
- Documentation should be entered in participant study charts in real-time (or close to real-time) should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network has developed and disseminated guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures due to COVID-19. Please contact the IMPAACT Operations Center Clinical Research Managers with any questions related to documentation and reporting requirements.

Appendix VII: Sample Informed Consent Form for Study Participation in Cohort 1

IMPAACT 2023
A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1

Version 2.0, 23 March 2022

Introduction

This form is for the parent or legal guardian of the baby and the mother of the baby who are being asked to participate in the research study named above.

Participants in this study may be babies and their mothers. For most participants, it is expected that the mother and/or other parent or legal guardian of the baby will provide informed consent for participation in the study. In this form, participants are referred to as "you" (for the mother), "baby", and "your baby" with the expectation that the mother and/or other parents and legal guardians will be reading the form.

This form gives information about the study. Please read it or have it read to you. 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.

Key Information

Here is a summary of important information about the study:

- The study is testing a study drug called dolutegravir. Dolutegravir is used to treat HIV. Dolutegravir has been tested and approved for treatment of HIV in adults and children over four weeks of age. This study is the first study to test dolutegravir when given to newborn babies.
- This study will look at whether dolutegravir can be safely used without any bad side effects when given to newborn babies. It will also look for the best amount of dolutegravir to give to newborn babies for prevention or treatment of HIV in the future.
- Mothers and babies will enter the study soon after the baby is born. Mothers will have one visit when they enter the study with blood drawn for laboratory tests. Babies will then have four visits over four months after they enter the study. At these visits, babies will have physical examinations and blood draws for laboratory tests. Mothers will answer questions about the baby's health, medicines and feeding methods.
- You and your baby will continue to take the HIV medicines given by your health care provider.
- There are possible risks for you and your baby. One possible risk is that dolutegravir could cause side effects. The most severe side effects include allergic reactions and liver problems. These side effects are rare.
- There may or may not be a direct benefit to you or your baby from being in the study. However, information learned in this study may benefit other babies in the future.
- Your decision to participate in the study will have no effect on the medical care that you and your baby receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in this form about the study, its risks, and benefits. You should feel that you understand the study before deciding whether to participate. If you decide to participate, you will be asked to sign or make your mark on this form and date it. You will be given a signed and dated copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *<<site name>>* are doing this study. The person in charge of the study at *<<site name>>* is *<<Investigator of Record name>>*.

This study will test an anti-HIV drug (ARV) for newborn babies. The study will include up to 108 mothers living with HIV and their newborn babies from Brazil, South Africa, Thailand, and the United States. Your baby will be in the study for approximately 16 weeks (four months) after they are born.

The United States National Institutes of Health (NIH) and the company that makes dolutegravir, ViiV Healthcare, are paying for the study.

1. The study is testing dolutegravir in newborn babies of mothers living with HIV.

Babies born to mothers who have HIV usually take ARVs to prevent passing HIV from the mother to baby. This is usually done in the first 4-6 weeks of the baby's life.

Only a small number of ARVs have been approved for use in newborn babies. This is because most ARVs have not been tested in babies. Dolutegravir, a newer ARV, is approved in the United States and other countries for adults and children at least four weeks of age living with HIV. This study will test dolutegravir in newborn babies under four weeks of age to inform future guidance for use of dolutegravir in newborn babies. This will be the first study of dolutegravir in newborn babies.

The study will look at different doses (amounts) of dolutegravir to find out the best dose for newborns and young babies. It will also look at whether dolutegravir can be safely used without causing bad effects when given to babies. The study will have two groups called Cohort 1 and Cohort 2. Cohort 1 will be done first. This part will include up to 36 babies and their mothers. Cohort 2 will be done after Cohort 1 is completed. Cohort 2 will include up to 72 babies and their mothers. This is a consent form for Cohort 1.

In Cohort 1, dolutegravir will be given once at two time points with other ARVs to babies. The results from Cohort 1 will help find doses of dolutegravir to use in Cohort 2. In Cohort 2, babies will take dolutegravir at multiple time points (such as every day or every 2-3 days) with other ARVs for up to four or six weeks. We will look at whether dolutegravir when given with other ARVs is safe when given to babies.

2. Only mothers and their babies who qualify can participate.

If you decide to join the study with your baby, we will first do some tests to see if you and your baby qualify. Some tests can be done while you are pregnant. Other tests will be done after your baby is born. More information about this is given in #4. If you and your baby qualify, you and your baby will be entered in the study. If you and your baby do not qualify, you and your baby cannot be entered in the study.

3. It is your decision whether you and your baby participate in the study.

Deciding to join the study is voluntary (your choice). You are free to join or not join. If you decide to join, you can change your mind later, and you and your baby can leave the study. Your decisions will have no effect on the medical care that you and your baby receive at this clinic. You and your baby's access to services, and the benefits and rights you and your baby 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 bring other people here to learn about the study with you.

No matter what you decide about the study, your baby should still take the ARVs in the first 4-6 weeks of life as instructed by your health care provider. You should also keep taking your ARVs. Taking ARVs is the best-known way for mothers living with HIV to stay healthy and avoid passing HIV to their babies.

You and your baby do not need to join this study to receive medical care and ARVs. You and your baby can keep receiving medical care and ARVs from outside the study. You and your baby may also qualify for other studies. Please ask any questions you may have about these types of alternatives.

Finding out if you and your baby qualify

4. We will review your medical records, ask questions, examine your baby, and test you and your baby's blood.

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

- Review your and your baby's medical records.
- Collect information about you and your baby, your pregnancy, your and your baby's health, the medications that you and your baby take, and your and your baby's exposure to ARVs.
- Ask about how you are (or will be) feeding your baby.
- Talk with you about the study requirements and if you are able to meet these requirements.
- If needed, we will draw your blood (up to 6 mL or about 1¼ teaspoons) for HIV testing to confirm that you have HIV. There are certain HIV tests that are required for mothers in this study. If the required tests are not in your medical records, we will do the tests that are needed.
- Give your baby a physical examination.
- Draw your baby's blood (4.5 mL or about 1 teaspoon) for tests. These tests will check:
  - Your baby's blood cells.
  - How well your baby's liver is working.
  - If your baby has HIV.

The above procedures to confirm if <u>you</u> qualify for the study may be done while you are pregnant and/or within five days after your baby is born. These procedures will take up to four hours.

If this visit takes place while you are pregnant, we will stay in contact with you through your delivery date and ask you to contact us when your labor begins. We will not be involved in the delivery of your baby. We will arrange to see you and your baby soon after your baby is born to complete remaining procedures to confirm if you both qualify for the study. You are welcome to contact us or return to the clinic at any time to talk about the study.

The above procedures to confirm if <u>your baby</u> qualifies for the study will take up to one or two hours.

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

The results of some of your baby's blood tests will be ready quickly and others may take a few days. We will review the results and all other information to determine if you and your baby qualify for the study.

- If you and your baby <u>do not</u> qualify, we will tell you this and give you information on where you and your baby can receive medical care and other services you and your baby may need. We will still use some information collected about you and your baby (for example, age, sex, and race). We will use

this information to look at patterns or common reasons for not entering the study. We will destroy any of your or your baby's blood samples remaining after testing.

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

Entering the study

6. If you and your baby qualify, you and your baby will enter the study within five days after delivery.

On the day when you and your baby enter the study, we will:
- Draw your blood (up to 6 mL or about 1¼ teaspoons) to test the amount of HIV in your blood.
- Collect updated information about your health, the medications that you are taking, and the ARVs you are taking.

When you complete these procedures, you will no longer be in the study, but your baby will continue in the study.

Your baby will receive their first dose of dolutegravir and then have blood drawn to test the amount of dolutegravir in the blood. More information about this test is given in #9.

If your baby enters the study on a different day from when your baby completed procedures to confirm if they qualified for the study, we will also:
- Review your baby's medical records.
- Ask you about your baby's health and medications.
- Give your baby a physical examination.

During the study

7. You and your baby will continue to take ARVs.

If you and your baby join the study, we will give your baby two doses of dolutegravir. The first dose will be given when you and your baby enter the study. The second dose will be given about one week later. On each day when dolutegravir is given, we will draw your baby's blood to measure the amount of study drug in your baby's blood. More information about this is given in #9.

Babies in this study will take dolutegravir in addition to the ARVs usually given to prevent HIV in the first 4-6 weeks of life. You and your baby should continue taking the ARVs you have been given outside of the study, as part of your regular medical care. Taking ARVs is the best-known way for women with HIV to stay healthy and to avoid passing HIV to babies. Please tell us if you have any questions about the ARVs you and your baby should be taking.

8. Your baby will have four study visits over approximately 16 weeks (4 months).

After your baby has entered the study, your baby will have four visits: Seven days after the first dose of dolutegravir, and at approximately 4, 6, and 16 weeks after birth. For some study visits, the visit may take place over more than one day.

During these visits, we will:

- Review your baby's medical records.
- Ask you about your baby's health and medications. If you are breastfeeding your baby, we may ask you about medications you are taking that your baby may be exposed to through breast milk.
- Give your baby a physical examination.
- Draw your baby's blood for tests. The amount drawn will range from 1.5 mL to 5 mL (less than ½ to about 1 teaspoon). At different visits, these tests will check:
  - Your baby's blood cells.
  - How well your baby's liver is working.
  - The amount of dolutegravir in your baby's blood after your baby receives a dose of dolutegravir (more information is given in #9 below).
  - If your baby has HIV.
  - If you agree, at one visit we will draw your baby's blood (about 0.5 mL or less than 1/8 teaspoon) for research to look at your baby's genes. More information on this test is given in #10 below.

Each of your baby's study visits will take up to 1 to 2 hours. Your baby may have more visits if they are sick or if we need to do more tests to check on their health.

9. Your baby will get two doses of dolutegravir, and we will very closely measure the amount of dolutegravir in your baby's blood.

One reason for doing this study is to find out the best dose of dolutegravir for newborn babies. To do this, we need to collect blood after babies take dolutegravir to measure the amount of dolutegravir in the blood. This is called a pharmacokinetic or "PK test." Both doses of dolutegravir will be given at the clinic at visits when babies will have a PK test.

The PK tests will take place within 0 to 5 days of your baby's birth (at the Entry visit) and approximately seven days after your baby's first dose of dolutegravir. At the Entry visit, your baby will have one sample collected before your baby is given dolutegravir at the clinic. Your baby will then have three samples collected for up to 13 hours after your baby takes the first dose of dolutegravir. Then your baby will have samples obtained two more times at 22-26 and 48-72 hours after your baby took the first dose of dolutegravir. If the study clinic is able to support this, you may be allowed to stay at the clinic the night before and during your first PK visit.

The second PK test will take place approximately seven days after your baby's first dose of dolutegravir. This PK test will take place over two days. On the first day, your baby will have one PK sample collected before your baby is given their second dose of dolutegravir at the clinic. Your baby will then have another sample collected 1-2 hours after your baby takes the second dose of dolutegravir. On the next day, your baby will need to return to the clinic 22-26 hours after your baby took dolutegravir. The PK test will then be finished with one more blood draw at this time.

Blood samples will be collected either by sticking a needle in your baby's vein or by a "heel stick." For a heel stick, your baby's heel is pricked and a small amount of blood is collected, usually with a small glass tube or filter paper. We will draw a few drops or about 0.25 mL of blood at six different time points during the first PK test (a total of 1.5 mL or less than ½ teaspoon) and at three time points during the second PK test (a total of about 0.75 mL or less than ¼ teaspoon) as described above. We will look at the amount of dolutegravir in your baby's blood at each of these times.

10. Different tests will be done at different laboratories

Testing During the Study

We will do most of the HIV tests and tests to check your baby's blood here at our laboratory, but some of the blood tests will be done elsewhere. Some tests will be done in the United States or other countries. We will give you the results of these tests at the next scheduled visit, or sooner, if necessary. We will also give the results to your and your baby's medical care providers. If the results show that your baby may need medical care that cannot be provided by the study, we will tell you where you can go for this care.

If your baby has a positive HIV test, resistance tests to dolutegravir and other HIV medications will be performed. All ARVs can cause some resistance. Resistance means that the ARVs may not work against HIV if it is taken again in the future. We will explain the results and give you counseling and provide referrals as needed.

Results of PK tests to measure dolutegravir in your baby's blood will not be given to you.

If you agree, we will also test 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. Differences in people's genes can also help explain why some people break down drugs differently and can affect the levels of drugs in their bodies. If you agree, your baby's blood would only be used to look at differences in specific genes that may affect the blood levels of dolutegravir. The results of these tests are for research purposes only and will not be given to the study staff or to you. Testing of all of your or your baby's genes, which is sometimes called whole genome sequencing, will not be done.

Future Testing

After your baby's blood is tested during the study, there may be some samples 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. It is your decision whether to allow extra samples to be kept and used for future research. You are free to say yes or no, and to change your mind at any time.

The extra samples may be used for future testing related to HIV, anti-HIV medicines (ARVs), the immune system, or other diseases. The testing may be done in laboratories in the United States or in other countries.

The extra samples may be used for tests of your baby's genes. Permission to store extra samples and use them for future testing is requested at the end of this form.

<<Sites insert one of the following two paragraph options. Non-US sites should select the option that applies based on whether local regulations do or do not permit specimen storage for future research in the US; if local regulations do not permit specimen storage for future research, this section of the form should be deleted.>>

If you agree to have extra samples stored for future testing, the extra samples will be kept in a repository. A repository is a secure facility used to store samples. The IMPAACT Network repository is in the United States. If you agree to have your baby's 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 modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

If you agree to have extra samples stored for future testing, the extra samples will be kept in a repository. A repository is a secure facility used to store samples. The IMPAACT Network repository is in the United States. However, our regulations require that samples be stored in our country. Therefore, if you agree to have your baby's specimens stored, they will be kept here at our laboratory. There is no limit on how long the samples will be kept. *<<Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

Future testing may not give information that is directly relevant to your baby's health. For this reason, the results of future tests will not be given to you. The results will not be placed in your baby's study records.

Your decision whether to allow your baby's extra samples to be kept and used for future research will not affect your baby's participation in the study. Your baby can be in the study, if your baby qualifies, whether you say yes or no. If you say no, all extra samples will be destroyed. You will record your decision at the end of this form.

11. We may stop one or both of your baby's dolutegravir doses.

We may stop giving your baby dolutegravir if:

- Your baby is not able to come to the study visits.
- Your baby is diagnosed with HIV.
- Your baby has bad effects from dolutegravir.
- Your baby needs to take medicine(s) that cannot be taken with dolutegravir.
- New data indicates dolutegravir should be discontinued.

Even if your baby stops taking dolutegravir, your baby will stay in the study with the same schedule of visits to monitor your baby's health, except that no further PK tests will be done.

If an HIV test shows that your baby has the HIV virus in their blood, we will ask you to bring your baby to the clinic for another test. You should stop giving your baby dolutegravir and your baby will have additional blood drawn (6 mL or 1¼ teaspoon) for another HIV test to confirm if your baby has HIV and to test for resistance to ARVs. If your baby has the HIV virus in their blood, your baby will stay in the study, with the same schedule of visits, but your baby will remain off dolutegravir. At these visits your baby will have all procedures done except no further PK tests will be done. The study cannot provide care and treatment for babies with HIV, but we will give information, counseling, and referrals to where your baby can get the care and treatment they need. The Investigator of Record at the site may be required by law to report the result of these tests to the local health authority.

12. We may take your baby off the study early.

Babies are expected to stay in the study for up to 140 days after birth. However, the study doctor may need to take your baby off the study early without your permission if:

- The study is stopped for any reason.
- You/your baby are not able to attend the study visits as required by the study or we determine that you/your baby cannot meet the study requirements.
- We determine that staying in the study might harm your baby.
- Your baby is not given the first dose of dolutegravir within five days of birth.

If your baby must leave the study early, we will explain this and tell you where your baby can go for the care and treatment your baby may need. We will ask you to bring your baby to the clinic to complete one

last visit. At this visit, we will perform the same procedures described in #8. We will answer any questions you may have and tell you how to contact us in the future if you wish.

13. Please tell us if you want your baby to leave the study.

You and your baby are free to leave the study at any time for any reason. You are also free to change your mind about storing your baby's extra samples for future testing. The medical care that you and your baby receive at this clinic will not be affected by your decisions, but it is important for us to know about your decision. We will record your decisions and ensure they are followed.

If your baby leaves the study early, we will ask you to bring your baby to the clinic to complete one last visit. At this visit, we will perform the same procedures described in #8. We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

If your baby leaves the study early, we will still use the information and samples already collected from your baby. However, if you do not agree to this, you can tell us and your decisions will be followed.

Risks of the study

Taking part in this study may involve some risks and discomfort.

14. Risk from blood draws.

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, low iron in the blood (anemia), or infection. If it is difficult to get blood from your baby, repeated attempts may be necessary.

15. There are risks from ARVs.

All ARVs can cause side effects. This includes ARVs your baby would receive outside the study. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects.

Some of the most common and most serious side effects of the study ARV, dolutegravir, are listed below in #16 and #17. This is based on what we know now about dolutegravir. There may be other side effects that we do not know. This may be especially true for babies, because this is one of the first studies of dolutegravir in babies.

This form does not list all possible side effects. If your baby joins the study, we will tell you about the side effects of dolutegravir that your baby will take. At each visit, we will check on whether your baby may be having side effects and tell you what to do if your baby has any side effects. If you have questions or concerns at any time, please tell us.

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

Because dolutegravir has been studied mostly in adults and older children, we do not know as much about how it will affect babies. We will tell you about the possible severe side effects of dolutegravir first. These effects are rare, but they can cause serious health problems and can result in death. Please contact us right away or go to the nearest hospital if your baby has any of these side effects.

In earlier studies of dolutegravir in children living with HIV/AIDS, some children experienced pneumonia (infection of the lung), vomiting and diarrhea with dehydration (a loss of water from the body), and increasing symptoms from other infections or diseases that they already had. Whether dolutegravir led to these events is uncertain, as they are common in children living with HIV/AIDS.

Dolutegravir can cause a severe allergic reaction. If your baby has an allergic reaction, your baby may have a rash, fever, poor appetite, upset stomach, vomiting (throwing up), diarrhea (loose or watery stools), or pain in the belly. Your baby may feel sick or tired or weak. Your baby may have aches or pains or have trouble breathing, a cough, or sore throat. Babies could also have blisters or sores in the mouth; blisters or peeling of the skin; redness or swelling of the eyes; swelling of the face, mouth, lips, or tongue. Contact us right away if your baby has any signs of a reaction.

Dolutegravir can cause severe liver problems. The liver is an organ near the stomach. It helps digest food and keep the body healthy. Problems of the liver can be seen with abnormal blood test results. Babies with liver problems may also have yellowing of the skin or eyes; dark or tea colored urine; pale colored stools; upset stomach or vomiting; poor appetite; weight loss; pain, aching, or tenderness in the belly, especially on the right side below the ribs. Babies may feel tired or weak or dizzy, or have difficulty feeding and/or breathing. When these types of problems happen, they can lead to failure of the liver and can result in death. Contact us right away if your baby has any signs of liver problems.

Bilirubin is a substance released by the liver when red blood cells are broken down by the liver. A possible problem is increased bilirubin in the blood, which can lead to newborn jaundice (yellow skin and eyes). Newborn jaundice is common in babies and if very bad may be treated with special lights or phototherapy. If the amount of bilirubin in the blood is very high for too long, this may sometimes result in brain injury. Babies with increased bilirubin may have poor feeding, sleepiness, vomiting, and/or high-pitched cry. Because dolutegravir has been studied mostly in adults, we do not know if it will increase bilirubin in the blood of infants. Newborn jaundice has not been seen so far due to dolutegravir, but it is possible and is being carefully looked for in this study.

17. There are also more common and not severe side effects from dolutegravir.

Other side effects have been seen in people taking dolutegravir. These side effects can be more or less common. They are not usually severe. The most common side effects seen in adults and older children on dolutegravir for a long time are listed below. There is no information on how often or what types of side effects occur in newborn babies.

The most common side effects in adults and older children for dolutegravir are:
- Cough
- Headache
- Upset stomach
- Diarrhea
- Trouble sleeping
- Tiredness

Other reported side effects of dolutegravir include:

- Rash
- Itching
- Gas or pain in the belly
- Loss of appetite
- Feeling sick or vomiting
- Fever
- Pain in the muscles or joints
- Abnormal dreams
- Depression or anxiety (feelings of fear or worry)
- Dizziness (feeling lightheaded)
- Excessive weight gain
- Changes in blood tests such as those suggesting problems with the liver, muscles, kidneys (organs that filter blood and make urine), pancreas (an organ involved in digestion and controlling blood sugar), white blood cell counts, and blood counts

Some other side effects have been reported in adults and older children living with HIV who take potent combinations of ARVs for a long time, but these side effects are unlikely to happen in newborn babies taking ARVs for only a few weeks, as in this study. These unlikely side effects include worsening of symptoms from current infections or diseases, abnormal placement or loss of fat in certain body areas, and changes in blood tests of fat or cholesterol levels.

If you become concerned about any side effects, please tell the study staff as soon as possible.

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

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

<<US sites insert this paragraph>> Your and your baby's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify you and 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 and your baby. The certificate does not protect against requests for information from the United States federal government. Regardless of the certificate, you can release information about you and your baby's participation in the study to others, if you wish.

The information we collect about you and your baby for this study will be combined with information collected about all other study participants. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your and your baby's information to this center. The information will be sent securely, following applicable laws and policies. Your and your baby's name and other information that could personally identify you and your baby will not be sent.

If there is any problem with the devices (for example, dosing cup, oral syringe, bottle adaptor) used to give dolutegravir to your baby, we may need to submit a report about this. The report will be sent to the company that makes dolutegravir (GSK/ViiV). Your and your baby's name and other information that could personally identify you and your baby will not be included in the report.

Information and samples collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any such research must be approved by the IMPAACT Network. Information and samples used for approved research will be labeled with a code number only. The only link between the code number and your and your baby's name will be kept here at this clinic. Your and your baby's name and other information that could personally identify you or your baby will not be given to other researchers.

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 could be treated badly or unfairly. You could feel stress or embarrassment.

19. There could be risks of genetic testing.

There may be some risks from tests of 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. You may decide that you do not want genetic testing for your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You and your baby can still join this study even if you do not agree to genetic testing. If you do agree to this testing, it will be done later in the study, so you will not receive the results of this testing, and the results will not go into your baby's medical records or have your or your baby's name attached to them.

Genetic information is unique to you and your family. Even without your or your baby's name or other identifiers, it may be possible to identify you, your baby, or other members of your family with your baby's genetic information. We will follow procedures so that people who work with your baby's DNA information for research cannot discover it belongs to your baby, unless you have given consent. However, new techniques may be developed that in the future make it easier to link your baby's genetic data to you or your baby, so we cannot promise that your baby's genetic information will never be linked to you or your baby.

Benefits of the study

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

By joining the study, you and your baby will be part of the search for anti-HIV medicines that may be better for babies born to mothers living with HIV. While there is no established direct benefit to you or your baby by participating in this study, DTG given with other HIV medicines may provide some benefit to your baby in preventing HIV in the body. Information learned may benefit other mothers living with HIV and their newborn babies in the future.

Your baby will have regular visits here and frequent checks on their health, including tests for HIV. It is possible that the examinations and tests done in the study may help your baby stay healthy. If these procedures show that your baby may need medical care that cannot be provided through the study, we will tell you where you can go for the care your baby needs. Information learned from this study may help others who are living with HIV.

Other information about the study

21. We will take precautions against COVID-19.

During this study, we will follow all applicable guidelines related to COVID-19. This may include asking you about symptoms of COVID-19 or doing procedures like taking your baby's temperature before study visits. If you and your baby need to quarantine because of COVID-19, we will work with you to determine how best to schedule your baby's study visits.

22. There are no costs from being in the study.

There is no cost for the study-related clinic visits, study drug, examinations, and laboratory tests in this study.

If you agree to have extra samples stored for future research, there is no cost to you or your baby for this. The extra samples will not be sold, and you will not be paid for the extra samples. It is possible that research done with the extra 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.

<<Sites insert information about compensation/reimbursement, for example>> You will be reimbursed for the cost of transport to study visits. For each visit, you will be given *[specify amount].>>*

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

Groups that oversee the study include:

- *<<US sites insert single IRB>>*
- *<<All sites insert applicable local IRBs/ECs>>*
- *<<All sites insert other applicable 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 U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- GlaxoSmithKline (GSK)/ViiV Healthcare (the company that makes dolutegravir)

The study staff and these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally. The same is true for research done in the future with stored extra samples.

A description of this study will be available on ClinicalTrials.gov as required by U.S. 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. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be disclosed to other authorities if required by law. *<<Sites may add other applicable local reporting requirements in this section.>>*

24. If your baby gets sick or injured, please contact us.

Your baby's health is important to us. If your baby gets sick or injured, contact us immediately. We will make every effort to protect your baby's well-being and minimize risks. It is possible, however, that your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of 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 your baby or tell you where you can get the treatment your baby needs. The cost for this treatment may be charged to you or your 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.

Whom to Contact About This Study:

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

- If you have questions about the study, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about future use of extra blood samples, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about your and your baby's rights as a study participant, or problems or concerns about how your baby is being treated in the study:
  <<insert name, phone number, and other relevant contact details of IRB/EC contact person or other appropriate person or organization>>

- If you or your baby have any health or other problems that may be related to study participation, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you want your baby and yourself to leave the study, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

Signatures:

If you decide that you and your baby will join this study, please sign and date or make your mark below.

Before deciding whether you and your baby will join this study, make sure you have read this form or had it read to you. Make sure all 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.

We will tell you any new information from this study or other studies that may affect your willingness to keep your baby in the study. You are welcome to ask questions or request more information at any time.

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

<<Sites insert initial and signature blocks as required by IRB/EC and institutional policies. Separate consent decisions must be documented for genetic testing of stored samples.>>

For participation in the study (both choices should be initialed/marked for participants to be enrolled)

_____ I agree to have myself and my baby join this study.

_____ I agree that myself and my baby's medical records may be reviewed and that information from these records can be recorded for this study.

For collection of infant blood (one of the two choices should be initialed/marked)

_____ I allow blood collected from my baby to be used for tests of my baby's genes for this study.

_____ I do not allow blood collected from my baby to be used for tests of my baby's genes for this study.

For storage of extra blood samples for future research (one of the three choices should be initialed/ marked)

_____ I allow extra blood collected from my baby to be stored for future research. I also allow my baby's extra blood to be used for tests of my baby's genes.

_____ I allow extra blood collected from my baby to be stored for future research. I do not allow my baby's extra blood to be used for tests of my baby's genes.

_____ I do not allow extra blood collected from my baby to be stored for future research.

Name of baby (print)

Name of Participant (mother) (print)	Participant (mother) Signature *(only for those who reach the legal age or circumstance to provide independent consent)*	Date
Name of Parent or Legal Guardian (print)	Parent or Legal Guardian Signature	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (if applicable; print)	Signature of Witness	Date

Appendix VIII: Sample Informed Consent Form for Study Participation in Cohort 2

IMPAACT 2023
A Phase I Study of the Safety, Tolerability, and Pharmacokinetics of Dolutegravir in Neonates Exposed to HIV-1

Version 2.0, 23 March 2022

Introduction

This form is for the parent or legal guardian of the baby and the mother of the baby who are being asked to participate in the research study named above.

Participants in this study may be babies and their mothers. For most participants, it is expected that the mother and/or other parent or legal guardian of the baby will provide informed consent for participation in the study. In this form, participants are referred to as "you" (for the mother), "baby", and "your baby" with the expectation that the mother and/or other parents and legal guardians will be reading the form.

This form gives information about the study. Please read it or have it read to you. 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.

Key Information

Here is a summary of important information about the study:

- The study is testing a study drug called dolutegravir. Dolutegravir is used to treat HIV. Dolutegravir has been tested and approved for treatment of HIV in adults and children over four weeks of age. This study is the first study to test dolutegravir when given to newborn babies.
- This study will look at whether dolutegravir can be safely used without any bad side effects when given to newborn babies. It will also look for the best amount of dolutegravir to give to newborn babies for prevention or treatment of HIV in the future.
- Mothers and babies will enter the study soon after the baby is born. Mothers will have one visit when they enter the study with blood drawn for laboratory tests. Babies will then have seven visits over four months after they enter the study. At these visits, babies will have physical examinations and blood draws for laboratory tests. Mothers will answer questions about the baby's health, medicines and feeding methods.
- You and your baby will continue to take the HIV medicines given by your health care provider.
- There are possible risks for you and your baby. One possible risk is that dolutegravir could cause side effects. The most severe side effects include allergic reactions and liver problems. These side effects are rare.
- There may or may not be a direct benefit to you or your baby from being in the study. However, information learned in this study may benefit other babies in the future.
- Your decision to participate in the study will have no effect on the medical care that you and your baby receive from your clinic. Your access to services, and the benefits and rights you normally have, will not be affected.

More information is given in this form about the study, its risks, and benefits. You should feel that you understand the study before deciding whether to participate. If you decide to participate, you will be asked to sign or make your mark on this form and date it. You will be given a signed and dated copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *<<site name>>* are doing this study. The person in charge of the study at *<<site name>>* is *<<Investigator of Record name>>*.

This study will test an anti-HIV drug (ARV) for newborn babies. The study will include up to 108 mothers living with HIV and their newborn babies from Brazil, South Africa, Thailand, and the United States. Your baby will be in the study for approximately 16 weeks (four months) after they are born.

The United States National Institutes of Health (NIH) and the company that makes dolutegravir, ViiV Healthcare, are paying for the study.

1. The study is testing dolutegravir in newborn babies of mothers living with HIV.

Babies born to mothers who have HIV usually take ARVs to prevent passing HIV from the mother to baby. This is usually done in the first 4-6 weeks of the baby's life.

Only a small number of ARVs have been approved for use in newborn babies. This is because most ARVs have not been tested in babies. Dolutegravir, a newer ARV, is approved in the United States and other countries for adults and children at least four weeks of age living with HIV. This study will test dolutegravir in newborn babies under four weeks of age to inform future guidance for use of dolutegravir in newborn babies. This will be the first study of dolutegravir in newborn babies.

The study will look at different doses (amounts) of dolutegravir to find out the best dose for newborns and young babies. It will also look at whether dolutegravir can be safely used without causing bad effects when given to babies. The two groups of the study are called Cohort 1 and Cohort 2. Cohort 1 was done first. This part included up to 36 babies and their mothers. Cohort 2 will be done after Cohort 1 is completed. Cohort 2 will include up to 72 babies and their mothers. This is a consent form for Cohort 2.

In Cohort 1, dolutegravir was given once at two time points with other ARVs to babies. Mothers and their babies continued to take other ARVs as prescribed by their doctors. The results from Cohort 1 helped find the best dose(s) of dolutegravir to use in Cohort 2. In Cohort 2, babies will take dolutegravir at multiple time points (such as every day or every 2-3 days) with other ARVs for up to four or six weeks. We will look at whether dolutegravir when given with other ARVs is safe when given to babies.

2. Only mothers and their babies who qualify can participate.

If you decide to join the study with your baby, we will first do some tests to see if you and your baby qualify. Some tests can be done while you are pregnant. Other tests will be done after your baby is born. More information about this is given in #4. If you and your baby qualify, you and your baby will be entered in the study. If you and your baby do not qualify, you and your baby cannot be entered in the study.

3. It is your decision whether you and your baby participate in the study.

Deciding to join the study is voluntary (your choice). You are free to join or not join. If you decide to join, you can change your mind later, and you and your baby can leave the study. Your decisions will have no effect on the medical care that you and your baby receive at this clinic. You and your baby's access to services, and the benefits and rights you and your baby 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 bring other people here to learn about the study with you.

No matter what you decide about the study, your baby should still take the ARVs in the first 4-6 weeks of life as instructed by your health care provider. You should also keep taking your ARVs. Taking ARVs is the best-known way for mothers living with HIV to stay healthy and avoid passing HIV to their babies.

You and your baby do not need to join this study to receive medical care and ARVs. You and your baby can keep receiving medical care and ARVs from outside the study. You and your baby may also qualify for other studies. Please ask any questions you may have about these types of alternatives.

Finding out if you and your baby qualify

4. We will review your medical records, ask questions, examine your baby, and test you and your baby's blood.

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

- Review your and your baby's medical records.
- Collect information about you and your baby, your pregnancy, your and your baby's health, the medications that you and your baby take, and your and your baby's exposure to ARVs.
- Ask about how you are (or will be) feeding your baby.
- Talk with you about the study requirements and if you are able to meet these requirements.
- If needed, we will draw your blood (up to 6 mL or about 1¼ teaspoons) for HIV testing to confirm that you have HIV. There are certain HIV tests that are required for mothers in this study. If the required tests are not in your medical records, we will do the tests that are needed.
- Give your baby a physical examination.
- Draw your baby's blood (4.5 mL or about 1 teaspoon) for tests. These tests will check:
  - Your baby's blood cells.
  - How well your baby's liver is working.
  - If your baby has HIV.

The above procedures to confirm if <u>you</u> qualify for the study may be done while you are pregnant and/or within five days after your baby is born. These procedures will take up to four hours.

If this visit takes place while you are pregnant, we will stay in contact with you through your delivery date and ask you to contact us when your labor begins. We will not be involved in the delivery of your baby. We will arrange to see you and your baby soon after your baby is born to complete remaining procedures to confirm if you both qualify for the study. You are welcome to contact us or return to the clinic at any time to talk about the study.

The above procedures to confirm if <u>your baby</u> qualifies for the study will take up to one or two hours.

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

The results of some of your baby's blood tests will be ready quickly and others may take a few days. We will review the results and all other information to determine if you and your baby qualify for the study.

- If you and your baby <u>do not</u> qualify, we will tell you this and give you information on where you and your baby can receive medical care and other services you and your baby may need. We will still use some information collected about you and your baby (for example, age, sex, and race). We will use

this information to look at patterns or common reasons for not entering the study. We will destroy any of your or your baby's blood samples remaining after testing.

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

Entering the study

6. If you and your baby qualify, you and your baby will enter the study within five days after delivery.

On the day when you and your baby enter the study, we will:
- Draw your blood (up to 6 mL or about 1¼ teaspoons) to test the amount of HIV in your blood.
- Collect updated information about your health, the medications that you are taking, and the ARVs you are taking.

When you complete these procedures, you will no longer be in the study, but your baby will continue in the study. Your baby will receive their first dose of dolutegravir after entering the study.

If your baby enters the study on a different day from when your baby completed procedures to confirm if they qualified for the study, we will also:
- Review your baby's medical records.
- Ask you about your baby's health and medications.
- Give your baby a physical examination.

During the study

7. You and your baby will continue to take ARVs.

If you and your baby join the study, we will give you dolutegravir for your baby. The study drug may be in the form of a liquid or a tablet that is dissolved in water. We will show you how to prepare the study drug and give it to your baby. We will give you devices such as cups, oral syringes, and/or bottle adaptors to be used when giving dolutegravir to your baby.

We will give you instructions for when to give dolutegravir to your baby. It is very important to give dolutegravir to your baby as instructed. We will take as much time as needed for you to understand the instructions. We will help you come up with strategies to give dolutegravir to your baby as instructed.

Babies in this study will take dolutegravir in addition to the ARVs usually given to prevent HIV in the first 4-6 weeks of life. You and your baby should continue taking the ARVs you have been given outside of the study, as part of your regular medical care. Taking ARVs is the best-known way for women with HIV to stay healthy and to avoid passing HIV to babies. Please tell us if you have any questions about the ARVs you and your baby should be taking.

8. Your baby will have seven study visits over approximately 16 weeks (4 months).

After your baby has entered the study, your baby will have seven visits: Two and seven days after the first dose of dolutegravir, and at approximately 4, 6, 8, 12 and 16 weeks after birth. For some study visits, the visit may take place over more than one day.

During these visits, we will:

- Review your baby's medical records.
- Ask you about your baby's health and medications. If you are breastfeeding your baby, we may ask you about medications you are taking that your baby may be exposed to through breast milk.
- Give your baby a physical examination.
- Ask you how easy or difficult it was for your baby to take dolutegravir when it is given to your baby at home.
- Draw your baby's blood for tests. The amount drawn will range from 0.5 mL to 5.25 mL (less than 1/8 to about 1 teaspoon). At different visits, these tests will check:
  - Your baby's blood cells.
  - How well your baby's liver is working.
  - The amount of dolutegravir in your baby's blood after your baby receives a dose of dolutegravir (more information is given in #9 below).
  - If your baby has HIV.
  - If you agree, at one visit we will draw your baby's blood (about 0.5 mL or less than 1/8 teaspoon) for research to look at your baby's genes. More information on this test is given in #10 below.

Each of your baby's study visits will take up to 1 to 2 hours. Your baby may have more visits if they are sick or if we need to do more tests to check on their health.

9. Your baby will get doses of dolutegravir every day, every two days (48 hours) or every three days (72 hours), and we will very closely measure the amount of dolutegravir in your baby's blood.

One reason for doing this study is to find out the best dose of dolutegravir for newborn babies. To do this, we need to collect blood after babies take dolutegravir to measure the amount of dolutegravir in the blood. This is called a pharmacokinetic or "PK test." The results of the PK tests for babies who participated in the first group of this study (Cohort 1) help determined the dose of dolutegravir for your baby and if your baby will take dolutegravir every day, every two days (approximately 48 hours) or every three days (approximately 72 hours).

PK tests will take place at approximately two and seven days after your baby's first dose of dolutegravir and also after a dose of dolutegravir at the Week 4 visit (23-33 days after birth). If your baby is taking dolutegravir through the Week 6 visit, as prescribed by your baby's doctor, then your baby will also have a PK test after the last dose of dolutegravir at the Week 6 visit (37-47 days after birth).

It is very important that you give your baby the doses of dolutegravir exactly as instructed and not miss any doses, except on the days of PK tests for the study visit that takes place approximately seven days after your baby's first dose of dolutegravir and at the Week 4 visit. On the days of these study visits with a PK test, we will ask that you <u>not</u> give your baby dolutegravir at home before coming to the clinic. On the day of these visits, you will bring your baby and dolutegravir to the clinic. The study staff will give

your baby dolutegravir or observe you giving your baby dolutegravir at the clinic. This is important so we know exactly what time dolutegravir is given to your baby on the day of the PK test.

At and/or before visits with a PK test, we will ask you when your baby took dolutegravir for the three doses before the visit date. For the three dolutegravir doses before a PK visit, it is **very important** that your baby takes dolutegravir on time. We will help you remember this before a PK visit.

For each PK test, blood samples will be collected either by sticking a needle in your baby's vein or by a "heel stick". For a heel stick, your baby's heel is pricked and a small amount of blood is collected, usually with a small glass tube or filter paper.

A PK test will take place approximately two days after your baby's first dose of dolutegravir. This PK test will take place on one day. Your baby will have one sample of blood drawn to measure the amount of dolutegravir in their blood. We will draw about 0.25 mL (a few drops of blood) for this test.

PK tests will also take place approximately seven days after your baby's first dose of dolutegravir and at the Week 4 visit (23-33 days after birth). These PK tests will take place over approximately one to three days. On the first day, your baby will have one sample collected before your baby is given dolutegravir at the clinic. Your baby will then have two samples collected for up to 10 hours after your baby takes dolutegravir. On the second day, your baby will need to return to the clinic at 22-26 hours after your baby took dolutegravir for one blood draw. If your baby is taking dolutegravir every day, the PK test will be finished after this blood draw. If your baby is taking dolutegravir every two or three days, your baby will return to the clinic for an additional blood draw before the next dose of dolutegravir should be given to complete the PK test. We will draw a few drops or about 0.25 mL of blood at each time point during these PK tests (a total of 1-1.25 mL or less than ½ teaspoon for each PK test).

A PK test will also take place at the Week 6 visit (37-47 days after birth) only if your baby is planned to take dolutegravir through six weeks after birth. This PK test will take place on one day. Your baby will have one sample of blood drawn to measure the amount of dolutegravir in their blood. We will draw about 0.25 mL (a few drops of blood) for this test. We will draw a few drops or about 0.25 mL of blood for this PK test.

10. Different tests will be done at different laboratories

Testing During the Study

We will do most of the HIV tests and tests to check your baby's blood here at our laboratory, but some of the blood tests will be done elsewhere. Some tests will be done in the United States or other countries. We will give you the results of these tests at the next scheduled visit, or sooner, if necessary. We will also give the results to your and your baby's medical care providers. If the results show that your baby may need medical care that cannot be provided by the study, we will tell you where you can go for this care.

If your baby has a positive HIV test, resistance tests to dolutegravir and other HIV medications will be performed. All ARVs can cause some resistance. Resistance means that the ARVs may not work against HIV if it is taken again in the future. We will explain the results and give you counseling and provide referrals as needed.

Results of PK tests to measure dolutegravir in your baby's blood will not be given to you.

If you agree, we will also test 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. Differences in people's genes can also help explain why some people break down drugs differently and can affect the levels of drugs in their bodies. If you agree, your baby's blood would only be used to look at differences in specific genes that may affect the blood levels of dolutegravir. The results of these tests are for research purposes only and will not be given to the study staff or to you. Testing of all of your or your baby's genes, which is sometimes called whole genome sequencing, will not be done.

Future Testing

After your baby's blood is tested during the study, there may be some samples 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. It is your decision whether to allow extra samples to be kept and used for future research. You are free to say yes or no, and to change your mind at any time.

The extra samples may be used for future testing related to HIV, anti-HIV medicines (ARVs), the immune system or other diseases. The testing may be done in laboratories in the United States or in other countries.

The extra samples may be used for tests of your baby's genes. Permission to store extra samples and use them for future testing is requested at the end of this form.

<<Sites insert one of the following two paragraph options. Non-US sites should select the option that applies based on whether local regulations do or do not permit specimen storage for future research in the US; if local regulations do not permit specimen storage for future research, this section of the form should be deleted.>>

If you agree to have extra samples stored for future testing, the extra samples will be kept in a repository. A repository is a secure facility used to store samples. The IMPAACT Network repository is in the United States. If you agree to have your baby's 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 modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

If you agree to have extra samples stored for future testing, the extra samples will be kept in a repository. A repository is a secure facility used to store samples. The IMPAACT Network repository is in the United States. However, our regulations require that samples be stored in our country. Therefore, if you agree to have your baby's specimens stored, they will be kept here at our laboratory. There is no limit on how long the samples will be kept. *<<Sites may modify the preceding sentence to specify time limits or additional site-specific requirements if required by local authorities.>>*

Future testing may not give information that is directly relevant to your baby's health. For this reason, the results of future tests will not be given to you. The results will not be placed in your baby's study records.

Your decision whether to allow your baby's extra samples to be kept and used for future research will not affect your baby's participation in the study. Your baby can be in the study, if your baby qualifies, whether you say yes or no. If you say no, all extra samples will be destroyed. You will record your decision at the end of this form.

11. We may stop your baby's dolutegravir.

We may stop giving your baby dolutegravir if:

- Your baby is not able to come to the study visits.

- Your baby is diagnosed with HIV.
- Your baby has bad effects from dolutegravir.
- Your baby needs to take medicine(s) that cannot be taken with dolutegravir.
- New data indicates dolutegravir should be discontinued.

Even if your baby stops taking dolutegravir, your baby will stay in the study with the same schedule of visits to monitor your baby's health, except that no further PK tests will be done.

If an HIV test shows that your baby has the HIV virus in their blood, we will ask you to bring your baby to the clinic for another test. You should stop giving your baby dolutegravir and your baby will have additional blood drawn (6 mL or 1¼ teaspoon) for another HIV test to confirm if your baby has HIV and to test for resistance to ARVs. If your baby has the HIV virus in their blood, your baby will stay in the study, with the same schedule of visits, but your baby will remain off dolutegravir. At these visits your baby will have all procedures done except no further PK tests will be done. The study cannot provide care and treatment for babies with HIV, but we will give information, counseling, and referrals to where your baby can get the care and treatment they need. The Investigator of Record at the site may be required by law to report the result of these tests to the local health authority.

12. We may take your baby off the study early.

Babies are expected to stay in the study for up to 140 days after birth. However, the study doctor may need to take your baby off the study early without your permission if:

- The study is stopped for any reason.
- You/your baby are not able to attend the study visits as required by the study or we determine that you/your baby cannot meet the study requirements.
- We determine that staying in the study might harm your baby.
- Your baby is not given the first dose of dolutegravir within five days of birth.

If your baby must leave the study early, we will explain this and tell you where your baby can go for the care and treatment your baby may need. We will ask you to bring your baby to the clinic to complete one last visit. At this visit, we will perform the same procedures described in #8. We will answer any questions you may have and tell you how to contact us in the future, if you wish.

13. Please tell us if you want your baby to leave the study.

You and your baby are free to leave the study at any time for any reason. You are also free to change your mind about storing your baby's extra samples for future testing. The medical care that you and your baby receive at this clinic will not be affected by your decisions, but it is important for us to know about your decision. We will record your decisions and ensure they are followed.

If your baby leaves the study early, we will ask you to bring your baby to the clinic to complete one last visit. At this visit, we will perform the same procedures described in #8. We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

If your baby leaves the study early, we will still use the information and samples already collected from your baby. However, if you do not agree to this, you can tell us and your decisions will be followed.

Risks of the study

Taking part in this study may involve some risks and discomfort.

14. Risk from blood draws.

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, low iron in the blood (anemia), or infection. If it is difficult to get blood from your baby, repeated attempts may be necessary.

15. There are risks from ARVs.

All ARVs can cause side effects. This includes ARVs your baby would receive outside the study. Some side effects are minor, others can be severe. Some side effects are common, others are rare. Some people have some of the side effects. Other people have no side effects.

Some of the most common and most serious side effects of the study ARV, dolutegravir, are listed below in #16 and #17. This is based on what we know now about dolutegravir. There may be other side effects that we do not know. This may be especially true for babies, because this is one of the first studies of dolutegravir in babies.

This form does not list all possible side effects. If your baby joins the study, we will tell you about the side effects of dolutegravir that your baby will take. At each visit, we will check on whether your baby may be having side effects and tell you what to do if your baby has any side effects. If you have questions or concerns at any time, please tell us.

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

Because dolutegravir has been studied mostly in adults and older children, we do not know as much about how it will affect babies. We will tell you about the possible severe side effects of dolutegravir first. These effects are rare, but they can cause serious health problems and can result in death. Please contact us right away or go to the nearest hospital if your baby has any of these side effects.

In earlier studies of dolutegravir in children living with HIV/AIDS, some children experienced pneumonia (infection of the lung), vomiting and diarrhea with dehydration (a loss of water from the body), and increasing symptoms from other infections or diseases that they already had. Whether dolutegravir led to these events is uncertain, as they are common in children living with HIV/AIDS.

Dolutegravir can cause a severe allergic reaction. If your baby has an allergic reaction, your baby may have a rash, fever, poor appetite, upset stomach, vomiting (throwing up), diarrhea (loose or watery stools), or pain in the belly. Your baby may feel sick or tired or weak. Your baby may have aches or pains or have trouble breathing, a cough, or sore throat. Babies could also have blisters or sores in the mouth; blisters or peeling of the skin; redness or swelling of the eyes; swelling of the face, mouth, lips, or tongue. Contact us right away if your baby has any signs of a reaction.

Dolutegravir can cause severe liver problems. The liver is an organ near the stomach. It helps digest food and keep the body healthy. Problems of the liver can be seen with abnormal blood test results. Babies with liver problems may also have yellowing of the skin or eyes; dark or tea colored urine; pale colored stools; upset stomach or vomiting; poor appetite; weight loss; pain, aching, or tenderness in the belly, especially on the right side below the ribs. Babies may feel tired or weak or dizzy, or have difficulty

feeding and/or breathing. When these types of problems happen, they can lead to failure of the liver and can result in death. Contact us right away if your baby has any signs of liver problems.

Bilirubin is a substance released by the liver when red blood cells are broken down by the liver. A possible problem is increased bilirubin in the blood, which can lead to newborn jaundice (yellow skin and eyes). Newborn jaundice is common in babies and if very bad may be treated with special lights or phototherapy. If the amount of bilirubin in the blood is very high for too long, this may sometimes result in brain injury. Babies with increased bilirubin may have poor feeding, sleepiness, vomiting, and/or high-pitched cry. Because dolutegravir has been studied mostly in adults, we do not know if it will increase bilirubin in the blood of infants. Newborn jaundice has not been seen so far due to dolutegravir, but it is possible and is being carefully looked for in this study.

17. There are also more common and not severe side effects from dolutegravir.

Other side effects have been seen in people taking dolutegravir. These side effects can be more or less common. They are not usually severe. The most common side effects seen in adults and older children on dolutegravir for a long time are listed below. There is no information on how often or what types of side effects occur in newborn babies.

The most common side effects in adults and older children for dolutegravir are:
- Cough
- Headache
- Upset stomach
- Diarrhea
- Trouble sleeping
- Tiredness

Other reported side effects of dolutegravir include:
- Rash
- Itching
- Gas or pain in the belly
- Loss of appetite
- Feeling sick or vomiting
- Fever
- Pain in the muscles or joints
- Abnormal dreams
- Depression or anxiety (feelings of fear or worry)
- Dizziness (feeling lightheaded)
- Excessive weight gain
- Changes in blood tests such as those suggesting problems with the liver, muscles, kidneys (organs that filter blood and make urine), pancreas (an organ involved in digestion and controlling blood sugar), white blood cell counts, and blood counts

Some other side effects have been reported in adults and older children living with HIV who take potent combinations of ARVs for a long time, but these side effects are unlikely to happen in newborn babies taking ARVs for only a few weeks, as in this study. These unlikely side effects include worsening of symptoms from current infections or diseases, abnormal placement or loss of fat in certain body areas, and changes in blood tests of fat or cholesterol levels.

If you become concerned about any side effects, please tell the study staff as soon as possible.

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

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

<<US sites insert this paragraph>> Your and your baby's privacy may also be protected by a Certificate of Confidentiality that helps us avoid being forced to release information that may identify you and 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 and your baby. The certificate does not protect against requests for information from the United States federal government. Regardless of the certificate, you can release information about you and your baby's participation in the study to others, if you wish.

The information we collect about you and your baby for this study will be combined with information collected about all other study participants. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your and your baby's information to this center. The information will be sent securely, following applicable laws and policies. Your and your baby's name and other information that could personally identify you and your baby will not be sent.

If there is any problem with the devices (for example, dosing cup, oral syringe, bottle adaptor) used to give dolutegravir to your baby, we may need to submit a report about this. The report will be sent to the company that makes dolutegravir (GSK/ViiV). Your and your baby's name and other information that could personally identify you and your baby will not be included in the report.

Information and samples collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about HIV. Any such research must be approved by the IMPAACT Network. Information and samples used for approved research will be labeled with a code number only. The only link between the code number and your and your baby's name will be kept here at this clinic. Your and your baby's name and other information that could personally identify you or your baby will not be given to other researchers.

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 could be treated badly or unfairly. You could feel stress or embarrassment.

19. There could be risks of genetic testing.

There may be some risks from tests of 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. You may decide that you do not want genetic testing for your baby. You may change your decision about having genetic testing at any time by contacting the study clinic. You and your baby can still join this study even if you do not agree to genetic testing. If you do agree to this testing, it will be done later in the study, so you will not receive the results of this testing, and the results will not go into your baby's medical records or have your or your baby's name attached to them.

Genetic information is unique to you and your family. Even without your or your baby's name or other identifiers, it may be possible to identify you, your baby, or other members of your family with your baby's genetic information. We will follow procedures so that people who work with your baby's DNA information for research cannot discover it belongs to your baby, unless you have given consent.

However, new techniques may be developed that in the future make it easier to link your baby's genetic data to you or your baby, so we cannot promise that your baby's genetic information will never be linked to you or your baby.

Benefits of the study

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

By joining the study, you and your baby will be part of the search for anti-HIV medicines that may be better for babies born to mothers living with HIV. While there is no established direct benefit to you or your baby by participating in this study, DTG given with other HIV medicines may provide some benefit to your baby in preventing HIV in the body. Information learned may benefit other mothers living with HIV and their newborn babies in the future.

Your baby will have regular visits here and frequent checks on their health, including tests for HIV. It is possible that the examinations and tests done in the study may help your baby stay healthy. If these procedures show that your baby may need medical care that cannot be provided through the study, we will tell you where you can go for the care your baby needs. Information learned from this study may help others who are living with HIV.

Other information about the study

21. We will take precautions against COVID-19.

During this study, we will follow all applicable guidelines related to COVID-19. This may include asking you about symptoms of COVID-19 or doing procedures like taking your baby's temperature before study visits. If you and your baby need to quarantine because of COVID-19, we will work with you to determine how best to schedule your baby's study visits.

22. There are no costs from being in the study.

There is no cost for the study-related clinic visits, study drug, examinations, and laboratory tests in this study.

If you agree to have extra samples stored for future research, there is no cost to you or your baby for this. The extra samples will not be sold, and you will not be paid for the extra samples. It is possible that research done with the extra 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.

<<Sites insert information about compensation/reimbursement, for example>> You will be reimbursed for the cost of transport to study visits. For each visit, you will be given *[specify amount].>>*

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

Groups that oversee the study include:

- *<<US sites insert single IRB>>*
- *<<All sites insert applicable local IRBs/ECs>>*
- *<<All sites insert other applicable 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 U.S., local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- GlaxoSmithKline (GSK)/ViiV Healthcare (the company that makes dolutegravir)

The study staff and these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your or your baby's name or identify you or your baby personally. The same is true for research done in the future with stored extra samples.

A description of this study will be available on ClinicalTrials.gov as required by U.S. 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. You can search this website at any time. If you want the results from this study, please tell the study staff.

Your or your baby's study information may be disclosed to other authorities if required by law. *<<Sites may add other applicable local reporting requirements in this section.>>*

24. If your baby gets sick or injured, please contact us.

Your baby's health is important to us. If your baby gets sick or injured, contact us immediately. We will make every effort to protect your baby's well-being and minimize risks. It is possible, however, that your baby could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of 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 your baby or tell you where you can get the treatment your baby needs. The cost for this treatment may be charged to you or your 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.

Whom to Contact About This Study:

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

- If you have questions about the study, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about future use of extra blood samples, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you have questions about your and your baby's rights as a study participant, or problems or concerns about how your baby is being treated in the study:

<<insert name, phone number, and other relevant contact details of IRB/EC contact person or other appropriate person or organization>>

- If you or your baby have any health or other problems that may be related to study participation, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

- If you want your baby and yourself to leave the study, contact:
  <<insert name, phone number, and other relevant contact details of investigator or other study staff>>

Signatures:

If you decide that you and your baby will join this study, please sign and date or make your mark below.

Before deciding whether you and your baby will join this study, make sure you have read this form or had it read to you. Make sure all 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.

We will tell you any new information from this study or other studies that may affect your willingness to keep your baby in the study. You are welcome to ask questions or request more information at any time.

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

<<Sites insert initial and signature blocks as required by IRB/EC and institutional policies. Separate consent decisions must be documented for genetic testing of stored samples.>>

For participation in the study (both choices should be initialed/marked for participants to be enrolled)

_____ I agree to have myself and my baby join this study.

_____ I agree that myself and my baby's medical records may be reviewed and that information from these records can be recorded for this study.

For collection of infant blood (one of the two choices should be initialed/marked)

_____ I allow blood collected from my baby to be used for tests of my baby's genes for this study.

_____ I do not allow blood collected from my baby to be used for tests of my baby's genes for this study.

For storage of extra blood samples for future research (one of the three choices should be initialed/ marked)

_____ I allow extra blood collected from my baby to be stored for future research. I also allow my baby's extra blood to be used for tests of my baby's genes.

_____ I allow extra blood collected from my baby to be stored for future research. I do not allow my baby's extra blood to be used for tests of my baby's genes.

_____ I do not allow extra blood collected from my baby to be stored for future research.

Name of baby (print)		
Name of Participant (mother) (print)	Participant (mother) Signature *(only for those who reach the legal age or circumstance to provide independent consent)*	Date
Name of Parent or Legal Guardian (print)	Parent or Legal Guardian Signature	Date
Name of Study Staff Conducting Consent Process Name (print)	Signature of Study Staff	Date
Name of Witness (if applicable; print)	Signature of Witness	Date