IMPAACT P1093

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

A Multicenter, Domestic & International Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Group (IMPAACT)

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID),
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IND#110,847 Held by NIAID
DAIDS Study ID #11773

Version 5.0

PROTOCOL SIGNATURE PAGE

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

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STUDY MANAGEMENT

- All questions concerning this protocol including questions regarding screening, clinical management of study participants should be sent via e-mail to impaact.teamp1093@fstrf.org. Remember to include the participant's PID when applicable. The appropriate team member will respond to questions via e-mail. A response should generally be received within 24 hours (Monday - Friday).

- For computer and screen problems email user.support@fstrf.org or call the DMC at (716) 834-0900 x7302.

- For questions or problems regarding study drug supplies, records, and returns, contact the DAIDS Protocol Pharmacist at sisetk@niaid.nih.gov or call (240) 292-4848.

- For Expedited Adverse Event (EAE) questions contact the DAIDS RSC Safety Office via email (RSCSafetyOffice@tech-res.com) or phone (1-800-537-9979 or +1-301-537-1709) or fax (1-800-275-7619 or +1-301-897-1710). For questions about the DAIDS Adverse Experience Reporting System (DAERS), email DAIDS-ESSupport@niaid.nih.gov. Questions may also be sent within the DAERS application.

- Email the Computer Support Group at the Data Management Center (DMC) (user.support@fstrf.org) to have relevant site personnel added to the protocol email group (impaact.protp1093@fstrf.org). Inclusion in the protocol email group will ensure that sites receive important information about the study during its implementation and conduct.

LIST OF COMMONLY USED ABBREVIATIONS AND DEFINITIONS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC_{0-24}	Area under the drug plasma concentration profile over time of dosing interval
BSA	Body Surface Area
C_0	Drug plasma concentration immediately prior to dosing
C_{max}	Maximal observed drug concentration during a dosing interval
C_{min}	Minimal observed drug concentration during a dosing interval
C_{24h}	Drug plasma concentration at the end of the 24 hour dosing interval
CAP	College of American Pathologists
CDC	Center for Disease Control and Prevention
cDNA	complementary DNA
CL/F	Apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
CPK	Creatinine phosphokinase
CRPMC	Clinical Research Products Management Center
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (United States)
DMC	Data Management Center
DNA	Deoxyribonucleic acid
DRV	Darunavir
DSMB	Data Safety and Monitoring Board
DTG	Dolutegravir
EAE	Expedited Adverse Event
EC	Ethics Committee
ECG	Electrocardiogram
EFV	Efavirenz
EIA	Enzyme Immunoassay
EMEA	European Medicines Agency
ETR	Etravirine
EU	European Union
EVG	Elvitegravir
FDA	US Food and Drug Administration
FPV	Fosamprenavir
FTC	Emtricitabine
GI	Gastrointestinal
GM	Geometric mean
GMR	Geometric mean ratio
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HHS	Department of Health & Human Services
IB	Investigator's Brochure

IC50	Half Maximal Inhibitory Concentration
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IgM	Immunoglobulin M
ICF	Informed Consent Form
IQ	Inhibitory Quotient
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
LAR	Legally Authorized Representative
LDH	Lactate dehydrogenase
LMC	low mineral content
LPV	Lopinavir
MSDF	Missing, Switch or Discontinuation = Failure
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
NVP	Nevirapine
OBT	Optimized Background Therapy
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
PID	Patient Identifier
PK	Pharmacokinetic
PRO	Protocol Registration Office
QD	Once daily
RAL	Raltegravir
RNA	Ribonucleic acid
RSC	Regulatory Support Center
RTV	Ritonavir
SAE	Serious Adverse Event
SDMC	Statistical and Data Management Center
SMC	Study Monitoring Committee
SUSAR	Suspected, Unexpected Serious Adverse Reaction
t_{max}	time Cmax occurs
t_{min}	time Cmin occurs
t1/2	half-life
TB	Tuberculosis
TDF	Tenofovir
TPV	Tipranavir
UAB	University of Alabama in Birmingham
UGT	UDP-glucuronosyltransferases
ULN	Upper Limit of Normal
US	United States
WB	Western Blot

SCHEMA

Phase I/II Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of Dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

DESIGN:

Phase I/II, multi-center, open-label, non-comparative intensive PK and safety study

Two formulations of dolutegravir (DTG), film-coated tablets and dispersible tablets (DT) will be evaluated under protocol Version 5.0. Evaluation of the film-coated tablet began under protocol Version 1.0; and evaluation of the DT formulation began under protocol Version 4.0. Evaluation of the granules for suspension formulation began under protocol Version 3.0; however, this formulation is no longer being developed for licensure.

DTG is evaluated in each age-based cohort, with the exception of IIB, in two sequential stages: Stage I and Stage II. Stage I examines the pharmacokinetic (PK) parameters from intensive PK sampling, the short-term tolerability and safety of DTG to determine a dose that is then studied with additional participants as Stage II. In version 5.0, doses will also be examined by weight band group.

POPULATION AND SAMPLE SIZE:

Up to 300 HIV-infected infants, children and adolescents aged ≥ 4 weeks to < 18 years of age enrolled in the age-specific cohorts specified below.

Cohort I: Adolescents ≥ 12 to <18 years of age
(film-coated tablets)

Cohort IIA: Children ≥ 6 to <12 years of age
(film-coated tablets)

Cohort IIB: Children ≥ 6 to <12 years of age
(granules for suspension or dispersible tablets)

Cohorts III: Children ≥ 2 to < 6 years of age
(granules for suspension)- Closed to Enrollment

Cohort IV: Children ≥ 6 months to < 2 years of age
(granules for suspension)- Closed to Enrollment

Cohort III-DT: Children ≥ 2 to < 6 years of age
(dispersible tablets)

Cohort IV-DT: Children ≥ 6 months to < 2 years of age
(dispersible tablets)

Cohort V-DT: Infants ≥ 4 weeks to < 6 months
(dispersible tablets)

Stage I enrollment into Cohorts III-DT, IV-DT, and V-DT continues until a minimum of 10 participants in each cohort AND a minimum of 8 participants in each of the weight band groups below, are enrolled:

a) 3 to < 6 kg
b) 6 to < 10 kg
c) 10 to < 14 kg
d) 14 to < 20 kg

When the PK parameters and safety are determined acceptable among participants enrolled in Stage I, additional participants will be enrolled to Stage II (if necessary) to achieve a minimum of 22 participants per cohort receiving the acceptable dose for long-term safety evaluation.

REGIMEN: Oral once daily dose of DTG film-coated tablets or dispersible tablets, or twice daily dosing, if indicated.

TREATMENT DURATION: Stages I and II: 48 Weeks

Long Term Safety Follow-up: All participants who successfully complete 48 weeks of DTG treatment will continue to receive DTG for up to, an additional, three years as part of long-term safety follow-up.

HYPOTHESIS: DTG will be generally well tolerated and demonstrate an acceptable safety profile, adequate PK and antiviral activity when used concurrently with an optimized background therapy (OBT) in HIV-1 infected infants, children and adolescents.

PRIMARY OBJECTIVES:

1. To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily dose in adults.
2. To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.
3. To evaluate the steady-state pharmacokinetics of DTG in combination with OBT in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C_{24h} and AUC_{0-24} PK parameters in this population.

SECONDARY OBJECTIVES:

1. To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.
2. To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.
3. To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure.
4. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.
5. To determine the extended long term (> 48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents.
6. To explore the relationship between DTG exposure and the antiviral activity.
7. To evaluate pharmacokinetic, safety and tolerability profile of DTG when dosed by weight bands.

1.0 INTRODUCTION

1.1 Background

Triple combination antiretroviral therapy including a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) has become the standard treatment of HIV-infected adults and children. In resource-advantaged countries, triple therapy with an integrase strand transfer inhibitor (INSTI) is now considered a preferred regimen in adults, adolescents and children (1). The World Health Organization (WHO) Treatment Guidelines still recommend triple therapy with a PI or NNRTI as preferred regimens; raltegravir is recommended as an alternative option in some children (2). Effective antiretroviral therapy results in a reduction in viral load with a concomitant increase in the CD4 cell count that has been associated with declining morbidity and mortality in HIV-1 infected adults and children (3, 4). However, very few third agents have approved dosing for children of all ages from birth to adulthood. Additionally, adherence, short and long-term toxicities and dosing intervals further complicate HIV management and may contribute to the development of drug resistance mutations further limiting treatment options in children. The establishment of dosing recommendations for new antiretrovirals in children is critically important, especially for children and adolescents who have failed or are unable to tolerate currently available antiretrovirals. In addition, newer agents with novel resistance patterns not overlapping with established classes of therapies are also needed.

Integrase, a viral enzyme essential for HIV-1 replication, mediates the integration of the viral DNA into the host genome. The primary role of the integrase enzyme is to catalyze the insertion of the viral cDNA into the chromosome of infected cells. This process requires two metal dependent consecutive steps in the viral replication cycle, 3'-processing and strand transfer. After the integration of the viral cDNA into the cell's chromosome, viral genome is transcribed and viral proteins are produced (6). Two metal integrase inhibitors preferentially block the strand transfer step.

Currently, four INSTI are approved and available for use. Raltegravir (MK-0518, Isentress, Merck) was the first approved HIV integrase strand transfer inhibitor and has demonstrated safety and efficacy in both treatment-naïve and highly antiretroviral (ARV) experienced adult participants. Elvitegravir (GS-9137, Gilead) also showed potent antiviral activity in adults (7) and adolescents (7). However, raltegravir needs to be administered twice a day in children and elvitegravir (EVG), though administered only once a day, requires a pharmacokinetic (PK) booster. Bictegravir (currently co-formulated with emtricitabine and tenofovir alafenamide [Biktarvy®], Gilead) was approved in 2018 for use in adults.

Clinical resistance to both raltegravir and elvitegravir has been reported in both treatment naïve and treatment experienced participants. Two mutation pathways emerged among participants experiencing virologic failure while on raltegravir. One pathway characterized by the N155H mutation lowered the susceptibility to raltegravir by 10-fold. The Q148H/R/K mutation pathway lowered the susceptibility to raltegravir by 25-fold. Additional mutations have decreased raltegravir susceptibility; the most common being the Q148H and G140S conferring >100 fold decrease susceptibility to raltegravir (8). Participants experiencing virologic failure while on elvitegravir have shown similar mutation pathways as seen with raltegravir (10). As the barrier to the above described resistance is low, there is a need for the development of new integrase inhibitors with different resistance profiles. Preliminary data suggests that elvitegravir exhibits similar resistance characteristics to raltegravir.

Dolutegravir (DTG) was the third approved INSTI and is a potent inhibitor of the HIV-1 integrase. When tested against a panel of 18 integrase resistant viruses from participants failing raltegravir or elvitegravir, DTG showed antiviral activity comparable to that seen against wild type viruses in 17 of 18 mutant viruses (7);(10). Regulatory approvals of DTG are based on studies showing clinical efficacy in treatment-naïve, treatment-experienced, and INSTI-resistant participants.

1.2 Clinical Efficacy

DTG is approved for the treatment of HIV-1 infection in adults and children weighing at least 15 kg in many countries but with a minimum weight of 30 kg in the US. The clinical development program for DTG was designed to support a broad patient population, from naïve to highly treatment experienced patients. The program involves 40 Phase I, 4 Phase II, and 15 Phase III/IIIb clinical trials as well as a Named Patient Program and an Expanded Access Program. The clinical pharmacology studies describe the PK and PD relationship of DTG in both healthy volunteers and special populations.

The supportive Phase II package for DTG (Studies 111521, ING112276, and ING112961) include initial safety data in ART-naïve, -experienced, and INI-resistant participants. In these supportive studies, participants were treated with doses of DTG from 2 mg daily up to 100 mg daily. These data informed the design and conduct of this study.

ING111521 was a proof of concept Phase IIA, dose-ranging, randomized, placebo-controlled study among 35 HIV infected adults. For ten days, participants received either DTG monotherapy at the doses of 2 mg, 10 mg, 50 mg or placebo. In the group receiving 50 mg of DTG monotherapy, the mean decline in HIV-1 was 2.5 log10 copies/mL and seven out of ten participants had a VL < 50 copies/mL during the study. DTG was well tolerated with only mild adverse events described including diarrhea, fatigue, and headache. No integrase signature resistance mutations were observed during the 10-day monotherapy study (11).

In this study, DTG demonstrated low PK variability and a steady-state half/life (t½) of 14 hours. At 50 mg once daily, the steady-state PK parameters (%CV) were; AUC0-24 43.4 (20%) µg h/mL, C_{max} of 3.34 (16%) µg/mL and C24h of 0.83 (26%) µg/mL. The ratio of the 10 and 50 mg C24h to the protein binding corrected IC90 (0.064 µg/mL), also defined as inhibitory quotient (IQ), were 3 and 13, respectively. Since the doses in this study covered a wide range of 25-fold (2 to 50 mg), a concentration-response relationship was observed between C24h and change in HIV-1 RNA from baseline to day 11 using a maximum effect (Emax) model. The concentration required to produce 50% of the maximum effect (EC50) was estimated to be 0.036 µg/mL (or 36 ng/mL) (12). These data provide a basis for an AUC0-24-and C24h-targeted trial in pediatric participants (Figure 1).

Figure 1: DTG Day 11 Log10VL Change

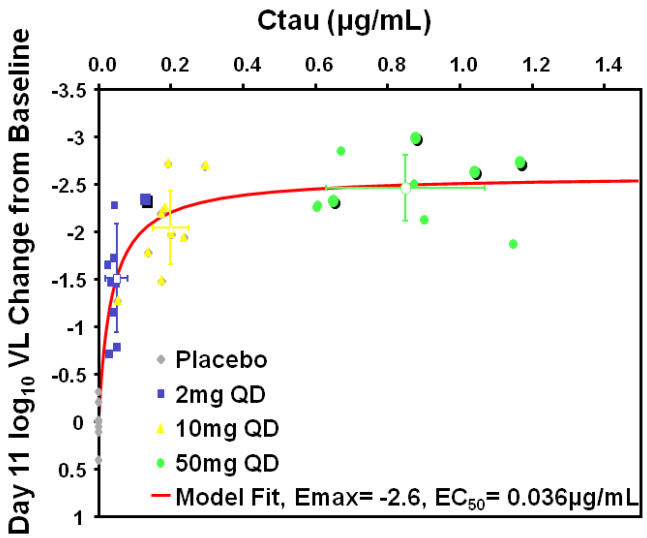


Table 1: Summary of DTG PK Parameters and Mean HIV-1 RNA Reduction from Baseline by Dose

Dose	AUC_{24} µg.h/mL	C_{max} µg/mL	C_{24} µg/mL	IQ	Δ Log_{10} HIV-1 RNA
2 mg QD N=9	2.56 (29%)	0.22 (25%)	0.04 (50%)	0.6	-1.51
10 mg QD N=7	10.1 (20%)	0.80 (23%)	0.19 (25%)	3	-2.03
50 mg QD N=10	43.4 (20%)	3.34 (16%)	0.83 (26%)	13	-2.46

Geometric mean (CV%); IQ=C_{24}/PA-IC_{90} = 0.064 µg/mL

Potent antiviral efficacy was demonstrated in treatment-naive and integrase-inhibitor resistant participants in Studies ING112276 (SPRING-1) and ING112961 (VIKING Pilot). In ING112276, a Phase IIb dose-ranging study in 205 treatment-naive, HIV-infected participants, rapid and sustained antiviral responses across all DTG doses (10 mg, 25 mg, and 50 mg) were observed; 93% of participants who received DTG achieved HIV-1 RNA <50c/mL by Week 16 and 91%, 88%, and 90% of participants, respectively, sustained this viral response to Week 48 (14). At Week 96, the proportion of participants with plasma HIV-1 RNA <50 c/mL was 79%, 78%, and 88% in the DTG groups compared with 72% for the EFV group (15). Neither dose trends nor differences were noted across DTG arms (10 mg, 25 mg, and 50 mg) for efficacy or safety. No clinically significant dose-related trends in Adverse Events (AEs) were observed, and fewer participants who received DTG withdrew because of AEs (3%) compared with EFV (10%) (16). All three doses of DTG were generally well tolerated through 48 weeks, and the 50 mg dose was selected for phase III evaluation.

Study ING112961 was a Phase IIb, open-label, single-arm, pilot study of HIV-infected participants with viral resistance to raltegravir (RAL) at Baseline. The primary endpoint was to assess the short-term antiviral activity of DTG plus a failing background regimen. Participants received DTG 50 mg once daily (Cohort I) or 50 mg BID (Cohort II) while continuing a failing regimen (without RAL) through Day 10. After Day 10, the background regimen was optimized, when feasible, for Cohort I, and at least one fully active drug was mandated for Cohort II. Cohort I enrolled 27 participants and Cohort II enrolled 24 participants. A rapid antiviral response was observed. More participants achieved the primary endpoint in Cohort II (96%), compared with Cohort I (78%) at Day 11. At Week 24, 41% and 75% of participants had an HIV-1 RNA load of <50 c/mL in Cohorts I and II, respectively (17). At Week 96, 26% of participants in Cohort I had an HIV-1 RNA load of <50 c/mL. At Week 48, 71% of participants in Cohort II had an HIV-1 RNA of <50 c/mL. Results from Study ING112961 concluded DTG 50 mg BID with an optimized background provided greater and more durable benefit than the once-daily regimen in patients with prior RAL treatment failure.

The Phase III/IIIb clinical development program for DTG comprised studies in antiretroviral therapy naïve and experienced adult participants in which DTG was compared to numerous therapies. DTG generally demonstrated non-inferior or superior efficacy in these studies (17).

1.3 Clinical Pharmacokinetics in Adults

Absorption and Effect of Formulation

Following oral administration, absorption is rapid with average t_{max} at one to two hours and subsequently the plasma drug concentration declines almost mono-exponentially with average terminal half-life estimated at ~14 hours, supporting once daily dosing. The oral bioavailability of the tablet was less than that of a suspension with a mean AUC (0-∞) decreased by 30% following administration of the tablet compared to the suspension under fasted conditions. The rate of absorption of DTG from the tablet was

slower than from the suspension; the median t_{max} for the suspension was 0.75 hours. DTG exhibited linear pharmacokinetics with dose proportional increases in plasma exposure at doses from 2 to 100 mg using the suspension formulation, with less than dose proportional PK between 100 mg and 250 mg. For the tablet formulation, PK was close to linear over the dosage range of 2 to 50 mg but less than dose proportional between 50 mg and 100 mg.

PK data (Week 2) are available across DTG doses from the Phase IIb SPRING-1 Study (ING112276) Table 2. At Week 2, serial samples were obtained in 46 participants and sparse samples were obtained in 90 participants for determination of PK parameters. DTG was less than dose-proportional between 10 mg and 25 mg but linear between 25 mg and 50 mg. PK parameters were similar to those reported in ING111521, although higher PK variability was observed around AUC and C_{max}. The increased variability is expected given that these are outpatient HIV-infected participants and the majority had sparse PK sampling.

Table 2: Summary of Week 2 DTG PK Parameters from ING112276

Dose	Tablet	Parameter	Cmax (µg/mL)	AUC (µg.h/mL)	Cτ (µg/mL)	Cmin (µg/mL)
10 mg	10 mg	N GeoMean CV%	15 1.10 37	15 16.0 40	47 0.30 71	15 0.33 64
25 mg	25 mg	N GeoMean CV%	15 1.71 43	15 23.1 48	44 0.54 67	15 0.44 68
50 mg	2 x 25 mg	N GeoMean CV%	15 3.40 27	15 48.1 40	44 1.20 62	15 0.94 74

Pharmacokinetics of DTG Granule Formulation

A granule formulation of DTG was developed as an alternative to tablets for use in pediatric populations. In a single-center, randomized, open-label, 5-way crossover study (ING114556) in healthy adults, 20 participants received a single dose of DTG 50 mg as the Phase III tablet and in 10 grams of granule (0.5% drug load) administered 1) direct to mouth; 2) with purified water; 3) with mineral water containing high cation concentrations; or 4) with a milk-based infant formula. Study treatments were separated by 7 days. Study data demonstrated that the plasma DTG exposures in all granule treatment arms exceeded those of the tablet formulation (Table 3). DTG PK exposure was similar when DTG was mixed with purified or cation-containing mineral water or given direct to mouth. Inter-participant variability was modest with CV% for AUC of 31-43%. DTG was well tolerated with no withdrawals due to AEs.

The exposure of DTG following administration of the granule formulation alone, with different types of water and with formula exceeded that of the tablet, and DTG exposure from granule formulation was similar when given direct to mouth, or with different types of water, indicating DTG granule can be given without restriction on the type of liquid, or can be administered directly to mouth (e.g., when water that is safe to drink is not available) (Table 3).

Table 3: Treatment Comparison of DTG PK Parameters (Study ING114556)

Comparison to Tablet	Geometric mean ratio (90%CI)	
	$AUC_{0-\infty}$	C_{max}
Granule direct to mouth	1.58 (1.46-1.71)	1.62 (1.49-1.77)
Granule with purified water	1.57 (1.45-1.70)	1.66 (1.52-1.81)
Granule with mineral water	1.55 (1.43-1.67)	1.65 (1.51-1.79)
Granule with formula	1.83 (1.69-1.98)	2.02 (1.86-2.20)

This adult relative bioavailability study utilized an early formulation in which the granules contained 0.5% DTG and were constituted as a suspension containing 2.5 mg/mL. The pediatric granule formulation used in the pediatric study had slightly different drug content with 0.4% of drug load (dosed as a 1.6mg/mL suspension).

However, based on input from the WHO, specifically that a dispersible tablet formulation is preferred to other pediatric appropriate formulations for ease of widespread distribution, stability and patient acceptability (e.g., liquids, granules for suspension), the manufacturer took the decision to develop a DTG dispersible tablet as the preferred formulation to make available globally.

Pharmacokinetics of DTG Dispersible Tablet Formulation (18)

A dispersible tablet formulation has been developed as an alternative to the pediatric granule formulation for administration in younger pediatric populations. In a single center, randomized, open-label, 5-period, single dose, crossover, relative bioavailability study (ING200401) in healthy adults, the PK of DTG given as dispersible tablet formulation was compared to a DTG pediatric granule formulation and effect of different types of water on the dispersible tablet in healthy adult participants was evaluated. Fifteen healthy participants were enrolled to provide data from at least 10 evaluable participants. Eligible participants were randomized to one of 5 treatment sequences. Participants received 1) DTG 20 mg of the pediatric granule formulation reconstituted with purified water (Treatment A); 2) DTG 20 mg of the dispersible tablet formulation dispersed in low mineral content (LMC) water and taken by participant immediately (Treatment B); 3) DTG 20 mg of the dispersible tablet formulation dispersed in Contrex mineral water (5% Contrex / 95% purified water) and taken by participant immediately (Treatment C); 4) DTG 20 mg of the dispersible tablet formulation dispersed in LMC water, held for 30 minutes, re-dispersed, and then taken by participant (Treatment D); 5) DTG 20 mg of the dispersible tablet formulation dispersed in Contrex mineral water, held for 30 minutes, re-dispersed, and then taken by participant (Treatment E). There were washout periods of at least 7 days between treatments. DTG PK parameters were determined from serial PK samples collected over a 48-hour dosing interval and compared between treatments. Study results are shown in Table 4:

- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in low mineral content water is equivalent to that following a single dose oral administration of 20 mg granule formation reconstituted with purified water.
- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in Contrex mineral water is equivalent to that following a single dose oral administration of 20 mg dispersible tablets dispersed in low mineral content water.
- DTG PK exposure following a single dose oral administration of 20 mg dispersible tablets dispersed in both low and high mineral content water held for 30 minutes before, re-dispersed, and then consumed is equivalent to that following a single dose oral administration of 20 mg dispersible tablets re-dispersed in both low or high mineral content water and consumed immediately.

Table 4: Treatment comparison of plasma DTG PK parameters

Treatment	GMR mean ratio (90%CI)	
	AUC0-∞	Cmax
Dispersible tablet in LMC[a] water	1.07 (1.01, 1.13)	1.13 (1.06, 1.20)
Dispersible tablet in Contrex water	0.944 (0.893, 0.999)	0.918 (0.863, 0.976)
Dispersible tablet in LMC, held for 30 minutes, then re-dispersed	1.03 (0.971, 1.09)	0.987 (0.928, 1.05)
Dispersible tablet in Contrex water, held for 30 minutes, then re-dispersed	1.05 (0.988, 1.11)	1.05 (0.986, 1.12)

a. LMC= low mineral content

In a 2-part phase I, single-dose crossover relative bioavailability (RBA) study, the 10 mg conventional film coated tablets were compared to the adult 50 mg tablet (Part 1), and the DTG 5 mg dispersible tablets were compared to a 25 mg tablet (Part 2) (ING205893). Part 2 of the study specifically evaluated the RBA of the dispersible tablet with 5 tablets administered as "dispense and immediately take" and 5 tablets taken direct to mouth against the DTG 25 mg film coated tablet taken direct to mouth. The geometric mean systemic exposure of DTG from the dispersible tablet was approximately 1.5 to 1.8-fold higher than that observed following administration of a single 25 mg conventional tablet taken direct to mouth. Comparable bioavailability was observed following disperse and immediate administration and direct to mouth administration. These data demonstrate that the 5 mg dispersible tablet can also be taken direct to mouth.

Effect of Food

The Phase III tablet formulation at a 50 mg dose demonstrated that low, moderate, and high fat meals increased DTG AUC (0-t) by 33%, 41%, and 65%, respectively. Such effect is not considered clinically significant based on accumulated toxicity data and safety and tolerability data in humans receiving DTG to date. DTG is licensed to be taken without regard to food.

Accumulation and Time-dependence

Following once daily dose administration, steady state was achieved after approximately 5 days of dosing. DTG (suspension and tablet formulations) showed time-invariant pharmacokinetics. The PK variability of DTG is between low to moderate with between-participant CV% for AUC and C_{max} of ~20 to 30% and for $C\tau$ of 30 to 50%.

Metabolism and Excretion

DTG is primarily metabolized via UGT1A1 with a minor CYP3A component. DTG is the predominant circulating compound in plasma and renal elimination of unchanged drug is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the feces, but unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate which can be further degraded to form the parent compound. Protein binding in human serum is 99.3%.

Drug Interaction Profile of DTG

The drug interaction profile of DTG has been evaluated in a number of clinical studies in healthy volunteers (Table 5).

Table 5: Effect of concomitant medications on DTG pharmacokinetics

Concomitant Drug	N	DTG Dose	GMR[1] (90% CI)			Conclusion
			$C\tau$ or C_{24h}	AUC	C_{max}	
TDF 300 mg QD	16	50 mg QD	0.920 (0.816-1.04)	1.01 (0.908-1.11)	0.969 (0.867-1.08)	No dose adjustment
DRV/r 600/100 mg BID	15	30 mg QD	0.620 (0.555-0.694)	0.782 (0.722-0.848)	0.892 (0.825-0.965)	No dose adjustment
LPV/r 400/100 mg BID	15	30 mg QD	0.944 (0.848-1.05)	0.973 (0.911-1.04)	1.00 (0.937-1.07)	No dose adjustment
ETV 200 mg BID	16	50 mg QD	0.121 (0.093-0.157)	0.294 (0.257-).337)	0.484 (0.433-0.542)	No dose adjustment
ETV 200 mg BID + LPV/r 400/100 mg BID	8	50 mg QD	1.28 (1.13-1.45)	1.10 (1.02-1.20)	1.07 (1.02-1.13)	No dose adjustment
ETV 200 mg BID + DRV/r 600/100 mg BID	9	50 mg QD	0.63 (0.52-0.76)	0.75 (0.69-0.81)	0.88 (0.78-1.00)	No dose adjustment
Multivitamin	16	50 mg single dose	0.679 (0.560-0.824)	0.668 (0.553-0.806)	0.646 (0.540-0.774)	No dose adjustment
Maalox	16	50 mg single dose	0.256 (0.211-0.311)	0.264 (0.218-0.318)	0.276 (0.231-0.331)	DTG should be taken 2 hrs. before or 6 hours after antacid
Maalox 2 hrs. after dolutegravir	16	50 mg single dose	0.703 (0.579-0.853)	0.743 (0.615-0.897)	0.821 (0.686-0.984)	
Calcium carbonate (fasted)	12	50 mg single dose	0.61 (0.47, 0.80)	0.61 (0.47, 0.79)	0.63 (0.50, 0.81)	DTG should be taken 2 hrs. before or 6 hours after supplement if taken without food or, alternatively, take with food
Calcium carbonate (fed)	11	50 mg single dose	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)	
Calcium carbonate 2 hrs. prior (fasted)	11	50 mg single dose	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.7, 1.29)	
Ferrous fumarate (fasted)	11	50 mg single dose	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)	DTG should be taken 2 hrs. before or 6 hours after supplement if taken without food or, alternatively, take with food
Ferrous fumarate (fed)	11	50 mg single dose	0.99 (0.80, 1.22)	0.87 (0.80, 1.19)	1.03 (0.85, 1.26)	
Ferrous fumarate 2 hrs. prior (fasted)	10	50 mg single dose	0.92 (0.74, 1.13)	0.95 (0.78, 1.15)	0.99 (0.81, 1.21)	
ATV/r 300/100 mg QD[2]	12	30 mg QD	2.21 (1.97-2.47)	1.62 (1.50-1.74)	1.33 (1.25-1.42)	No dose adjustment
ATV 400 mg QD	12	30 mg QD	2.80 (2.52-3.11)	1.91 (1.80-2.02)	1.49 (1.40-1.59)	No dose adjustment
Omeprazole 40 mg QD	12	50 mg single dose	0.954 (0.752-1.21)	1.00 (0.808-1.25)	0.915 (0.754-1.11)	No dose adjustment
Tipranavir/RTV 500/200 mg BID	13	50 mg QD	0.24 (0.21-0.27)	0.41 (0.38-0.44)	0.53 (0.50-0.57)	DTG 50 mg BID
Efavirenz 600 mg QD	12	50 mg QD	0.25 (0.18-0.34)	0.43 (0.35-0.54)	0.61 (0.51-0.73)	DTG 50 mg BID

Table 5: Effect of concomitant medications on DTG pharmacokinetics

Concomitant Drug	N	DTG Dose	GMR[1] (90% CI)			Conclusion
			$C\tau$ or C_{24h}	AUC	C_{max}	
FPV/RTV 700/100 mg BID	12	50 mg QD	0.51 (0.42-0.63)	0.65 (0.54-0.78)	0.76 (0.63-0.92)	INI naïve: No dose adjustment INI-resistant: Alternative combination that do not include FPV/RTV should be used where possible
Rifampin	11	50 mg BID	1.22 (1.01, 1.48)	1.33 (1.15, 1.53)	1.18 (1.03, 1.37)	DTG 50 mg BID
	11	50 mg BID	0.28 (0.23, 0.34)	0.46 (0.38, 0.55)	0.57 (0.49, 0.65)	
Rifabutin	9	50 mg QD	0.70 (0.57, 0.87)	0.95 (0.82, 1.10)	1.16 (0.98, 1.37)	No dose adjustment
Prednisone	12	50 mg QD	1.17 (1.06, 1.28)	1.11 (1.03, 1.20)	1.06 (0.991, 1.14)	No dose adjustment
Boceprevir	13	50 mg QD	1.08 (0.911, 1.28)	1.07 (0.948, 1.20)	1.05 (0.960, 1.15)	No dose adjustment
Telaprevir	15	50 mg QD	1.37 (1.29, 1.45)	1.25 (1.20, 1.31)	1.19 (1.11, 1.26)	No dose adjustment
Rilpivirine	16	50 mg QD	1.22 (1.15, 1.30)	1.12 (1.05, 1.19)	1.13 (1.06, 1.21)	No dose adjustment
Carbamazepine	14	50 mg QD	0.27 (0.24, 0.31)	0.51 (0.48, 0.55)	0.67 (0.61, 0.73)	DTG 50 mg BID
Daclatasvir	12	50 mg QD	1.45 (1.25, 1.68)	1.33 (1.11, 1.59)	1.29 (1.07, 1.57)	No dose adjustment

[1]GMR = geometric mean ratio

DTG has a low propensity to cause drug interactions. In a metabolic probe substudy, DTG did not alter the pharmacokinetics of midazolam, demonstrating that DTG does not induce or inhibit CYP3A4. In vitro studies in liver microsomes against other CYP isozymes demonstrate that DTG would not be expected to affect the exposure of concomitant medications that are metabolized by CYP450 enzymes. In addition, in vitro data demonstrate that DTG did not inhibit UGT2B7 and had only a 20% inhibition of UGT1A1, and this occurred at concentrations (IC_{50} > 100 μM) that are not clinically relevant. DTG also had no significant effect on tenofovir exposure (Table 6).

Table 6: Effect of DTG on the Pharmacokinetics of Concomitant Medications

Concomitant Drug	N	DTG Dose	GMR[1] (90% CI)			Conclusion
			Cτ	AUC	C_{max}	
Midazolam 25 mg	10	25 mg once daily	ND	0.953 (0.790-1.15)	ND	No effect on MDZ
TDF 300 mg QD	16	50 mg once daily	1.19 (1.04-1.35)	1.12 (1.01-1.24)	1.09 (0.974-1.23)	No TDF dose adjustment
Methadone	11	50 mg twice daily				No methadone adjustment
Oral contraceptive[2]	15	50 mg twice daily	1.02 (0.93, 1.11)	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)	No OC adjustment
Rilpivirine	16	50 mg once daily	1.21 (1.07, 1.38)	1.06 (0.98, 1.16)	1.10 (0.99, 1.22)	No RPV adjustment
Metformin	14	50 mg once daily	NA	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)	Consider metformin dose adjustment/reduction when starting or stopping co-administration with DTG to maintain glycemic control
Metformin	14	50 mg twice daily	NA	2.45 (2.25, 2.66)	2.11 (1.91, 2.33)	
Daclatasvir	12	50 mg once daily	1.06 (0.88, 1.29)	0.98 (0.83, 1.15)	1.03 (0.84, 1.25)	No DCV adjustment

[1]GMR = geometric mean ratio
[2]ethinyl estradiol

With respect to DTG exposures, no clinically significant drug interactions requiring a dosage change have been observed with lopinavir/ritonavir, darunavir/ritonavir, atazanavir (ATV), atazanavir/ritonavir (ATV/r), fosamprenavir/ritonavir (FPV/RTV), tenofovir, and omeprazole.

It is recommended that the dose of DTG be increased to twice daily in participants receiving EFV, FPV/r, or TPV/r concomitantly. The DTG unit dose in mg will still be based on weight banding per the IMPAACT P1093 Dosing Table Appendix, which is available at http://impaactnetwork.org/studies/P1093.asp.

As the key of the PK evaluation in the pediatric study is to evaluate the impact of development (organ maturation, age, or body size) on DTG in order to guide dose selection, it would be optimal to limit other confounding factors that introduce variability as much as possible, especially during the intensive PK evaluation/dose determination in Stage 1. Therefore, use of ATV, boosted (ritonavir or cobicistat) ATV, FPV, TPV/r, FPV, and EFV will be disallowed during the intensive PK assessment in Stage 1.

DTG is recommended to be taken at least two hours prior or 6 hours after antacids due to reduced absorption resulting from chelation with metal cations in antacids (12). However, DTG can be taken with proton pump inhibitors and H_2 blockers without restriction. Concomitant administration with a multivitamin containing metal cations modestly decreased DTG AUC (0-τ) by 33% and DTG may be administered concurrently with multivitamins. These dosing recommendations are supported by clinical data (19). Concomitant administration with an antacid, Maalox Maximum Strength, decreased the AUC (0-τ) of DTG by 74%. The reduction in exposure was decreased to 26% when DTG was administered 2 hours before the antacid.

Effect of Rifampin on DTG

Rifampin induces UGT1A1 and CYP3A4 which are involved in DTG metabolism. In an open-label, three-period, fixed-sequence drug interaction study, 11 healthy participants received DTG 50 mg once daily for seven days (period 1), then DTG 50 mg twice daily for seven days (period 2), then DTG 50 mg twice daily together with rifampin 600 mg once daily (period 3) for 14 days. Twice daily DTG plus rifampin achieved mean PK parameters that were 18-33% higher than once daily dosing alone. Therefore, a dose of DTG 50 mg twice daily is recommended when co-administered with rifampin.

1.4 Clinical Pharmacokinetics in P1093

Available data from P1093 as of 14 April 2018 are summarized below:

Table 7: Pharmacokinetic Data Available from P1093

Age Cohort	DTG Dose (once daily)	DTG PK Parameter Estimates Geometric Mean (CV%)		
		$AUC_{0\text{-}24}$ µg.hr/mL	**C_{max} ng/mL**	**C_{24h} ng/mL**
12 to 18 yrs[1], (n=10)	50 mg (n=9) 35 mg (n=1)	46.0 (43)	3490 (38)	900 (59)
6 to < 12 yrs[1] (n=11)	50 mg (n=5) 35 mg (n=2) 25 mg (n=4)	50.5 (64)	3960.6 (50)	920 (89)
2 to < 6 yrs[2] (n=11)	20 mg (n=1) 15 mg (n=9) 10 mg (n=1)	43.5 (43)	4239 (41)	504 (61)
6 mos to < 2 yrs[2] (n=13)	15 mg (n=5) 10 mg (n=7) 5 mg (n=1)	55.9 (61)	4691 (45)	807 (87)
4 wks to < 6 mos[2] (n=10)	10 mg (n=4) 5 mg (n=6)	61.2 (44)	4459 (38)	1207 (55)

[1] DTG film coated tablets
[2] DTG dispersible tablets

Dosing recommendations for DTG in adolescents and in children ≥15 kg have been approved in the EU based on these data, and ≥30 kg in the U.S. Assessment of DTG dosing in the youngest children is ongoing.

1.5 Summary of Safety in Clinical Trials

Summaries of findings from both clinical and non-clinical studies conducted with DTG can be found in the IB version 11 and product labels. The following section outlines select summaries of safety for DTG. Where available, the approved country product label should be referenced.

DTG has been administered to a total of 6004 participants (4814 HIV-infected and 1190 healthy) cumulative to 16 July 2017 in ongoing and completed ViiV sponsored and clinical trials ranging from Phase I to IIIb and the DTG compassionate use program. DTG exposure has occurred among a total of 1190 healthy adults in Phase I clinical trials; 4814 HIV-infected adults in Phase IIa-IIIb studies; 514 HIV-infected adults via either the Named Patient Program or Expanded Access Program; and 121 HIV-infected children and adolescents via the P1093 Study.

Meta-Analysis of 26 Completed Phase I/IIa Clinical Pharmacology Adult Studies

Based on a safety meta-analysis of 26 clinical pharmacology Phase I/IIa studies using DTG single entity, the most commonly reported adverse events (AEs) were headache (14%), nausea (6%), and diarrhea (4%). These AEs are comparable to those seen in adult HIV clinical trials. Headache and nausea were the only AEs reported with greater frequency among participants receiving DTG compared to placebo, among common AEs reported in at least 5% in any analysis group (headache 14% vs 3%, and nausea 6% vs 3%). Withdrawals due to AEs were infrequent (2%), and the majority of AEs were Grade 1. A total of two SAEs were reported and both were unrelated to DTG.

In summary, the safety profile for DTG in healthy adult participants participating in phase I/IIa clinical pharmacology studies was similar to that observed in HIV-infected adults in the Phase IIb/III clinical adult program.

Phase IIb to IIIb Adult Clinical Studies and Compassionate Use Program

The integrated safety output (ISO) for the ART-naïve adult population is derived from four randomized controlled trials (ING112276, ING113086, ING114467, and ING114915), comprising a total of 1222 participants who received DTG once daily. The ART-experienced population was comprised of 621 participants from four trials (ING112961, ING112754, ING111762, and ING116529). For both ART-naïve and ART-experienced (INI-naïve) patients, the ISO was similar to both RAL and DRV/RTV, and the most frequently observed AEs were diarrhea, nausea and headache, which tended to be Grade 1 or 2 in severity and typically did not require discontinuation from study.

There has been a total of 13 deaths up to 16 July 2017 across the DTG pivotal and supporting clinical trials. One death was considered related to investigative product (IP) (a 40-year-old male with renal failure, ING114467). Few participants receiving DTG have developed AEs requiring permanent discontinuation of study drug and withdrawal from study. Please refer to the DTG Investigator Brochure v11 for a complete listing of SAEs and AEs leading to withdrawals.

Pregnancy Outcome data from the Tsepamo Study in Botswana

In May of 2018, a preliminary analysis of the Tsepamo Study, a large observational study of pregnant women in Botswana, showed an increased rate of neural tube defects (NTDs) among infants born to women who started DTG at the time of conception.

The Tsepamo birth outcomes surveillance study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to EFV from conception. Botswana's HIV program moved to universal ART with DTG/FTC/TDF provided as the first-line regimen for patients starting ART, including pregnant women, in May 2016 (women already on other regimens were not switched to a DTG-containing regimen). The previous first-line regimen was EFV/FTC/TDF. Almost all women on DTG-based and EFV-based ART took these drugs in combination with FTC/TDF. More than 95% of women in Botswana deliver in-hospital, and obstetric records are available for more than 99% of women. The Tsepamo study is conducted at eight of the largest public maternity wards across Botswana, representing approximately 45% of all births in the country. Research assistants extract exposure data from maternity cards for all consecutive in-hospital deliveries. Trained nurse midwives perform systematic infant surface examinations of all newborns, whether stillborn or live born. Reports and photographs (when available) of major abnormalities are reviewed by an experienced medical geneticist who is blinded to exposure information (20) (22) (22).

A preliminary unscheduled analysis of the Tsepamo study data collected between 15 August 2014 and 1 May 2018 was recently performed at the request of colleagues who were preparing for a WHO meeting. This analysis identified four infants with NTDs born to 426 women who became pregnant while taking DTG (prevalence 0.94%, 95% CI 0.37%, 2.4%). In comparison, 14 infants with NTDs were born to 11,300 women who became pregnant while taking a non-DTG-containing three-drug ART regimen (prevalence 0.12%, 95% CI 0.07%, 0.21%); approximately half of these women were taking an EFV-containing regimen). No NTDs were identified among infants born to 2,812 women who started DTG-containing ART during pregnancy (including 280 women who started DTG-containing ART during the first trimester). (23)

At this time, only a small amount of additional data exists regarding birth outcomes among women taking DTG from conception, from multiple sources of varying data quality and completeness; from these sources, only one NTD was reported among infants born to approximately 323 women taking DTG from conception (24). Additional data will continue to be collected — in Botswana and ideally in other settings — to try to determine whether this signal for NTDs with DTG exposure from conception persists, and whether it is found in different populations.

The Tsepamo study had previously showed similar rates of other adverse pregnancy outcomes (stillbirth, neonatal death, preterm or very preterm birth, small for gestational age or very small for gestational age) among 845 women initiating DTG/TDF/FTC (at median 19 weeks gestation) compared with 4593 women initiating EFV/TDF/FTC (at median 21 weeks gestation) in pregnancy. Among 512 women initiating ART in the first trimester of pregnancy (116 DTG/TDF/FTC, 396 EFV/TDF/FTC), one major congenital abnormality was identified (skeletal dysplasia in an EFV-exposed infant) (25).

Although there is limited experience with the use of DTG in pregnancy, the data analyzed prior to May of 2018 from all sources including the Antiretroviral Pregnancy Registry (26), other clinical trials and post marketing use has not indicated a similar potential safety issue.

Additional Pregnancy and Lactation Data

Sixty-nine pregnancies were reported across ViiV Healthcare (sponsored clinical trials and compassionate use program) up to 16 July 2017. Few cases resulted in an adverse pregnancy outcome, such as an ectopic pregnancy or spontaneous abortion. One congenital anomaly was reported for a participant who was taking DTG + ABC + ATV + RTV during the first month of gestation. A diagnosis of double-outlet right ventricle with ventricular septal defect was made on routine ultrasound at 31 weeks gestation. Surgery was performed for the defect following delivery of the infant but the infant died at day of life 4 due to post-operative complications. The investigator considered the congenital anomaly to be unrelated to IP. With the exception of this case, no other congenital anomalies have been reported in clinical trials.

Post-marketing data identified a total of 235 pregnancies relating to the use of DTG in pregnant women (17).

It is expected that DTG will be secreted into human milk based on animal data, though this has not yet been confirmed in humans (27).

DTG was tested in a complete package of reproductive toxicology studies including embryofetal development studies. In reproductive toxicology studies in animals, DTG was shown to cross the placenta. However, no adverse development outcomes, including NTDs, were identified from reproductive toxicology studies performed in animals.

Recognized Risks with Dolutegravir

The following risks have been recognized for DTG and are summarized cumulatively from the clinical development program.

Hypersensitivity Reaction*:* in the latest integrated analyses performed for DTG single entity, there were 17 adult participants with AE preferred terms of "drug hypersensitivity" or "hypersensitivity" or who had a syndrome of drug hypersensitivity in 1856 cases (0.91%) exposed to at least one dose of DTG in ViiV-sponsored IIb-IIIb clinical trials. DTG as a contributing factor to the event could not be ruled out in all but 5 cases (0.27%), these were all potentially confounded by other ARVs (ABC, ETV, and/or DRV for which HSR and rash are possible outcomes). Thus, the frequency of HSR with DTG in clinical trials remains low, and SAE reports are generally confounded by concurrent ART.

Rash**:** The overall rate for rash reported in the most recent ISO was 5% (91/1843) and was similar when taken once daily (5%) compared to twice daily (6%).

Hepatobiliary Disorders: for ART-naïve participants, the incidence of grade 3 and 4 liver chemistry toxicities in the most recent ISO was low (<2%) for all liver chemistries across all treatment groups in the Phase III and IIIb studies. For ART-experienced participants, safety data suggests no excess risk of hepatic toxicity for DTG. In most cases where liver abnormalities have been present, one or more of the following have been present: history of hepatitis virus co-infection; medical history of alcohol abuse, or ART included drugs with well-described bilirubin or liver enzyme elevation. Please refer to the IB v11 for further information on hepatobiliary disorders in HBV and HCV-co-infected participants.

Renal Function: small increases in mean serum creatinine have been observed in participants on DTG across the entire clinical development program, related to a likely benign effect on creatinine secretion via blockade of the OCT2 receptor. Phase I studies on iohexol and para-aminohippurate clearance have confirmed, however, that there is no effect on GFR.

Psychiatric Disorders including Suicidality: Patients with HIV infection may occasionally experience symptoms of depression and/or suicidal ideation. In the most recent ISO, the psychiatric profile for DTG was favourable compared to EFV and similar to RAL and DRV/r. There was no excess risk of DTG 50 mg BID compared to 50 mg QD. The adverse drug reaction of depression, suicidal ideation, and suicidal behaviors were added to the Company Global Data Sheet (GDS) and Reference Safety Information (RSI) after a review of cumulative data on depression, suicide, and self-harm with DTG up to November 21, 2014. It was determined that a causal association could not be ruled out, though it is not considered to suggest a change in the positive risk benefit assessment for DTG as psychiatric events have already been recognized as potential risks and alternative backbone drugs for HIV treatment already have these adverse reactions in their labelling [ie – RAL, EVG, EFV]. Furthermore, the risk is primarily in those participants with a pre-existing history of depression or psychiatric illness. Thus, it is important to monitor participants being treated with DTG for depression, suicidal ideation, and behaviour, before and during the clinical study. Insomnia is listed as a common non-serious adverse reaction associated with DTG based on clinical trials and post-marketing experience. Additionally, it was observed at a greater frequency with the combination of DTG + ABC/3TC vs Atripla in one study, SINGLE (ING114467), but the incidence has been lower and similar to comparators in all other Phase III studies to date, including ARIA (ING117172), which compared TRIUMEQ with ATV/r +TDF/FTC (28). In the latest ISO, the psychiatric profile for DTG, which includes insomnia, was favourable compared with EFV, and similar to RAL and DRV/RTV. There was no excess risk of DTG 50 mg BID compared to 50 mg once daily.

Clinical Laboratory Evaluations**:** No clinically significant trends in treatment emergent hematology abnormalities, electrolytes, or vital signs have been in any integrated safety analyses or across studies.

There was no evidence of a clinically significant impairment of the lipid profile by DTG treatment in the Phase III/IIIb studies. Lipase elevations have been noted among ART-naïve participants in the Phase IIb and Phase III studies though most have been transient. There is no evidence to suggest a higher rate of clinical pancreatitis with DTG vs comparator ARVs.

Immune Reconstitution Inflammatory Syndrome (IRIS): Based on medical adjudication by the Phase III clinical trial Independent Data Monitoring Committee, despite the rapid decline in HIV-1 RNA observed on DTG, IRIS cases were generally infrequent on DTG, and the rates of IRIS on DTG were comparable to those observed on RAL, EFV, and DRV/RTV.

Post-Marketing Data Sources (Spontaneous Reporting)

DTG was approved by the US FDA in August 2013, by Health Canada in October 2013, and by the European Medicines Agency (EMA) in January 2014. As of 16 July 2017, DTG has been approved in all EU member states, the US, and Japan, as well as 70 other countries. The best estimates of post-marketing experience with the 50 mg once daily and BID doses are 275,818 and 13,164 patient-years, respectively, as calculated from Intercontinental Medical Statistics (IMS) Health "Sales Data" available from licensure until 31 March 2017.

No new safety concerns emerged from an analysis of psychiatric diagnoses in patients prescribed DTG in the OPERA observational database, which indicated that use of DTG was not associated with an increased risk of psychiatric symptoms compared to other ARVs. These findings are also discussed in a paper published by the Marketing Authorization Holder (MAH) (28). As a result of a subsequent MAH review of psychiatric events with DTG, the term "anxiety" was added to the expected adverse reactions in the global datasheet for DTG-containing drugs, and has been reported with a frequency of "common". These reactions were generally not severe, and were often seen in participants with a history of anxiety. Anxiety has been added to the Investigator's Brochure as a non-serious adverse drug reaction, and, as such, is not considered to impact the Clinical Trial Reference Safety Information used for expectedness assessment of 'suspected serious adverse reactions'. ViiV Healthcare does not consider the addition of anxiety to the list of adverse drug reactions to change the overall benefit risk for participants in ongoing clinical studies.

Conclusion

DTG based regimen have demonstrated good tolerability as shown by the analyses of clinical trial data presented in the DTG IB v 11. No other new significant safety concerns or new potential or identified risks were identified from Post-Marketing experience or the analyses of clinical safety data, for the most recent Development Safety Update Report to Regulatory Agencies, with a Data Lock Point of 16 July 2017. The safety data were consistent with the known safety profile of the DTG single entity and/or the treatment populations.

1.6 Rationale

The accelerated development of DTG dosing recommendations for the treatment of HIV-1 infection in children of all ages is needed. A limited number of ARV medications have approved dosing for children; not all agents are available globally; and there remains an unmet international medical need for novel and potent ARV therapy for children with drug resistance or toxicity, or who are failing their current ARV regimen. Potential participants are often heavily pre-treated and have limited therapeutic options. In addition, younger children, who are infected despite exposure to ARVs in utero and after birth for prevention of perinatal transmission may have virus that is resistant to currently available medications.

Drugs with new mechanisms of action, such as the HIV integrase inhibitors, demonstrate activity even in participants with resistance to currently available reverse transcriptase and protease inhibitors.

The purpose of P1093 is to determine the appropriate dose for the pediatric DTG formulations and acquire short and long-term safety data, intensive and population PK data, and efficacy experience with DTG in HIV-1 infected children. These data are needed to guide potential use in children ages 4 weeks through adolescence. Results from this trial are intended to support a regulatory filing for DTG use across the pediatric age spectrum.

P1093 participants are enrolled in two stages. The objectives of Stage I are to examine PK parameters after intense sampling and to evaluate the short-term tolerability and safety of DTG in approximately 10 participants per cohort allowing for the selection of a dose. Longer term safety, tolerability, and efficacy of that dose is then studied in additional participants enrolled in Stage II. The intensive PK evaluation of Stage I is performed on days 5-10 to minimize the risk of sub-optimal doses (as identified by real-time PK evaluation) being used for prolonged periods of time. A number of agents are prohibited during the intensive PK evaluation in Stage I, refer to Concomitant Medication Guidelines in Section 4.3 to minimize the impact of drug-drug interactions that might increase PK variability including ritonavir or cobicistat boosted ATV, NVP, FPV or TPV, or ATV, EFV and FPV. However, concomitant introduction of NRTI agents or lopinavir/r is not expected to alter steady state DTG levels.

Two sets of PK exposure criteria are developed: the minimal and maximal exposure and the target population exposure. The minimal and maximal exposure is developed for patient management in case of extreme exposure which prevents the participant to be considered as evaluable. The target population exposure (range) is developed for dose selection for the population.

1.6.1 Rationale for Pharmacokinetic Exposure Targets

The goal of P1093 is to determine the doses for children that approximate DTG exposures (AUC_{0-24} and C_{24h}) observed in adults who received 50 mg once daily in the Phase I to III trials of DTG. Steady state intensive PK data of weight-based dosing for children will be collected in P1093 under fasting condition. Two sets of PK exposure criteria are used in this protocol. The geometric mean of participant C_{24h} and AUC_{0-24} are used to assess population exposures for dose determination. In addition, ranges of acceptable individual C_{24h} and AUC_{0-24} values have been separately designated to ensure the safe management of participants.

Minimal and Maximal Exposure

Since pediatric pharmacokinetics tend to be more variable than adults, a lower threshold range for both the AUC_{0-24} and C_{24h} have been identified. Using maximum effect (E_{max}) models, the estimated AUC_{0-24} required to produce 95% of the maximum virologic response (EC_{95}) is 25µg.h/mL, and the EC_{95} for the C_{24h} is 0.5µg/mL. These are to be considered the lowest threshold exposures acceptable in this study. This lower threshold is in place to ensure minimum exposure criteria are met in case, for some reason, the targeted range cannot be met in an individual using the selected dose for the population. Similarly, the maximal exposure (upper threshold) is also defined to ensure participants are not exposed to extremely high drug concentrations which may cause safety concerns. Based on accumulated data in adults (in Phase I and IIb) to date, DTG is generally well tolerated with no significant safety issues identified. A dose of DTG 50 mg BID was studied in ING112961 (VIKING) and ING112574 (VIKING3) in adult HIV-infected participants. The exposure (geometric mean, 80% CI) at steady state following 50 mg BID exposure was 75.6 (48.8-115) µg.h/mL. The minimum-maximum AUC0-24 range was 28.4-214 µg.h/mL following 50mg BID dosing. Therefore, the maximal exposure

target is 213 µg.h/mL for AUC0-24. Such upper threshold may be adjusted upon availability of further clinical data.

An exception to the minimum exposure target may be allowed. When a participant has a low drug exposure, after consideration of the clinical, pharmacologic, immunologic and virologic data, and upon agreement of the site investigator, study co-chairs, pharmacologist and medical officers, a given participant may be allowed to continue with the study drug at the initial dosing that resulted in the exposures below the minimum target. Individual participants with extreme PK values (less than the minimal and greater than the maximal exposure as defined above) using the selected dose for the population are eligible for individual dosage adjustment.

Target Population Exposure

Steady state C_{24h} and AUC_{0-24} are the key PK parameters utilized to compare drug exposures in P1093 to those obtained after 50 mg once daily dosing in adults. The geometric mean (GM) of C_{24h} and AUC_{0-24} will be utilized to assess population exposure in study cohorts, with C_{24h} as the primary target and the AUC_{0-24} as secondary target.

DTG demonstrated good short-term safety/tolerability and antiviral activity as monotherapy and combination therapy in Phase IIb and Phase III trials in adults and adolescents (30). Based on Phase III trial data, a dose of 50 mg once daily dose is FDA approved for INI-naïve adult patients. The proof of concept (POC) study (ING111521) used doses of 2, 10, and 50 mg once daily as monotherapy for 10 days in treatment naïve participants. Spring-1 (ING112276) was a Phase IIb trial where treatment naïve participants received 10, 25, or 50 mg once daily for 96 weeks. There was no difference among these regimens with participants on all three doses achieving high rates of virologic suppression at 96 weeks. Table 8 summarizes the steady state pharmacokinetic parameters from 25 participants at the 50 mg once daily dose (combining these two studies).

Table 8: Statistic Summary of DTG PK Exposure from Combined Data in ING111521 and ING112276

PK Parameter*	Dose (mg)	N Obs	Mean	Std Dev	Median	10th Pctl	25th Pctl	75th Pctl	90th Pctl	Geometric Mean	CVb (%)
AUC_{0-24}	50.00	25	48.333	14.629	47.732	30.670	42.324	55.957	67.222	46.1385	32.8404
C_0	50.00	24	1090	597	1017	464	667	1318	1869	946.3	59.6907
C_{max}	50.00	25	3464	838	3464	2630	3042	3713	4069	3377.9	22.7659
C_{24}	50.00	25	1084	560	957	604	803	1165	2260	955.5	56.9724

*Units: ug.h/mL for AUC (=AUC 0-24), and ng/mL for C_0, C_{max}, and C_{24}

The P1093 target population exposure (GM) for C_{24h} is 995 ng/mL, with an acceptable range of 697 – 2260 ng/mL. The C_{24h} population exposure (GM) target is selected as 995 ng/mL based on PK data from phase III adult studies ING111762 (SAILING) and ING113086 (SPRING-2) where the PK of DTG was characterized without regard to food. The primary difference between phase III studies and P1093 study is the collection of the PK under fed/fasted conditions. In phase III studies, PK was characterized without regard to food while in P1093 study, under fasting conditions. Notably, the PK of DTG varies with the ingestion of food in adult participants. DTG C24h showed ~33% - ~73% increase with low to high fat meals, respectively (ING113674). The acceptable range for GM C_{24h} target is selected as 697-2260 ng/mL. The lower limit is the 70th percent of geometric mean and the upper limit is the upper 80th percentile of observed C_{24h} concentrations from combined data in ING111521 and ING112276. The lower

limit is still significantly above the *in vivo* EC90 (300 ng/mL) from day 11 data in monotherapy (PoC) study, and there have been no toxicities observed at the upper limit. This range for GM C_{24h} also approximates values seen in adults receiving 50 mg once daily and are based on Emax modeled data as well as data collected in P1093 thus far; the upper value is approximately the 95th percentile of observed C_{24h} concentration in pediatric participants in study P1093.

The P1093 target population exposure (GM) for AUC_{0-24} target is 46 µg.h/mL, with an acceptable range of 37-134 µg.h/mL. The AUC_{0-24} target of 46 µg.h/m is from combined data in ING111521 and ING112276 and was similar to seen in adults following 50 mg once daily dosing. To accommodate variability around this target and the high mg/kg dosing required to meet the higher C_{24h} target, the acceptable range for AUC_{0-24} is defined as follows. The lower limit for GM AUC_{0-24} is selected as 80% of the target (37 µg.h/mL). The upper limit (134 µg.h/mL) is selected based on the upper 95th percentile of AUC obtained at steady state following 50 mg BID dosing. A DTG dose of 50 mg BID was studied in ING112961 (VIKING) and ING112574 (VIKING3) in adult HIV-infected participants. In the VIKING study (ING112961), the 50 mg BID dose was tolerated as well as the 50 mg QD dose; the observed AUC24 (min, max) from the 50 mg BID dose was in the range of 28.4-214 µg.h/mL. The AUC_{0-24} (geometric mean, 90% CI) at steady state following 50 mg BID exposure (from VIKING and VIKING 3) was 75.1 (40-134) µg.h/mL

P1093 is designed to characterize the PK of DTG in pediatric participants comparing it to the PK obtained in adult participants for dose selection for children. In protocol versions 1-4, AUC_{0-24} was considered the primary target parameter and C_{24h} was the secondary target parameter. Recently, a regulatory agency suggested that C_{24h} be elevated to a primary target. Therefore, in protocol Version 5, C_{24h} is selected as a primary target parameter for PK comparison, with AUC_{0-24} secondary.

Emerging data from Cohort IIA through V-DT showed that C_{24h} (primary PK endpoint) was not comparable to the predefined target in pediatric participants weighing <30kg. Higher doses were selected to achieve a predefined C_{24h} target based on modeling and simulation. Simulations from the interim population PK model showed that the proposed doses will provide trough concentrations in the target range. However, targeting a higher trough concentration may result in the expected geometric mean AUC_{0-24} being approximately 1.33-2 fold higher.

Acceptable Individual Minimal and Maximal Exposure

To ensure the safety and optimal management of participants, the P1093 protocol has specified ranges of acceptable C_{24h} and AUC_{0-24} values for individuals. The acceptable ranges have changed with different protocol versions based on evolution and accumulation of safety and efficacy data both in P1093 and outside studies, refer to Table 9.

Table 9: IMPAACT P1093 C_{24} and AUC_{0-24} Parameters

P1093 Protocol	Version 3	Version 4	Version 5
C_{24}			
Target for GM	960 ng/mL	750 ng/mL	995 ng/mL
Range for GM	770-2260 ng/mL	500 – 2600 ng/mL	697 – 2260 ng/mL
MIN-MAX for individual	MIN 500 ng/mL	MIN 400 ng/mL	MIN 500 ng/mL
AUC $_{0-24}$			
Target for GM	46 µg.h/mL	46 µg.h/mL	46 µg.h/mL
Range for GM	37 – 67 µg.h/mL	37 – 86 µg.h/mL	37 – 134 µg.h/mL
MIN-MAX for individual	25 – 92 µg.h/mL	25 – 115 µg.h/mL	25 – 214 µg.h/mL

Owing to difference in PK collection between the phase III studies and the pediatric study and relatively higher variability in the trough concentrations, these targets will be used as guide for dose selection. The individual data from participants will also be considered in final dose determination for age group and weight bands. Doses for each weight band will be selected taking the entirety of the PK and safety data into consideration.

1.6.2 Rationale for Selection of Initial Dose(s)

The initial starting dose(s) for Cohort I and Cohort IIA using the film-coated tablet formulation is presented in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp and labelled Table A. Starting doses in subsequent cohorts are outlined in tables also on this study specific web page.

While this study is enrolled based on age cohorts to meet regulatory standards, weight-based dosing is also being evaluated in Version 5 in accord with WHO consensus guidelines. The 5 mg dispersible tab was formulated to facilitate storage and administration globally.

As the granule and the dispersible tablet formulations demonstrated higher exposure than the tablet formulation, the proposed initial doses using the granule formulation for Cohort IIB and successive cohorts was calculated by adjusting the tablet dose(s) by a common factor with the goal to match target exposures in adults. As DTG exposure from granule and dispersible tablet formulations given direct to mouth or with different types of water were similar and demonstrated 55-58% higher exposure than the tablet formulation, initial doses for these formulations were obtained by dividing the tablet doses by a common factor of 1.55 for each weight band. Under protocol Version 3.0, the PK targets for Cohort IIB Stage I and Cohort III Stage I were met, but required an increased dose of ~0.8 mg/kg (granule formulation); there were no safety concerns in either Cohort. Under protocol Version 4.0, Cohort IV Stage I (≥ 6 months to < 2 years of age) opened with an initial dose of ~0.8 mg/kg (granule formulation). In order to achieve higher C_{24}concentrations higher doses were evaluated in Version 4.0.

1.6.3 Rationale for the Enrollment of HIV-infected Children < 2 years of age

There is a need for new ARVs like DTG to treat HIV-infected children < 2 years of age. Access to ARVs for pregnant women has increased and rates of vertical transmission have decreased globally (30). However, the expanded use of NNRTIs has also corresponded with rising rates of ARV resistance that limit the utility of NVP and other NNRTI for the treatment of infected infants (32, 33). LPV/r is recommended by the WHO as first line for treatment of children < 2 years (33), but there are persistent concerns about the storage requirements and palatability (35).

The management of young HIV-infected children is distinguished by the clinical urgency with which treatment must be initiated. HIV-infected children < 2 years of age suffer extreme viremia, rapid disease progression and high mortality rates (36). Current guidelines recommended treatment for all HIV-infected children, but initiation is considered “urgent” for children < 2 years of age by the WHO (33) and US Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (36). Accordingly, national guidelines in limited resource countries often recommend initiation of ART on the basis of a single positive HIV nucleic acid based test, rather than waiting for confirmatory results (37, 38).

Version 4.0 of P1093 expanded eligibility to include children < 2 years who were ART-naïve or for those who recently started ART (< 4 weeks prior) so that treatment initiation be in accord with current guidelines and standard of care. In P1093, children < 2 years of age can enroll and initiate an ART with only a single positive nucleic acid test if a confirmatory test was pending; these participants started background regimens that were empiric or based on national guidelines while the results of genotype testing drawn at screening were pending. Background regimens are subsequently optimized based upon the results of the genotype.

1.6.4 Rationale for Including ARV Naïve Participants

In Versions 1.0-3.0 of P1093, only treatment-experienced children were eligible for enrollment. In Version 4.0, the enrollment criteria were expanded to include treatment-naïve children < 2 years old. In Version 5.0, treatment-naïve children can enroll in any treatment group open for enrollment. The inclusion of treatment-naïve children is based on cumulative safety data, and the rationale that it is likely to be used and recommended as first line therapy in children consistent with DTG now being recommended as first line therapy for adolescents and adults in U.S. Public Health guidelines (39). Cumulative safety and efficacy from P1093 cohorts I and IIA contributed to European Medicines Agency approval of DTG for children > 6 years of age (40)as well as FDA approval for children 30 kg and above (41).

1.6.5 Rationale for Adding Dose Analysis by Weight Band in Version 5.0

The P1093 protocol is designed to enroll participants and analyze data based on age cohorts. Since the study was first initiated, the WHO (42) and other guideline groups around the world have advocated moving away from age-based dosing to one based upon weight band dosing. Regulatory Agencies are increasingly expecting to receive and analyze pediatric data by weight band to facilitate dosing recommendations in product labelling, based on this standard. Rather than completely modifying the P1093 study design from age-based cohorts to weight-based enrollment, analysis of WHO-recommended weight bands is included as a key secondary consideration in Version 5.0. Therefore, enrollment into P1093 will be monitored to ensure that minimum numbers of participants are accrued into both age based cohorts as well as each relevant WHO weight band to facilitate gathering robust weight-based data to allow flexible treatment recommendations. The fundamental design of the study remains unchanged.

1.7 Hypothesis

DTG will be generally well tolerated and demonstrate an acceptable safety profile, adequate PK and antiviral activity when used concurrently with an optimized background therapy (OBT) in HIV-1 infected infants, children and adolescents.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To select a dose for each formulation of DTG for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily adult dose.

2. To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.

3. To evaluate the steady-state pharmacokinetics of DTG in combination with OBT in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C_{24h} and AUC_{0-24} PK parameters in this population.

2.2 Secondary Objectives

1. To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks.

2. To evaluate the effect on immunologic response from baseline to 24 and 48 weeks.

3. To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure.

4. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population PK analysis.

5. To determine the extended long term (≥48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents.

6. To explore the relationship between DTG exposure and the antiviral activity.

7. To evaluate pharmacokinetic, safety and tolerability profile of DTG when dosed by weight bands.

3.0 STUDY DESIGN

P1093 is a Phase I/II multi-center, open-label, non-comparative study of pharmacokinetic (PK) parameters, safety, tolerability, and efficacy of DTG in pediatric populations. Formulations will be evaluated in age-specific cohorts as shown below.

Cohort I: Adolescents ≥ 12 to <18 years of age (film-coated tablets)
Cohort IIA: Children ≥ 6 to <12 years of age (film-coated tablets)
Cohort IIB: Children ≥ 6 to <12 years of age (granules for suspension or dispersible tablets)
Cohorts III: Children ≥ 2 to < 6 years of age (granules for suspension) – closed to enrollment
Cohort III-DT: Children ≥ 2 to < 6 years of age (dispersible tablets)
Cohort IV: Children ≥ 6 months to < 2 years (granules for suspension) – closed to enrollment
Cohort IV-DT: Children ≥ 6 months to < 2 years of age (dispersible tablets)
Cohort V-DT: Infants ≥ 4 weeks to < 6 months (dispersible tablets)

Participants receiving the film-coated tablet formulation were initially enrolled sequentially into Cohorts I and IIA. Granules for suspension were introduced in Protocol Version 3.0. When it subsequently became clear that dispersible tablets (DT) would be the commercially available pediatric formulation, new cohorts for DT were opened in Protocol Version 4.0 (Section 3.3). Under protocol Version 5.0, two formulations of DTG (film-coated tablets and dispersible tablets) will be evaluated; the target enrollment in Stage I was increased to allow for additional examination of PK, safety, and tolerability by weight bands, including participants from all of Cohorts III-DT, IV-DT, and V-DT (Section 3.4). The approach for currently open cohorts III, IV and V is described below (Section 3.1). However, additional cohorts and weight-band

groups might be opened or reopened to investigate data gaps or new modifications to dosing, for example, regarding fasting requirements or background regimens.

The fundamental procedure for evaluation of DTG doses has remained unchanged through all protocol versions. Each cohort is enrolled in two sequential stages: Stage I and II. (The only exception is Cohort IIB which only enrolled through Stage I). In Stage I, participants undergo intensive PK sampling and are monitored for the safety and tolerability of DTG; to accept or reject a dose, the Protocol Team evaluates PK parameters exposures (Section 8.5) and 4-week safety and tolerability data (Section 9.3). Once a treatment dose has been accepted, enrollment to Stage II begins to complete the cohort. Participants in Stage II will be followed for 48-weeks and evaluated for PK parameters (using population PK methods), safety and tolerability. After study week 48 all Stage I and Stage II participants transition to long-term follow-up and remain on study for approximately three additional years (144 additional weeks of follow-up, for a total of 192 on study). Study drug is provided for the duration of the study. Thereafter, participants are transitioned into care outside of the study (Section 10.6).

3.1 Stage I Study Design

The primary objective of Stage I enrollment is to enable selection of a treatment dose. Participants enrolled during Stage I undergo intensive PK sampling and are monitored to determine the safety and tolerability of the study dose of DTG, as summarized in Figure 2. If the Protocol Team determines the PK parameters, safety or tolerability data to be unacceptable at any point, Stage I enrollment is stopped. A new mini-cohort might be opened to evaluate new dosing that might include changes in the weight band dosing tables available on the study-specific website at http://impaactnetwork.org/studies/P1093.asp or other modifications including the potential of an alteration in recommendations for food ingestion with study drug. This cyclic process continues until the PK parameters, safety and tolerability are considered acceptable for all doses evaluated by cohort and weight band groups.

Mini-Cohort Analysis

The first analysis of participants enrolled in Stage I includes the "mini-cohort" of the first 4 participants who have evaluable PK parameters and 4-week safety and tolerability data. The purpose of this mini-cohort analysis is to promptly identify concerning safety or PK signals. If data from the mini-cohort are acceptable, per the Protocol Team (as per Sections 8.5 and 9.3), Stage I enrollment continues in that cohort with participants receiving the same dose. If data from the mini-cohort analysis are deemed unacceptable, Stage I enrollment to that cohort is stopped, and new dosing is selected for evaluation. In Version 5.0 up to a maximum of seven participants can enroll while waiting for the mini-cohort analysis of the week 4 PK and safety analyses of the first four participants with evaluable data. Allowing enrollment to continue prevents delays in this early safety analysis that can occur when participants with unevaluable data (i.e. inadequate PK collection, incomplete adherence) must be replaced by new enrollees. The Protocol Team is continuously monitoring safety of all participants real tine.

Interim Cohort Analysis

The next analysis is an interim analysis that includes PK parameters and 4-week safety and tolerability of a dose given to the first 10 participants in each cohort with evaluable data, according to criteria outlined in Sections 8.5 and 9.3. If PK parameters safety and tolerability data in this interim analysis are considered unacceptable by the Protocol Team, Stage I enrollment to that cohort is stopped, and new dosing is selected for evaluation and the process restarts.

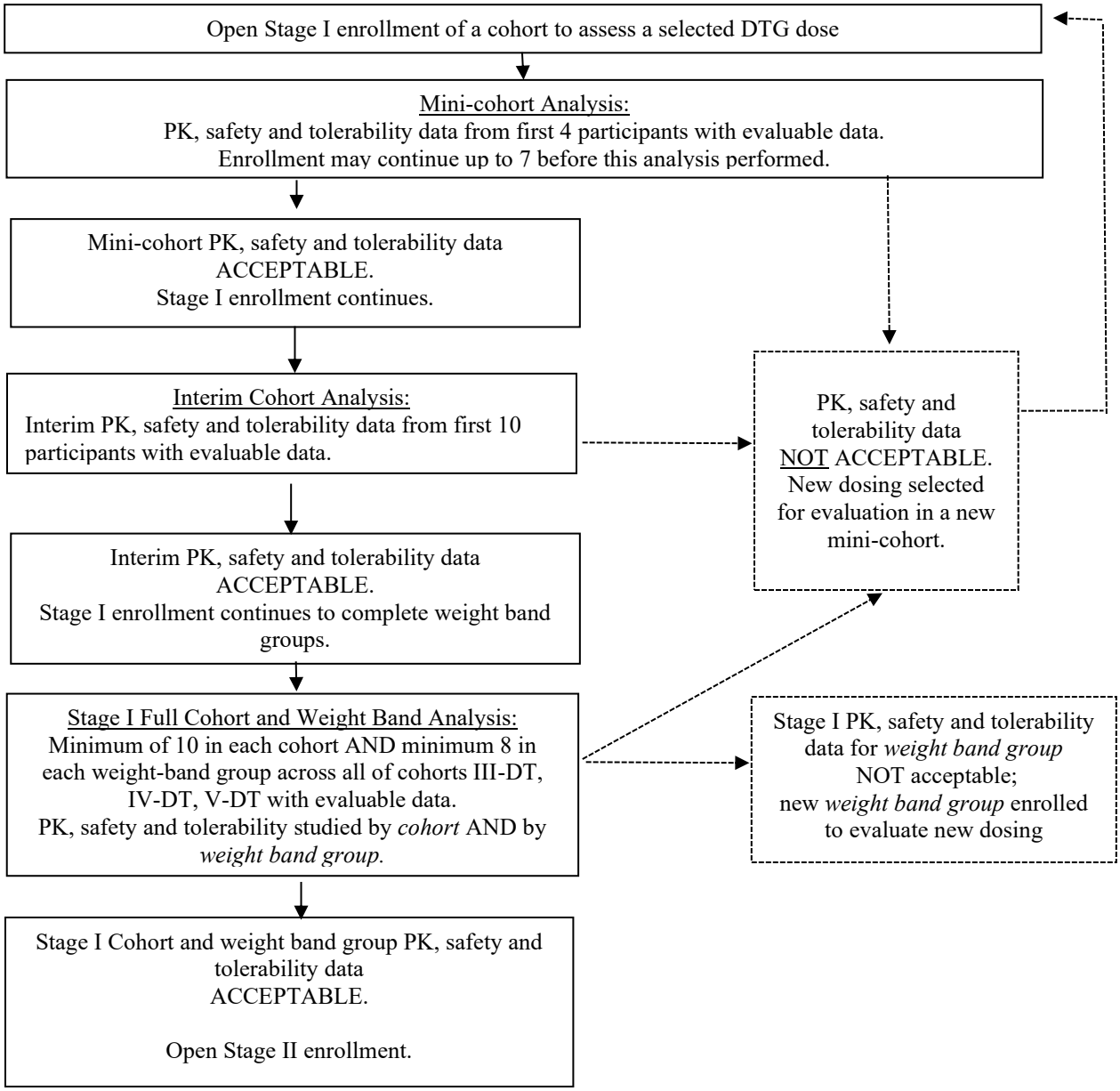
Stage 1 Full Cohort and Weight-band Analysis

The study aims to ensure that adequate numbers of participants are enrolled into each of the age-defined cohorts as well as each of the weight-band groups. To this end, once 10 participants with evaluable data are enrolled into a cohort, additional enrollments into that cohort are only permitted if a participant will be

contributing to achieve the minimum enrollment of 8 evaluable in a weight-band group. To ensure continuous enrollment into cohorts during Stage 1, enrollment does not close until it has been confirmed that 8 participants with evaluable data have been enrolled and completed PK and safety assessments into a weight band, up to a maximum of an additional 2 participants while waiting for these results to become available.

Stage I enrollment of all three Cohorts III-DT, IV-DT and V-DT will therefore be considered complete when two conditions are met simultaneously: at least 10 participants have enrolled in each of the three cohorts AND a minimum of 8 participants have enrolled in each of the four weight bands (Section 3.4). At this point, the team will perform Stage I analyses of PK, safety, and tolerability of all three age cohorts (III-DT, IV-DT and V-DT) and all 4 weight band groups together. At this point, the Protocol Team could pass all groups together, could "fail" a dose applied to cohort or weight band and enroll additional participants to investigate additional dosing questions. New cohorts or weight-band groups will be evaluated in the same manner (minimum 10 for age, and minimum 8 for weight, with mini-analysis after first 4).

Figure 2: Algorithm for STAGE I Enrollment and Analysis



3.2 Stage II Study Design

Stage II enrollment opens once a dose has been accepted based on analysis of data from Stage I enrollments. The additional enrollments during Stage II are intended to complete a full cohort of participants receiving the accepted study dose who are followed for long-term safety, tolerability and efficacy outcomes. Enrollment during Stage II for each cohort will progress independently until the target of 22 per cohort is met; therefore, the number enrolled during Stage II varies depending on the number enrolled during Stage I, as described in Table 10.

Table 10: Target Accrual at the Accepted Dose in Stages I and II

Cohort	Cohort Description	Approximate Accrual at the Accepted Dose	
		Minimum Stage I Participants	Total Stage I and II Participants[3]
I	Adolescents ≥ 12 to <18 years of age (Film-coated Tablet formulation)	10	22
IIA	Children ≥ 6 to <12 years of age (Film-coated Tablet formulation)	10	22
IIB	Children ≥ 6 to <12 years of age (Granules for Suspension or Dispersible Tablets)[1]	10	10
III	Children ≥ 2 to < 6 years of age (Granules for Suspension- closed to enrollment)	10	22
III-DT	Children ≥ 2 to < 6 years of age (Dispersible Tablets)	10[2]	22
IV	Children ≥ 6 months to < 2 years (Granules for Suspension-closed to enrollment)	10	22
IV-DT	Children ≥ 6 months to < 2 years (Dispersible Tablets)	10[2]	22
V-DT	Infants ≥ 4 weeks to < 6 months (Dispersible Tablets)	10[2]	22

Note: Enrollment of children into cohorts using the granules for suspension was stopped in protocol Version 4.0; therefore, Cohorts III, and IV did not reach full enrollment targets.

[1] Dispersible tablets may also be evaluated in this cohort if requested by the regulatory authorities.

[2] Under Version 5.0, accrual into Cohorts III-DT, IV-DT, and V-DT will be continued until a minimum of 10 participants per cohort at the accepted dose and a minimum of 8 participants per weight band is achieved as per Section 3.4.

[3] Additional participants might be enrolled to a cohort for additional evaluation of weight band dosing and/or if requested by the regulatory authorities and/or to fill a data gap (Section 3.1).

3.3 Protocol Version 4.0 – Addition of Dispersible Tablets

In addition to the film-coated tablet and granules for suspension, dispersible tablets (DT) were introduced for study under Protocol Version 4.0. The DT formulation is being proposed as the commercially available pediatric formulation. In a relative bioavailability study in adults, the dispersible tablets resulted in PK exposure that was, on a 'mg to mg' basis, equivalent to granules and there were no observed adverse events. Based on this PK equivalency and safety data the mini-cohorts for the dispersible tablets could enroll simultaneously if the dose from the respective age-equivalent granules for suspension mini-cohort was approved under Version 4.0. With varying timelines for IRB approvals and drug importation at U.S. and non-U.S. sites, it was anticipated that DTG dispersible tablets would not be available to all sites simultaneously. Therefore, enrollment into cohorts for granules for suspension was continued with approval from the Protocol Team until all sites obtained the DT formulation. In January 2018, all participants on granules were recommended to transition to DT formulations. Participants who switched form granules for suspension to dispersible tablets had additional evaluations as follows:

- On the day of switch, the initial dose of dispersible tablets should be given in the study clinic and observed by study staff.
- Two weeks after switching to dispersible tablets, the participant should have an additional 'Switch Visit' during which a palpability assessment and RNA PCR test will be done; if this visit falls within the window for another scheduled visit, a combined visit can be completed to avoid duplication of procedures.
- For participants who have completed 24 weeks of follow-up at the time of the 'Switch Visit' in addition to the procedures mentioned above, these participants will have population PK specimens collected at the two-week post switch visit and at the next regularly scheduled visit.

3.4 Protocol Version 5.0 – Addition of Evaluation by Weight Band or other Factors

As described in Section 1.6.5 there is increased interest globally in dosing DTG by weight band (independent of age). To facilitate analysis of the PK, safety, efficacy, and tolerability data by weight band, target enrollment in Cohorts III-DT, IV-DT and V-DT is expanded in Version 5.0 to ensure that a minimum of 8 participants in each following weight bands will be enrolled into Stage I:

a) 3 to < 6 kg
b) 6 to < 10 kg
c) 10 to < 14 kg
d) 14 to < 20 kg

Note that individual participants within a given weight band group are also included in an age-based cohort for analysis. Additional groups of participants based on weight band alone, also generally including a minimum of 8 might be enrolled if dosing within a specific weight band appears concerning during the full cohort analysis at the end of Stage 1 or if requested by the regulatory authorities. Such weight band groups will be evaluated in a similar manner as the cohorts that are based on age, with analysis of PK parameters and 4-week safety and tolerability data from a minimum of 8 participants have evaluable data.

Instructions for intensive PK sampling are provided in Section 9.2.1. Initially, PK sampling will be done in a fasting state. If, upon review of PK data, the Protocol Team determines that an additional evaluation of PK should be performed with and without fasting, the team will notify the sites to which cohorts or weight band groups this will apply and sites will follow new instructions for non-fasting around PK sampling.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants, who fail the study inclusion / exclusion criteria for viral load or toxicities at screening, may be rescreened after 4 weeks. NOTE: Genotypes do not need to be repeated at screening if they were acceptable at the previous screen.

4.1 Inclusion Criteria

4.1.1 Age: ≥ 4 weeks to <18 years at study entry.

4.1.2 Confirmed HIV-1 infection

- Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. All test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT central laboratory.
- Sample #1 may be tested by non-study public or PEPFAR programs. However, both the result and the assay date must be recorded in the participant's chart. Source documentation (patient's medical record/chart, in-country Ministry of Health registers, laboratory results, etc.) must be available if requested.
- Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites) or in a laboratory that operate according to GCLP guidelines and participates' in appropriate external quality assurance program (for non-US sites).

4.1.2.1 Acceptable tests when participants are ≤ 18 months of age:

Sample #1 and Sample #2 may be tested using any of the following:

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid

Note: Participants ≤ 18 months of age can be enrolled on the basis of one positive test result (from Sample #1) if the results from Sample #2 are pending. The HIV RNA test required at screening per the Schedule of Evaluations may serve as Sample #2 and may be pending at the time of enrollment. However, any participant in whom infection is not confirmed by the results of Sample #2 should discontinue study drug, per Section 6.9 and be followed per Appendix IF

4.1.2.2 Acceptable tests when participants are > 18 months of age:

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

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

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

- Rapid antibody test. If this option is used in combination with the two tests for Sample #1, at least one of the three rapid antibody tests for Sample #1 must be FDA approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence

- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid

4.1.3 Participants must belong to one of the ARV exposure groups below:

4.1.3.1 ARV-treatment experienced (not including receipt of ARVs as prophylaxis or for prevention of perinatal transmission)

— Previously took ARVs for treatment, but not currently taking ARVs:
- Must have been off treatment ≥ 4 weeks prior to screening.

OR

— Currently taking ARVs for treatment but failing:
- Must be on an unchanged, failing therapeutic regimen within the 4 to 12 weeks prior to screening (≤1 log drop in HIV-1 RNA within the 4 to 12 weeks prior to screening).

NOTE: To meet this criterion, two HIV RNA levels are required: one from a date between 4-12 weeks prior to study screening and a second one at study screening. The HIV RNA level at screening must be higher than, equal to or ≤ 1 log lower than the prior HIV RNA level.

NOTE: Dose adjustments for growth or formula substitutions (i.e. switching from single agent to fixed dose combination) during this 4 to 12-week period, substitutions of one ARV within the same class for toxicity or tolerability management, or discontinuation of ARVs are permitted between the HIV RNA measurements and screening or enrollment.

OR

— For participants < 2 years of age, initiated ARVs for treatment < 4 weeks prior to screening.

4.1.3.2 ARV treatment naïve (no exposure to ARVs for treatment; could have received ARVs for prophylaxis or prevention of perinatal transmission)

4.1.4 If an infant has received NVP as prophylaxis to prevent perinatal transmission, he or she must have not received NVP for at least 14 days prior to enrollment into Stage I or II.

4.1.5 HIV-1 RNA viral load greater than 1,000 copies/mL of plasma at screening

NOTE: For participants enrolling into cohorts IV, IV-DT, and V-DT, the HIV RNA test performed at screening may be pending at the time of enrollment. If the screening HIV RNA is ≤ 1000 c/mL, the participant should discontinue study drug, per Section 6.9 and be followed per Appendix IF

4.1.6 Demonstrated ability or willingness to swallow assigned study medications.

NOTE: Film coated tablets MAY NOT be crushed or dissolved. Dispersible tablets MAY NOT be cut and must be used in five milligram intervals.

4.1.7 Parent or legal guardian able and willing to provide signed informed consent.

4.1.8 Female participants of reproductive potential, defined as having reached menarche, and who are engaging in sexual activity that could lead to pregnancy must agree to use two contraceptive methods while on study and for two weeks after stopping study drug.

4.1.9 Males engaging in sexual activity that could lead to HIV-1 transmission must use a condom.

4.1.10 Optimized background therapy (OBT):

- Participants who are both ≥ 2 years of age and ARV-treatment experienced (meeting entry criterion 4.1.3.1) must have available at least one fully active drug for the OBT to enroll. If screening genotype testing is inconclusive, historical genotypes obtained within 1 year of screening will be considered by the Protocol Team for determination of fully active drugs.
- Participants who are ≥ 2 years of age and ARV-treatment naïve (meeting entry criterion 4.1.3.2) can enroll if genotype testing has been obtained with results pending.
- Participants < 2 years of age (either ARV-treatment experienced or ARV treatment naïve) can enroll if genotype testing has been obtained with results pending.

4.2 Exclusion Criteria

4.2.1 Presence of any active AIDS defining opportunistic infection

4.2.2 At enrollment, participant < 3.0 kg

4.2.3 Known Grade 3 of any of the following laboratory toxicities within 30 days prior to study entry: neutrophil count, hemoglobin, platelets, AST, ALT, lipase, serum creatinine and total bilirubin. A single repeat within the 30 days is allowed for eligibility determination.

NOTE: Grade 3 total bilirubin is allowable, if the participant is on ATV.

4.2.4 ANY known Grade 4 laboratory toxicities within 30 days prior to study entry.

NOTE: Grade 4 total bilirubin is allowable, if the participant is on ATV.

4.2.5 The following liver toxicities within 30 days prior to study entry: ALT > 3x ULN AND direct bilirubin is > 2x ULN

4.2.6 Any prior history of malignancy, with the exception of localized malignancies such as squamous cell or basal cell carcinoma of the skin

4.2.7 Clinical or symptomatic evidence of pancreatitis, as determined by the clinician

4.2.8 Use of any disallowed medications at time of screening (see Section 4.3.2 for a complete list of disallowed medications)

4.2.9 Known history of exposure to integrase inhibitor treatment by the participant or participant's mother prior to delivery/cessation of breast feeding

4.2.10 Known resistance to an integrase inhibitor

4.2.11 Women who are pregnant or breastfeeding

4.2.12 Participant is currently participating in or has participated in a study with a compound or device that is not commercially available within 30 days of signing informed consent, unless permission from both Protocol Teams is granted

4.2.13 Participant is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study to a non-IMPAACT study site

4.2.14 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator's opinion, would compromise the outcome of this study

4.2.15 Participant has used, or anticipates using, chronic systemic immunosuppressive agents or systemic interferon (e.g., for treatment of HCV infection) within 30 days prior to beginning DTG study drug. Systemic corticosteroids (e.g., prednisone or equivalent up to 2 mg/kg/day) for replacement therapy or short courses (≤30 days) are permitted. (See disallowed medications Section 4.3.2)

4.2.16 Any condition that would, in the opinion of the site investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol.

4.2.17 Active TB disease and/or requirement for treatment that includes rifampin at the time of the screening visit. However, participants who need rifampin treatment while on DTG will be allowed to continue in P1093 provided the DTG dose is adjusted according to Section 6.1.8.

4.3 Concomitant Medication Guidelines

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Disallowed Medications section below.

4.3.1 Precautionary Medications

DTG should be administered two hours before or six hours after taking any products containing divalent cations. Examples include antacids containing aluminum, calcium, magnesium and supplements that contain zinc or iron. Proton pump inhibitors and H_2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable.

It is the responsibility of the investigator to check on potential drug-drug interactions between background ARV therapy and other concomitant therapies, before placing a participant on a specific medication.

4.3.2 Disallowed Medications

For clarity, the following information on disallowed ARV medications is summarized in Table 11.

Disallowed ARV Medications for Stage I Participants BEFORE the Intensive PK Only
The following medications are disallowed prior to the initial intensive PK evaluation for Stage I participants only, since they could significantly increase or decrease the levels of DTG due to enzyme induction or inhibition and result in increased PK variability. However, these medications ARE allowed in Stage I participants as part of OBT after the intensive PK evaluation has been completed:

Atazanavir (ATV)
Boosted (ritonavir or cobicistat) Atazanavir
Efavirenz (EFV)
Boosted (ritonavir or cobicistat) Fosamprenavir
Fosamprenavir (FPV)
Boosted (ritonavir or cobicistat) Tipranavir

Disallowed ARV Medications for Participants on Stage I (BEFORE and AFTER the Intensive PK) and Stage II participants
When constructing a participant's background ART regimen, the following medications are prohibited for Stage I and Stage II participants because no PK data about co-administration are available and/or they could significantly decrease the levels of DTG due to enzyme induction:

- Nevirapine (NVP): Nevirapine has significant drug-drug interactions with DTG resulting in lowered DTG exposure. The expectation that PK interaction data would become available, led protocol Version 3.0 to allow concurrent therapy with increased (BID) DTG dosing. Data has not been become available and concomitant DTG and nevirapine use is not permitted in protocol Version 4.0. Prior historical NVP treatment is permitted but NVP treatment must be discontinued 14 days prior to initiation of DTG.
- Etravirine (ETR): Etravirine UNLESS it is co-administered with lopinavir/ritonavir or darunavir/ritonavir; these boosted protease inhibitors have been shown to counteract etravirine enzyme induction. Thus, DTG may be co-administered with etravirine if the participant is receiving concomitant lopinavir/ritonavir or darunavir/ritonavir.
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Bictegravir (BIC)
- Other INSTI drugs, including long acting preparations

Additionally, due to their enzyme induction potential, the following medications, or their equivalents, must NOT be administered concurrently with DTG:

- Barbiturates
- Oxcarbamazepine
- Pioglitazone

- Troglitazone
- Rifampin (NOTE: see Section 6.1.8 regarding TB exclusion)
- Rifabutin
- Phenytoin
- Phenobarbital
- Carbamazepine
- St. John's wort

Dolutegravir may inhibit the renal tubular secretion of dofetilide resulting in increased dofetilide concentrations and potential for toxicity.

- Dofetilide

The following medications are also prohibited:

- Medications for HCV therapy

Table 11: Summary of Disallowed ARV Medications

Medication	STAGE I		STAGE II
	Allowed Prior to Intensive PK	Allowed After Intensive PK (OBT)	
Efavirenz (EFV)	No	Yes*	Yes*
Atazanavir (ATV)	No	Yes	Yes
Atazanavir /Ritonavir (ATV/r)	No	Yes	Yes
Tipranavir / Ritonavir (TPV/r)	No	Yes	Yes
Nevirapine (NVP)**	No	No	No
Fosamprenavir / Ritonavir (FPV/r)	No	Yes	Yes
Fosamprenavir (FPV)	No	Yes	Yes
Etravirine (ETR)	No	No	No
Etravirine with Lopinavir / Ritonavir (ETR/ LPV/r)	Yes	Yes	Yes
Etravirine with Darunavir / Ritonavir (ETR/ DRV/r)	Yes	Yes	Yes
Raltegravir (RAL)	No	No	No
Elvitegravir (EVG)	No	No	No
Bictegravir (BIC)	No	No	No

*May NOT be given as part of OBT if it is in combination with TPV/r
**Prior historical NVP treatment is permitted but NVP treatment must be discontinued 14 days prior to initiation of DTG.

4.4 Protocol Registration and Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity.

Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS

PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

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

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Participants meeting the study eligibility criteria will be enrolled through the Data Management Center (DMC) registration screens. Written informed consent for study participation must be obtained before any study related procedures are performed.

Sites interested in screening potential participants into MUST request and receive permission from the Protocol Team in order to proceed with screening visits. Prior to emailing the team to get permission to screen a patient the sites must complete the PS2001 IMPAACT Screening Checklist within the Participant Enrollment System to obtain a screening number, which should be included in the screening request. For all participants from whom informed consent is obtained, but who are deemed ineligible or who do not enroll into the protocol for any reason, a Screening Failure Results form must be completed and keyed into the database.

NOTE: If the participant has a milestone birthday that will change cohort assignment, it is the site's responsibility to notify the DMC data manager to request a cohort assignment change.

4.5 Co-enrollment Procedures

Co-enrollment is permitted except for protocols that would violate the exclusion criteria and where permitted by local/country regulations. All co-enrollments in protocols require the assent of the protocol chairs of the main protocol and the co-enrollment protocols.

5.0 STUDY TREATMENT

Study treatment is defined as DTG film-coated tablets, DTG granules for suspension (granules mixed with liquid) for oral administration or DTG dispersible tablets. Refer to Section 6.3 for further instructions regarding the timing of initiation of DTG and OBT.

5.1 Drug Regimens

All dosing tables referenced below are available in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp.

Weight will be measured and recorded at each visit to verify the participant is receiving the appropriate dose based on the current dosing table. If a participant's weight change requires a dose adjustment, the dose adjustment should be made, the Protocol Team must be notified, although Protocol Team approval for a weight-based dose adjustment is not required. Dose adjustments for weight decreases will only be made if the weight decrease persists for two consecutive study visits.

Participants enrolled into a given age cohort will remain in that cohort throughout their participation in the study. It is possible that the dose chosen for one age cohort (based upon a "mg/kg" target) may differ from the accepted target dose for the next older age cohort. In this case, the participant will stay on their current dose and will "grow" into any subsequent increase in dosing, as per the original dosing table; their dose should not be automatically decreased as they age. This approach is supported by acceptable safety and tolerance observed in adults treated with DTG 50 mg PO BID. The Protocol Team will continue to monitor protocol safety and, if any signals are noticed that require a modification to this approach; the sites will be contacted as to any necessary changes for individual participants or cohorts, see Section 6.4.

Stage 1

Participants enrolled to Stage I of the study will be stratified at screening into one of the age specific cohorts as shown below. Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily. Beginning with protocol version 5, Stage I enrollment into Cohorts III-DT, IV-DT and V-DT will continue until a minimum of 10 participants in each cohort and a minimum of 8 participants in each of the following weight band-groups are enrolled: 3 kg to <6 kg, 6 kg to < 10 kg, 10 kg to <14 kg and 14 kg to < 20 kg

Cohort I: Adolescents ≥ 12 to <18 years of age

- Dolutegravir film-coated tablets
- Participants will take an initial starting dose orally of dolutegravir tablet(s) at approximately 1 mg/kg once daily per Table A in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp.

Cohort IIA: Children ≥ 6 to <12 years of age

- Dolutegravir film-coated tablets
- Participants will take an initial starting dose orally of dolutegravir tablet(s) at approximately 1 mg/kg once daily per Table A in the IMPAACT P1093 Dosing Table Appendix posted on the study-specific web page: http://impaactnetwork.org/studies/P1093.asp.

Cohort IIB: Children ≥ 6 to <12 years of age

- Dolutegravir granules for suspension (1.6 mg/mL). Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.
- Participants will take an oral starting dose* of dolutegravir granules for suspension or dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies.
- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff.

Cohort III: Children ≥ 2 to < 6 years of age (Closed to Enrollment)

- Dolutegravir granules for suspension (1.6 mg/mL)
- Participants will take an oral starting dose* of dolutegravir granules for suspension or dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff for tolerability.

Cohort III-DT: Children ≥ 2 to < 6 years of age

- Dolutegravir dispersible tablet
- Participants will take an oral starting dose* of dolutegravir dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff for tolerability.

Cohort IV: Children ≥ 6 months to < 2 years (Closed to Enrollment)

- Dolutegravir granules for suspension (1.6 mg/mL).
- Participants will take an oral starting dose* of dolutegravir granules for suspension or dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.

Cohort IV-DT: Children ≥ 6 months to < 2 years

- Dolutegravir dispersible tablet
- Participants will take an oral starting dose* of dolutegravir dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.
- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff for tolerability.
- Refer to Section 5.2.3 for additional administration procedures.

Cohort V-DT: Infants ≥ 4 weeks to < 6 months

- Dolutegravir dispersible tablet
- Participants will take an oral starting dose* of dolutegravir dispersible tablets once daily (or twice daily as indicated below) per the dose determined by review of all available data, as well as any relevant bioavailability studies. Refer to the selected Dosing Table.

- Participants who add EFV, FPV/r, or TPV/r as part of OBT after intensive PK will have the frequency of the dose of DTG changed to twice daily.
- The initial dose of dispersible tablets will be administered in the clinic and observed by study staff for tolerability.
- Refer to Section 5.2.3 for additional administration procedures.

*Note: The initial starting Cohort dose selected and any Cohort dose adjustments will be communicated to study sites by the Protocol Team. For individual participant dose adjustments, sites will be notified by a PID specific e-mail from the Protocol Team, see Section 6.4.

Stage II

Beginning with protocol Version 5, upon the confirmation of an acceptable cohort dose in Stage I, additional participants will be enrolled to Stage II (if necessary) to achieve the targeted number of participants per cohort (refer to Section 3.2). Participants enrolling to Stage II of each of the following cohorts will receive the Stage I accepted DTG dose to be administered orally once daily or if on EFV, FPV/r, or TPV/r as part of OBT, DTG will be dosed twice daily, as shown below.

Cohort I:	Adolescents ≥ 12 to <18 years of age – dolutegravir film-coated tablets.
Cohort IIA:	Children ≥ 6 to <12 years of age – dolutegravir film-coated tablets
Cohort III:	Children ≥ 2 to < 6 years of age – dolutegravir granules for suspension
Cohort III-DT:	Children ≥ 2 to < 6 years of age – dolutegravir dispersible tablets
Cohort IV:	Children ≥ 6 months to < 2 years of age – dolutegravir granules for suspension
Cohort IV-DT:	Children ≥ 6 months to < 2 years of age – dolutegravir dispersible tablets
Cohort V-DT:	Infants ≥ 4 weeks to < 6 months of age – dolutegravir dispersible tablets

Changing Dolutegravir Study Product Formulation

Provisions for changing study product formulations is outlined below.

- Participants entering Cohorts III-DT, IV-DT and V-DT and receiving dispersible tablets must continue to receive the dispersible tablets through Week 48. After Week 48, those participants who reach the appropriate age and weight may elect to change to film-coated tablets upon approval of the Protocol Team.
- Participants receiving granules will switch to dispersible tablets, see Section 3.3.
- The Protocol Team will retain the ability to modify participants' dose and formulation as per the protocol, based on PK data, age, weight, and/or other variables.

5.1.1 Duration of Study Product Regimen

Stage I and Stage II: 48 weeks

Long term follow-up: Participants who successfully complete 48 weeks of DTG treatment will continue to receive DTG as part of long term safety follow-up. For additional information please refer to Section 6.6.

Vomiting or Missed Doses

If a participant spits out a dose of DTG or vomits within 4 hours after taking DTG, the participant should take a full replacement dose. If vomiting occurs more than 4 hours after taking study product, a replacement dose should not be taken (the next scheduled dose should be taken).

If a participant misses a dose of DTG the participant should take DTG as soon as possible, provided the next dose is not due within 4 hours. If the next dose is due within 4 hours, the participant should not take the missed dose and simply resume the usual dosing schedule.

5.2 Study Product Formulations and Administration

5.2.1 Dolutegravir Film-coated Tablets

Dolutegravir film-coated tablets in 10 mg, 25 mg, and 50 mg per tablet. Store at 15°C to 30°C (59°F to 86°F). Dispense and store only in the original manufacturer's container. If provided, the desiccant should remain in the bottle.

5.2.2 Dolutegravir Granules for Oral Suspension

Dolutegravir granules for suspension 1.6 mg/1mL suspension. When the granules in the bottle are reconstituted with 73mL of potable (drinkable) water as directed, each container contains 160 mg per 100mL. Once reconstituted, the suspension is stable for 12 weeks in the manufacturer's container. The reconstituted product should be stored at temperatures up to 30ºC (86ºF). Storage in a refrigerator is fully acceptable and preferred, if available.

Preparation of oral suspension by the site pharmacist

In order for the product to be dosed as 1.6 mg/mL suspension in glass bottles: The DTG pediatric granules 0.4% w/w are to be reconstituted into a suspension containing 1.6mg/mL through the addition of water by the site pharmacist as follows:

Using a graduated syringe, the dispensing pharmacist, will measure 73mL of potable (drinkable) water (in two portions) to mix with the DTG granules; the resulting concentration of the suspension after it is mixed is 1.6mg/mL of DTG if reconstituted as directed. Insert a bottle adapter into the neck of the bottle and replace the child resistant cap. The bottle must be shaken for about one minute to ensure homogeneity. After shaking, visually check to ensure that there is no non-dispersed material adhering to the bottom or sides of the bottle. If non-dispersed material is observed, additional shaking is required as above. The maximum in use period of the pediatric formulation after it has been reconstituted with water is 12 weeks and may be refrigerated or stored at room temperature up to 30ºC (86ºF). The suspension should not be frozen. The DTG pediatric suspension reconstituted from granules should be dispensed in the same amber glass bottle in which the granules were mixed with water. An oral dispenser will also be provided with each bottle. The suspension must be retained within the bottle in which it is dispensed and not transferred to any other container except the dosing syringe used for administration. The reconstituted suspension should be used within 12 weeks of the initial reconstitution, but preferably within a single month. Following reconstitution, the suspension in EVERY glass bottle should be shaken EVERY day, irrespective of whether doses are being taken from that particular bottle. Failure to follow this instruction may lead to variability in dosing.

5.2.3 Dolutegravir Dispersible Tablets

Dolutegravir dispersible tablet, 5 mg per tablet. Product may be stored at temperatures up to 30ºC (86ºF). Storage in a refrigerator is fully acceptable, if available. Once a bottle is opened the product has an in-use shelf life of 60 days providing the product is stored in the original package to protect from moisture, with the bottle tightly closed. Do not remove the desiccant.

In Stage I and prior to intensive PK sampling each tablet is to be dispersed using 2 to 5mL of water. There are two options for dispensing described below.

- Option 1: for older children, pour drinking water into the dosing cup. For 1-2 tablets use 5mL of water. For 3-4 tablets use 10mL of water and for 5-6 tablets use 15mL of water. Add the prescribed number of tablets to the water. Swirl the cup gently for 1-2 minutes to fully disperse the tablets. The medicine will be cloudy. If any lumps of tablet remain, swirl the cup gently until they are gone. Give the prepared dose to the child. Rinse the dosing cup before next use.

- Option 2: for infants and younger children, prepare medicine in dosing cup as directed in Option 1. Draw up all the medicine into the syringe. Place the tip of the syringe against the inside of the infant's cheek to give the dose slowly. Swirl a further 2mL of water into the dosing cup, draw it into the syringe, and give it all to the infant. Wash cup and syringe thoroughly.

After intensive PK sampling and in Stage II each tablet can continue to be dispersed as described above or each tablet can be placed directly on the tongue and directly swallowed.

Dispersible tablets may be given as multiples (up to a maximum of 6 tablets), depending on the weight of the child. Once dispersed, the medication should be consumed from the supplied dosing cup or syringe within five minutes.

5.3 Study Product Supply, Acquisition and Accountability

5.3.1 Study Product Supply and Acquisition

Dolutegravir study products will be supplied by GSK. All DTG study products are available through the NIAID Clinical Research Products Management Center (CRPMC).

Other components of the ARV regimen will not be supplied by the protocol.

The IMPAACT pharmacist can obtain DTG by following the instructions in the manual "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Management.

Oral syringes and dosing cups in which to measure water for dispersion and to administer the dispersed product will be packaged with the dispersible tablets and will be provided to the parent/caregiver. Additional instructions for administration of DTG for the parent/caregiver can be found in the Manual of Procedures.

5.3.2 Study Product Accountability

The IMPAACT pharmacist is required to maintain complete records of all study products received from CRPMC. All unused DTG must be returned to the CRPMC after the study is completed or terminated at domestic sites. The procedures to be followed are given in the manual, "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks" in the section Study Product Control.

Non-US IMPAACT pharmacists should follow the instructions on the Study Product Destruction Form. The only study products for this protocol to be included on the Study Product Destruction Form are the DTG study products. The procedures to be followed are given in the manual, "Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks".

6.0 PARTICIPANT MANAGEMENT

6.1 Toxicity Management

Refer to Section 7.3 for guidance on toxicity grading. Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Alternate explanations for clinical and laboratory abnormalities must be sought. Laboratory normal ranges will be the institutional values. Abnormal clinical and laboratory findings should be followed until resolution to < Grade 2.

The remainder of this section provides further guidance on reporting and management of adverse events. General guidance is provided in Sections 6.1.1 and 6.1.2. With respect to management, the guidance in 6.1.2 should be followed for all adverse events except the following:

- Liver toxicity (follow Section 6.1.3)
- Decline in renal function (follow Section 6.1.4)
- Proteinuria (follow Section 6.1.5)
- Peptic ulcer disease (follow Section 6.1.6)
- Abacavir hypersensitivity (follow Section 6.1.7)

Additional considerations for management of participants co-infected with TB are provided in Section 6.1.8.

6.1.1 Reporting

All adverse events occurring from the start of DTG study drug and until the final follow-up visit will be source documented and recorded on case report forms (CRFs).

- Grades 1 and 2: All AEs should be recorded on Case Report Forms (CRFs) at each visit.

- Grades 3, 4 and 5:

    - All AEs should be recorded on CRFs at each visit.
    - The Protocol Team must be notified of AEs within 72 hours of awareness.
    - The investigator should attempt to confirm any laboratory test results, as soon as possible, but always within 72 hours.

6.1.2 Management

Grade 1 – Continue study drug; routine monitoring.

Grade 2 – Continue study drug; monitor closely with more frequent visits as per site PI, work-up to exclude other causes.

For Grade 3 laboratory AEs – Continue study drug while awaiting confirmatory results unless the clinician believes that remaining on study drug would be unsafe and that continuing them would pose little additional risk. Notify the Protocol Team of the confirmatory results within 72 hours of awareness.

For Grade 3 clinical AEs and confirmed Grade 3 laboratory AEs – hold the study drug and concomitant ARV therapy until the abnormalities decrease to a Grade 2 or below unless the site clinician believes holding ARV therapy (including study drug) would be harmful to the participant and that continuing them would pose little additional risk.

The Protocol Team should be informed of all Grade 3 clinical AEs and confirmed Grade 3 laboratory AEs, within 72 hours of awareness, and the site's plan to hold or continue study drug and concomitant ARV therapy.

Grade 4 – Hold study drug and concomitant ARVs immediately unless the site clinician believes that holding ARV therapy (including study drug) would be harmful to the participant and that continuing them would pose little additional risk. Attempt to confirm Grade 4 laboratory AEs as soon as possible, but always within 72 hours of the initial result.

The Protocol Team should be notified of the initial and confirmatory results within 72 hours of awareness.

For Grade 4 clinical AEs and confirmed Grade 4 laboratory AEs that are determined to be probably or definitely related to study drug, study drug should be permanently discontinued. For Grade 4 adverse events that are determined to be possibly, probably not, or not related to study drug, the site investigator should contact the team to determine whether and when study drug may be safely continued (if not previously held) or resumed (if held).

All ARV therapy including study drug should be started or stopped together whenever possible, except when one ARV agent can be substituted for another within class when the etiology of the toxicity can be determined.

6.1.3 Liver Toxicities

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology. If any of the following liver chemistry stopping criteria are met study drug (DTG) should be held unless continuation is approved by the Protocol Team:

- Hy's Law: ALT>3xULN and bilirubin>2xULN; Direct Bilirubin > 35% of Total Bilirubin. NOTE: Hy's Law is a prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10-50%. Increased ALT or total bilirubin are relatively common (in HIV/AIDS) but the combination of ALT>3xULN and total bilirubin >2xULN is rare in drug development and of clinical concern.

- ALT ≥ 10xULN; In this case, if another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team.
- ALT > 3xULN with symptoms of hepatitis or hypersensitivity (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia). In this case, if another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team.
- ALT > 5xULN for more than 2 weeks. In this case, if another cause of ALT elevation is identified, the participant may be re-challenged after receiving the approval of the Protocol Team. Participants who develop ALT ≥ 5xULN should be followed weekly until resolution or stabilization (ALT < 5xULN on 2 consecutive evaluations).

If any of the above liver chemistry stopping criteria are met, sites are instructed to do the following:

- Immediately hold study drug unless continuation is approved by the Protocol Team.
- Report the event to the Protocol Team by email within 24 hours of learning of its occurrence.
- Report Hy's Law liver toxicities (see above) to the RSC as an EAE
- If possible, collect a 2-mL blood draw for pharmacokinetic analysis from the participant within 72 hours of the last dose taken, and record the date and time of the last dose taken as well as the date and time of the pharmacokinetic sample collected. NOTE: If the timeframe is greater than 72 hours since the last dose, the specimen should not be collected.
- Complete and submit the liver toxicity CRFs within 1 week to the DMC

6.1.4 Decline in Renal Function

Participants who experience an increase to Grade 2 from a baseline normal or Grade 1 serum creatinine level, or an increase to Grade 3 or higher from a baseline Grade 2 level, must return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio, as well as serum creatinine should be done at this confirmatory visit. If the creatinine elevation is confirmed (with or without proteinuria), the investigator should contact the Protocol Team to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (calculated by the Schwartz formula) of <50mL/min ($1.73m^2$) must return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine microalbumin/creatinine ratio should be done at this confirmatory visit (in addition to the serum creatinine). If an estimated GFR of <50mL/min ($1.73m^2$) is confirmed, then DTG should be withheld and the investigator should contact the Protocol Team to discuss additional follow-up and management, which may include resumption of DTG if agreed to be appropriate.

Schwartz formula: GFR (mL/min/ 1.73 m^2) = K x Ht cm/P_{creat}

K=constant	Cr mg/mL
Infants < 1 year	0.45
Children 1-12 years	0.55
Female 13-21 years	0.55
Males 13-21 years	0.70

Consideration for confounding factors (e.g. background ART therapy; other medications; dehydration and concurrent conditions) should be considered, and a nephrology consult may be obtained. If participants are also receiving TDF, then a switch to an alternative nucleoside should

be considered if restarting DTG. Current local prescribing information should be consulted for additional details on dosing background ART therapy in renal-impaired participants. If DTG is re-initiated, it should have been withheld for no more than 4 weeks, unless approved by the P1093 Team.

6.1.5 Proteinuria

Participants with an abnormal urine microalbumin/creatinine ratio (>300 mcg/mg) that represents a change from a normal baseline and no associated increase in creatinine should have a repeat spot urine microalbumin/creatinine ratio and serum creatinine assay performed within 2 to 4 weeks. If confirmed, the investigator should contact the Protocol Team to discuss additional follow-up and management. Additional follow-up may include nephrology referral. Participants with an abnormal urine microalbumin/creatinine ratio (>300 mcg/mg representing a change from baseline) and a serum creatinine increase to grade 2 toxicity or above, should have confirmation of both results within 2 to 4 weeks. If confirmed, DTG should be held, and the investigator should immediately contact the Protocol Team to discuss additional follow-up and management, which may include resumption of DTG if agreed to be appropriate.

6.1.6 Peptic Ulcer Disease

Symptoms suggestive of peptic ulcer disease (e.g., epigastric pain, nausea, vomiting, bloating, etc.) are relatively common but are also non-specific.

Participants with such symptoms should be treated symptomatically as appropriate (e.g., H_2 blockers or proton pump inhibitors) and be evaluated and treated as appropriate for *H. pylori*. However, patients with these symptoms should not be prescribed cation-containing antacids for concomitant use, because significant reduction in DTG exposure has been observed when these drugs were co-administered. If deemed necessary, DTG should be administered 2 hours before or 6 hours after taking antacid products.

If symptoms consistent with peptic ulcer disease persist or worsen on symptomatic therapy, the investigator should consult the Protocol Team to discuss additional management, which may include but is not limited to discontinuation of DTG.

6.1.7 Abacavir (ABC) Hypersensitivity (HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR).

Where HLA-B*5701 screening is considered standard of care, it is recommended that investigators screen for the presence of the HLA-B*5701 allele in any participant for whom an Abacavir (ABC)-containing product (e.g., ZIAGEN™, TRIZIVIR™, EPZICOM™, KIVEXA™) may be considered as part of the optimized background regimen and *HLA-B*5701* status is unknown (even if the participant has previously tolerated ABC). Use of ABC in participants known to carry HLA-B*5701 is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and only under close medical supervision.

Reporting of Abacavir Hypersensitivity Reactions

All cases of potential abacavir hypersensitivity MUST be reported as an EAE, refer to Section 7.2. In addition, the ABC HSR CRF must be completed and submitted to the DMC within one week of the onset of the hypersensitivity reaction.

6.1.8 Management of Participants Co-infected with TB

Participants presenting at the Screening visit with active Tuberculosis (TB) co-infection are not eligible to participate in the study due to multiple drug interactions, overlapping toxicities, and other complications affecting treatment outcomes. Participants who are already enrolled and are on therapy who become exposed to TB, and subsequently require an anti-TB treatment that includes the use of rifampin, may be allowed to continue in the study if their ART options are compatible with co-administration of rifampin. Continuation requires the approval of the Protocol Team. Management of these participants is as follows:

- When administration of the rifampin-containing anti-TB treatment begins, participants will switch to the Schedule of Evaluations in Appendix IG
  Schedule of Evaluations
  Participants who Start Rifampin as Part of Treatment for Active Tuberculosisand will increase their DTG dose from once daily to twice daily (dose is based on weight). DTG study drug continues to be administered twice daily while participant is on the rifampin containing anti-TB therapy.

- While on the rifampin-containing anti-TB therapy, to ensure the DTG dose is appropriate, intensive pharmacokinetic sampling will occur two weeks after the start of anti-TB treatment at the following times, per Appendix IG : Pre-dose, and at 1, 2, 3, 4, 6, 8, and 12 hours post-dose will be performed.

- Individual dose adjustments may be made to the initial DTG dose following the Week 2 intensive pharmacokinetic study and is participant to approval of the Protocol Team. If the participant assessed is adherent to therapy but does not achieve the minimum AUC_{0-24} of 25 µg.h/mL after dose adjustment they may continue on study drug after consideration of the clinical, pharmacologic, immunologic and virologic data, and upon agreement of the site investigator, study co-chairs, pharmacologist and medical officers, a given participant may be allowed to continue with the study drug at the dosing that resulted in the exposures below the minimum target.

- Population PK time points at weeks 4 and 12 should remain the same as the Schedule of Evaluations (Appendix IG).

- It is estimated the participant will be on anti-TB treatment for approximately 24 weeks. Upon discontinuation of the rifampin containing anti-TB therapy, the participant's DTG dose will revert back to once daily administration unless on EFV, FPV/r, or TPV/r. The participant should complete the remainder of the first 48 weeks of DTG therapy on their original schedule of evaluations, or if they have completed 48 weeks of DTG therapy, they should move to long term follow-up (Appendix IE). For example, if the participant was at week 16 when they were started on rifampin, and they complete 24 weeks of rifampin therapy, they would then go back to week 40 of their original Schedule of Evaluation (SoE).

6.2 Screening

The DMC will maintain a web page informing sites as to the availability of enrollment slots per cohort. Participants screened for enrollment in the mini-cohort of Stage I but cannot enroll because the mini-cohort is filled will be given priority to enroll when the remaining slots are opened for that cohort. If Stage I enrollment is completed before a screened participant can enroll, that participant will be given priority for enrollment on Stage II. The Protocol Team will maintain a waiting list for each cohort to ensure facilitated enrollment as well as informing sites and potential participants as to the status of the various cohorts and stages as the study progresses.

Participants will be asked to undergo the following evaluations at screening to be eligible for enrollment:

- Medical history and physical exam
- Pregnancy test (for females of child bearing age)
- Confirmation of two methods of contraception for participants of reproductive potential and who are engaging in sexual activity that could lead to pregnancy
- Hematology, chemistries, lymphocyte subsets and lipid profiles
- Urinalysis
- Confirmation of HIV-infection
  NOTE: for participants ≤ 18 months of age results may be pending at the time of enrolment: see Section 4.1.2.
- HIV-1 RNA PCR
  NOTE: for participants < 2 years of age results may be pending at the time of enrolment: see Section 4.1.5.
- Real time genotyping for resistance testing
  NOTE: for all naïve participants and participants < 2 years of age (Cohorts IV, IV-DT, and V-DT) results may be pending at the time of enrolment; see Section 4.1.10.
- Phenotyping where possible

6.3 Initiation of Dolutegravir and Management of Background ART

DTG is initiated by all participants on the day of enrollment. Additional ARV's taken as background ART vary depending on timing during follow up, age, ARV-treatment history, and availability of genotype results. Detailed instructions on DTG and background ART administration follow.

6.3.1 Optimized Background Therapy (OBT)

The OBT regimen should ideally include one ARV with predicted antiviral activity and (at least) one additional ARV, for a total two ARV drugs given in addition to DTG. The HIV-1 genotype obtained at screening, as well as participant history of virologic and medication tolerance should be used to determine an appropriate OBT regimen. All OBT regimens must be approved by the Protocol Team. Sites are requested to send the proposed OBT regimen along with resistance profiles by email to the Protocol Team for approval, as soon as possible, once screening genotype results are available; the team will respond within two business days. Additional details about the OBT are based on cohort and ARV experience, as follows.

- The OBT regimen for ARV-treatment-experienced participants in Cohorts I, II, III, III-DT must contain at least one fully active drug AND one additional drug, and be approved by the Protocol Team.

- The OBT regimen for ARV-treatment-experienced participants in Cohorts IV, IV-DT, and V-DT AND treatment naïve participants in all cohorts will ideally contain AT LEAST one fully active drug AND one additional drug, and be approved by the Protocol Team. The determination of OBT for these cohorts can be made before enrollment (if genotype results are available) or after enrollment (once screening genotype results are available); at either time point, the site proposes an OBT regimen that must be approved by the Protocol Team. Notably, the protocol permits Stage I participants to be receiving empiric regimens while awaiting genotype results and OBT determination. If the screening genotype results ultimately do not demonstrate any available active drugs, a participant can either discontinue DTG (Section 6.9) or can continue on the regimen until the 4-week HIV RNA testing results are available. At that point the site should propose OBT and the Protocol Team will make a case-specific determination of OBT acceptability taking into consideration results of the screening genotype, historical genotypes (up to one year prior), 4-week virologic response (e.g. viral load decrease of > 1 log drop or a VL <400 at the four week visit), and other clinical factors.
- For participants in Cohorts I, II, III, III-DT, the prescriptions should have already been obtained from a pharmacy and the drugs must be available during the intensive PK visit to have the first dose observed immediately upon completion of the PK evaluations. For participants in Cohorts IV, IV-DT, and V-DT, the PK should be completed on day 5-10, and OBT initiated as soon as possible thereafter when results are back from screening genotype and when agents are available, as outlined below.
- To minimize the impact of drug-drug interactions on PK variability, use of ATV, FPV, EFV, boosted (ritonavir or cobicistat) ATV, FPV, and TPV will not be allowed PRIOR to the initial PK evaluation in Stage I but may be added as part of the OBT regimen after completing the intensive PK or as part of the OBT regimen for those in Stage II. Refer to Section 4.3.2 and Table 11 for a description of the medications that are disallowed during Stage I and/or Stage II of each cohort.

6.3.2 Empiric Background Therapy

For ART naïve participants and ARV experienced participants < 2 years of age (Cohorts IV and V) the empiric background therapy regimen should be chosen by site investigators, per country guidelines and provider discretion. In choosing the regimen consideration should be given to the regimen most likely to be considered effective, but it must not include disallowed medications (Section 4.3.2 and Table 11) and must be approved by the Protocol Team.

6.3.3 Stage I: Initiation of DTG

The timing and management of DTG and background ART is outlined in Table 12 below. Note that age ≥ 2 years effectively applies Cohorts I, II, and III-DT and age < 2 year applies to participants in Cohorts IV-DT and V-DT.

Table 12. Stage I Timing and Management of DTG and Background ART

ARV Exposure Group (Section 4.1)	Age at Enrollment	ARV at Entry	ARV Management Immediately after Intensive PK Visit on day 5-10	Subsequent ARV Modifications Based on Screening Genotype (if necessary)
ARV-treatment experienced participants, not currently receiving ARVs	≥ 2 years	Start DTG alone. No other ARVs.	Continue DTG. Start OBT.	Not applicable
	< 2 years	Start DTG. Start empiric background ART.	Continue DTG. Either change background ART to OBT, or continue empiric ART (if screening genotype results pending).	Change background ART to OBT when genotype available and OBT approved.
ARV-treatment experienced participants currently receiving a failing regimen of ARVs (all ages) or who recently started an empiric regimen (<2 years old only).	≥ 2 years	Start DTG. Continue current ARV regimen.	Continue DTG. Change background ART to OBT.	Not applicable
	< 2 years	Start DTG. Continue current ARV regimen.	Continue DTG. Either change background ART to OBT, or continue empiric ART (if screening genotype results pending)	Change background ART to OBT when genotype available and OBT approved.
ARV-naïve participants	≥ 2 years	Start DTG alone. No other ARVs.	Continue DTG. Start OBT or start empiric background ART if screening genotype results pending.	Change background ART to OBT when genotype available and OBT approved.
	< 2 years	Start DTG. Start OBT or empiric background ART if screening genotype results pending.	Continue DTG. Continue OBT, start OBT or continue empiric background ART if screening genotype results pending.	Change background ART to OBT when genotype available and OBT approved.

6.3.4 Stage II: Initiation of DTG

During stage II, all participants initiate DTG on enrollment. ARV-treatment experienced participants in Cohorts I, II, III and III-DT will be based on screening results, and the regime will start simultaneously with DTG. ARV-naïve participants of Cohorts II and III, and all participants in Cohorts IV, IV-DT, and V-DT can start OBT on enrollment, or start empiric ART and change to OBT as soon as genotype results are available.

6.3.5 Permitted Changes to ARV Regimens (Stages I and II)

No changes, re-optimization or intensification in background ARV therapy after initial optimization will be permitted prior to protocol-defined virologic failure, with the exception of a single substitution of a component of OBT with another approved compound for the management of drug toxicity. Formula substitutions (substituting single agents for fixed dose combinations and

vice versa of the same ARV) are not classified as a change and are permitted during the study. Any changes must be discussed with the Protocol Team. Unless the change is specifically permitted, participants who have one or more new agents added to the optimized background HAART regimen will be considered virologic failures.

6.4 Dose Adjustments

Dose modifications will be considered after the Protocol Team reviews the intensive PK parameters and safety data as part at any stage of analysis (mini-cohort, interim, full cohort or weight band group) in Stage I. If a dose is deemed unacceptable then the Team will review the clinical, virologic and PK data for individual participants who are currently receiving the dose deemed unacceptable and decide whether a modification is in the participant's best interest. If the dose is modified in these participants, additional PK sampling may be requested by the team. The type of PK sampling (intensive, specific timed samples) will be determined by the Protocol Team on an individual basis and communicated to the site. Participants who undergo a dose increase will have an additional study visit four weeks after the dose modification to monitor safety and then continue follow-up with no further changes in the visit schedule. Refer to schedule of evaluations for procedures indicated for a dose modification.

In addition, at any point during study follow-up, an individual participant's dose may be modified on a case-by-case basis by the Protocol Team if determined to be in the individual's best interest. As specified above, the Protocol Team may request additional PK sampling and all participants who undergo a dose increase will have an additional visit for safety.

6.5 Virologic Failure for Participant Management

All HIV-1 RNA PCR test results should be reviewed and entered into the Lab Data Management System (LDMS) within two weeks of specimen collection. If extenuating circumstances prevent results from being entered during this timeframe, the Protocol Team should be notified.

Virologic FAILURE in this study is defined as:

- A confirmed decrease in HIV RNA of < 1.0 log10 at or after week 12 unless the HIV RNA is < 400 copies/mL.

OR

- A confirmed HIV RNA > 400 copies/mL starting at Week 24 or beyond on 2 consecutive measurements at least 1 week and within 4 weeks apart;

Virologic REBOUND in this study is defined as:

- Confirmed HIV-1 RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after an initial confirmed response (on 2 consecutive measurements at least 1 week apart) of HIV-1 RNA < 400 copies/mL;

OR

- Confirmed > 1.0 log10 increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart). For the purposes of this study, nadir is defined as the lowest HIV-1 RNA while on study drug that is > 400 copies/mL.

NOTE: A confirmatory HIV-1 RNA sample is to be collected ≥ 1 week to ≤ 4 weeks after the date of the HIV sample suggesting HIV virologic failure or rebound.

NOTE: Participants should continue to be evaluated for virologic failure beyond Week 48 as part of their schedules of evaluations. This includes participants who experience their initial or subsequent virologic failure (if they suppressed after a prior failure), provided that at least 24 weeks have lapsed from the prior virologic failure drug resistance samples.

Participants, who are confirmed as virologic failures as defined above, should undergo a Virologic Failure Visit, as described in the Schedules of Evaluations. At this visit, a specimen should be drawn for resistance testing (genotyping and phenotyping), as described in the Schedules of Evaluations. Sites should notify the Protocol Team of all virologic failures. Participants may then, at the discretion of the participant's clinician and with the approval of the Protocol Team:

- Be taken off study drug and followed as per Appendix IF .

OR

- Have background therapy re-optimized, with the participant remaining on study drug;

OR

- Continue with no changes made to the current regimen.

Any re-optimization of background therapy must first be approved by the Protocol Team.

6.5.1 Viral Resistance Samples/Testing

For all participants, blood samples for viral resistance assays and integrase resistance will be collected and stored at entry. In addition, to evaluate development of resistance to DTG and to other ARV therapies, used in the treatment regimen, blood samples will be collected at the Virologic Failure visit (as defined above) and at the Premature Discontinuation of Study Drug (if not already obtained at virologic failure) to assess development of genotypic or phenotypic resistance to DTG and/or OBT.

6.5.2 Algorithm for Resistance Testing

- If a participant reaches virologic failure at or after 24 weeks and discontinues because of viral failure, the earliest sample with a corresponding HIV-1 RNA result above 400 copies/mL should be sent for all resistance testing, as outlined in the Laboratory Processing Chart which can be found on the P1093 protocol specific webpage: http://impaactnetwork.org/studies/P1093.asp

- If a participant is a virological failure but continues in the study (on study drug), the second consecutive sample with a corresponding HIV RNA result above 400 copies /mL will be sent for all testing. In addition, resistance testing will be done for participants who continue on study after confirmation of virologic failure if HIV RNA is >400 copies/mL.

- If a participant discontinues from the study early, a sample will be sent for resistance testing if the participant's HIV RNA level is above 400 copies /mL at the time of discontinuation.

6.6 Long Term Safety Follow-up

Participants who successfully complete 48 weeks of DTG treatment will continue on the study in long-term follow-up and will be seen in clinic every 12 weeks for approximately 3 additional years (192 weeks total follow-up) per Appendix IE Appendix IE Schedule of Evaluations
Long-term Safety Follow-up for Participants Who Continue to Receive DolutegravirStudy drug will be provided for the duration of the study. Thereafter, participants will be transitioned into care and treatment outside of the study, refer to Section 10.7.

6.7 Pregnancy and Contraception

6.7.1 Pregnancy Testing and Contraception

A female participant is considered to be of reproductive potential if she has reached menarche. The protocol includes multiple measures to prevent and monitor for pregnancy in study participants, as there is concern for potential toxicity of DTG early in gestation (Section 1.5).

During follow-up, all female participants over the age of 9 years are asked about menarche at each visit (until it occurs).

At each visit, all female participants of reproductive potential

- must have a test for pregnancy
- are asked about sexual activity that could lead to pregnancy
- must have their choice of TWO contraceptives (see below) documented if they are currently or could possibly be engaging in sexual activity that could lead to pregnancy
- are reminded that if they change their minds (since enrollment) and now seek pregnancy they should inform the study staff

One of the TWO forms of contraception must be highly effective, such as hormonal birth control (e.g., pills, shots, or slow release inserts placed under/on the skin) and/or an intrauterine device (IUD). The second form contraception is ideally an accepted barrier method (e.g. female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm [excluding nonoxydyl-9]). Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission. Use of an IUD may increase the risk of pelvic inflammatory disease.

Female participants with reproductive potential who are currently or could possibly engage in sexual activity that could lead to pregnancy and are unable to utilize two forms of contraception for some reason (such as local availability), *alternative contraceptive management can be discussed with and approved by the Protocol Team*. Any female participant with reproductive potential who is sexually active in a way that could lead to pregnancy AND is unwilling or unable to take effective contraception must stop taking DTG.

Pregnancy testing will be conducted, per the relevant Schedule of Evaluations for females with reproductive potential and at any time during the study when pregnancy is suspected. Additionally, a pregnancy test should also be performed prior to DTG re-administration, when dosing is disrupted for more than 7 days. Pregnancy tests may be performed on either blood or urine. At every visit (or some other more frequent interval), pregnancy prevention will be

discussed with the participants, including specific counseling, provision of information and advice as needed. This discussion should be documented in the participant's study record.

6.7.2 Pregnancy

Any participant who becomes pregnant while participating in this study should discontinue study drug immediately. However, these participants should remain on study but off study drug and followed per Appendix IF Appendix IF Schedule of Evaluations
Participants who Prematurely Discontinue Dolutegravir, to monitor for any safety issues until the birth of the baby. Any pregnancy that occurs during study participation must be reported to the Protocol Team. All pregnancy complications, elective terminations for medical reasons and spontaneous abortions must be reported as an EAE.

Pregnancy test results and pregnancy outcomes should be ascertained and entered into eCRFs. Outcomes may be ascertained based on maternal report but medical records should be obtained whenever possible to supplement maternal reports.

Note: Study sites will also be encouraged to prospectively register the participant's pregnancy in the Antiretroviral Pregnancy Registry: http://www.apregistry.com/ (in U.S.: 1-800-258-4263; non-US: 1-910-679-1598).

6.8 Criteria for Study Discontinuation

6.8.1 The participant or legal guardian refuses further treatment and/or follow-up evaluations.

6.8.2 The participant fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

6.8.3 The participant requires treatment with medications that are disallowed while on this study.

6.8.4 Virologic failure and participant does not meet the criteria for continuation of study drug.

6.8.5 Non-adherence of study medications.

6.8.6 The Protocol Team has determined that there would be no benefit to continue on study and receive DTG.

6.9 Criteria for Treatment Discontinuation

6.9.1 Pregnancy, refer see Section 6.7.

6.9.2 New data become available that indicate treatment should be discontinued.

6.9.3 Drug toxicity that requires permanent study drug discontinuation, see Section 6.1.

6.9.4 Liver toxicities, see Section 6.1.3.

6.9.5 The investigator determines that further participation would be detrimental to the participant's health or well-being.

6.9.6 HIV infection not confirmed, see Section 4.1.2.

6.9.7 Participant was enrolled but found to have HIV RNA ≤ 1000 copies /mL at screening (applies only to Cohorts IV, IV-DT, and V-DT).

6.9.8 Participant was enrolled but found to have no active drugs per genotype performed at screening (applies only to Cohorts IV, IV-DT, and V-DT who enrolled with genotype results pending); and whom the Protocol Team determined the proposed OBT as non-acceptable, see Section 6.3.1.

NOTE: In the event of treatment discontinuation, participants will be asked to continue on study for 4 weeks after they discontinue study drugs or until the adverse event resolves.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

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

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

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

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

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which expedited reporting are required are DTG tablets, DTG granules for suspension (granules mixed with liquid) and DTG dispersible tablets for oral administration.

In addition to the EAE Reporting Category identified above, other adverse events that must be reported in an expedited manner are:

- All grade 4 toxicities,
- Hy's law liver toxicities, see Section 6.1.3,
- Abacavir (ABC) hypersensitivity (HSR), see Section 6.1.7, and
- All pregnancy complications, elective terminations and spontaneous abortions.

7.3 Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, will be used to grade all adverse events except for psychiatric events listed in Table 13 below, which will be graded as shown. The DAIDS AE Grading Table is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting.

Table 13: Supplemental Table for Grading of Psychiatric Events

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the duration of the study.
- After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

NOTE: For reporting of all adverse experiences the Investigator will determine the causality and relationship to study drug. However, regarding participant safety and PK evaluations which will support the selection of a dose for a given cohort, the Protocol Team will also have input as to the causality and drug relation of specific adverse experiences.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II study whose primary objectives are to assess the safety and pharmacokinetics of DTG administered to HIV-1-infected infants, children and adolescents with ages ranging from 4 weeks to < 18 years. The sample will be stratified into the following groups:

Cohort I: Adolescents ≥ 12 to <18 years of age (tablets)

Cohort IIA: Children ≥ 6 to <12 years of age (tablets)

Cohort IIB: Children ≥ 6 to <12 years of age (granules for suspension)

Cohorts III: Children ≥ 2 to < 6 years of age (granules for suspension or dispersible tablets)

Cohort III-DT: Children ≥ 2 to < 6 years of age (dispersible tablets)

Cohort IV: Children ≥ 6 months to < 2 years (granules for suspension)

Cohort IV-DT: Children ≥ 6 months to < 2years of age (dispersible tablets)

Cohort V-DT: Infants ≥ 4 weeks to < 6 months (dispersible tablets)

A minimum of ten participants will be enrolled into each age cohort in Stage I for purposes of dose finding. Under Version 5, for stage I enrollment intro Cohorts III-DT, IV-DT, and V-DT, there is also a requirement to enroll a minimum of eight participants (which may include those already enrolled into the age cohort) into each of the following weight band groups:

1) 3 to <6 kg
2) 6 to <10 kg
3) 10 to <14kg
4) 14 to <20 kg

To this end, once a cohort has enrolled 10 participants, additional participants will be allowed to enroll during Stage I only if their weights fall within a weight band that has not yet reached its enrollment target of N=8 with evaluable PK and safety data; enrollment of up to 2 additional participants to a total of 10 per weight band will be allowed while evaluation of the minimum of 8 is ongoing (i.e. to confirm data are evaluable). Additional participants will be enrolled into Stage II of the study and treated at the doses determined optimal for their cohorts based on Stage I results. The total sample will provide a minimum of 120 evaluable participants (Stage I + Stage II) who have been treated exclusively at the doses judged to be optimal for their age cohorts (see Schema for breakdown by cohort) and weight band groups.

Under previous protocol versions, accrual to Stage I followed an algorithm in which younger children's exposure to the study medication was contingent upon success in meeting safety and pharmacokinetic guidelines in the older strata. Thus, Cohort I was the first to opened with enrollment in Cohort IIA contingent upon whether members of Cohort I met the guidelines for safety and PK parameters. Cohort IIB then opened once members of Cohort IIA passed safety and PK criteria and a pediatric formulation was available. A similar approach was used for the rest of the younger cohorts, each of whose opening was contingent upon successful results from the next older age cohort. Because data have already now

been obtained from all cohorts, under protocol Version 5.0 accrual to Stage I for Cohorts III-DT, IV-DT and V-DT will be simultaneous, rather than sequential.

The data from Stage I is analyzed in three steps, a mini-cohort analysis, an interim cohort analysis, and the full cohort and weight band group analysis (Section 3.1). For the *mini-cohort analysis*, the overall safety and PK data of the first 4 participants with evaluable data in a given cohort will be evaluated with respect to the safety guidelines, per Section 8.5 and the PK guidelines, per Section 9.3. If the first 4 evaluable participants of this cohort meet both sets of guidelines, then accrual will continue and no dose adjustments will be made. If the first 4 evaluable participants of the older cohort fail either the safety or the PK guidelines in this initial test, then the starting dose will be adjusted in the appropriate direction, (e.g. upwards for inadequate PK values; downwards for safety failure), if this is feasible. New doses will be tested in the same manner, enrolling new participants and reviewing PK and safety data from the first 4 participants with evaluable data. The evaluation will proceed as described above.

The *interim cohort* analysis occurs when there are 10 participants with evaluable data in an age cohort. Data will be evaluated, and safety guidelines, per Section 8.5 and the PK guidelines, per Section 9.3. If there are no concerns, enrollment continues but additional participants can only into a cohort if they also contribute to meeting the weight band group minimums.

For the *full Stage I cohort and weight band group* analysis, the starting dose of fully accrued cohorts are evaluated by BOTH cohort and weight band group on the basis 4 week safety (as per Section 8.5) and intensive PK data (as per Section 9.3). As of Version 5.0, the full analysis of Stage I data for Cohorts III-DT, IV-DT and V-DT occurs when all cohorts and weight band groups have met minimum enrollment targets and achieved 4-weeks of follow up (See Section 3.1 for more details). The purpose of this review process is to take account of all available information in determining whether the dose finding algorithm has converged on the best dose for further study in Stage II or whether adjustments are needed. As part of this review process, safety and PK data will be broken down based on the dosing adjustments that have been made because of the inducing or inhibiting effects of the background regimens. If there is evidence that some adjustments may have been associated with undesirable PK levels or with safety concerns, these adjustments may be modified for Stage II or further data may be gathered prior to opening Stage II.

If a dose is "failed" by the Protocol Team, considering the safety and/or PK targets (refer to Section 3.1) at the mini-cohort, interim or full cohort analysis stages, a new test dose will be examined. New participants will be started on the new dose and evaluations will proceed as described above. For participants who meet PK targets, safety will be evaluated based on all available data collected through 4 weeks on that dose. For participants who fail to meet PK targets and are required to have a dose adjustment, safety will be evaluated based on data gathered until the time of the visit at which the dose is adjusted.

If the Protocol Team deems a given participant's PK data to be unevaluable (e.g., because of reported non-adherence or PK results that would be physiologically implausible with good adherence), that participant will be replaced for dose finding purposes (but will continue in the study and contribute to the safety analyses). Note that the participant would be replaced for evaluating safety, as well as PK, criteria, if unevaluable PK data reflect uncertainty about appropriate exposure to the study medication.

If the dosing recommendation for a given subgroup of participants should differ between that based on age cohort vs. that based on weight band, the Protocol Team will review all relevant data and make a final dosing recommendation. In a situation where a final dosing recommendation cannot be made with available data, the Protocol Team can enroll additional cohorts or weight band groups until a dosing recommendation can be made.

Participants accrued to Stage II of the study will be administered the doses determined for their age cohorts, with no individual dose adjustments based on PK allowed. For purposes of analysis, data from these participants will be combined with the data from the Stage I participants who have been treated at the doses accepted for their cohorts and weight bands and who have not required individual PK determined dose adjustments, such that their total exposure to the study drug has been at the accepted dose. Sensitivity analyses will be performed to determine whether the exclusion of participants whose doses have been adjusted creates a selection bias which impacts upon any results.

Participants who switched formulation will be included in sensitivity analyses whose purpose would be to (1) identify safety issues for all children exposed to the study drug, and (2) determine whether the results of those switching formulations differed descriptively from those of the primary analysis.

Participants with no study drug dose adjustments, except for those due to change in age and/or weight where the adjusted doses conform those to be recommended for the resulting group, will be included in the primary analysis and classified in the original cohort and weight band in which they enrolled. For participants whose study drug dose is adjusted due to PK outcomes (after the week 4 visit), safety data up to the date of dose adjustment will be analyzed in the original cohort/weight band, and sensitivity analyses will be performed to assess whether conclusions drawn from primary dose confirmation evaluations would be affected by inclusion of these data.

Study accrual is designed to yield at least 120 evaluable participants for the weeks 24 and 48 safety analyses: some participating in Stage I and some participating in Stage II. In order to ensure that the primary safety analyses will yield results that can be generalized to the overall patient population, the "evaluable" participants for the primary analysis will be defined as those participants whose treatment will conform to the final dosing recommendation that will result from this protocol. This sample will consist of participants: 1) whose starting dose was the dose determined to be the final confirmed starting dose of DTG for their cohort/weight band; 2) whose dose may have been changed, due to changes in age and/or weight, provided that the dose they received at that cohort/weight band is the dose that will be recommended for members of the treatment population who experience a similar progression. Participants whose treatment regimens conform to those described in #1 and #2, above, but who leave the study due to treatment failure or toxicity prior to completing 24 weeks or 48 weeks of treatment, will be included in the sample for the primary analyses and will be treated as failures in those analyses."

8.2 Endpoints and Outcome Measures

For safety reporting and monitoring purposes, a drug related adverse event is defined as an adverse event that is judged to be definitely, probably, or possibly related to the study drug. Endpoints and outcome measures are generally to be assessed by cohort, unless otherwise specified.

8.2.1 Primary Endpoints - presented aggregated and by cohort

8.2.1.1 Toxicity through Week 24

- All adverse events or lab toxicities of Grade 3 or higher severity
- Adverse events or lab toxicities of Grade 3 or higher severity judged to be at least possibly attributable to the study medication
- Termination from treatment due to a drug-related adverse event
- Death

8.2.2 Primary Response Variables

8.2.2.1 Pharmacokinetics

- C_{24h}, AUC_{0-24}

8.2.3 Secondary Endpoints - presented aggregated, by cohort, and by weight band

8.2.3.1 Toxicity through week 48 and beyond

- All adverse events or lab toxicities of grade 3 or higher severity.
- Adverse events or lab toxicities of grade 3 or higher severity judged to be at least possibly attributable to the study medication.
- Termination from treatment due to a drug-related adverse event.
- Death

8.2.3.2 Plasma HIV-1 RNA (copies/mL) <400 copies/mL and <50 copies/mL

8.2.3.3 Pharmacokinetics

- AUC_{0-24}, C_{24h}, C_0, C_{min}, C_{max}, CL/F, Vz/F and $t_{1/2}$

8.2.4 Secondary response variables

- CD4/8 counts and percent
- Genotypic and phenotypic measures of resistance at baseline and at virologic failure
- Disease progression as measured by change in CDC category

8.3 Randomization and Stratification

There will be no randomization. In each stage, participants will be stratified into cohorts defined by age and formulation, as described in Section 8.1. In addition, under Version 5, enrollment of participants by weight band will be monitored.

8.4 Sample Size and Accrual

Total accrual will depend upon the number of participants who must be accrued to yield at least 120 evaluable participants for purposes of the primary safety analyses and the regulatory submissions. There is some uncertainty concerning the number needed to complete the dose finding procedures in Stage I and the number who may be lost to follow-up for reasons other than treatment failure. Each successful cohort on Stage I will include a minimum of 10 participants; the majority of whom will have been treated continuously on the dose that has been chosen for Stage II. This will likely yield additional participants from Stage I who will contribute to the evaluation of the optimal dose. Thus, approximately300 participants will be accrued to ensure that the total sample includes at least 120 evaluable participants who have been treated only on the optimal dose and that the quotas for each cohort, specified in the Schema, have been filled.

The selection of a sample size of ten participants in Stage I for each age cohort is based on feasibility and the historical pediatric recruitment experience of GSK and IMPAACT, as well as justification to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance (CL/F) and volume of distribution (Vd) for DTG with an at least 78% power.

Variability (CV%) in CL/F and Vd for each age cohort are predicted based on the population PK model developed using adult data from ING111521 and ING112276. In the adult population PK model, CL/F and Vd are modeled as the following:

CL/F (L/hr) = 0.873 * (WT/70)^0.713*EXP(eta1), eta1 ~ N (0, 0.0857)
Vd (L) = 17.5 * (WT/70)^1.02 * EXP(eta2) + 1.6, eta2 ~ N (0, 0.0365) where WT is body weight in kg.

Using predicted variability in CL/F and Vd, simulations (10,000 simulations with a sample size of 10 for each simulation) were performed to estimate % chance for 95% CI of geometric mean estimates of simulated CL/F and Vd to fall within 60% to 140% of the point estimates (equivalent to power).

Table 14 presents the projected weight range, predicted mean and variability (coefficient of variability, CV) in CL/F and Vd, and estimated power for a sample size of 10 in each age cohort.

Table 14: Power Estimation based on Proposed Sample Size of 10 Per Cohort for Stage I

Age Cohort	Projected Weight Range (kg)	PK Parameter	Predicted Mean	Predicted CV	Power (%)
12-18yr	30-100	CL/F	0.85	0.38	94.1
		Vd	18.1	0.34	98.5
6-<12yr	17-52	CL/F	0.54	0.38	95.1
		Vd	10.3	0.30	99.7
2-<6yr	10.7-23	CL/F	0.21	0.34	98.4
		Vd	5.77	0.21	100
6mo-<2yr	6.75-15.1	CL/F	0.13	0.34	98.2
		Vd	4.28	0.19	100
4wk-<6mo	3.77-9.26	CL/F	0.084	0.35	97.5
		Vd	3.18	0.16	100

Power for a sample size of 10 and CV of 0.45, which is 20% higher than the highest predicted CV, was estimated to be >78%. Power for a sample size of 9 and CV of 0.45, was estimated to be >68%.

8.5 Safety Guidelines for the Evaluation of Stage I Starting Doses

The attribution of serious adverse events to study drug for the purposes of employing the start, stop and pause rules will be by consensus among the site investigator and the Protocol Team. If unanimous agreement between them cannot be established, the relevant data will be reviewed by the P1093 Study Monitoring Committee, which will make the final judgment concerning the relationship between study drug and the adverse event. Within this committee the decision will be determined by the majority opinion of the P1093 Study Monitoring Committee clinicians. Gradation of relationship will use the following terminology: 'Not related', 'Probably not related', 'Possibly related', 'Probably related' or 'Definitely related'.

Table 15 and Table 16 below use a multinomial response model to assess the probability of failing the safety criteria under each of the hypothetical situations specified in those tables. The calculations are performed as follows: Each of the total number of participants represents a trial, which may have 1 of 3 mutually exclusive outcomes: (1) a life threatening drug-related adverse event or a grade 4 event judged to be at least probably related to treatment; (2) a Grade 3+ event, not satisfying the criteria set forth in #1, immediately above, but judged to be at least possibly related to study drug and resulting in termination of

study drug; and (3) a relatively benign outcome, satisfying neither the criteria in #1 nor #2, immediately above.

Each table has its sets of results under which the set of trials would pass the safety criteria. The probability of passing the safety criteria represents the sum of the probabilities of these sets of results, and "1 minus the probability of passing the safety criteria" represents the probability of failing them. The "True Toxicity Rates" presented in the tables, along with the true rate of having neither of the types of toxicity represented by the true toxicity rates (which is 1 - the sum of the true toxicity rates), provide the probabilities for the outcomes which are used in the multinomial calculations for each of the hypothetical situations.

8.5.1 Safety Guidelines for the First Four Participants Started at a Given Dose Level in Each Stage I Cohort

For each Cohort, for the mini-cohort analysis (see Stage I Study Design3.1), the frequency of adverse reactions to the starting dose of the study medication will be evaluated on the first 4 participants with evaluable data. The data will extend to the week 4 visit for participants not requiring PK determined dose adjustment or until the visit on which the dose is adjusted, as described above. Further accrual into this cohort will be contingent upon meeting the following safety guidelines.

If any of the first 4 participants has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication, or in the first four evaluable participants 2 or more have terminated study drug due to a grade 3+ drug-related adverse event stop accrual into this dose group, until a safety review by the Protocol Team has been conducted. All of the relevant safety and pharmacokinetic data will be reviewed to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make any changes in the dosing and monitoring procedures which have been judged to be necessary. If there are any concerns regarding safety, the P1093 Study Monitoring Committee will then review all relevant safety and pharmacokinetic data, along with the recommendations of the Protocol Team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

The protocol will only proceed if this review has led to a recommendation that it is safe to do so and the team agrees. The safety review may lead to a recommendation that the dose be de-escalated. Before implementing such a recommendation, the Protocol Team will review the PK data to determine whether a lower dose is likely to achieve adequate drug exposure.

If none of the first 4 participants has experienced a life-threatening drug-related adverse event or a Grade 4 event that is probably or definitely attributable to the study medication and fewer than 2 of these 4 participants have terminated study drug due to a grade 3+ drug-related adverse event, then this group has passed the initial interim safety guidelines. If these 4 participants also meet the PK guidelines, the cohort will continue to enroll a minimum of 10 participants to evaluate the safety and PK.

Given the small sample sizes within each cohort, the information available for preliminary safety decisions will be imperfect. Two types of sampling errors are possible:

1) In a group where the true rate of toxicity is too high to warrant increased exposure to the current starting dose of the medication, the sample data may pass the safety guidelines;
2) In a group where the true rate of toxicity is low enough that further exposure to the current starting dose is warranted, the sample data may fail the guidelines.

The extent to which the safety guidelines protect against the errors described above can be assessed by examining various hypothetical rates of "true toxicity" which could occur, if the study medication were used extensively among the participant population at the dose level under question. The hypothetical situations presented in Table 15 range from conditions under which a given dose level would cause a high incidence of severe and life threatening drug-related adverse events to conditions under which severe drug-related adverse events would be relatively rare and would not be life threatening. For each of these hypothetical situations, a sample of four participants is drawn from the participant population and that the safety guidelines is assumed, summarized above, are followed.

For example, Table 15 shows that there is a 78% chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening drug-related adverse event is 50%.

Table 15: Probability of Failing Dose Escalation Guidelines under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-Life Threatening drug-related adverse events that would result in Tx discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	**Life Threatening drug-related adverse events (including death) or Grade 4 events probably or definitely attributable to study medication**	
.50	.00	.69
.50	.05	.78
.50	.25	.96
.25	.00	.26
.25	.05	.42
.25	.25	.81
.05	.00	.01
.05	.05	.20
.05	.25	.69
.00	.05	.19
.00	.25	.68

Assuming that it would be undesirable to accrue additional participants at a dose that had these true rates of adverse events, the 22% chance of NOT failing the safety guidelines would represent the probability of error. The table also shows that there is a 1 % chance of failing, when the true rate of non-life threatening drug-related adverse events is only 5% and the true rate of life threatening drug-related adverse events is zero. Assuming that the potential benefits associated with exposing additional participants to this dose of the drug would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

8.5.2 Safety Guidelines for the Interim and Full Cohort Analyses, with a Minimum of Ten Participants Started at a Given Dose Level in Each Stage I Cohort

The safety guidelines applied to a given starting dose of the study medication within a cohort for either the interim cohort analysis or full cohort analysis (see Section 3.1), will make use of data from all participants started at that dose. The data will extend to the week 4 visit for participants not requiring PK determined dose adjustment or until the visit on which the dose is adjusted, as

described above. If any of these participants has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication, or more than 25% terminated study drug due to grade 3+ drug-related adverse event, this starting dose will fail the safety guidelines for the cohort under investigation. If none of these participants has experienced a life-threatening drug-related adverse event or a Grade 4 event that is probably or definitely attributable to the study medication and no more than 25% terminated study drug due to Grade 3+ drug-related adverse events, then this starting dose will pass the safety guidelines for the group under investigation.

If any of these participants has a life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication or more than 25% terminated study drug due to Grade 3+ drug-related adverse event, this starting dose will fail the safety guidelines for the cohort under investigation. Should this occur, the Protocol Team will review all the relevant safety and pharmacokinetic data to determine whether it is safe to continue the attempt to find an optimal dose for this cohort. If the team determines that it is safe to proceed, it will make any changes in dosing and monitoring procedures which are judged to be necessary. If there are any concerns regarding safety, the P1093 Study Monitoring Committee (SMC) will then review all of the relevant safety and pharmacokinetic data, along with the recommendations of the Protocol Team, and will determine whether and under what conditions further dose finding activities for this cohort may proceed.

Following Table 16, the hypothetical rates of "true toxicity" which could occur if the study medication were used extensively among the participant population at the dose level are again presented in Table 16, this time assuming that a sample of ten participants is drawn from the participant population and the safety guidelines allows no participant with life threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication or no more than 2 participants who terminated study drug due to Grade 3+ drug-related adverse event.

Table 16: Probability of Failing Dose Escalation Guidelines Under Potential Rates of True Toxicity with n=10 participants

True Toxicity Rates		Probability of Failing Safety Guidelines
Non-life threatening drug-related adverse event that would result in treatment discontinuation, excluding Grade 4 events probably or definitely attributable to study medication	Life threatening drug-related adverse event or Grade 4 events probably or definitely attributable to study medication	
.50	.00	.95
.50	.05	.98
.50	.25	1.00
.25	.00	.47
.25	.05	.71
.25	.25	.98
.05	.00	.01
.05	.05	.41
.05	.25	.95
.00	.05	.40
.00	.25	.94

For example, Table 16 shows that there is a 98 % chance of failing the safety guidelines under conditions in which the true rate of life-threatening toxicity is 5% and the rate of non-life threatening drug-related adverse event is 50%.

8.5.3 Safety Guidelines for Minimum Eight Participants Started at a Given Dose Level in Each Weight Band

Under protocol Version 5, a secondary examination of safety data by weight band will be performed. An additional safety assessment of a given starting dose of the study medication within a weight band will make use of data from all participants within that weight band who started at that dose. The data will extend to the week 4 visit for participants not requiring PK determined dose adjustment or until the visit on which the dose is adjusted, if adjustment occurs prior to 4 weeks on study. If any of these participants has a life-threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication, or more than 25% terminated study drug due to grade 3+ drug-related adverse event, this dose will fail the safety guidelines for the weight band under investigation. If none of these participants has experienced a life-threatening drug-related adverse event or a Grade 4 event that is probably or definitely attributable to the study medication and no more than 25% have terminated study drug due to Grade 3+ drug-related adverse events, then this dose will pass the safety guidelines for the weight band under investigation.

If any of these participants has a life-threatening drug-related adverse event or any Grade 4 event that is probably or definitely attributable to the study medication or more than 25% terminated study drug due to Grade 3+ drug-related adverse event, this dose will fail the safety guidelines for the weight band under investigation. Should this occur, the Protocol Team will review all the relevant safety and pharmacokinetic data to determine whether it is safe to continue the attempt to find an optimal dose for this weight band. If the team determines that it is safe to proceed, it will make any changes in dosing and monitoring procedures which are judged to be necessary. If there are any concerns regarding safety, the P1093 SMC will then review all the relevant safety and pharmacokinetic data, along with the recommendations of the Protocol Team, and will determine whether and under what conditions further dose finding activities for this weight band may proceed.

8.6 Analyses

8.6.1 Summary of Dose Finding Data

The analysis of dose finding data will consist of descriptive statistics summarizing the safety and PK data from the dose finding phase of the study, see Section 0 for PK analysis. The safety data will be broken down by cohort and by weight band, and will present the results of the safety evaluations applied to each starting dose tested within each cohort/weight band, including information indicating which starting doses have passed or failed the safety guidelines. For each starting dose within each cohort/weight band, every adverse event of Grade 3 or higher will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event and the Protocol Team's assessment of the probability that this event was due to the study drug (not related, possibly related, probably related or definitely related).

8.6.2 Analysis of Data Representing Exposure to the Doses Judged to be Optimal for Each Cohort

These analyses will be stratified by Age Cohort. The findings will be presented both in aggregate and broken down by this stratification factor, with estimates bounded by 95% confidence limits.

Given that the small sample sizes within strata will provide limited power for statistical tests of differences across age groups, interpretation of the results will depend upon whether differences across strata are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across strata to a clinically important extent, interpretation of results should take account of the issues represented by the stratification factor.

8.6.2.1 Primary Analyses (performed on data through the Week 24 visit)

Safety

The primary safety analysis will include only participants whose starting doses have been those judged to be optimal for their groups. Stage I participants whose doses have been adjusted for inadequate PK will be excluded. Stage I participants who have been removed from treatment due to toxicities while on the optimal dose will be included and treated as safety failures in the primary safety analysis. Sensitivity analyses will be performed to determine whether the exclusion of participants whose doses have been adjusted creates a selection bias which impacts upon any results.

Each participant's safety data will be summarized as: the worst grade of adverse event experienced during the first 24 weeks (and 48 weeks) of exposure to the optimal dose of the study drug and the worst grade of adverse event judged to be at least possibly due to study drug during this time period. Frequency distributions of these safety outcomes will be presented in the aggregate and broken down by age cohort. Listings of all Grade 3+ events will be provided, broken down by type of toxicity (hepatic, hematologic, etc.).

The proportions of participants experiencing Grade 3+ adverse events will be presented in aggregate and broken down by age, with these proportions bounded by exact 95% confidence intervals. Similar analyses will present the proportions of participants exhibiting Grade 3+ events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals.

Table 17: Percent of Participants Experiencing Grade 3+ Adverse Events (or Grade 3+ Adverse Events Attributed to the Study Medication) With Exact 95% Confidence Intervals

N	% With Grade 3+ Adverse Events	95% C.I.
10	0%	0% -- 31%
20	0%	0% -- 17%
40	0%	0% -- 9%
60	0%	0% -- 6%
90	0%	0% -- 4%
150	0%	0% -- 2%
10	10%	0.3% -- 45%
20	10%	1% -- 32%
40	10%	3% -- 24%
60	10%	4% -- 21%
90	10%	5% -- 18%
150	10%	6% -- 16%
10	20%	3% -- 56%
20	20%	6% -- 44%
40	20%	9% -- 36%
60	20%	11% -- 32%
90	20%	12% -- 30%
150	20%	14% -- 27%
10	30%	7% -- 65%
20	30%	12% --54%
40	30%	17% -- 47%
60	30%	19% -- 43%
90	30%	21% -- 41%
150	30%	23% -- 38%

Table 17 presents exact 95% confidence intervals around various potential rates of grade 3+ adverse events which might be observed in a total sample of 100 evaluable participants, a sample of 10 participants representing the minimal sample that could be accrued within any of the Stage I stratification factors and potential sample sizes that might occur if subgroups are analyzed (N = 20, 40, 60, 90) This table indicates that confidence intervals will be quite wide around the minimal sample size of 10 participants within a given stratum, but would be reasonably precise around samples of 90-150 participants.

8.6.2.2 Key Secondary Analyses

Safety

Safety assessments will be performed on data collected through Week 48 and on long term data. These analyses will be similar to the Week 24 analyses described in Section

8.6.2 above. In addition, these analyses will also be performed with participants classified by weight band.

Viral Load

Virologic outcomes, based on HIV-1 RNA (copies/mL), will be assessed at weeks 24 and 48. Virologic outcomes at additional time points might also be evaluated. For regulatory submission purposes, at both of these time points the primary definition of virologic outcome will be calculated according to FDA's snapshot algorithm. Participants will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest. (This window will be defined in the analysis plan.) In addition, participants will be classified as virologic failures at either of these time points if they meet any of the following conditions prior to that time point:

a) Discontinuation of drug;
b) Change in background therapy not allowed in the protocol;
c) Change in background ART substitutions permitted per protocol, unless the decision to switch is documented as being before or at the first on-treatment visit after switching to OBT where HIV-1 RNA is assessed (Week 4) or participant's HIV-RNA is <400/<50 copies/mL before the switch.

Participants who only discontinued a background ARV or who had formula substitutions (substituting single agents for fixed dose combinations and vice versa of the same ARV) in their OBT are not considered as having OBT changes and will not be analyzed as virologic failures. Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the visit of interest window. The proportions of participants meeting the criteria for virologic success at each of these time points will be bounded by exact 95% confidence intervals, and will be presented in the aggregate and broken down by age cohort and by weight band.

Table 18: Percent of Participants Meeting Criterion for Virologic Success with Exact 95% Confidence Intervals

N	% Undetectable RNA	95% C.I.
10	10%	0.3% -- 45%
20	10%	1% -- 32%
40	10%	3% -- 24%
60	10%	4% -- 21%
80	10%	4% -- 19%
100	10%	5% -- 18%
10	30%	7% -- 65%
20	30%	12% -- 54%
40	30%	17% -- 47%
60	30%	19% -- 43%
80	30%	20% -- 41%
100	30%	21% -- 40%
10	50%	19% -- 81%
20	50%	27% -- 73%
40	50%	34% -- 66%
60	50%	37% -- 63%
80	50%	39% -- 61%
100	50%	40% -- 60%
10	70%	35% -- 93%
20	70%	46% -- 88%
40	70%	53% -- 83%
60	70%	57% -- 81%
80	70%	59% -- 80%
100	70%	60% -- 79%
10	90%	55% -- 99.7%
20	90%	68% -- 99%
40	90 %	76% -- 97%
60	90%	79% -- 96%
80	90%	81% -- 96%
100	90%	82% -- 95%

Table 18 presents exact 95% confidence intervals around various potential rates of virologic success which might be observed in a total sample of 100 participants or in subsamples of various sizes (N=10, 20, 40, 60, 80). Participants whose OBT is changed after initial optimization will be considered treatment failures in these analyses, unless the change is one specifically allowed by the protocol.

CD4/8

Change in CD4/8 count and percent from baseline to weeks 24 and 48 will be bounded by 95% confidence intervals and presented in the aggregate and broken down by age cohort, by accrual to Stage I vs. Stage II and by weight band.

HIV Drug Resistance

The incidence of HIV drug resistance will be presented descriptively at baseline and at the point of failure for participants who meet the criteria for virologic failure. Participants will be evaluated for HIV genotypic and phenotypic drug resistance to the OBT and to DTG. Analysis results will be presented in aggregate, by cohort and by weight band.

Interim Analysis of Data from Cohort I

An interim analysis based upon the 24 week data from Cohorts I and IIA was performed. This focus of this analysis was primarily on safety data, presented as described in Section 8.6.2.1 and pharmacokinetic data, as described in Section 0. A secondary analysis of virologic success, as described in Section 8.6.2.2 was also performed. The results of these analyses were used as part of a regulatory submission for pediatric use of DTG.

8.7 Monitoring

The study will be monitored by the Protocol Team, which includes Protocol Co-Chairs, Medical Officers, Pharmacologists, Statisticians, Data Managers, and GlaxoSmithKline representatives. The Protocol Team will review safety and pharmacokinetic data with the aim of determining the optimal dose for each cohort and weight band, while protecting participant safety.

Participant Safety

The Protocol Team will closely monitor participant safety through routine review of safety and toxicity reports summarizing laboratory and clinical data from the study database (CRFs and laboratory data). The Protocol Team will review these reports via conference call or other meeting at least twice a month during the dose finding stage (Stage I) and less frequently thereafter. The data required for the toxicity reports must be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.

In addition to regular safety and toxicity reviews by the Protocol Team, according to standard IMPAACT procedures an SMC will provide impartial independent reviews in situations where participant safety is in question.

If the Protocol Team identifies any potentially treatment-related toxicities, which may compromise participant safety, it will determine whether the study needs to be suspended or modified. If this occurs, the SMC will review all relevant data and will determine whether, and under what conditions, the study will be allowed to proceed.

8.7.1 Rules for Suspending Accrual to Assess Safety Following an Adverse Event

Accrual will be temporarily suspended if any participant has a life threatening drug-related adverse event or any Grade 4 event that may not be judged to be life-threatening but is judged to be probably or definitely attributable to the study medication. Following temporary suspension of accrual, the team will further review the safety data within 48 hours of notification of the event to determine if continuation of accrual is appropriate. If the team agrees that the study drug is likely to be safe for additional participants, they may allow accrual to resume. The SMC will be informed of this decision, and the study will not reopen without the approval of the SMC. Regulatory agencies will be notified of the event and the team's decision after this review of the safety data has taken place.

8.7.2 Accrual Rate Evaluation

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. The team will monitor feasibility quarterly based on accrual. If any open Cohort has not accrued half its participants within 6 months of opening, the team will identify the reasons for lack of accrual and determine whether/how the issues can be addressed with the SMC.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

The clinical pharmacology objectives are:

1. To evaluate the steady-state pharmacokinetics of DTG and its various formulations in combination with other ARVs in treatment-experienced HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves a targeted C_{24h} (primary PK endpoint) and AUC_{0-24} (secondary PK endpoint) in this population.

2. To evaluate the steady state plasma concentration profiles and pharmacokinetic parameters of DTG administered as the film-coated tablet, the oral-granules for suspension and the dispersible tablet - pediatric formulations.

3. To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population pharmacokinetic analysis.

9.2 Primary and Secondary Data

All concentration-time samples will be registered in the LDMS database. All PK samples (including intensive and population PK) will be sent to the University of Alabama (UAB) Laboratory (see the Laboratory Processing Chart). The study database will be kept up to date by close tracking of samples. As part of Stage I, the intensive PK sample assays and pharmacokinetic calculations will be performed in real-time and the results will be reported and discussed with the Protocol Team.

9.2.1 Intensive PKs (Stage I only)

Steady-state pharmacokinetic parameters will be determined from plasma concentration-time profiles using non-compartmental methods (Phoenix WinNonlin 8.0, Certara, Princeton, NJ). Calculated pharmacokinetic parameters will be: area-under-the-curve (AUC_{0-24}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), plasma concentration observed at end of 24 hour dosing interval (C_{24h}), plasma concentration observed immediately to dosing of 24 hour dosing interval (C_0), minimum plasma concentration (C_{min}), apparent clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half-life ($t_{1/2}$). AUC_{0-24} will be determined using the linear-log trapezoidal rule. C_{max}, T_{max} , C_0, C_{24h}, and C_{min} will be taken directly from the observed concentration-time data.

Intensive PK sampling will be conducted between days 5 and 10, after study drug initiation, and over the course of approximately 24 hours. The pharmacokinetic evaluation should be scheduled so that a witnessed dosing of DTG is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. One sample will be collected pre-dose and 7 samples will be collected post-

dose, at 1, 2, 3, 4, 6, 8 and 24 hours post-dosing, per footnotes in Appendix IA and Appendix IC The 24-hour sample must be collected prior to the next dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 24-hour sample within a window of 22-26 hours. Actual sampling time will be recorded and used in the PK analysis. US sites will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to the BRI repository for a 'pass-through' (see LPC for instructions).

Study staff will review the regimen, dosage, dosing intervals, and timing relative to meals with participants or their caregivers in advance of the visit. The importance of adherence to the study drug and of reporting non-adherence will be emphasized. The date and time of doses taken 3 days prior to the PK visit should be recorded. The actual sampling time recorded on the CRF will be used in the PK analysis. Participants should have no missed doses 3 days prior to the scheduled intensive PK visit. The PK visit should be scheduled so that the pre-dose PK samples and the witnessed dosing of DTG are as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Participants should have been adherent in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled. Participants who vomited within 4 hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following 7 days.

Additionally, any participant who cannot have the intensive PK visit completed within 5-10 days of study drug initiation, must have the visit completed within 17 days of study drug initiation. The participant will remain on study and be included for safety analyses but will be replaced for PK analyses.

Intensive PK sampling will be done in a fasting state and sites will follow the instructions as described below in Sections 9.2.1.1 and 9.2.1.2. If upon review of PK data, the Protocol Team determines that an additional evaluation of PK should be performed in a non-fasted state, the team will notify the sites to which cohorts or weight bands this will apply and sites will follow the instructions in Section 9.2.1.3.

9.2.1.1 Sampling with Fasting (Cohorts I, II III, and III-DT)

The guidelines for intensive PK sampling in Cohorts I, II, III and III-DT while fasting follow:

- Participants must be fasted for 6 hours prior to dosing on the intensive PK day.
- ≥6 hours PRIOR to dosing – participants may eat and drink without restriction
- ≥4 to <6 hours PRIOR to dosing – milk, apple/orange juice and water may be consumed; No food
- <4 hours PRIOR to dosing – water ONLY
- From dosing to <2 hours POST dose – apple/orange juice and water may be consumed; No food
- From ≥2 to <4 hours POST dose – participants may drink apple/orange juice and eat a snack/light meal (around 100-150 calories). High fat foods should be avoided.
- From ≥4 hours POST dose onwards – participants may eat and drink without restriction

9.2.1.2 Sampling with Fasting (Cohorts IV, IV-DT, and V-DT)

The guidelines for intensive PK sampling in Cohorts IV, IV-DT, and V-DT while fasting follow:

- Participants should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day.
- Water and other fluids (i.e. apple/orange juice (with the exception of grapefruit juice) and oral rehydration solution)) can be taken at any time.
- Participants may consume a light meal of their choice four hours after dosing on the intensive PK day.

9.2.1.3 Sampling Non-Fasting (All Cohorts)

If upon review of PK data, the Protocol Team determines that collected PK data supports an additional evaluation of PK in a non-fasted state, the Protocol Team will notify the sites to which cohorts or weight band groups this will apply. Sites will be informed if there are restrictions on the choice or quantity of food permitted prior to, and during the day of intensive PK sampling. However, all food must be consumed within 30 minutes prior to dose administration. All PK sample collection and processing procedures will remain the same as for fasting.

9.2.2 Population PK (Stage I and II)

Population pharmacokinetic evaluations will be scheduled at Weeks 4, 12 and 24. In addition population PK sampling will be scheduled for participants who have completed 24 weeks of follow-up and who have switched from granules for suspension to dispersible tablets. Population PK will be collected at the 2-week post-switch visit and at the next scheduled visit per footnotes in the relevant Schedules of Evaluations. These evaluations should be scheduled so that the pre-dose PK sample and the witnessed dosing of DTG are as close to possible to 24 hours (generally 22-26 hours) after the previous dose.

9.2.2.1 Cohorts I, II, and III

In all cases, the participant will need to provide a self-reported time and date of their last dose. Appendix IA and Appendix IB footnotes describe the sampling time points for Stage I and II respectively.

9.2.2.2 Cohorts IV, IV-DT and V-DT

In all cases, the participant will need to provide a self-reported time and date of their last dose. Appendix IC andAppendix ID Schedule of Evaluations
Cohorts IV, IV-DT, and V-DT – Stage IIAppendix ID footnotes describe the sampling time points for Stage I and II respectively.

These data will be pooled to build a population pharmacokinetic model to assess pediatric DTG exposure and possible changes in exposure during the study. This population pharmacokinetic model will be created using NONMEM version VII (or similar software) or higher software program. The model may also be used to determine if covariates, such as age, weight, sex, BSA, and concomitant medications alter DTG pharmacokinetic parameters in pediatric participants.

9.3 Evaluation of PK Exposures for Cohorts and Weight Bands

The target population exposure (GM) for C_{24h} is 995 ng/mL, with an acceptable range of 697– 2,260 ng/mL. The target population exposure (GM) for AUC_{0-24} target is 46 µg.h/mL, with an acceptable range of 37-134 µg.h/mL. Rationale for these targets is provided in Section 1.6. At the mini-cohort stage, the PK parameters for the four participants will be reviewed to ensure that individual PK parameter values are not so extreme as to be unsafe for the participant or make attainment of the target values for the population exposure - the GM of all participants at the end of Stage I - unlikely. At the completion of Stage I, the GMs of C_{24h} and AUC_{0-24} of cohorts and independent weight bands will be evaluated by the Protocol Team to determine if a dose is acceptable or not for that respective group. As the primary target, the GM C_{24h} will be weighted most heavily in this decision, but AUC_{0-24} as well as participant specific factors that may have altered the PK data will also be considered.

If on review of all PK and safety data the dose is not acceptable, a new test dose (i.e. dosing table) will be determined.

The ultimate decision about a new test dose may also be guided by other data from this study (e.g. drug clearance, CV in different ages) as well as information about DTG metabolism, safety, or efficacy generated outside the context of this protocol. Additionally, PK modeling work will be used to assist in new dose decisions. If there is disagreement among the Protocol Team, the study monitoring committee (SMC) will be asked to review the data. Further information on the SMC can be found in Section 8.7.

Of note, DTG is dosed for P1093 participants according to dosing tables in which participants within a given weight range are given the same quantity of a formulation (DT, film-coated tablets). While dosing tables may target a certain mg/kg dose overall, individual participants with weights on the edges of weight bands will inevitably receive a range of mg/kg dosing which may result in a wide range of drug exposure, especially in younger populations. The Protocol Team will monitor the range of exposures within age cohorts and within weight band groups that cross age cohorts. In addition, enrollment within a cohort or weight band might be evenly distributed or skewed towards an extreme, which could limit generalization for populations likely to be treated with DTG in the future. The Protocol Team will continue to monitor enrollment to ensure that information from a normally distributed population is collected so that appropriate dosing guidelines can be formulated If this goal is not being met, the Protocol Team reserves the right to reopen an age or weight band cohort to include a subset of participants who were underrepresented in that full group's analysis. For example, this may include the smallest infants within the 3-6 kg weight band.

9.4 Evaluation of PK Exposures for Individual Dose Modification

If the C_{24h} and/or AUC_{0-24} of any individual participant falls outside of the individual target ranges (refer to Table 9) the Protocol Team will consider all clinical, pharmacologic, immunologic and virologic data to determine if it in the participants best interest to continue or if the dose should be modified. Additional PK sampling may be performed, at the discretion of the Protocol Team and site investigators, if felt to be in the best interest of participants, refer to Section 6.4.

10.0 HUMAN SUBJECTS PROTECTIONS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs / ECs for the recruitment of prisoners.

10.1 Institutional Review Board/Ethics Committee Review and Approval

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

All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from the IRBs/ECs must be maintained in site essential document files. Sites must submit documentation of both initial review and approval and continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Manual (see also Section 4.4).

10.2 Vulnerable Participants

The NIH is mandated by law to ensure that children be included in clinical research when appropriate. This study responds to that mandate and will provide clinical research data to inform ARV treatment guidelines for pediatric populations. Nonetheless, the children who take part in this study are considered vulnerable participants per the U.S. Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to infant and child participants as described in 45 CFR 46 Subpart D (for children).

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

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

10.3 Informed Consent

Written informed consent for study participation will be obtained before any study-specific procedures are performed. The informed consent process will be conducted prior to screening.

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. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the

procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant (or parent or legal guardian).

Participants providing assent or parents or legal guardians will also be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been completed. Future research testing of residual specimens may be declined with no impact on other aspects of study participation.

It is generally expected that only one parent or legal guardian will provide informed consent for the child's participation in this study. However, parental consenting requirements at each site will depend on the IRB/EC risk determination described in Section 10.2; all IRB/EC requirements will be followed.

Should the consenting parent (or guardian) of a participant die sites should follow the guidelines described by their IRBs/ECs. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 10.2, all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child or adolescent, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

Participants may also reach the legal age of consent during follow-up. In this case, written informed consent for continued participation and specimen storage and future use will be obtained from participants once they reach legal age at their next study visit. If participants do not consent for continued study participation, they should be discontinued from the study; similarly, if they do not consent for specimen storage and future use, all specimens will be destroyed after all protocol-related testing is complete.

10.4 Essential and Source Documents and Access to Source Data

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

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

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

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

10.5 Participant Confidentiality

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. If any photographs of observed reactions are taken, standard precautions will be followed to ensure that participant privacy and confidentiality are protected.

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

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

10.6 Study Discontinuation

The study may be discontinued at any time by NIAID, the IRB or EC, GSK, the FDA, OHRP, IMPAACT or other country-specific governmental agencies as part of their duties to ensure that research participants are protected.

10.7 Access to Dolutegravir at the Close of the Study

Participants will be transitioned into care and treatment outside of the study at the end of the study as per local standards. If the DTG formulations are not locally available for a participant completing study then DTG will be provided by the pharmaceutical partners following the participant's completion of the study through a mechanism outside of the protocol, or until one or more of the following events occur:

- Until the age-appropriate formulations provided by the study are available from another source (e.g. government programs, aid programs, assistance programs etc.) to all participants in each specific country; OR
- Until participants are no longer deriving benefit; OR
- Until clinical development of DTG is terminated.

10.8 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 informed consent forms and/or other materials as applicable per IRC/EC policies and procedures.(3)

10.9 Management of New Information Pertinent to Study Participation

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

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the GlaxoSmithKline prior to submission.

12.0 BIOHAZARD CONTAINMENT

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

All infectious specimens will be transported in compliance with Federal Regulations and the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g. Federal Express or Airborne) for specific instructions and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at:
http://www.hanc.info/labs/labresources/procedures/Pages/actnShippingDemo.aspx

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Appendix IA Schedule of Evaluations
Cohorts I, IIA, IIB, III and III-DT – Stage I

Screen through Week 48

	Screen [1]	Entry [12] Day 0	Intensive PK Day 5-10	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48
Visit Windows	-	-	-	±1 wk	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks
	CLINICAL EVALUATIONS										
Informed Consent	X										
History and Physical exam [2]	X	X	X	X	X	X	X	X	X	X	X
Tanner Staging [3]		X									X
Adherence Questionnaire			X	X	X	X	X	X	X	X	X
CDC Classification		X						X			
Palatability Assessment			X	X				X			
	LABORATORY EVALUATIONS										
Hematology	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Chemistries [4]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Lipid profiles [5]	1mL							1mL			1mL
PBMCs / plasma for storage (includes integrase resistance sample)		7mL						6.5mL			6.5mL
Urinalysis	X				X			X			X
Microalbumin/creatinine ratio urine[6]		X			X			X			X
Pregnancy test[7]	X	X	X	X	X	X	X	X	X	X	X
	Virology										
HIV-1 RNA PCR	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
Genotyping	2mL										
Phenotyping [8]	2mL										
	Immunology										
Lymphocyte subsets [9]	1mL	1mL				1mL		1mL	1mL	1mL	1mL
	Pharmacokinetic studies										
STAGE I - Intensive PK [10]			4mL								
STAGE I - Population PK [11]				1mL		0.5mL		1mL			
Total Maximum Blood Volumes [20]	11mL	13mL	9mL	6mL	5mL	6.5mL	5mL	14.5mL	6mL	6mL	13.5mL

Appendix IA Schedule of Evaluations (cont'd)
Cohorts I, IIA, IIB, III and III-DT – Stage I
Virologic Failure, Dose Adjustment and Premature/DC of Study Drug Visits

	Confirm Suspected virologic failure [13]	**Virologic Failure [14]**	**[Dose Adjustment PK Visit] [15]**	**[Dose Adjustment Safety Visit] [16]**	**Premature/DC of Study Drug On study [17]**
Visit Windows		-	If requested, 5 to 14 days after initiation of the dose adjustment	4 weeks post dose modification (-1 wk/+ 2 wk)	-
	CLINICAL EVALUATIONS				
Informed Consent					
History and Physical exam [2]		X		[X]	X
Tanner Staging [3]					
Adherence Questionnaire		X		[X]	X
CDC Classification		X			X
Palatability Assessment					
	LABORATORY EVALUATIONS				
Hematology		1mL			1mL
Chemistries [4]		1mL			1mL
Lipid profiles [5]					
PBMCs / plasma for storage (includes integrase resistance sample)		6.5mL			
Urinalysis					
Microalbumin/creatinine ratio - urine[6]					
Pregnancy test[7]		X			X
	Virology				
HIV-1 RNA PCR	3mL	3mL			3mL
Genotyping		2mL[18]			2mL[18,19]
Phenotyping [8]		2mL			2mL[19]
	Immunology				
Lymphocyte subsets [9]		1mL			1mL
	Pharmacokinetic studies				
STAGE I - Intensive PK [10]			[4mL]		

STAGE I - Population PK [11]			[0.5 – 1mL]		
Total Maximum Blood Volumes [20]	3mL	16.5mL	[0.5 – 4mL]		10mL

Appendix IA Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure), occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing. For female participants 9 years of age and older, menarche status and for participants who have reached menarche; sexual activity and contraceptive use.

3. For information on Tanner Staging assessment, see P1093 MOP.

4. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all participants in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

5. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a participant has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

6. M/C ratio – microalbumin / creatinine ratio (mcg/mg creatinine)

7. Pregnancy test (urine or serum beta hCG) must be performed on all females of reproductive potential within 72 hours prior to enrollment. Subsequent tests should be performed at each visit. If a blood test is performed, collect 1.0mL in a red top serum tube.

8. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the Protocol Team.
9. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

10. Refer to Section 9.2 for additional instructions around intensive PK sampling.

    The pharmacokinetic evaluation should be scheduled so that witnessed dosing of DTG is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Participants should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled.

    Intensive PK should be done in a fasted state following the guidelines below and Section 9.2.1.1, unless instructed otherwise by the Protocol Team.

- ≥6 hours PRIOR to dosing – participants may eat and drink without restriction
- ≥4 to <6 hours PRIOR to dosing – milk, apple/orange juice and water may be consumed; No food
- <4 hours PRIOR to dosing – water ONLY
- From dosing to <2 hours POST dose – apple/orange juice and water may be consumed; No food
- From ≥2 to <4 hours POST dose – participants may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
- From ≥4 hours POST dose onwards – participants may eat and drink without restriction

For participants who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5mL) will be collected at the following timepoints: pre-dose, 1, 2, 3, 4, 6, 8 and 24 hours post dosing. The 24-hour sample must be collected prior to the next dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 24-hour sample with a window of 22-26 hours. US sites will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a 'pass-through' (see LPC for instructions).

11. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. Participants will have 2 blood sample collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the LPC. For sample collection timepoints for the 'Two Weeks Post Switch Visit' and 'Next Scheduled Visit after Post Switch Visit' refer to footnotes 14 and 15 below. For participants on BID dosing refer to the study MOP for sampling time points.

12. Entry must occur within 30 days of screening.

13. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of specimen collection of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks.

14. If a participant is confirmed as having virologic failure, as defined in Section 6.5, conduct a Virologic Failure Visit at least one week and within four weeks later.

15. Per Section 6.4, participants who underwent a dose modification and for whom additional PK sampling (intensive or population sampling) was requested by the Protocol Team collect intensive or population PK samples (per Protocol Team request only) 5 – 14 days after initiation of the DTG dose adjustment. (If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.)

16. Per Section 6.4, for participants who underwent a dose modification, as requested by the Protocol Team, a safety visit should be done 4 weeks (- 1 wk/+ 2 wks) after initiation of the DTG dose adjustment. (If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.)

17. Participants, who discontinue study drug early, should remain on study and follow Appendix IF .

18. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

19. Only if not done at virologic failure.

20. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.

Appendix IB Schedule of Evaluations
Cohorts I, IIA, III and III-DT – Stage II

	Screen[1]	Entry[11] Day 0	Day 10	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48	Confirm Suspect Virologic Failure[12]	Virologic failure[13]	Pre-mature DC of Study Drug/ On study[14]
Visit Windows	-	-	±3 days	±1 wk	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	-	-	-
CLINICAL EVALUATIONS														
Informed Consent	X													
History and Physical exam[2]	X	X	X	X	X	X	X	X	X	X	X		X	X
Tanner Staging [3]		X									X			
Adherence Questionnaire			X	X	X	X	X	X	X	X	X		X	X
CDC Classification	X	X						X					X	X
Palatability Assessment			X	X				X						
LABORATORY EVALUATIONS														
Hematology	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL		1mL	1mL
Chemistries[4]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL		1mL	1mL
Lipid profiles[5]	1mL							1mL			1mL			
PBMCs / plasma for storage (includes integrase resistance sample)		7mL						6.5mL			6.5mL		6.5mL	
Urinalysis	X				X			X			X			
Microalbumin/creatinine ratio - urine [6]		X			X			X			X			
Pregnancy test [7]	X	X	X	X	X	X	X	X	X	X	X		X	X
Virology														
HIV-1 RNA PCR	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
Genotyping	2mL												2mL[15]	2mL[15,16]
Phenotyping [8]	2mL												2mL	2mL[16]
Immunology														
Lymphocyte subsets [9]	1mL	1mL				1mL		1mL	1mL	1mL	1mL		1mL	1mL
Pharmacokinetic studies														
STAGE II - Population PK[10]				1mL		0.5mL		1mL						

Total Maximum Blood Volumes [17]	11mL	13mL	5mL	6mL	5mL	6.5mL	5mL	14.5 mL	6mL	6mL	13.5 mL	3mL	16.5mL	10mL

Appendix IB Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing. For female participants 9 years of age and older, menarche status and for participants who have reached menarche; sexual activity and contraceptive use.

3. For information on Tanner assessment, see P1093 MOP.

4. Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. “ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all participants in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

5. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a participant has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

6. M/C ratio – microalbumin / creatinine ratio

7. Pregnancy test (urine or serum beta hCG) must be performed on all females of reproductive potential within 72 hours prior to enrollment. Subsequent tests should be performed at each visit. If a blood test is performed, collect 1.0mL in a red top serum tube.

8. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the Protocol Team.

9. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

10. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All participants will have 2 blood sample collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the Laboratory Processing Chart (LPC). For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 13 and 14 below. For participants on BID dosing refer to the study MOP for sampling time points.

11. Entry must occur within 30 days of screening.

12. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks)

13. If a participant is confirmed as having virologic failure as defined, in Section 6.5, conduct a Virologic Failure Visit at least one week and within four weeks.

14. Participants, who discontinue study drug early, should remain on study and follow Appendix IF Appendix IF Schedule of Evaluations Participants who Prematurely Discontinue Dolutegravir.

15. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left-over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

16. Only if not done at virologic failure.

17. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.

Appendix IC Schedule of Evaluations
Cohorts IV, IV-DT, and V-DT– Stage I
Screen through Week 48

	Screen[1]	Entry[10] Day 0	Intensive PK: Day 5-10	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 48
Visit Windows	-	-	-	±1 wk	±1 wk	±1 wk	±1 wk	±2 wk	±2 wk	±2 wk	±2 wk
CLINICAL EVALUATIONS											
Informed Consent	X										
History and Physical exam [2]	X	X	X	X	X	X	X	X	X	X	X
Adherence Questionnaire			X	X	X	X	X	X	X	X	X
CDC Classification		X						X			
Palatability Assessment			X	X				X			
LABORATORY EVALUATIONS											
Hematology	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL
Chemistries [3]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL
Lipid profiles[4]	1mL							1mL			1mL
PBMCs / plasma for storage (includes integrase resistance)		5mL						4.5mL			4.5mL
Urinalysis	X				X			X			X
Microalbumin/creatinine ratio -urine[5]		X			X			X			X
Virology											
HIV-1 RNA PCR	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
Genotyping	2mL										
Phenotyping[6]	2mL										
Immunology											
Lymphocyte subsets[7]	1mL	1mL				1mL		1mL	1mL	1mL	1mL
Pharmacokinetic studies											
STAGE I - Intensive PK[8]			4mL								
STAGE I – Population PK[9]				1mL		0.5mL		1mL			
Total Maximum Blood Volumes[18]	10.5mL	10.5 mL	8.5mL	5.5mL	4.5mL	6.0mL	4.5mL	12mL	5.5mL	5.5mL	11mL

Appendix IC Schedule of Evaluations (cont'd)
Cohorts IV, IV-DT, and V-DT– Stage I
Virologic Failure, Dose Adjustment and Premature/DC of Study Drug Visits

	Confirm Suspected virologic failure[11]	**Virologic Failure[12]**	**[Dose Adjustment PK Visit][13]**	**[Dose Adjustment Safety Visit][14]**	**Premature/DC of Study Drug On study[15]**
Visit Windows		-	If requested, 5 to 14 days after initiation of the dose adjustment	4 weeks post dose modification (-1 wk/+ 2 wk)	-
CLINICAL EVALUATIONS					
Informed Consent					
History and Physical exam [2]		X		[X]	X
Adherence Questionnaire		X		[X]	X
CDC Classification		X			X
Palatability Assessment					
LABORATORY EVALUATIONS					
Hematology		0.5mL			0.5mL
Chemistries [3]		1mL			1mL
Lipid profiles [4]					
PBMCs / plasma for storage (includes integrase resistance sample)		4.5mL			
Urinalysis					
Microalbumin/creatinine ratio - urine[5]					
Virology					
HIV-1 RNA PCR	3mL	3mL			3mL
Genotyping		2mL[16]			2mL[16,17]
Phenotyping [6]		2mL			2mL[17]
Immunology					
Lymphocyte subsets [7]		1mL			1mL
Pharmacokinetic studies					
STAGE I - Intensive PK [8]			[4mL]		
STAGE I - Population PK [9]			[0.5 – 1mL]		
Total Maximum Blood Volumes[18]	3mL	14mL	[0.5 – 4mL]		9.5mL

Appendix IC – Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. "ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all participants in the study, using the same source all the way through the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a participant has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the Protocol Team.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. Refer to Section 9.2 for additional instructions around intensive PK sampling.

   The pharmacokinetic evaluation should be scheduled so that witnessed dosing of DTG is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Participants should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled.

   Intensive PK should be done in a fasted state following the guidelines below and Section 9.2.1.1, unless instructed otherwise by the Protocol Team.

   - Participants should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day.
   - Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time.
   - Participants may consume a light meal of their choice four hours after dosing on the intensive PK day.

   For participants who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5mL per sample) will be collected at the following time points: pre-dose, 1, 2, 3, 4, 6, 8 and 24 hours post dosing. The 24-hour sample must be collected prior to the next dose. To allow for some flexibility,

the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 24-hour sample with a window of 22-26 hours. US sites will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a 'pass-through' (see Laboratory Processing Chart (LPC).

9. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All participants will have 2 blood samples collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood sample will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the LPC. For sample collection timepoints for the 'Two Weeks Post Switch Visit' and 'Next Scheduled Visit after Post Switch Visit' refer to footnotes 13 and 14 below. For participants on BID dosing refer to the study MOP for sampling time points.

10. Entry must occur within 30 days of screening

11. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of specimen collection of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks).

12. If a participant is confirmed as having virologic failure, as defined in Section 6.5, conduct a Virologic Failure Visit at least one week later, and within four weeks.

13. Per Section 6.4, participants who underwent a dose modification and for whom additional PK sampling (intensive or population sampling) was requested by the Protocol Team collect intensive or population PK samples (per Protocol Team request only) 5 – 14 days after initiation of the DTG dose adjustment. (If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.)

14. Per Section 6.4, for participants who underwent a dose modification, as requested by the Protocol Team, a safety visit should be done 4 weeks (- 1 wk/+ 2 wks) after initiation of the DTG dose adjustment. (If this visit is scheduled to occur during another scheduled visit a combined visit can be done and procedures do not need to be duplicated.)

15. Participants, who discontinue study drug early, should remain on study and follow Appendix IF

16. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the Laboratory Processing Chart (LPC) for additional details.

17. Only if not done at virologic failure.

18. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.

Appendix ID Schedule of Evaluations
Cohorts IV, IV-DT, and V-DT – Stage II

	Screen[1]	**Entry**[9] **Day 0**	**Day 10**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**	**Week 32**	**Week 40**	**Week 48**	**Confirm Suspected Virologic Failure**[10]	**Virologic failure**[11]	**Premature DC of Study Drug/ On study**[12]
Visit Windows	-	-	±3 days	±1wk	±1wk	±1wk	±1wk	±2wk	±2wk	±2wk	±2wk		-	-
CLINICAL EVALUATIONS														
Informed Consent	X													
History and Physical exam[2]	X	X	X	X	X	X	X	X	X	X	X		X	X
Adherence Questionnaire			X	X	X	X	X	X	X	X	X		X	X
CDC Classification		X						X					X	X
Palatability Assessment			X	X				X						
LABORATORY EVALUATIONS														
Hematology	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL	0.5mL		0.5mL	0.5mL
Chemistries[3]	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL	1mL		1mL	1mL
Lipid profiles[4]	1mL							1mL			1mL			
PBMCs / plasma for storage Includes integrase resistance)		5mL						4.5mL			4.5mL		4.5mL	
Urinalysis	X				X			X			X			
Microalbumin/ creatinine ratio assay - urine[5]		X			X			X			X			
Virology														
HIV-1 RNA PCR	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
Genotyping	2mL												2mL[13]	2mL[13,14]
Phenotyping[6]	2mL												2mL	2mL[14]
Immunology														
Lymphocyte subsets[7]	1mL	1mL				1mL		1mL	1mL	1mL	1mL		1mL	1mL
Pharmacokinetic studies														
STAGE II - Population PK [8]				1mL		0.5mL		1mL						
Total Maximum Blood Volumes[15]	10.5mL	10.5mL	4.5mL	5.5mL	4.5mL	6mL	4.5mL	12mL	5.5mL	5.5mL	11mL	3mL	14mL	9.5mL

Appendix ID – Footnotes

1. After obtaining Informed Consent, evaluations should be completed within 30 days prior to study entry.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Blood Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. “ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all participants in the study, using the same source all the way through the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a participant has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Phenotyping will occur where there is sufficient blood volume collected. HIV-1 phenotyping will NOT be performed in real time and will NOT be used to determine optimized background therapy (OBT). Specimens should be stored at the local site and shipped in batches when requested by the Protocol Team.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. Blood samples (0.5mL per sample) will be collected per time point at Weeks 4, 12 and 24. All participants will have 2 blood samples collected at week 4: pre-dose and 2-4 hours post dose. At week 12, 1 blood samples will be collected at any time point post dose. At week 24, 2 blood samples will be collected two hours apart between 12 and 26 hours post-dose. Samples to be batched and shipped as described in the LPC. For sample collection timepoints for the ‘Two Weeks Post Switch Visit’ and ‘Next Scheduled Visit after Post Switch Visit’ refer to footnotes 11 and 12 below. For participants on BID dosing refer to the study MOP for sampling time points.

9. Entry must occur within 30 days of screening.

10. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of specimen collection of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks).

11. If a participant is confirmed as having virologic failure, as defined in Section 6.5, conduct a Virologic Failure Visit at least one week later, and within four weeks.

12. Participants, who discontinue study drug early, should remain on study and follow Appendix IF

13. A baseline specimen should also be sent with the genotype virologic failure specimen. This specimen may be a baseline (Day 0 entry) storage sample or left over sample from baseline genotyping (screening). Please refer to the LPC for additional details.

14. Only if not done at virologic failure.

15. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: hematology; chemistry; pharmacokinetic studies; HIV-1 RNA; genotyping; lymphocyte subsets; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.

Appendix IE Schedule of Evaluations
Long-term Safety Follow-up for Participants Who Continue to Receive Dolutegravir

	Every 12 Weeks [Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, 168,180, and 192(End of Study Visit)]	**Every 48 Weeks [Weeks 96, 144 and 192 (End of Study Visit)]**	**Confirm suspected virologic failure[6]**	**Virologic failure[7]**	**Premature Discontinuation of Study Drug/On Study[9]**
Visit Windows	±4 wks	±4 wks			
CLINICAL EVALUATIONS					
History and Physical[1]	X			X	X
Adherence Questionnaire	X			X	
Palatability Assessment					
LABORATORY EVALUATIONS					
HIV-1 RNA PCR	3mL		3mL	3mL	
PBMCs/plasma for storage				6.5mL	
Genotyping		2mL[2]		2mL[3]	2mL[3,4]
Phenotyping				2mL	2mL[4]
Lipid profiles		1mL			
Pregnancy test[5]	X	X		X	X
Total Maximum Blood Volumes[8]	3mL	3mL		13.5mL	4mL

Appendix IE - Footnotes:

1. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure, occurrence of adverse events since last study visit and any HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing. For female participants 9 years of age and older, menarche status and for participants who have reached menarche, sexual activity and contraceptive use.
2. Genotyping to be done for participants post virologic failure, ONLY if requested to do so by the Protocol Team.
3. Specimens for genotyping and phenotyping should be obtained and stored at this visit, but only sent for processing if the confirmatory HIV RNA test at this visit is > 400 c/ml. Please refer to the Laboratory Processing Chart (LPC) for additional details.
4. Only if not done at virologic failure visit.
5. Pregnancy testing, after the initial 48 weeks of study drug, should be determined as per local practice. If pregnancy occurs, it is an event that should be captured on the CRFs.
6. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of specimen collection of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks)
7. If a participant is confirmed as having virologic failure, as defined in Section 6.5, conduct a Virologic Failure Visit at least one week and within four weeks.
8. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: pharmacokinetic studies; HIV-1 RNA; genotyping; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.
9. Participants, who discontinue study drug early, should remain on study and follow Appendix IF

Appendix IF Schedule of Evaluations
Participants who Prematurely Discontinue Dolutegravir

Participants who continue DTG will be followed as per Appendix IE

	4 Week Follow-Up Visit[2]	**Every 3 months until resolved (if applicable)[3]**
Visit Windows	±2 wks	±4 wks
History and Physical[1]	X	X

Appendix IF - Footnotes:

1. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and any HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

2. This follow up visit should be performed 4 weeks after the participant's last exposure to DTG.

3. Participants who are pregnant or who have a drug related adverse event that has not resolved within 3 months of stopping study drug, should come back to clinic every 3 months for follow-up until the AE is resolved or the mother delivers the baby. Study required tests are an interim history and physical exam at these visits. If sites perform safety tests at these visits as a result of standard of care, sites should document all results in the case report forms. If the participant discontinues for any reason other than pregnancy or drug related AE, no other visit after the 4 week visit is required.

Appendix IG
Schedule of Evaluations
Participants who Start Rifampin as Part of Treatment for Active Tuberculosis

	Study Visits Following Initiation of Rifampin Therapy					Confirm Suspected Virologic Failure[10]	Virologic failure [11]	Premature Discontinuation of Study Drug/ On study [12]
	Day 1 of rifampin therapy [1]	**Week 2**	**Week 4**	**Week 12**	**Every 8 weeks until end of rifampin therapy**			
Visit Windows		±1 wk	±1 wk	±1 wk	±2 wks		-	-
CLINICAL EVALUATIONS								
History and Physical exam [2]	X	X	X	X	X		X	X
Adherence Questionnaire	X	X	X	X	X		X	X
LABORATORY EVALUATIONS								
Hematology	1mL	1mL	1mL	1mL	1mL		1mL	1mL
Chemistries[3]	1mL	1mL	1mL	1mL	1mL		1mL	1mL
Lipid profiles[4]	1mL			1mL				
Microalbumin/creatinine ratio assay – urine[5]			X	X	X		X	
PBMCs / plasma for storage							6.5mL	
Pregnancy test[6]	X	X	X	X	X		X	X
Virology								
HIV-1 RNA PCR	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL
Immunology								
Lymphocyte subsets[7]				1mL	1mL		1mL	1mL
Pharmacokinetics								
Intensive PK[8]		8mL						
Population PK [9]			1mL	1mL				
Total Maximum Blood Volumes [13]	6mL	13mL	6mL	8mL	6mL		12.5mL	6mL

NOTE: Participants who are diagnosed with active tuberculosis while taking DTG as part of P1093, will have their medications changed as per Section 6.1.8 and should be followed as per Appendix IG . It is estimated the participant will be on anti-TB treatment for approximately 24 weeks. Upon discontinuation of the rifampin containing anti-TB therapy, the participant's DTG dose will revert back to once daily administration. The participant should complete the remainder of the first 48 weeks of DTG therapy on their original schedule of evaluations, or if they have completed 48 weeks of DTG therapy, they should move to long- term follow-up (Appendix IE). For example, if the participant was at week 16 when they were started on rifampin, and they complete 24 weeks of rifampin therapy, they would then go back to week 40 of their original SOE.

Appendix IG Footnotes:

1. Participants who are already enrolled in P1093 and become exposed to TB, and subsequently require an anti-TB treatment that includes the use of rifampin, may be allowed to continue in the study if their ART options are compatible with co-administration of rifampin. Continuation requires the approval of the Protocol Team.

2. History and physical exam (including height, weight, vital signs [temperature, pulse, respirations and blood pressure], occurrence of adverse events since last study visit and HIV-1 associated conditions). Weight should be measured without shoes and with minimal clothing.

3. Chemistries will be performed at all visits. Electrolytes (sodium, potassium, and HCO_3), glucose, creatinine, lipase, phosphorus, and LFTs. LFTs should include total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, and albumin. If indirect bilirubin is not reported by the site laboratory, it should be calculated at the site and documented.

   The following (listed in order of preference) should be used to determine the upper limit of normal (ULN) values for indirect bilirubin.
   a. "ULN" values reported by the laboratory report for the test, or
   b. “ULN" values routinely used/established by the site, or
   c. "ULN" values as per the Harriet Lane Handbook (e.g. the current "ULN" for indirect bilirubin as per Harriet Lane Handbook is 0.4)

   Sites must be consistent with the way toxicities are evaluated for all participants in the study; sites should use the same source throughout the study. Remember to have documentation of calculated indirect bilirubin and source of "ULN", when not reported by your laboratory.

4. Lipid Profile (triglycerides, cholesterol, HDL, LDL) will be drawn in a non-fasting state. However, if triglycerides are grade 2 (using DAIDS toxicity table for fasting triglycerides), a complete fasting state lipid profile (triglycerides, cholesterol, HDL, and LDL) must be drawn. Fasting intervals will be overnight or at least 8 hours. After a participant has had a grade 2 triglycerides in non-fasting state, all future triglycerides must be obtained in fasting state.

5. M/C ratio – microalbumin / creatinine ratio

6. Pregnancy test (urine preferably) must be performed on all females of reproductive potential at each visit. If a serum beta hCG test is performed, collect 1.0mL in a red top serum tube.

7. Lymphocyte subset blood samples should be collected in EDTA tubes. These samples will be analyzed for CD4 and CD8.

8. The pharmacokinetic evaluation should be scheduled so that witnessed dosing of DTG is as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Participants should have been compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit should be re-scheduled. For participants who vomit within 4 hours after dosing; PK must be cancelled and may be rescheduled. Blood samples (0.5mL per sample) will be collected at the following time points: pre-dose, and at 1, 2, 3, 4, 6, 8, and 12 hours post-dose. To allow for some flexibility, the 8-hour sample can be collected with a window of 7-9 hours post-dose and the 12 hour sample with a window of 11-13 hours. US sites

will ship intensive PK samples in real time to UAB; all non-US sites will ship PK samples in real time to BRI repository for a 'pass-through' (see LPC for instructions). See dosing and fasting instructions for Cohorts I-III and Cohorts IV-V-DT, below.

Instructions for Cohorts I-III:

- ≥6 hours PRIOR to dosing – participants may eat and drink without restriction
- ≥4 to <6 hours PRIOR to dosing – milk, apple/orange juice and water may be consumed; No food
- <4 hours PRIOR to dosing – water ONLY
- From dosing to <2 hours POST dose – apple/orange juice and water may be consumed; No food
- From ≥2 to <4 hours POST dose – participants may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
- From ≥4 hours POST dose onwards – participants may eat and drink without restriction

Instructions for Cohorts IV-V-DT:

Participants should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time.

9. All participants will have 2 blood samples (0.5mL per sample) collected at weeks 4 and 12: pre-dose and 8-14 hours post dose. Samples to be batched and shipped as described in the LPC.

10. If a participant meets a criterion for suspected virologic failure, as defined in Section 6.5, collect a confirmatory HIV-1 RNA PCR sample at least 1 week but not more than 4 weeks from the date of specimen collection of the initial RNA PCR test. If a sample cannot be obtained within weeks, samples should be collected as soon as possible beyond 4 weeks)

11. If a participant is confirmed as having virologic failure, as defined in Section 6.5, conduct a Virologic Failure Visit at least one week and within four weeks.

12. Participants who discontinue study drug (DTG) early are required to come back to clinic four weeks after stopping study drug or after resolution of any adverse event.

13. The blood volumes listed are ideal, but may not always be possible due to site-specific regulations or challenges with phlebotomy in certain participants. For insufficient blood draws, priorities are as follows: pharmacokinetic studies; HIV-1 RNA; genotyping; plasma and PBMCs/plasma for storage; phenotyping; lipid profiles.

Appendix II
Sample Consent Form for Participants Enrolling in Stage I

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Participants Enrolling in STAGE ONE
P1093 Version 5.0, dated 12 July 2018

SHORT TITLE FOR THE STUDY: Safety and PK of dolutegravir in HIV-1 Infected Children

INTRODUCTION
You are/your child is being asked to take part in this research study because you have /your child has the Human Immunodeficiency Virus (HIV), which is the virus that causes AIDS, and because the drugs currently available may not keep the amount of HIV in your / your child's blood low enough or may cause side effects too difficult to deal with. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?
This study is being done to study a new antiretroviral HIV medication called dolutegravir. This drug is a type of medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein that HIV needs to enter human cells and make more copies of itself. The study will help find the best amount or dose of dolutegravir for infants, children and teenagers, when it is taken on its own as well as with other antiretroviral medications. This study will also find out the safety of using this medication in infants, children and adolescents and if there are any side effects from the medication. Dolutegravir has been tested in adults and children. The study drug (dolutegravir) is approved for use in children 12 years and older by the FDA [and/or local regulatory authorities].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE IS IN THIS STUDY?
If you decide to (allow your child to) enroll in this study, you / your child will be asked to come to the clinic at least 10 times over 48 weeks and then every 12 weeks for three more years. You / your child will be given dolutegravir and you / your child will be asked to take it once or twice a day for the entire study, in addition to your / your child's regular HIV medicines. Dolutegravir is available in 3 different formulations: 1) a film-coated tablet which cannot be crushed or dissolved, 2.) a liquid suspension and, 3) a tablet that can be dissolved in water. If you are/your child is 12 up to 18 years old, you/your child will take the film-coated tablet formulation of dolutegravir. You will be given instructions on how to give dolutegravir to your child and how to store the dolutegravir. If your child is between 6 to less than 12 years of age and was prescribed the liquid or dissolvable tablets of dolutegravir he/she may be allowed to switch to the film-coated tablet formulation at a later time. The study staff will let you know when your child can switch and if you request to do so.

Although the study will provide you/your child with dolutegravir, other antiretrovirals will not be provided by the study.

This study will be done in two parts – Stage one and Stage two. Stage one will enable the doctors to find the right dose of study drug for you/your child and then will keep you on that dose to look for any side effects that you/your child might experience. In Stage two the doctors will know the right dose to put you/your child on and will look at any side effects that you / your child might experience as well as how well the drug is controlling your HIV infection. You/your child will be enrolled into either Stage one or Stage two, depending on when you/your child enroll and your age / the age of your child. This consent form is for Stage one.

In this study there are 8 cohorts in Stage I – enrolling infants, children, and adolescents from 4 weeks to less than 18 years of age. Participants who have had their 18th birthday by the entry visit will not be enrolled into the study.

Screening:
If you are interested in taking part / allowing your child to enroll in this study, we will see if you are / your child is eligible for the study:

- We will ask your / your child's medical history including questions about your /your child's health and what symptoms, medications, and illnesses you have/your child has had.
- We will do a physical exam including height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate). Doses may be modified based on the results of the weight.
- We will take a little more than 2 teaspoons (11mL) of blood, to check for the following:
    - The amount of HIV in the blood,
    - The amount of cholesterol and triglycerides (types of fat) in the blood,
    - How well your immune system, liver and kidneys are working,
    - Other routine tests.

You will be given the results of these tests. We will also ask you/your child to provide a urine sample for routine tests. Girls and women who can have a baby will also be asked to provide a urine or blood sample to test for pregnancy. If you are / your child is engaged in sexual activity that could lead to pregnancy, you / your child will be asked to take birth control precautions throughout the study period.

On Study:
If you are/your child is eligible for this study, you/your child will come to the clinic at least 10 times in about 1 year. Most of the visits will last about 1-2 hours. More visits will be needed if the amount of study drug in your blood is too low or too high and your dose needs to be adjusted. You/your child will come to the clinic for the first study visit within 30 days of the screening visit.

- At each visit, a medical history will be taken and you/your child will have a physical exam. At the enrollment visit and at the week 48 visit, you/your child's stage of sexual development will be determined. For girls/women, this will be done by looking at how developed the breasts are. For boys/men, this will be done by measuring the size of the testes.

- We will draw blood at each visit. Depending upon your/your child's age, between 1- 4 teaspoons (5-17mLs) of blood will be drawn at these visits; you will be informed of results of routine blood tests. Some of the blood drawn will be stored and tested to find out how your/your child's immune system is affected by the study drug. This testing will be done after the study is over, and you will not be given the results of these tests.
- A palatability assessment will be done at Day 10, Week 4 and Week 24 to find out what you/your child thinks about the taste of the study drug.
- You/your child will be asked to come to the clinic to have blood drawn 8 times over 24 hours during one visit, approximately 5-10 days after you / your child started taking the study medication. This visit is known as an 'intensive PK visit'. Depending on your/your child's age, up to 9mLs (about 2 teaspoons) of blood will be drawn at this visit and you will be asked to withhold certain liquids and food. The study staff will give you instructions about this. These blood tests are done to measure the amount of study drug in your/your child's blood. A small plastic catheter (a needle that is placed in a vein for an extended period of time, so that blood can be drawn multiple times, without having to stick you with a needle several times) will be placed in your/your child's arm to draw these blood samples. The needle will stay in place until all of the blood samples are drawn.
- If the amount of study drug in your/your child's blood is not enough or is too high, you/your child may be asked to take a different dose and may be asked to return to the clinic for another 'intensive PK visit'. You/your child may have blood to be drawn again 8 times over 24 hours. This is to make certain that the new dose is safe. The same procedures above will be followed.
- The current instructions on what you/your child can eat and drink around the intensive PK draws are below, but these may change. If these instructions change, the study staff will let you know and provide you with different instructions.

  If you are/your child is older than 2 years old and having intensive PKs done you/your child may be asked to follow the guidelines below regarding eating and drinking around the intensive PK visit.

  - ≥6 hours PRIOR to taking your medication – you/your child may eat and drink without restriction
  - ≥4 to <6 hours PRIOR to taking your medication – milk, apple/orange juice and water may be consumed; No food
  - <4 hours PRIOR to taking your medication – water ONLY
  - From dosing to <2 hours AFTER taking your medication – apple/orange juice and water may be consumed; No food
  - From ≥2 to <4 hours AFTER taking your medication – you may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
  - From ≥4 hours AFTER taking your medication onwards – you may eat and drink without restriction

  If your child is 4 weeks to less than 2 years old and having intensive PKs done, you/your child may be asked to follow the guidelines below regarding eating and drinking around the intensive PK visit.

- No breastmilk, formula or any other high fat food/liquid for 2 hours prior to and 1 hour after dosing on the intensive PK day.
- Water and other fluids (i.e. apple/orange juice and oral rehydration solution) can be taken at any time.

- You will have extra blood draws at three visits (week 4, week 12 and week 24). At weeks 4 and 24, you will have two blood draws. At week 12 you will only have one blood draw. The amount of blood drawn at the different study visits will be less than 1 teaspoon (0.5-1mL) depending on your /your child's age.
- If the amount of HIV virus in your/your child's blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood. If the level of HIV virus in your blood is still too high, your study doctor may ask you to stop taking the study medicine and to come back to the clinic for another visit. As part of this visit, you/your child will have an interim medical history, physical exam and approximately 3 teaspoons of blood (14-16.5mL) will be drawn for testing and storage.
- If you/your child experiences a severe liver reaction or inflammation while on the study, you/your child may be asked to come back to clinic to have less than one teaspoon of blood (2mL) drawn to check the level of dolutegravir in the blood. Additional testing as part of routine assessments for liver inflammation (e.g. checking for viruses that cause liver inflammation) may be performed as well.

Long Term Follow-Up
After you have been on study drug for approximately 48 weeks, you will enter the long term follow-up phase of the study. You will be asked to come back into clinic every 12 weeks (every 3 months) for 3 more years. Most visits will last about 30 mins.

- At each visit, a medical history will be taken and you/your child will have a physical exam. You will also be asked if you have missed taking any of your medications.
- We will draw less than 1 teaspoon of blood (3-4mL) at each visit. You will be informed of results of routine blood tests.
- As before, if the amount of HIV virus in your/your child's blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood (see above).

You/your child must continue to take your/his/her anti-HIV medications during the study as prescribed by your/your child's HIV care provider. If your/your child's HIV care provider changes your/your child's anti-HIV medications during the study, you/your child can still take the study drug. You/your child will be asked questions about taking your/his/her anti-HIV medications and the times you take/he/she takes them and if you have/he/she has missed any medications.

If you/your child can become pregnant, we will collect urine or blood to test for pregnancy at each visit. We will also ask you/your child about contraception use. If you think you/if your child thinks she may be pregnant at any time during the study, tell the study staff right away.

Blood and Urine Samples
Some of your / your child's blood and urine samples will be shipped out of the country to the USA for specialized tests. These tests will tell the doctors how much study drug is in your / your child's blood and if the study drug is causing any changes in your kidneys.

For Participants Receiving Granules for suspension only

If your child is receiving the liquid he/she will need to switch to the dissolvable tablet. The study staff will inform you when your child will need to switch. This is because the company will not be making the (granule) liquid form of dolutegravir any longer. The study staff will provide instructions on how to dispense the dissolvable tablet and on the day you are scheduled to come to the clinic to begin taking the dissolvable tablets you will be asked to not give the (granule) liquid dose to your child. The first dose of the dissolvable tablet will be given in the clinic. You will be asked to come back to the clinic about 2 weeks later and will have a palatability assessment and blood drawn to confirm the level of HIV in your child's blood. If you have been on the study for more than 24 weeks at each of these visits, blood samples will be drawn at two separate times. The amount of blood drawn will be less than 1 teaspoon (0.5 -1mL)].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE BECOMES INFECTED WITH TUBERCULOSIS WHILE ON THIS STUDY?

If you become/your child becomes exposed to Tuberculosis (TB) while on study and requires anti-TB treatment that includes Rifampin you/your child will have to increase the dose of dolutegravir from once a day to twice a day while taking Rifampin. After you/your child complete(s) treatment with Rifampin, you/your child will go back to taking the dolutegravir once a day depending on what other medications you/your child is taking.

You/your child will also be required to return for at least five additional follow-up visits after starting Rifampin.

- At each of these visits, a medical history will be taken and you/your child will have a physical exam and a pregnancy test. We will draw approximately 1-3 teaspoons of blood to look at the following:
    - The amount of HIV, cholesterol and triglycerides (types of fat) in your blood
    - How well your immune system, liver and kidneys are working, as well as other routine tests
- At each visit you will be asked whether you are taking your medication as instructed.
- You/your child will be asked to come to the clinic to have blood drawn 8 times over 12 hours during one visit, approximately 5-10 days after you/ your child started taking anti-TB medication. For this visit, you/your child will be asked to fast for 6 hours before your daily dose of study medication.
- The study staff will give you more instructions about this. Depending on your/your child's age, up to 13mL (about 3 teaspoons) of blood will be drawn at this visit.
- You will have extra blood draws at two visits. At weeks 4 and 12, you will have two blood draws - blood will be drawn once before you take dolutegravir and about 12 hours later. The amount of blood drawn at the different study visits will be less than 1 teaspoon (1mL) depending on your /your child's age.

OTHER INFORMATION

The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 300 children and adolescents will take part in this study

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
You/your child is enrolling in Stage I of the study, and so will be in the study for at least 48 weeks After that time you/your child will enter the long-term safety follow-up phase of the study. During this time, you / your child will continue to take study-provided dolutegravir and will be asked to come to clinic every 12 weeks for three more years.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THE STUDY DRUG / THIS STUDY EARLY?
The study doctor may need to take you/your child off the study drug early, without your permission, if:

- Continuing the study drug may be harmful to you / your child
- You become / your child becomes pregnant while on study
- If you elect not to attend repeat PK evaluations as part of the study

The study doctor may need to take you/your child off the study early, without your permission, if:

- You are/ your child is not able to attend the study visits as required by the study
- You need / your child needs a treatment that you / your child may not take while on the study
- You are / your child is not able to take the study drug as required by the study
- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), other country specific governmental agencies, IMPAACT, the drug company supporting this study (GSK), or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB or EC is a committee that watches over the safety and rights of research participants

If your doctor wants you / your child to stop taking the study drug, you/your child will be asked to return to the clinic once more, four weeks after your last dose of dolutegravir, to make sure you are/your child is continuing to do well. This visit will include a history and physical exam, a blood draw and a review of your medical records.

IF MY CHILD HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE I LEAVE THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?

During the study:
If you / your child must permanently stop taking study-provided dolutegravir before your/your child's study participation is over, the study staff will discuss other options that may be of benefit to you/your child.

After the study:
Once you / your child leaves the study, if you/they are gaining benefit from the study-provided drug, this drug may continue to be provided until it is available to you in your country, but there is no guarantee. Study clinicians will work to ensure that you/your child continue to receive appropriate care and treatment outside of the study.

WHAT ARE THE RISKS OF THE STUDY?
The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this drug. These lists include the more serious

or common side effects with a known or possible relationship. It is very important that you tell your study doctor of any changes in your/your child's medical condition while taking part in the study. At any time during the study, if you believe you are/your child is experiencing any of these side effects, you have the right to ask questions on possible and /or known risks.

Possible Risks Associated with Dolutegravir

The drug used in this study, dolutegravir, has been administered to a total of 6004 participants (4814 HIV-infected and 1190 healthy) cumulative to 16 July 2017 in ongoing and completed ViiV sponsored and clinical trials ranging from Phase I to IIIb and the dolutegravir compassionate use program. The following side effects have been seen with dolutegravir:

Very Common (expected in about 100 of every 1000 people taking DTG (10%))
Nausea or feeling sick
Headache
Diarrhea or loose stools

Common (expected in about 10 of every 1000 people taking DTG (1%))
Cold symptoms like runny nose and sore throat; cough; flu
Dizziness or feeling light headed
Trouble sleeping; abnormal dreams
Rash
Feeling tired
High temperature
Pain in the stomach; vomiting
Changes in kidney, liver and muscle blood tests
Ocular icterus (yellowing of the whites of the eyes)
Itching (pruritus)
Feelings of deep sadness and unworthiness (depression)
Flatulence (gas or wind)
Increase in the level of liver enzymes
Increase in the level of enzymes produced in the muscles (creatinine phosphokinase)
Anxiety (fear, worry)

Uncommon (expected in about 1 of every 1000 people taking DTG (0.1%)
Allergic reaction (see below)
Liver toxicity (see below)
An inflammatory condition which may develop as the immune system becomes stronger (immune reconstitution syndrome or 'IRIS' (see below)
Suicidal thoughts and behaviors (mainly in patients who have had depression or mental health problems before) (see below)

Most of the side effects listed above have been mild or moderate, and have not generally stopped HIV-infected patients treated with dolutegravir from getting on with their lives as normal.

In one animal study, gastric erosion (irritation of the stomach lining) was seen. This finding has not been seen in adults in studies to date. However, if you or your child feels heartburn or stomach pain or has vomiting, please contact your/your child's study doctor.

Other side effects that may show up in blood tests:

- An increase in bilirubin (a pigment produced from the breakdown of red blood cells) in the blood,
- An increase in the level of creatinine, a waste product in the blood that gets filtered by the kidneys.

Dolutegravir Hypersensitivity Reaction

Hypersensitivity reactions have also been reported with integrase inhibitors, including dolutegravir, with signs and symptoms including general feeling of being sick, skin rash, a high temperature (fever), lack of energy (fatigue), swelling sometimes of the face or mouth (angioedema) causing difficulty in breathing, blisters or peeling skin, mouth ulcers, conjunctivitis (sore eyes), and muscle or joint aches. If you/your child develop(s) any of these signs and symptoms during the study, contact you/your child's study doctor immediately, who may decide to carry out tests on you/your child liver, kidneys or blood.

Mental illness

Some people with HIV infection occasionally have feelings of depression or may have thoughts of hurting or killing themselves (committing suicide). A small number of people being treated with integrase inhibitors for HIV infection, including dolutegravir, have had suicidal thoughts and behaviors, particularly patients with a prior history of depression or mental health illness. People with HIV taking integrase inhibitors including dolutegravir have also reported depression.

Tell the study doctor if you/your child have a history of mental illness. If you/your child have thoughts of hurting or killing yourself or have any other unusual or distressing thoughts or feelings at any time during the study, you/your child should tell the study staff or go to the nearest hospital immediately.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Some patients taking combination anti-HIV therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-HIV therapy, corticosteroid use, drinking alcohol, severe reduction in ability to fight off infection, higher body weight, among others, may be risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you/your child notice any of these symptoms, please inform your doctor

Liver Toxicity

Liver toxicity in the form of abnormal liver enzymes, inflammation of the liver (hepatitis) and liver failure have occurred in HIV-infected patients receiving regimens containing dolutegravir. The liver toxicity usually occurs in the first few weeks or months of taking anti-HIV medications. These patients were also generally either taking other medications (both HIV treatment and non-HIV treatment) that are also known to cause significant liver inflammation and/or allergic reaction, or already had liver problems

(such as hepatitis B or hepatitis C), or drank too much alcohol or had a combination of these. Cases of liver toxicity have also occurred in patients who do not have these risk factors.

If you/your child have (has) an unanticipated need for hepatitis C virus (HCV) therapy during the conduct of the study, the study doctor will discuss specific HCV treatment options with you. In case you/your child experience liver toxicity, the study doctor can decide to stop the administration of the study drug in order to assure your/your child's safety.

Other Risks

There is the risk of serious and/or life threatening side effects when non-study medications are taken with the study drug. For your/your child's safety, you must tell your/your child's HIV care provider and the study doctor or nurse about all medications you take/your child takes before the start of this study and also before starting any new medications while you are/your child is on the study. In addition, you must tell the study doctor or nurse before you enroll/enrolling your child in any other clinical trials while on this study. The use of highly active HIV medications may also be associated with altered fat metabolism including increased triglycerides (fatty acid in the blood) and/or increased cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child's doctor immediately. It is also important that while participating in the study, you do not/your child does not take any other prescription drugs or over-the-counter medications without first talking to your/your child's doctor or study nurse.

With any drug for HIV, there is a risk that the virus in your body will become resistant, which means that the drug will be less effective or not effective against your HIV. The risk that taking part in this study will cause your HIV to develop resistance to the study drug is unknown and will depend on how well the study drug works against your virus and whether instructions are followed for taking the study drug.

Blood Drawing and Heparin Lock Risks:
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur when a needle enters the body.

ARE THERE RISKS RELATED TO PREGNANCY?
It is not known if the drug or drug combinations in this study harm fetuses. Tests in pregnant animals do not show risk to the mother. Early results from a large study in Botswana of pregnant women showed a possible increased risk of certain types of serious birth defects involving the brain, and spinal cord in babies born to women who received dolutegravir at the time of becoming pregnant. No cases of babies born with these types of birth defects have been reported among women who started dolutegravir later in pregnancy.

If you are/your child is having sex that could lead to pregnancy, you/your child must agree not to become pregnant.

Because of the risk involved, you and your partner, or your child and their partner must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until two weeks after stopping study drug. Options for birth control methods include these listed below:

- Birth control drugs that prevent pregnancy given by pills, shots, placed on the skin (e.g. patch) or placed under the skin

- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

Some of these are better than others in preventing pregnancy. You/your child will work with study staff to pick the options best for you. All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

If you think you/your child may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your/your child's choices. You/your child will be tested at each study visit if it is possible that you/she may be pregnant.

If you are /your child becomes pregnant while on study, you/she will not be allowed to continue on the study drug but will be asked to remain on study and come in for study visits as planned in case of safety concerns and so that the doctors can follow your/her pregnancy until your / your child's baby is born.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you / your child take(s) part in this study, the amount of HIV in your / your child's body may go down and your/your child's immune system may become stronger, but no guarantee can be made. You/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I / DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to you/your child
- Treatment with other experimental drugs, if you/your child qualify(ies)
- No treatment (NOT recommended)

Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

(For US Sites Only)

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your/your child's records include the U.S. Food and Drug Administration and other U.S., local and international regulatory entities, the Office of Human Research Protections (OHRP), the site IRB /EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, drug companies supporting the study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an

insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(For sites outside the U.S.)
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name of identify you personally.

Your records may be reviewed by the Ministry of Public Health in your country, the FDA and other U.S., local and international regulatory entities, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB/EC, study staff, study monitors and the drug companies supporting this study.

WHAT ARE THE COSTS TO ME / MY CHILD?
There are no costs to you/your child for the study drug, study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications arise or if your doctor decides extra tests are needed. In some cases, it is possible that your insurance company will not pay for these costs because [you are/ your child is] taking part in a research study.

WILL I RECEIVE ANY PAYMENT?
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

WHAT HAPPENS IF I AM / MY CHILD IS INJURED?
If you are / your child is injured as a result of being in this study, you / your child will be given immediate treatment for your/his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your/your child's legal rights by signing this consent form.

WHAT ARE MY / MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

(For legal guardians, as applicable)
If your child reaches the legal age of consent during the study [he/she] will be asked to provide independent consent at their next visit.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your/your child's/baby's rights as a research participant, contact:

- Name or title of person on the Institutional Review Board (IRB), Ethics Committee (EC) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Participant's Legal Guardian (print) (As appropriate)	_____ Legal Guardian's Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature and Date
_____ Witness' Name (print) (As appropriate)	_____ Witness's Signature and Date
_____ Second Guardian (print) (If required)	_____ Second Guardian's Signature and Date

Appendix III
Sample Consent Form for Participants Enrolling in Stage II

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

Participants Enrolling in STAGE TWO
P1093 Version 5.0, dated 12 July 2018

SHORT TITLE FOR THE STUDY: Safety and PK of dolutegravir in HIV-1 Infected Children

INTRODUCTION
You are/your child is being asked to take part in this research study because you have /your child has the Human Immunodeficiency Virus (HIV), which is the virus that causes AIDS, and because the drugs currently available may not keep the amount of HIV in your / your child's blood low enough or may cause side effects too difficult to deal with. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?
This study is being done to study a new antiretroviral HIV medication called dolutegravir. This drug is a type of medicine called an integrase inhibitor. Integrase inhibitors work by blocking integrase, a protein that HIV needs to enter human cells and make more copies of itself. The study will help find the best amount or dose of dolutegravir for infants, children and teenagers, when it is taken on its own as well as with other antiretroviral medications. This study will also find out the safety of using this medication in infants, children and adolescents and if there are any side effects from the medication. Dolutegravir has been tested before in adults and children. The study drug (dolutegravir) is approved for use in children 12 years and older by the FDA [and/or local regulatory authorities].

WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE IS IN THIS STUDY?
If you decide to (allow your child to) enroll in this study, you / your child will be asked to come to the clinic at least 10 times over 48 weeks and then every 12 weeks until the end of the study. You / your child will be given dolutegravir and you / your child will be asked to take it once or twice a day for the entire study, in addition to your / your child's regular HIV medicines. Dolutegravir is available in three different formulations: 1) a film-coated tablet that cannot be crushed or dissolved**,** 2) a liquid suspension and 3) a tablet that can be dissolved in water. You will be given instructions on how to give dolutegravir to your child. If your child is between 6 to less than 12 years of age and was prescribed the liquid or dissolvable tablet tablets of dolutegravir he/she may be allowed to switch to the film-coated tablet formulation, at a later time. The study staff will let you know when your child can switch, if you request to do so.

Although the study will provide you/your child with dolutegravir, other antiretrovirals will not be provided by the study.

This study will be done in two parts – Stage One and Stage Two. Stage One will enable the doctors to find the right dose of study drug for you/your child and then will keep you on that dose to look for any side effects that you/your child might experience. In Stage Two the doctors will know the right dose to put you/your child on and will look at any side effects that you / your child might experience as well as how well the drug is controlling your HIV infection. You/your child will be enrolled into Stage One or Stage Two, depending on when you enroll /your child enrolls and your age / the age of your child. This consent form is for Stage Two.

In this study there are 7 cohorts in Stage II – enrolling infants, children, and adolescents from 4 weeks to less than 18 years of age. Participants who have had their 18th birthday by the entry visit will not be enrolled into the study.

Screening:
If you are interested in taking part / allowing your child to enroll in this study, we will see if you are / your child is eligible for the study:

- We will ask your / your child's medical history including questions about your /your child's health and what symptoms, medications, and illnesses you have/your child has had.

- We will do a physical exam including height, weight and vital signs (temperature, blood pressure, pulse and respiratory rate). Doses may be modified based on the results of the weight.

- We will take about 3 teaspoons (11mLs) of blood, to check for the following:
    - The amount of HIV in the blood,
    - The amount of cholesterol and triglycerides (types of fat) in the blood,
    - How well your immune system, liver and kidneys are working,
    - Other routine tests.

You will be given the results of these tests. We will also ask you to provide a urine sample for routine tests. Girls and women of childbearing age will also be asked to provide a urine or blood sample to test for pregnancy. If you are / your child is engaged in sexual activity that could lead to pregnancy, you / your child will be asked to take birth control precautions throughout the study period.

On Study:
If you are/your child is eligible for this study, you/your child will come to the clinic at least 8 times in 48 weeks. Most of the visits will last about 1-2 hours. You/your child will come to the clinic for the first study visit within 30 days of the screening visit.

- At each visit, a medical history will be taken and you/your child will have a physical exam. If you are/your child is older than 2 years of age, at the enrollment visit and at the week 48 visit, you/your child's stage of sexual development will be determined. For girls/women, this will be done by looking at how developed the breasts are. For boys/men, this will be done by measuring

the size of the testes. Girls and women of childbearing age will also be asked to provide a urine or blood sample to test for pregnancy at each visit.

- We will draw blood at each visit. Depending upon your/your child's age, between 1-5 teaspoons (5-17mLs) of blood will be drawn at these visits. You will be informed of results of routine blood tests. Some of the blood drawn will be stored and tested to find out how your/your child's immune system is affected by the study drug. This testing will be done after the study is over, and you will not be given the results of these tests.
- A palatability assessment will be done at Day 10, Week 4 and Week 24 to assess what you/your child thinks about the taste of the study drug**.**
- At two visits (week 4 and week 24), blood samples will be drawn two separate times. At week 12, you will only have one blood draw. The amount of blood drawn at the different study visits will be less than 1 teaspoon (0.5-1mL) depending on your /your child's age.
- If the amount of HIV virus in your/your child's blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood. If the level of HIV virus in your blood is still too high, your study doctor may ask you to stop taking the study medicine and to come back to the clinic for another visit. As part of this visit, you/your child will have an interim medical history, physical exam and approximately 4 teaspoons of blood (14-17mL) will be drawn for testing and storage.
- If you/your child experiences a severe liver reaction or inflammation while on the study, you/your child may be asked to come back to clinic to have less than one teaspoon of blood (2mL) drawn to check the level of dolutegravir in the blood. Additional testing as part of routine assessments for liver inflammation (e.g. checking for viruses that cause liver inflammation) may be performed as well.

Long Term Follow-Up
After you have been on study drug for approximately 48 weeks, you will enter the long term follow-up phase of the study. You will be asked to come back into clinic every 12 weeks (every 3 months) for 3 more years. Most visits will last about 30 minutes.

- At some visits, a medical history will be taken and you/your child will have a physical exam. You will also be asked if you have missed taking any of your medications.
- We will draw less than 1 teaspoon of blood (3-4mL) at some visits. You will be informed of results of routine blood tests.
- As before, if the amount of HIV virus in your/your child's blood increases too much while on this study drug, you/your child may be asked to come back to clinic to have your blood drawn to confirm the level of HIV in your blood (see above).

You/your child must continue to take your/his/her anti-HIV medications during the study as prescribed by your/your child's HIV care provider. If your/your child's HIV care provider changes your/your child's anti-HIV medications during the study, you/your child can still take the study drug. You/your child will be asked questions about taking your/his/her anti-HIV medications and the schedule you take/he/she takes them on and if you have/he/she has missed any medications.

If you/your child can become pregnant, we will collect urine or blood to test for pregnancy at each visit. We will also ask your child about contraception use. If you think you/if your child thinks she may be pregnant at any time during the study, tell the study staff right away.

Blood and Urine Samples
Some of your / your child's blood and urine samples will be shipped out of the country to the US for specialized tests. These tests will tell the doctors how much study drug is in your / your child's blood and if the study drug is causing any changes in your kidneys.

[For Participants Receiving Granules for suspension only]

[If your child is receiving the (granule) liquid he/she will need to switch to the dissolvable tablet. The study staff will inform you when your child will need to switch. This is because the company will not be making the liquid form of dolutegravir any longer. The study staff will provide instructions on how to dispense the dissolvable tablet and on the day you are scheduled to come to the clinic to begin taking the dissolvable tablets you will be asked to not give the (granule)liquid dose to your child. The first dose of the dissolvable tablet will be given in the clinic. You will be asked to come back to the clinic about 2 weeks later and will have a palatability assessment and blood drawn to confirm the level of HIV in your child's blood. If you have been on the study for more than 24 weeks at each of these visits, blood samples will be drawn at two separate times. The amount of blood drawn will be less than 1 teaspoon (0.5-1mL) depending on your /your child's age.]

<u>WHAT DO I / DOES MY CHILD HAVE TO DO IF I AM / HE / SHE BECOMES INFECTED WITH TUBERCULOSIS WHILE ON THIS STUDY?</u>
If you become/your child becomes exposed to Tuberculosis (TB) while on study and requires anti-TB treatment that includes Rifampin you/your child will have to increase the dose of dolutegravir from once a day to twice a day while taking Rifampin. After you/your child complete(s) treatment with Rifampin, you/your child may go back to taking the dolutegravir once a day, depending on what other medications you/your child is taking.

You/your child will also be required to return for at least five additional follow-up visits after starting Rifampin.

- At each of these visits, a medical history will be taken and you/your child will have a physical exam and we will draw approximately 1-3 teaspoons of blood to look at the following:
    - The amount of HIV, cholesterol and triglycerides (types of fat) in your blood
    - How well your immune system, liver and kidneys are working, as well as other routine tests
- At each visit you will be asked whether you are taking your medication as instructed.
- You/your child will be asked to come to the clinic to have blood drawn 8 times over 12 hours during one visit, approximately 5-10 days after you/ your child started taking anti-TB medication. For this visit, you/your child will be asked to fast for 6 hours before your daily dose of study medication.
- The study staff will give you more instructions about this. Depending on your/your child's age, up to 13mL (a little more than 4 teaspoons) of blood will be drawn at this visit.

- You will have extra blood draws at two visits. At weeks 4 and 12, you will have two blood draws – blood will be drawn once before you take dolutegravir and about 12 hours later. The amount of blood drawn at the different study visits will be less than 1 teaspoon (1mL).

OTHER INFORMATION
The information collected in this study may be used for other IMPAACT-approved HIV-related research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 300 children and adolescents will take part in this study

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
By signing this consent form, you are agreeing to / allow your child to participate in Stage II of the study. You/your child will stay in the study for at least 48 weeks. After that time After that time you/your child will enter the long-term safety follow-up phase of the study. During this time, you / your child will continue to take study-provided dolutegravir and will be asked to come to clinic every 12 weeks for three more years.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THE STUDY DRUG / THIS STUDY EARLY?

The study doctor may need to take you/your child off the study drug early, without your permission, if:

- Continuing the study drug may be harmful to you / your child
- You become / your child becomes pregnant while on study

The study doctor may need to take you/your child off the study early, without your permission, if:

- You are/ your child is not able to attend the study visits as required by the study
- You need / your child needs a treatment that you / your child may not take while on the study
- You are / your child is not able to take the study drug as required by the study
- If you elect not to attend repeat PK evaluations as part of the study

The study doctor may need to take you/your child off the study early, without your permission, if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), other country specific governmental agencies, IMPAACT, the drug company supporting this study (GSK), or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB or EC is a committee that watches over the safety and rights of research participants

If your doctor wants you / your child to stop taking the study drug, you/your child will be asked to return to the clinic once more, four weeks after your last dose of dolutegravir, to make sure you are/your child is continuing to do well. This visit will include a history and physical exam, a blood draw and a review of your medical records.

IF MY CHILD HAS TO PERMANENTLY STOP TAKING STUDY-PROVIDED MEDICINE, OR ONCE I LEAVE THE STUDY, HOW WOULD THE STUDY MEDICINE BE PROVIDED?

During the study:
If you / your child must permanently stop taking study-provided dolutegravir before your/your child's study participation is over, the study staff will discuss other options that may be of benefit to you/your child.

After the study:
Once you / your child leaves the study, if you/they are gaining benefit from the study-provided drug, this drug may continue to be provided until it is available to you in your country, but there is no guarantee. Study clinicians will work to ensure that you/your child continue to receive appropriate care and treatment outside of the study.

WHAT ARE THE RISKS OF THE STUDY?
The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this drug. These lists include the more serious or common side effects with a known or possible relationship. It is very important that you tell your study doctor of any changes in your/your child's medical condition while taking part in the study. At any time during the study, if you believe you are/your child is experiencing any of these side effects, you have the right to ask questions on possible and /or known risks.

Possible Risks Associated with Dolutegravir

DTG has been administered to a total of 6004 participants (4814 HIV-infected and 1190 healthy) cumulative to 16 July 2017 in ongoing and completed ViiV sponsored and clinical trials ranging from Phase I to IIIb and the DTG compassionate use program.

The following side effects have been seen with dolutegravir:

Very Common (expected in about 100 of every 1000 people taking DTG (10%))
Nausea or feeling sick (mild to moderate)
Headache (mild to moderate)
Diarrhea or loose stools

Common (expected in about 10 of every 1000 people taking DTG (1%))
Cold symptoms like runny nose and sore throat; cough; flu
Dizziness or feeling light headed
Trouble sleeping; abnormal dreams
Rash
Feeling tired
High temperature
Pain in the stomach; vomiting
Changes in kidney, liver and muscle blood tests
Ocular icterus (yellowing of the whites of the eyes)
Itching (pruritus)
Feelings of deep sadness and unworthiness (depression)
Flatulence (gas or wind)
Increase in the level of liver enzymes
Increase in the level of enzymes produced in the muscles (creatinine phosphokinase)
Anxiety (fear, worry)

Uncommon (expected in about 1 of every 1000 people taking DTG (0.1%))
Allergic reaction (see below) Liver toxicity (see below) An inflammatory condition which may develop as the immune system becomes stronger (immune reconstitution syndrome or 'IRIS' (see below) Suicidal thoughts and behaviors (mainly in patients who have had depression or mental health problems before) (see below)

Most of the side effects listed above have been mild or moderate, and have not generally stopped HIV-infected patients treated with dolutegravir from getting on with their lives as normal.

In one animal study, gastric erosion (irritation of the stomach lining) was seen. This finding has not been seen in adults in studies to date. However, if you or your child feels heartburn or stomach pain or has vomiting, please contact your/your child's study doctor.

Other side effects that may show up in blood or urine tests:

- An increase in bilirubin (a pigment from the breakdown of red blood cells) in the blood.
- An increase in the level of creatinine, a waste product in the blood that gets filtered by the kidney

Dolutegravir Hypersensitivity Reaction
Hypersensitivity reactions have also been reported with integrase inhibitors, including dolutegravir, with signs and symptoms including general feeling of being sick, skin rash, a high temperature (fever), lack of energy (fatigue), swelling sometimes of the face or mouth (angioedema) causing difficulty in breathing, blisters or peeling skin, mouth ulcers, conjunctivitis (sore eyes), and muscle or joint aches. If you/your child develop(s) any of these signs and symptoms during the study, contact you/your child's study doctor immediately, who may decide to carry out tests on your/your child's liver, kidneys or blood.

Mental illness
Some people with HIV infection occasionally have feelings of depression or may have thoughts of hurting or killing themselves (committing suicide). A small number of people being treated with integrase inhibitors for HIV infection, including dolutegravir, have had suicidal thoughts and behaviors, particularly patients with a prior history of depression or mental health illness. People with HIV and taking integrase inhibitors including dolutegravir have also reported depression.

Tell the study doctor if you/your child have a history of mental illness. If you/your child have thoughts of hurting or killing yourself or have any other unusual or distressing thoughts or feelings at any time during the study, you/your child should tell the study staff or go to the nearest hospital immediately.

Use of Combination Antiretroviral Drugs

Immune Reconstitution Syndrome: In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs, and arms
- Breast enlargement

Some patients taking combination anti-HIV therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination anti-HIV therapy, corticosteroid use, drinking alcohol, severe reduction in ability to fight off infection, higher body weight, among others, may be risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you/your child notice any of these symptoms, please inform your doctor.

Liver Toxicity

Liver toxicity in the form of abnormal liver enzymes, inflammation of the liver (hepatitis) and liver failure have occurred in HIV-infected patients receiving regimens containing dolutegravir. The liver toxicity usually occurs in the first few weeks or months of taking anti-HIV medications. These patients were also generally either taking other medications (both HIV treatment and non-HIV treatment) that are also known to cause significant liver inflammation and/or allergic reaction, or already had liver problems (such as hepatitis B or hepatitis C), or drank too much alcohol or had a combination of these. Cases of liver toxicity have also occurred in patients who do not have these risk factors.

If you/your child has an unanticipated need for hepatitis C virus (HCV) therapy during the conduct of the study, the study doctor will discuss specific HCV treatment options with you. In case you/your child experience liver toxicity, the study doctor can decide to stop the administration of the study drug in order to assure your/your child's safety.

Other Risks

There is the risk of serious and/or life threatening side effects when non-study medications are taken with the study drug. For your/your child's safety, you must tell your/your child's HIV care provider and the study doctor or nurse about all medications you take/your child takes before the start of this study and also before starting any new medications while you are/your child is on the study. In addition, you must tell the study doctor or nurse before you enroll/enrolling your child in any other clinical trials while on this study.

The use of potent antiretroviral drug combinations may also be associated with altered fat metabolism including elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol.

Other side effects besides those listed and side effects from taking these drugs together may occur. If any unusual symptoms or changes happen, you should call your/your child's doctor immediately. It is also important that while participating in the study, you do not/your child does not take any other prescription drugs or over-the-counter medications without first talking to your/your child's doctor or study nurse. With any drug for HIV, there is a risk that the virus in your body will become resistant, which means that the drug will be less effective or not effective against your HIV. The risk that taking part in this study will cause your HIV to develop resistance to the study drug is unknown and will depend on how well the study drug works against your virus and whether instructions are followed for taking the study drug.

Blood Drawing and Heparin Lock Risks:

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the needle enters the body or there may be swelling in the

area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm fetuses. Tests in pregnant animals do not show risk. Early results from a large study in Botswana of pregnant women showed a possible increased risk of certain types of serious birth defects involving the brain, and spinal cord in babies born to women who received dolutegravir for HIV treatment at the time of becoming pregnant. No cases of babies born with these types of birth defects have been reported among women who started dolutegravir later in pregnancy.

If you are/your child is having sex that could lead to pregnancy, you/your child must agree not to become pregnant or make a female pregnant.

Because of the risk involved, you and your partner, or your child and their partner, must use two methods of birth control that you discuss with the study staff. You must continue to use both methods until two weeks after stopping the study drug. Options for birth control methods include these listed below:

- Birth control drugs that prevent pregnancy given by pills, shots, placed on the skin (e.g. patch) or placed under the skin
- Male or female condoms with or without a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

Some of these are better than others in preventing pregnancy. You/your child will work with study staff to pick the options best for you. All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

If you think you/your child may be pregnant at any time during the study, tell the study staff right away. The study staff will talk to you about your/your child's choices. You/your child will be tested at each visit during the study if it is possible that you/she may be pregnant. If you are /your child becomes pregnant while on study, you/she will not be allowed to continue on the study drug but will be asked to remain on study and come in for study visits as planned in case of safety concerns and so that the doctors can follow your/her pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you / your child take(s) part in this study, the amount of HIV in your / your child's body may go down and your/your child's immune system may become stronger, but no guarantee can be made. You/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to you/your child
- Treatment with other experimental drugs, if you/your child qualify(ies)
- No treatment (NOT Recommended)

Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

(For U.S. sites only)

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your/your child's records include the U.S. Food and Drug Administration and other U.S., local, and international regulatory entities, the Office of Human Research Protections (OHRP), the site IRB /EC (insert name of site IRB/EC), the National Institutes of Health, study staff, study monitors, drug companies supporting the study, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(For sites outside the U.S.)

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name of identify you personally.

Your records may be reviewed by the Ministry of Public Health in your country, the FDA and other US, local, and international regulatory entities, the Office of Human Research Protections (OHRP), the NIH, (insert name of site) IRB/EC, study staff, study monitors and the drug companies supporting this study.

WHAT ARE THE COSTS TO ME / MY CHILD?

There are no costs to you/your child for the study drug, study visits or study procedures. However, taking part in this study may lead to added costs to you and your insurance company if medical complications arise or if your doctor decides extra tests are needed. In some cases it is possible that your insurance company will not pay for these costs because you/ your child are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

WHAT HAPPENS IF I AM / MY CHILD IS INJURED?

If you are / your child is injured as a result of being in this study, you / your child will be given immediate treatment for your/his/her injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your/your child's legal rights by signing this consent form.

WHAT ARE MY / MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

(For legal guardians, as applicable)
If your child reaches the legal age of consent during the study [he/she] will be asked to provide independent consent at their next visit.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your/your child's/baby's rights as a research participant, contact:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date
_____	_____
Second Guardian (print) (If required)	Second Guardian's Signature and Date

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

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

Phase I/II, Multi-Center, Open-Label Pharmacokinetic, Safety, Tolerability and Antiviral Activity of dolutegravir, a Novel Integrase Inhibitor, in Combination Regimens in HIV-1 Infected Infants, Children and Adolescents

P1093 Version 5.0, dated 12 July 2018

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

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

(For legal guardians, as applicable)
If your child reaches the legal age of consent during the study [he/she] will be asked to provide independent consent at their next visit.

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

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

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

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

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

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

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

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

4. There is little risk to you/your child.

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

There may be some risks from tests of you/your child's genes. If others found out the results of these tests, they could treat you badly or unfairly. However, this is almost impossible because the results of these tests will not be in you/your child's study records and they will not be given to you.

5. There may be no benefit to you/your child.

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

6. You will not be paid for use of your/your child's samples.

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

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

These groups include:

- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other local, US, and international regulatory entities

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

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

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

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

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

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

[sites insert name and telephone number of IRB contact person or other appropriate person/organization].

9. Signatures

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

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

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

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

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