IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

IND#: 141,131
DAIDS Study ID #38504

This file contains the current IMPAACT 2019 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #2, dated 14 August 2020
- Clarification Memorandum #1, dated 11 June 2020
- Protocol Version 2.0, dated 4 September 2019

Clarification Memorandum #2 for:

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, dated 4 September 2019

DAIDS Study ID #38504
IND #141,131

Clarification Memorandum Date: 14 August 2020

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Summary of Clarifications

This Clarification Memorandum (CM) is being issued to safeguard the health and well-being of IMPAACT 2019 study participants in the context of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease 2019 (COVID-19).

As the study Sponsor, the Division of AIDS (DAIDS) has determined that this CM should be implemented immediately upon issuance. Consistent with United States Food and Drug Administration guidance, institutional review board/ethics committee (IRB/EC) approval of this CM is not required by the Division of AIDS prior to implementation. However, given the context of COVID-19 and the importance of the guidance provided in this CM, sites should submit this CM to IRBs/ECs for their information or, if required by the IRBs/ECs, for their review and approval.

The purpose of this CM is to provide operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug and to prioritize the conduct of clinically and scientifically important evaluations. The CM also updates the Protocol Team Roster.

Please file this CM and any applicable IRB/EC correspondence in your essential document files for IMPAACT 2019.

Implementation

This CM provides operational guidance to study sites from the IMPAACT 2019 Protocol Team. This guidance is provided in a new protocol appendix, Appendix VII, as shown in Section A. This guidance to be followed at sites experiencing operational disruptions due to COVID-19. Sites should continue to follow protocol specifications for communication with the Protocol Team and/or Clinical Management Committee (CMC) and should contact the CMC (impaact.2019cmc@fstrf.org) with any questions or concerns regarding this CM or the management of study participants.

This CM also updates the Protocol Team Roster, as shown in Section B.

A. Addition of Protocol Appendix VII

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

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

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the IMPAACT 2019 Protocol Team. Should a determination be made in the future that the guidance provided in this appendix is no longer applicable, sites will be formally notified and instructed to inform their IRBs/ECs and other applicable regulatory entities.

Visit Scheduling

- Sites are advised that potential participants who are screened for the study should only be enrolled if the site investigator has confidence that local conditions will allow for, at a minimum, the Week 1 and Week 4 Visits to be conducted in-person at the study site. For participants who will be undergoing intensive PK evaluations at the Week 1 Visit, the site investigator should also have confidence that directly observed dosing can be performed and that intensive PK samples can be collected, processed, and shipped consistent with protocol Section 6 and relevant sections of the study-specific Manual of Procedures and Laboratory Processing Chart. In the absence of such confidence, screening and enrollment should not proceed.
- Sites are advised to make use of the allowable visit windows specified in protocol Section 6 when scheduling study visits during periods of operational disruption. For example, sites that are able to anticipate operational disruptions are advised to conduct study visits early in the allowable visit window before the disruption occurs. Visits conducted outside of allowable windows are also preferred to missed visits. In the event of a missed visit (i.e., visit not conducted before the allowable window closes) or in situations of overlapping windows, the CMC should be contacted for guidance on visit completion on a case-by-case basis.
- When visits must be delayed or missed, sites should make every effort to avoid gaps in study drug supply (see further guidance for study drug supply below).

Prioritization of Study Visit Procedures

- If it is not possible to conduct study visits in-person at the study site, visit procedures may be performed off-site or remotely (e.g., by telephone) as described below. Site investigators must ensure that standard operating procedures (SOPs) are in place for off-site and remote procedures. These SOPs must include feasible options for measurement of participant weight to guide weight-based prescribing and dosing of study drug.
- Sites may conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, site staff should communicate with participant families to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Off-site visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site investigator, with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the site investigator as needed.
- As indicated under Visit Scheduling, it is generally expected that Week 1 and Week 4 Visits will be conducted in-person at the study site. For subsequent visits, sites with limited capacity to conduct in-person visits should perform safety evaluations to the extent possible and should prioritize laboratory evaluations consistent with protocol Section 6.20.1. If laboratory tests cannot be performed consistent with a site's Protocol Analyte List, the tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing). Sites should identify feasible options for performing pregnancy testing for female participants of reproductive potential, including use of home test kits. When necessary:
  - Medical and medication histories may be obtained remotely.
  - Adherence assessment, counseling, and support may be performed remotely.
  - Contraception counseling may be performed remotely. Sites should discuss options for and assist with ongoing access to contraception throughout the duration of study participation.
  - Questionnaires may be administered remotely or may be skipped.

Study Drug Supply

- Sites are advised to maintain frequent communication with participant families (e.g., by telephone) to inquire about each participant's health, use of study drug, and study drug supplies.
- Study visits are scheduled at Week 1 and Week 4 and then approximately quarterly, with additional visits for selected participants. To avoid gaps in study drug supply, sites are encouraged to dispense study drug in quantities sufficient for at least three months; quantities sufficient for up to six months should be considered at the Week 24 Visit. As noted above, SOPs must be in place to guide weight-based dosing of study drug; when dose adjustments are needed due to participant growth, site investigators must provide appropriate instructions to caregivers and actively follow-up to ensure correct understanding and implementation of these instructions.
- Sites are encouraged to implement study drug dispensing and delivery options involving outdoor pick-up or drop-off. Sites are also advised that, when other options are not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants. This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Guidelines* for additional details on this method.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT 2019.
- Documentation should be entered in participant study charts in real-time (or close to real-time) if any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network has developed and disseminated guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures due to COVID-19. Please contact the IMPAACT Operations Center Clinical Trials Specialists with any questions related to documentation and reporting requirements.

B. Protocol Team Roster Updates

To reflect current Protocol Team membership, Rohan Hazra, Rajendra Singh, and Dale Dayton are removed from the roster (deletions not shown) and the persons listed below are added; Dwight Yin, Sai Majji, and Jack Moye are also added to the protocol cover page.

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Clarification Memorandum #1 for:

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, dated 4 September 2019

DAIDS Study ID #38504
IND #141,131

Clarification Memo Date: 11 June 2020

Summary of Clarifications

This Clarification Memorandum (CM) clarifies the types of tests that may be used for confirmation of HIV-1 infection in participants who are less than two years of age or have been exposed to breast milk in the past 28 days.

Implementation

Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the study sponsor prior to implementation; however, sites may submit it to IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation. The information included in this memorandum will be incorporated into the next protocol amendment.

Inclusion criterion 4.1.7 specifies the tests that may be performed to confirm HIV-1 infection prior to enrollment in the study. For participants who are less than two years of age, or who have been exposed to breast milk in the past 28 days, nucleic acid tests must be used for this purpose. These tests are indicated with an asterisk (*****) in the protocol text shown below; added protocol text is shown using bold type.

In protocol Section 4.1, Inclusion Criteria

4.1.7 Confirmed HIV-1-infection based on documented testing of two samples collected at different time points:

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

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

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

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

For participants who are less than two years of age, or who are two years of age and older with any exposure to breast milk in the past 28 days, HIV-1 infection must be confirmed using the tests indicated above with an asterisk (*) for Sample #1 and Sample #2.

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

IMPAACT 2019

Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

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

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

Study Drug Provided by:
ViiV Healthcare Ltd

DAIDS Study ID #38504
IND #141,131 Held By DAIDS

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Final Version 2.0
4 September 2019

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

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DAIDS Study ID #38504

Version 2.0
Protocol Signature Page

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

_____ _____

Signature of Investigator of Record Date

_____

Name of Investigator of Record
(printed)

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AE	Adverse event
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 to 24 hours
C_{24h}	Concentration at 24 hours post-dose
CBC	Complete blood count
CFR	Code of Federal Regulations
CRF	Case report form
C_{max}	Maximum concentration
DAIDS	Division of AIDS
DAERS	DAIDS Adverse Event Reporting System
DBS	Dried blood spot
DTG	Dolutegravir
EC	Ethics committee
eCRF	Electronic case report form
FDA	United States Food and Drug Administration
HIV	Human Immunodeficiency Virus
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IRB	Institutional review board
INSTI	Integrase strand inhibitor
LPC	Laboratory processing chart
MOP	Manual of procedures
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
PID	Participant identification number
PIP	Paediatric Investigative Plan
PBMC	Peripheral blood mononuclear cell
PSP	Pediatric Study Plan
RBC	Red blood cell
SES	Subject Enrollment System
SOP	Standard operating procedure
US	United States

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IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

SCHEMA

Purpose: To assess the pharmacokinetics (PK), safety, and tolerability of fixed dose combination abacavir (ABC)/ dolutegravir (DTG)/ lamivudine (3TC) in HIV-1-infected children

Design: Phase I/II, multi-site, open-label, multiple dose, non-comparative study

Study Population: HIV-1-infected children less than 12 years of age

Sample Size: Up to 75 to achieve at least five dose-evaluable participants in each weight band and at least 50 participants overall (at least 25 less than six years of age and at least 25 six to less than 12 years of age)

Study Drug: Dispersible tablets containing 60 mg ABC, 5 mg DTG, and 30 mg 3TC and immediate release tablets containing 600 mg ABC, 50 mg DTG, and 300 mg 3TC, administered for at least 48 weeks and up to 144 weeks in weight bands as follows:

Weight Band		Formulation (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	3 dispersible tablets (180/15/90 mg)
#2	10 to less than 14 kg	4 dispersible tablets (240/20/120 mg)
#3	14 to less than 20 kg	5 dispersible tablets (300/25/150 mg)
#4	20 to less than 25 kg	6 dispersible tablets (360/30/180 mg)
#5	25 kg or greater	1 immediate release tablet (600/50/300 mg)

Study Duration: Up to approximately 48 months total. Accrual is expected to require approximately 12 months; enrolled children will be followed for at least 48 and up to 144 weeks.

Primary Objectives

- To determine the steady-state $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} of ABC, DTG, and 3TC and confirm the dosing of ABC/DTG/3TC dispersible and immediate release tablets that achieves protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age
- To evaluate the safety profile of 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

Secondary Objectives

- To determine the PK of ABC, DTG, and 3TC, and the clinical covariates that influence PK disposition, among children less than 12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with ABC/DTG/3TC dispersible and immediate release tablets
- To evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To evaluate virologic and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To evaluate changes in lipid profiles at 24 and 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To evaluate adherence to and palatability and acceptability of ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age at 4, 24 and 48 weeks of treatment
- To evaluate HIV-1 genotypes and phenotypes among children less than 12 years of age who experience virologic failure while receiving treatment with ABC/DTG/3TC dispersible tablets or ABC/DTG/3TC immediate release tablets

Exploratory Objectives

- To describe central nervous system effects, including sleep and behavioral changes, that may occur over 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To describe pharmacogenetic associations among children less than 12 years of age receiving treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets
- To determine concentrations of phosphorylated ABC and 3TC anabolites in PBMCs and DBS over 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To examine relationships between PK-based adherence measures and other adherence measures

1 INTRODUCTION

1.1 Background

Three drug therapy consisting of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) is the standard of care worldwide for the treatment of HIV-1 infection across the age spectrum (1-3). Many factors including patient age, co-morbidities, antiretroviral (ARV) safety, dosing recommendation, drug-drug interactions, prior ARV exposure and viral resistance are considered when selecting a HIV-1 treatment regimen. INSTIs block the integrase enzyme, and in so doing prevent the integration of viral genome into the host cell. Raltegravir was the first INSTI approved in the United States (US) in 2007. Since then, three additional INSTIs — elvitegravir (EVG; approved by the US Food and Drug Administration (FDA) in 2012), dolutegravir (DTG; approved by the FDA in 2014), and bictegravir (BIC; approved by the FDA in 2018) — have been marketed. Based on their potency, safety profile and lack of drug-drug interactions, INSTIs are currently recommended as part of preferred or alternative regimens for adults, children, and infants (from birth). DTG can be administered once daily without boosting and has a higher genetic barrier to resistance than RAL and EVG (4). The availability of a once daily immediate release tablet containing DTG, abacavir (ABC) and lamivudine (3TC) has resulted in increasing popularity of the regimen.

DTG is currently available in three formulations: a single agent film-coated tablet containing 10 mg, 25 mg, or 50 mg marketed in the US and European Union as Tivicay®; a fixed dose combination immediate release tablet containing DTG (50 mg), ABC (600 mg), and 3TC (300 mg) marketed as Triumeq®, and a fixed dose combination tablet containing DTG (50 mg) and rilpivirine (25 mg) marketed as Juluca®. A 5 mg dispersible tablet is currently being evaluated for pediatric use in other studies. This study, IMPAACT 2019, will evaluate two fixed dose combination formulations of DTG, ABC, and 3TC for pediatric use, a dispersible tablet formulation and the immediate release tablet formulation marketed as Triumeq®. The objectives and design of this study correspond with ViiV Healthcare Ltd's currently agreed Paediatric Investigation Plan (PIP; dated 23 June 2017) and Pediatric Study Plan (PSP; dated 9 November 2017).

1.2 Prior Research

1.2.1 Efficacy and Safety of DTG in Adults

Three large clinical trials support the efficacy and safety of DTG in HIV-1 infected adults. The design and key findings of these trials are summarized in Table 1. In all three trials, DTG was well-tolerated; the most common adverse events involved headache, fatigue, and insomnia, all of which were reported in less than 3% of participants.

Table 1. Adult Clinical Trials of DTG Film-Coated Tablets

	SPRING-2[5]	SINGLE[6,7]	FLAMINGO[8-10]
DTG-Based Regimen	DTG 50 mg once daily + (ABC/3TC or TDF/FTC)	DTG 50 mg once daily + ABC/3TC	DTG 50 mg once daily + (ABC/3TC or TDF/FTC)
Comparator ARV Regimen	RAL 400 mg twice daily + (ABC/3TC or TDF/FTC)	EFV 600 mg + TDF/FTC once daily	DRV/r 800/100 once daily + (ABC/3TC or TDF/FTC)
Sample Size	822	833	484
Duration	96 weeks	144 weeks	96 weeks
Key Findings	DTG non-inferior to RAL	DTG regimen superior to EFV regimen at 48 and 144 weeks. Time to viral suppression shorter and discontinuation of regimen for toxicity less frequent with DTG regimen.	DTG non-inferior to DRV/r at 48 weeks and superior at 96 weeks

ABC = abacavir, ARV = antiretroviral, DC = discontinuation, DRV/r – darunavir boosted with ritonavir, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, RAL = raltegravir, TDF = tenofovir disoproxil fumarate, 3TC = lamivudine

1.2.2 PK and Safety of DTG in Pediatric Populations

IMPAACT P1093 (NCT01302847) is a Phase I/II, multi-center, open-label study of the pharmacokinetics (PK), safety, tolerability, and antiviral activity of DTG in combination regimens among HIV-1 infected infants, children, and adolescents. In Stage I of this study, a dose of DTG is studied among ten children with intensive PK and four weeks of safety data. If exposures and safety data are acceptable, Stage II enrollment begins and additional participants are evaluated over 48 weeks of follow-up. The study's PK targets are specified to achieve a concentration-time profile similar to that observed in adults at the approved dose of 50 mg daily.

Data from IMPAACT P1093 have led to FDA-approved dosing with DTG film-coated tablets for children weighing at least 30 kg (35 mg or 50 mg once daily based on weight). Doses of 20 mg, 25 mg, and 35 mg daily have been approved by the European Medicines Agency (EMA) for children at least six years of age weighing at least 15 kg (based on age and weight) (5). Pediatric friendly dosing options for younger children who are unable to swallow film-coated tablets — granules for suspension and dispersible tablets — have also been evaluated in IMPAACT P1093. PK data currently available from IMPAACT P1093 for all three formulations are presented in Table 2. The granule formulation has been phased out of development, with regulatory approval planned to be sought for the dispersible tablet formulation.

In addition to IMPAACT P1093, PENTA's ODYSSEY study (NCT02259127) is also evaluating DTG-based ART in children. This study includes two groups of children, those ART-naïve and those in need of second line ART. Participants are randomized to initiate or switch to a regimen containing DTG tablets or to receive standard of care ART with a boosted PI, an NNRTI, or another INSTI. The study also includes two PK sub-studies of DTG film coated tablets for weight bands from 14 kg to less than 40 kg. WB-PK1 is examining the PK of DTG in children weighing 3 kg to less than 25 kg according to WHO weight bands. WB-PK2 is a crossover study examining the PK of DTG in children weighing 25 kg to less than 40 kg switching to the 50 mg film-coated tablet (6). Available results are summarized in Table 2.

Table 2. DTG Pharmacokinetics by Age or Weight and Formulation in IMPAACT P1093 and ODYSSEY

Cohort	n	Formulation	Age or Weight	Dose (mg/kg)	C_{max} (µg/mL)	C_{24h} (µg/mL)	AUC_{0-24h} (µg*hr/mL)
IMPAACT P1093							
I	10	Film Coated Tablet	≥12 to <18 yrs	0.88 [0.55, 1.09]	3.49 [38]	0.902 [59]	45.97 [43]
IIA	11	Film Coated Tablet	≥6 to <12 yrs	1.09 [0.93, 1.25]	3.96 [50]	0.926 [89]	50.46 [64]
IIB	11	Granules		0.93 [0.78, 1.06]	4.95 [30]	0.643 [77]	53.62 [47]
III	10	Granules	≥2 to <6 yrs	0.84 [0.58, 1.06]	4.41 [32]	0.507 [55]	44.68 [37]
III-DT	10	Dispersible Tablet		1.07 [0.80, 1.55]	3.94 [31]	0.461 [59]	40.49 [36]
IV	7	Granules	≥6 mos to <2 yrs	1.35 [1.02, 1.56]	4.99 [33]	0.567 [48]	53.47 [36]
IV-DT	10	Dispersible Tablet		1.21 [1.02, 1.40]	4.40 [27]	0.711 [60]	50.52 [38]
V-DT	10	Dispersible Tablet	≥4 wks to <6 mos	1.17 [0.88, 1.68]	4.46 [38]	1.207 [55]	61.20 [44]
ODYSSEY							
WB-PK1	14	Film Coated Tablet	20 to <25 kg	1.1 [1.0, 1.2]	3.20 [40]	0.32 [94]	30.1 [41]
WB-PK1	8	Dispersible Tablet	20 to <25 kg	1.4 [1.3, 1.5]	7.42 [25]	0.71 [74]	71.8 [28]
WB-PK1	7	Film Coated Tablet	20 to <25 kg	2.2 [2.0, 2.4]	6.07 [29]	0.77 [51]	62.8 [30]
WB-PK2	9	Film Coated Tablet	30 to <40 kg	1.1 [0.9, 1.2]	3.98 [28]	0.45 [63]	40.3 [35]
	10	Film Coated Tablet	30 to <40 kg	1.5 [1.3, 1.7]	5.22 [25]	0.63 [49]	53.5 [32]
	17	Film Coated Tablet	25 to <30 kg	0.9 [0.8, 1.0]	3.16 [24]	0.38 [48]	33.1 [23]
	16	Film Coated Tablet	25 to <30 kg	1.8 [1.6, 2.0]	5.41 [25]	0.75 [42]	58.7 [27]

PK parameters are presented as Geometric mean [%CV];
Dose is presented as Geometric mean [min, max]

Based on adult data, the initial dose of the granules studied in IMPAACT P1093 for children two to less than six years was approximately 0.8 mg/kg. The C_{24h} was below the target (0.51 µg/mL with target minimum of 0.77 µg/mL) but above the pharmacodynamic threshold of approximately 0.3 µg/mL reported in adults (7). In bioavailability studies of the granules for suspension in adults, plasma DTG exposure exceeded that of the tablet formulation by 55-83% regardless of the type of fluid suspended in or administration directly into the mouth (8).

ODYSSEY also identified challenges with achieving target trough concentrations in children, resulting in additional studies to assess the use of 50 mg adult dose in children weighing at least 25 kg. A recent PK sub-study in children weighing 20 to less than 25 kg demonstrated similar AUC and trough concentrations with both DTG 30 mg dispersible tablets and DTG 50 mg film-coated tablets (6). Exposures for both formulations were within the range of exposures measured in adults receiving DTG 50 mg once or twice daily. Trough concentrations were also comparable to historical data in adults and were markedly higher than trough concentrations with the 25 mg film-coated tablets in children weighing 20 to less than 25 kg. However, peak concentrations in children with the 50 mg film-coated tablet were ~12-82% higher than those measured in adults on DTG 50 mg once or twice daily. In children receiving 30 mg dispersible tablets, peak concentrations were 37-122% higher than historical data. Children in both groups were followed for a median of 12-13 weeks, and no drug discontinuations or serious adverse events occurred during this period.

The PK of a dispersible tablet formulation, developed as an alternative to the granule for suspension formulation, has also been evaluated in an adult study. The DTG dispersible tablet showed equivalent exposures compared to the granule formulation following oral administration in adults, indicating these two formulations are interchangeable (9).

An additional relative bioavailability study in adults compared single doses of the immediate release ABC/DTG/3TC (Triumeq®) formulation with the dispersible tablet formulation as a dispersion or directly to mouth, and to dispersible DTG with 3TC alone using a four-period crossover design. DTG exposures with the dispersible ABC/DTG/3TC tablet were 65% higher when dispersed in water compared to the immediate release ABC/DTG/3TC tablet. When dispersible ABC/DTG/3TC tablets were administered direct-to-mouth, DTG exposures were 25% higher compared to the immediate release ABC/DTG/3TC tablet. ABC and 3TC exposures were bioequivalent to the immediate release ABC/DTG/3TC tablet whether administered as a dispersion or direct-to-mouth (10).

1.2.3 DTG in Pregnancy

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 were taking DTG at the time of conception (11-13). This analysis included data collected between 15 August 2014 and 1 May 2018. Among women taking DTG at conception, the prevalence of NTDs was 0.94% (95% CI 0.37%, 2.4%) compared to 0.12% (95% CI 0.07%, 0.21%) among women taking a non-DTG-containing regimen. This signal had not been seen in other post marketing surveillance (14). The Tsepamo study was expanded from eight to eighteen sites in 2018, and additional results were reported in July 2019 (15, 16). From August 2014 through March 2019, surveillance captured 119,477 deliveries. The prevalence of NTD among women taking DTG at conception (0.30%, 95% CI 0.13%, 0.69%) remained higher than among women taking a non-DTG-containing regimen at conception (0.10%, 95% CI 0.06%, 0.17%). Although the prevalence of NTDs appears to be slightly higher among women taking DTG at conception, the WHO has noted that the absolute risk is very low and has re-confirmed

their recommendation for use of DTG-containing regimens as preferred for first- and second-line ART across all populations, including pregnant women (17). Ongoing surveillance will continue to inform these recommendations.

1.2.4 ABC/3TC in Pediatric Populations

ABC and 3TC form the backbone of several recommended ART regimens. These medications are available separately in tablet and liquid formulations and have also been co-formulated in fixed dose combination tablets (ABC/3TC). Currently, ABC and 3TC are approved for use in children, ABC from three months of age and 3TC from birth. ABC and 3TC were initially approved for pediatric use in 1997 and 1998, respectively, for twice-daily dosing. Support for once-daily dosing in this population originated from multiple PK and efficacy studies, primarily PENTA 13 (18), PENTA 15 (19), and ARROW (20, 21). PENTA 13 examined the PK of once-daily ABC/3TC in children 2-12 years of age, and PENTA 15 examined the PK in children 3 to less than 36 months of age. ARROW found bioequivalent AUCs between once-daily and twice-daily dosing in addition to determining that once-daily dosing was non-inferior to twice-daily dosing with regard to virologic suppression and grade 3 and grade 4 adverse events (20).

Efficacy and PK of ABC/3TC

ABC is administered at doses of 16 mg/kg/day (maximum dose of 600 mg/day), and 3TC is dosed at 8 mg/kg/day (maximum dose of 300 mg/day) per the FDA-approved dosing nomograms for these agents. The WHO weight bands fall in line with this dosing schema, and are expected to yield mean AUC_{24} exposures of ~7.9-13.6 µg·h/mL for 3TC, and ~13.8-19.4 µg·h/mL for ABC in patients <35 kg based on population PK modeling simulations (see Table 3). Peak absorption of ABC occurs 0.6-2.5 hours after oral administration, and between ~1-2 hours with 3TC. The plasma half-lives of ABC and 3TC in children are relatively short, at ~1.2 and ~1.5-2 hours, respectively. The active moieties of these agents, carbovir-triphosphate and lamivudine-triphosphate, have longer half-lives of ~14.1 and 17.7 hours, respectively, in PBMCs (22).

Exposure-response analyses with ABC suggest a weak relationship between the PK parameters of AUC_{24} and C_{tau} and virologic response in HIV-infected adults (23, 24). Carbovir-triphosphate, the active ABC moiety, also does not show a relationship between intracellular PBMC levels and plasma exposures to the parent drug, though differences in intracellular levels were detected between males and females (22). ABC 50% maximal effect (EC_{50}) values against HIV-1 clades A-G range from 0.00042 to 0.29 µg/mL (25), with a reported mean of 0.07 µg/mL against clinical isolates (26).

Dose-response data for 3TC in pediatrics primarily originated from a study that examined doses of 1-20 mg/kg/day divided twice daily for 24 weeks (27). Optimal virologic responses were seen at doses above 4 mg/kg/day, though other studies pointed to a concern of pancreatitis at higher doses. Collectively, studies in pediatric and adult patients led to doses of ~8 mg/kg/day being identified as an optimal target that balanced both therapeutic efficacy and possible safety concerns with this agent. Exposure-response data with 3TC have not been published to date. However, intracellular levels of lamivudine-triphosphate in PBMCs have been shown to correlate with its anti-HIV activity (28). Relationships between antiviral activity and plasma levels of 3TC in its parent form were not seen. EC_{50} values reported for 3TC range between 0.0007 and 0.021 µg/mL (29).

Table 3. Predicted Once-Daily ABC and 3TC Exposures in Children Using WHO Dosing Nomogram

Weight Band	Daily Dose (mg/kg)	AUC_{0-24h} (·µg•h/mL)	C_{max} (µg/mL)	C_{24h} (µg/mL)
ABC				
<14kg[a]	16.4 (15.8-17.3)	13.8[a] (5.3, 34.2)	5.0 (2.1, 11.3)	0.03 (0.001, 0.22)
14- <20kg	17.9 (15.3-21.2)	16.9 (6.3, 42.1)	6.6 (2.8, 14.8)	0.021 (NQ, 0.18)
20- <25kg	20.3 (18.0-22.5)	19.9 (7.5, 49.9)	7.9 (3.3, 7.9)	0.02 (NQ, 0.13)
25- <35kg	18.5 (11.1-23.7)	19.3 (7.1, 50.4)	7.9 (3.2, 18.5)	0.01 (NQ, 0.13)
Adult	600 mg	9.3 (4.6, 14.8)	4.3 (2.1, 6.0)	NQ (NQ, 0.03)
3TC				
<14kg[a]	8.5 (7.8-9.3)	7.9 (4.5, 14.6)	1.8 (0.9, 3.4)	0.05 (0.02, 0.13)
14- <20kg	9.0 (7.6-10.6)	11.6 (6.3, 21.9)	2.8 (1.4, 5.4)	0.05 (0.02, 0.14)
20- <25kg	10.1 (9.0-11.2)	13.8 (7.3, 26.2)	3.4 (1.7, 6.4)	0.05 (0.02, 0.14)
25- <35kg	9.3 (5.6-11.8)	13.6 (7.0, 26.5)	3.4 (1.6, 6.7)	0.05 (0.02, 0.14)
Adult	300 mg	8.4 (7.0, 11.7)	2.0 (1.3, 3.0)	0.04 (0.03, 0.07)

Table adapted from Clinical Pharmacology Review for Ziagen® (abacavir sulfate) and Epivir® (lamivudine) to support once-daily dosing in pediatric populations. Daily dose reported as median (range), PK parameters reported as median (90% CI).
[a]Levels with oral solution.
NQ=not quantifiable.

Safety of ABC/3TC

The most common side effects reported with ABC include nausea, vomiting, diarrhea, headache, fever, and rash. Nausea may be an exposure-related effect, particularly AUC and C_{max}, based on previous dose-finding studies in adults (23, 24). No relationships with other commonly reported side effects in these studies were found. Rare but potentially fatal hypersensitivity reactions can occur and are associated with the presence of the HLA-B*5701 allele. Other rare but serious side effects of ABC include elevated liver transaminases, hyperglycemia, hypertriglyceridemia, lactic acidosis, severe hepatomegaly with steatosis, and pancreatitis.

Common side effects of 3TC include headache, nausea, diarrhea, and insomnia. Less common but more severe side effects include peripheral neuropathy, lipodystrophy, and elevated liver transaminases. Decreases in neutrophil counts by ~30% from baseline were observed in adults at doses of 20 mg/kg/day (mean ± SD AUC_{24h} 29.1 ± 9.1 µg·h/mL) (30). Pancreatitis was also reported in pediatric patients in 3TC dose-finding studies, though this finding was also attributed to advanced HIV disease and the presence of opportunistic infections associated with an increased risk of developing this condition (27).

Available data from the APR show no difference in the overall risk of birth defects for ABC or 3TC compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program reference population (29).

1.3 Rationale

1.3.1 Overall Rationale

To date, DTG has only been studied as a single ARV formulation in children. ABC/DTG/3TC (immediate release tablet marketed as Triumeq®) is a safe, effective, and well-tolerated "one pill, once daily" regimen approved by the FDA and EMA for use in adults and children weighing at least 40 kg (the EMA approval for pediatric use is limited to children at least 12 years of age). DTG has rapidly become a "preferred" agent for initial treatment of HIV in adults, and more recently, children and adolescents six years of age and older. Much of the safety, PK and dose-finding evaluation for DTG in children was completed in the ongoing IMPAACT P1093 and ODYSSEY studies. Internationally, the WHO supports harmonization of ARV regimens across populations including using the same regimen of ARVs in adult and pediatric populations. As more experience with INSTIs become available, it is presumed that this drug class will be identified as the candidate for a universal regimen for adults, pregnant women and children. To facilitate this goal, the safety and PK of dispersible tablet ABC/DTG/3TC in young children must be defined.

This Phase I/II study will investigate the PK, safety and tolerability of ABC/DTG/3TC in HIV-infected children less than 12 years of age. Given that DTG has demonstrated excellent virologic activity in P1093 and has an increasing role as initial ARV therapy in adults and older children, this study will include both ART-naïve and ART-experienced children. ABC/DTG/3TC will be dosed by weight bands across the age spectrum, consistent with the intended future marketing of the product. Age-based quotas have been specified to help ensure that adequate PK, safety, and tolerability data are collected among children less than six years of age as well as children six years of age and older.

Previous experience in adults has demonstrated that the exposure to DTG, ABC and 3TC in a fixed dose combination formulation is consistent with each drug administered individually. This information was provided as part of the application for Triumeq®. Therefore, the DTG dosing recommendations from IMPAACT P1093 are not expected to differ when DTG is administered in a fixed dose combination. Nonetheless, a subset of children in each weight band will undergo intensive PK approximately one week after initiating ABC/DTG/3TC to evaluate for similar exposure to DTG. Population PK will be evaluated among all study participants.

1.3.2 Rationale for Initial Dose Selection

The DTG doses selected for evaluation in this study are expected to achieve DTG exposures similar to those observed with DTG 50 mg twice-daily in adults. The DTG doses are higher than those previously evaluated but consistent with doses currently being studied in IMPAACT P1093. The higher expected exposures of DTG are due to the coformulation of DTG, ABC, and 3TC in a single tablet; whereas the doses of 3TC and ABC increase in sync to each other with body weight, the increase is not the same for DTG. Safety data available from adults with higher DTG doses and exposures support the DTG doses selected for evaluation in this study (31-33).

The DTG doses selected for evaluation in this study are specified within weight bands and are expected to be applicable to children less than 12 years of age who weigh at least 6 kg. However, as of the date of this protocol, limited data are available on DTG dosing for children less than six months of age. Additional data from the IMPAACT P1093 and ODYSSEY studies are expected to become available for this age group in the near future. When these data become available, the IMPAACT 2019 Protocol Team will review them to determine whether the dosing specified for this study is appropriate for children less than six months of age. Until this review is conducted, accrual into this study will be restricted to children six months of age and older. Once this review is conducted, if the Protocol Team determines that the dosing specified for this study is appropriate for children less than six months of age, the restriction on accrual will be lifted. If the Protocol Team determines that the dosing is not appropriate for children less than six months of age, the restriction on accrual will be maintained while alternative dosing and/or other protocol modifications are developed for children less than six months of age. Study sites will be notified of the outcome of the team's review and decision-making via email.

The doses of ABC/3TC proposed for use in this study are consistent with WHO recommended doses of ~16 mg/kg for ABC and ~8 mg/kg for 3TC in children. Exposures from these doses are expected to achieve AUCs similar to those measured in ARROW, PENTA13, and PENTA15, which examined the PK and efficacy of once-daily ABC/3TC in pediatric patients. A relative bioavailability study is planned to provide reassurance of similar exposures of ABC/3TC with use of the dispersible fixed dose combination tablet compared with the marketed immediate release fixed dose combination tablet.

1.3.3 Rationale for PK Targets

A minimum of five children in each weight band will undergo intensive PK sampling with real time testing and review of intensive PK outcomes for ABC, DTG, and 3TC to confirm appropriate dose selection for each weight band. Dose confirmation for each weight band will be based on PK ($AUC_{0\text{-}24h}$ for ABC, DTG, and 3TC, in addition to C_{24h} for DTG) and safety outcomes. Dose confirmation based on all three agents reflects ViiV's currently agreed PIP and PSP.

As indicated in Table 4 and Table 5, the goal is to achieve the following:

- Geometric mean DTG $AUC_{0\text{-}24h}$ between 35.1 and 134 μg·h/mL
- Geometric mean DTG C_{24h} between 0.67 and 2.97 μg/mL
- Geometric mean ABC $AUC_{0\text{-}24h}$ between 6.3 and 50.4 μg·h/mL
- Geometric mean 3TC $AUC_{0\text{-}24h}$ between 6.3 and 26.5 μg·h/mL

Table 4. Weight Band and Individual $AUC_{0\text{-}24h}$ and C_{24h} Targets Based on Adult Exposure Data

PK Parameter	DTG Values in Adults[a]		Weight Band Targets		Individual Targets	
	Once-daily DTG	Twice-daily DTG	Lower Bound	Upper Bound	Lower Bound[b]	Upper Bound
$AUC_{0\text{-}24h}$ (μg·h/mL)	53.6 (26.9%)	75.1 (35.1%)	35.1[c]	134[d]	25.0	134[d]
C_{24h} (μg/mL)	1.11 (46%)	2.12 (47%)	0.67[e]	2.97[f]	0.5	—

[a]Geometric mean (CV%) value reported in adults [b]Estimated $AUC_{0\text{-}24h}$ and C_{24h} values to produce EC_{95} [c]Lower 90% CI bound for once-daily DTG exposures in adults [d]Upper 90% CI bound for twice-daily DTG exposures in adults [e]Targets based on 60% of once-daily DTG exposures in adults [f]Targets based on 140% of twice-daily DTG exposures in adults

Table 5. Weight Band $AUC_{0\text{-}24h}$ Targets Based on Pediatric Exposure Data

ARV Agent	ARROW PK results (n=35)[a]	Predicted $AUC_{0\text{-}24h}$ Values by Weight Band[b]			Weight Band Targets[c]	
		14 to <20 kg	20 to <25 kg	≥25 kg	Lower Bound	Upper Bound
ABC	15.3 (42%)	16.9 (6.3, 42.1)	19.9 (7.5, 49.9)	19.3 (7.1, 50.4)	6.3	50.4
3TC	13.0 (38%)	11.6 (6.3, 21.9)	13.8 (7.3, 26.2)	13.6 (7.0, 26.5)	6.3	26.5

[a]Mean (CV%) values measured in children enrolled in ARROW [b]Median (90% CI) predicted values based on population PK modeling of ARROW, PENTA13, PENTA15, and other single-dose PK studies in children [c]Minimum lower and maximum upper 90% CI bounds for predicted once-daily exposures in children

The DTG targets are similar to current targets for IMPAACT P1093. These targets will continue to be evaluated and updated if needed based on new findings from P1093. The weight band target $AUC_{0\text{-}24h}$ target range for DTG is based on the lower and upper bounds of the 90% CIs for once- and twice-daily DTG dosing in adults, respectively. The weight band target C_{24h} target range for DTG is based on 60% of once-daily geometric mean exposures and 140% of twice-daily geometric mean exposures in adults. The ABC and 3TC $AUC_{0\text{-}24h}$ targets are based on the minimum lower and maximum upper bounds of the 90% CIs for predicted exposures with once-daily ABC/3TC weight band dosing with the tablet formulation in children (summarized Table 3). If the geometric mean $AUC_{0\text{-}24h}$ for ABC, DTG, or 3TC and/or C_{24h} for DTG among the dose-evaluable (refer to Section 3.2) children in each weight band falls outside of the targeted range, the Protocol Team will re-evaluate the dose for that weight band using all available PK data from this study in addition to PK results from previous and ongoing studies of ABC, DTG, and 3TC. Individual dose adjustments may also be performed if a child's DTG $AUC_{0\text{-}24h}$ or C_{24h} falls outside of the individual target ranges outlined in Table 5. If a child requires an individual dose adjustment, a repeat PK assessment may be performed for that child, with an appropriate sampling strategy determined by the Protocol Pharmacologists.

1.3.4 Rationale for Deferred Enrollment of Children Switching from an NNRTI-Containing Regimen

Children switching to the study drug regimen from an NNRTI-containing regimen (particularly a regimen containing etravirine, efavirenz, or nevirapine) will not be included in the intensive PK sampling as they may have decreased DTG exposure subsequent to enzymatic induction by these agents. These children, however, will have additional sparse sampling to better understand the PK of DTG when switching from an NNRTI-containing regimen. A sub-study in adult patients switched from efavirenz or nevirapine to DTG with rilpivirine (SWORD 1 and 2) examined trough levels at Weeks 2, 4, 8, 24, and 48 following the switch, and revealed that DTG trough concentrations were similar to levels in patients not on an NNRTI regimen by Week 4 (34). No dose adjustments to DTG were made following the transition from efavirenz or nevirapine to DTG with rilpivirine, and trough levels remained above the DTG IC_{90} at all time points examined.

Note: Under certain pre-specified conditions, and in consultation with the Study Monitoring Committee (SMC), the Protocol Team may consider expanding intensive PK sampling to children switching to the study drug regimen from an NNRTI-containing regimen; refer to Section 9.5.1 for more information regarding this potential option.

1.3.5 Rationale for Exploratory Evaluations

In addition to plasma PK evaluations, this study will characterize phosphorylated 3TC and ABC moieties in PBMCs and dried blood spots (DBS). The active moieties of ABC and 3TC are found intracellularly and have been shown to correlate with ARV activity in previous studies (28). Thus, examining intracellular levels of carbovir-triphosphate and lamivudine-triphosphate in PBMCs may provide additional insight into exposure-response relationships at the site of action with these agents.

DBS will be collected to characterize drug levels in this matrix and compare levels to self-reported adherence. This approach has been studied with tenofovir disoproxil fumarate, tenofovir alafenamide, and emtricitabine, for which concentrations of the phosphorylated moieties can serve as measures of long- and short-term adherence to ARV therapy, respectively (35-37). Tenofovir-diphosphate concentrations increase proportionally with the number of doses taken per week, and thus this measure has been integrated as a surrogate measure of adherence and treatment outcomes in several HIV pre-exposure prophylaxis (PrEP) (25, 38-40) and treatment (41, 42) studies. This same approach could be applied with the phosphorylated moieties of ABC and 3TC.

Pharmacogenetic analyses will focus on single nucleotide polymorphisms (SNPs) in genes that encode drug transporters and metabolizing enzymes involved in the PK disposition of ABC, DTG, and 3TC. The primary focus for initial pharmacogenetic analyses will focus on SNPs that influence the PK of DTG, such as UGT1A1 (rs8175317), for which individuals with low and reduced activity (presence of *28 and/or *37 alleles) exhibit slower clearance and higher DTG exposure (43).

1.3.6 Rationale for Adherence Evaluations

A variety of methods will be used to evaluate adherence to daily administration of ABC/DTG/3TC in this study. For all children, questionnaires will be administered at time points designated in the Schedule of Evaluations. In addition, for children undergoing intensive PK sampling, more objective methods of assessing adherence such as texted video, video streaming, and in-person directly observed therapy will be used to confirm daily dosing between enrollment and the day of intensive PK sampling. Data obtained through these methods will assist with determining whether failure to reach PK targets is due to challenges with adherence or administration versus actual PK differences in the pediatric study population. Relationships between PK-based adherence measures and other adherence measures will be explored, which may provide useful insights into selection of adherence measures to be used in future pediatric studies.

1.4 Hypotheses

The hypotheses of this study are:

- Selected doses of ABC/DTG/3TC dispersible and immediate release tablets will achieve protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age

- ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets will be described as safe for treatment in children less than 12 years of age

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

2.1.1 Determine the steady-state $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} of ABC, DTG, and 3TC and confirm the dosing of ABC/DTG/3TC dispersible and immediate release tablets that achieves protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age

2.1.2 Evaluate the safety profile of 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 Determine the PK of ABC, DTG, and 3TC, and clinical covariates that influence PK disposition, among children less than 12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with ABC/DTG/3TC dispersible and immediate release tablets

2.2.2 Evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.2.3 Evaluate virologic and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.2.4 Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.2.5 Evaluate adherence to and palatability and acceptability of ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age at 4, 24 and 48 weeks of treatment

2.2.6 Evaluate HIV-1 genotypes and phenotypes among children less than 12 years of age who experience virologic failure while receiving treatment with ABC/DTG/3TC dispersible tablets or ABC/DTG/3TC immediate release tablets

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

2.3.1 Describe central nervous system effects, including sleep and behavioral changes, that may occur over 24 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.3.2 Describe pharmacogenetic associations among children less than 12 years of age receiving treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets

2.3.3 Determine concentrations of phosphorylated ABC and 3TC anabolites in PBMCs and DBS over 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age

2.3.4 Examine relationships between PK-based adherence measures and other adherence measures

3 STUDY DESIGN

3.1 Overview

This is a Phase I/II, multi-site, open-label, multiple dose, non-comparative PK and safety study of ABC/DTG/3TC dispersible tablets and immediate release tablets in ART-naïve and ART-experienced HIV-1-infected children less than 12 years of age.

The study will be conducted among at least 50 and up to 75 children. Refer to Section 4 for the study eligibility criteria and a description of the study recruitment, screening, and enrollment process. Children are expected to be enrolled at study sites in Botswana, South Africa, Thailand, and the US.

At least 25 children will be less than six years of age and at least 25 will be six to less than 12 years of age. Children will be enrolled in weight bands and will receive study drug as shown in Table 6. Two alternative dispersion volumes for preparation of dispersible tablets will be considered, as described in Sections 5.2.1 and 9.6.2.

Accrual into all weight bands will occur concurrently, and the age-based quotas will apply across weight bands. Accrual into the study overall will continue until study drug dosing has been confirmed for each weight band and the age-based quotas have been met. There is no pre-specified maximum number of children who may be enrolled in each weight band; the Protocol Team will closely monitor accrual into each weight band and may pause and subsequently close or resume accrual into individual weight bands in an effort to assure balance across the weight bands (as described further in Sections 9.4.1 and 9.5.1).

Table 6. IMPAACT 2019 Weight Band Dosing of Study Drug

Weight Band		Study Drug Formulation (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	3 dispersible tablets (180/15/90 mg)
#2	10 to less than 14 kg	4 dispersible tablets (240/20/120 mg)
#3	14 to less than 20 kg	5 dispersible tablets (300/25/150 mg)
#4	20 to less than 25 kg	6 dispersible tablets (360/30/180 mg)
#5	25 kg or greater	1 immediate release tablet (600/50/300 mg)

At the outset of study implementation, accrual into weight band #1 will be restricted to children six months (180 days) of age and older (see Section 1.3.2). Once the Protocol Team has confirmed that data are available to support the specified weight band dosing for children less than six months of age, this restriction will be lifted. If the Protocol Team determines that the specified dosing is not appropriate for children less than six months of age, the restriction on accrual will be maintained while alternative dosing and/or other protocol modifications are developed for children less than six months of age.

ART-naive children will initiate treatment with the study drug regimen, ABC/DTG/3TC, at enrollment. ART-experienced children will switch from their pre-study ART regimen to ABC/DTG/3TC at enrollment. For all children, the first dose of study drug is expected to be taken on the day of enrollment or the day after enrollment.

Use of ABC/DTG/3TC and evaluations to assess safety, adherence, tolerability (i.e., palatability and acceptability), virologic and immunologic response, and lipid profiles will continue through 48 weeks of follow-up. Specimen collection for PK evaluations will also continue through 48 weeks of follow-up. Scheduled follow-up is generally expected to be completed at the Week 48 Visit, but may be continued for up to an additional 96 weeks for children who are deriving benefit from ABC/DTG/3TC but do not otherwise have access to ABC/DTG/3TC from a non-study source (see also Sections 6.13 and 13.11). For these children once ABC/DTG/3TC becomes available from a non-study source, study participation will be discontinued with transition into local standard HIV care and treatment. For children who are not deriving benefit from ABC/DTG/3TC, or who are deriving benefit and have access to ABC/DTG/3TC from a non-study source, the transition into local standard HIV care and treatment will occur upon completion of the Week 48 Visit.

Refer to Sections 5, 9, and 10, respectively for more detailed information on study drug considerations, data analysis and statistical considerations, and pharmacology considerations,

3.2 Approach to Dose Confirmation

Accrual will begin with enrollment of children who will undergo intensive PK sampling approximately one week after initiating ABC/DTG/3TC and will continue while intensive PK evaluations are performed and the appropriateness of each weight band dose is determined. Accrual will continue (i.e., will not be paused) while intensive PK evaluations are performed

because there is no evidence to suggest that PK, safety, or efficacy activity will differ when ABC, DTG, and 3TC are administered as a fixed dose combination rather than as individual agents.

A minimum of five **dose-evaluable** children will be enrolled in each weight band. The term dose-evaluable is used in this protocol to refer to children who will be included in the dose confirmation analyses described in Section 9.5.1. To be considered dose-evaluable, children must be both safety-evaluable and PK-evaluable for the study drug dose being evaluated for their weight band. Safety-evaluable and PK-evaluable are defined as follows:

- **Safety-evaluable:** To be considered safety-evaluable, children must have exclusively received the study drug dose being evaluated for their weight band between study Entry and the Week 4 Visit or have experienced a grade 3 or higher adverse event that is assessed as related to study drug or an adverse event assessed as related to study drug that results in permanent discontinuation of study drug prior through the Week 4 Visit.

- **PK-evaluable:** To be considered PK-evaluable, children must have exclusively received the study drug dose being evaluated for their weight band, administered as described in Section 5.2, between study Entry and the day of intensive PK sampling. Children must have an observed dose on the day of intensive PK sampling; blood samples collected; and ABC, DTG, and 3TC concentration data available from all intensive PK sampling time points specified in Section 6.3. Profiles with missing samples will be assessed for evaluability by the Protocol Team on a case-by-case basis. Every effort should be made to collect all time points of interest. If the Protocol Team determines that intensive PK sampling was performed incorrectly or that results seem inaccurate, participants may be asked to repeat the sampling within 5-10 days after receipt of the team's recommendation to repeat the sampling. In this case, the child must continue to exclusively receive the study drug dose being evaluated for their weight band until the day of repeat intensive PK sampling.

The first five children enrolled in each weight band will undergo intensive PK sampling; the sixth and seventh children enrolled in each weight band may also undergo intensive PK sampling as described below. Intensive PK samples will be tested in real time and the number of safety-evaluable, PK-evaluable, and dose-evaluable children enrolled in each weight band will be closely monitored by the Protocol Team. The Protocol Team will provide frequent updates to study sites as enrollment proceeds.

If the first five children enrolled in a given weight band have been confirmed as dose-evaluable before additional children are enrolled in that weight band, intensive PK sampling will not be performed among the sixth and seventh children enrolled in that weight band. Alternatively, if the first five children enrolled in a given weight band have not (yet) been confirmed as dose-evaluable before the sixth and seventh children are enrolled in that weight band, intensive PK sampling will be performed among the sixth and seventh children enrolled. If fewer than five of the first seven children enrolled in each weight band are determined to be dose-evaluable, additional children (beyond the first seven) will be enrolled and undergo intensive PK sampling to achieve five dose-evaluable in that weight band. Additional children may also be enrolled and undergo intensive PK sampling if, in the opinion of the Protocol Pharmacologists, a confident determination regarding achievement of PK targets cannot be made based on the first 5-7 dose-evaluable children in a given weight band.

Guidelines for determining the appropriateness of the weight band doses are provided in Section 9.5.1. Safety-related guidelines are based on the occurrence of adverse events through the Week 4 Visit. PK-related guidelines are based on DTG, ABC, and 3TC exposures. Because prior use of NNRTIs may affect observed concentrations of DTG (as described in Section 1.3.4), and thereby affect variability and interpretation of PK outcomes, children who undergo intensive PK sampling will either be ART-naïve or will be switching to the study drug regimen from a non-NNRTI-containing regimen. Further requirements for administration of study drug to children undergoing intensive PK sampling are provided in Sections 5.2 and 10.3.

Note: Under certain pre-specified conditions, and in consultation with the SMC, the Protocol Team may consider expanding intensive PK sampling to children switching to the study drug regimen from an NNRTI-containing regimen; refer to Section 9.5.1 for more information regarding this potential option.

If the safety and PK guidelines are met for a given weight band, the restriction on enrollment with respect to prior NNRTI exposure will be lifted for that weight band. If these guidelines are not met, dosing for the weight band may be adjusted and additional children may be enrolled in the weight band and undergo intensive PK sampling.

4 STUDY POPULATION

This study will be conducted among at least 50 and up to 75 HIV-1-infected children who will be selected according to the criteria in Sections 4.1 and 4.2 and the guidelines in Section 4.3. At least 25 children will be less than six years of age and at least 25 will be six to less than 12 years of age. The study-specific approach to recruitment, screening, and enrollment is described in Section 4.4. Considerations related to monitoring enrollment within and across weight bands are provided in Section 9.5.1. Considerations related to participant retention and withdrawal/termination from the study are provided in Sections 4.5 and 4.6, respectively.

4.1 Inclusion Criteria

Potential participants must meet all of the following criteria to be included in this study; in these criteria, "at entry" is used to refer to the day of enrollment in the study:

4.1.1 Less than 12 years of age at entry

Note: Accrual will initially be restricted to children six months (180 days) of age and older. Once the Protocol Team has confirmed that data are available to support the specified weight band dosing for children less than six months of age, this restriction will be lifted.

4.1.2 Weight 6 kg to less than 40 kg at entry

4.1.3 ART-naïve at entry or has been taking a stable ART regimen for at least six consecutive months at entry

Note: For ART-naïve children, receipt of ARV prophylaxis prior to diagnosis of HIV infection is permitted. For these children, ascertainment of this criterion may be based on parent or guardian report only, but available medical records should also be reviewed in relation to this criterion.

Note: For ART-experienced children (on a stable ART regimen), dose and formulation changes (e.g., for growth) within the six months prior to entry are permitted. For these children, ascertainment of this criterion must be based on medical records.

4.1.4 For ART-experienced children (on a stable ART regimen), has had a suppressed HIV viral load (HIV-1 RNA less than 200 copies/mL) for at least six consecutive months prior to entry

Note: To fulfill this criterion, at least two documented HIV-1 RNA results less than 200 copies/mL must be available, one based on a specimen collected at least six months prior to entry and one based on a specimen collected within 30 days prior to entry.

Note: Any documented HIV-1 RNA result greater than or equal to 200 copies/mL based on a specimen collected within six months prior to entry is exclusionary (see exclusion criterion 4.2.2).

4.1.5 At screening, has normal, Grade 1, or Grade 2 laboratory test results for all of the following, based on testing of specimens collected within 30 days prior to entry and grading per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (refer to Section 7.3.3 for guidance on severity grading):

4.1.5.1 Hemoglobin (≥8.5 g/dL or ≥5.25 mmol/L)
4.1.5.2 Absolute neutrophil count (≥600 cells/mm^3 or ≥0.600 x 10^9 cells/L)
4.1.5.3 Platelet count (≥50,000 cells/mm^3 or ≥50.00 x 10^9 cells/L)
4.1.5.4 Estimated glomerular filtration rate (eGFR; bedside Schwartz formula; ≥60 ml/min/1.73 m^2)
4.1.5.5 ALT (<5.0 x ULN)
4.1.5.6 AST (<5.0 x ULN)
4.1.5.7 Total bilirubin (<2.6 x ULN)
4.1.5.8 Direct bilirubin (≤ULN)

Note: Laboratory tests may be repeated during the screening period (i.e., within 30 days prior to entry), with the latest results used for eligibility determination.

Note: For treatment-experienced children on an atazanavir-containing ART regimen, Grade 3 or higher total bilirubin is permitted.

4.1.6 At screening, has a negative test result for hepatitis B surface antigen based on testing of a specimen collected within 30 days prior to entry

4.1.7 Confirmed HIV-1-infection based on documented testing of two samples collected at different time points:

Sample #1 may be tested using any of the following:
- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One enzyme immunoassay OR Western Blot OR immunofluorescence assay OR chemiluminescence assay
- One HIV DNA polymerase chain reaction (PCR)
- One quantitative HIV RNA PCR (above the limit of detection of the assay)

- One qualitative HIV RNA PCR
- One HIV total nucleic acid test

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

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

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

4.1.8 HLA-B*5701-negative based on documented testing at any time prior to entry

Note: Documented testing is required even if the potential participant has received ABC prior to study entry.

4.1.9 *For females of reproductive potential (defined as having experienced menarche),* not pregnant based on testing performed at screening

4.1.10 *For females of reproductive potential who are engaging in sexual activity that could lead to pregnancy,* willing to use two methods of contraception while receiving study drug, based on participant and parent or guardian report at entry

One of the two methods must be highly effective; highly effective methods include surgical sterilization (i.e., hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy) and the following:

- Contraceptive intrauterine device or intrauterine system
- Subdermal contraceptive implant
- Progestogen injections
- Combined estrogen and progestogen oral contraceptive pills
- Percutaneous contraceptive patch
- Contraceptive vaginal ring

The highly effective method must be initiated prior to study entry. The second method should ideally be a barrier method. Male or female condom use is recommended with all other methods of contraception for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections.

4.1.11 Based on parent or guardian report at entry, child is expected to be available for 48 weeks of follow-up

4.1.12 Parent or legal guardian is willing and able to provide written informed consent for child's study participation and, when applicable per local institutional review board/ethics committee (IRB/EC) policies and procedures, child is willing and able to provide written informed assent for study participation

4.2 Exclusion Criteria

Children must be excluded from this study if any of the following are identified any time prior to study entry:

4.2.1 Documented resistance to ABC, DTG, or 3TC

Note: Testing to rule out resistance is not required, and the M184V resistance mutation is not exclusionary.

4.2.2 For ART-experienced children (on a stable ART regimen), documented HIV-1 RNA result greater than or equal to 200 copies/mL based on a specimen collected within six months prior to entry

4.2.3 History of any of the following as determined by the site investigator based on participant/parent/guardian report and available medical records:

4.2.3.1 Malignancy (ever)
4.2.3.2 Hypersensitivity reaction to ABC (ever)
4.2.3.3 Receipt of any prohibited medication (refer to Section 5.7) within 30 days prior to study entry
4.2.3.4 Receipt of systemic interferon or any chronic systemic immunosuppressant medication within 30 days prior to study entry

Note: Systemic corticosteroids (e.g., prednisone or equivalent up to 2 mg/kg) taken for replacement or short course therapy are permitted. Intranasal or inhaled steroid use is also permitted.

4.2.4 Has any of the following as determined by the site investigator based on participant/parent/guardian report and available medical records

4.2.4.1 Current clinical evidence of pancreatitis
4.2.4.2 Currently-active TB and/or currently receiving rifampicin-containing TB treatment
4.2.4.3 Currently-active AIDS-defining (WHO Clinical Stage 4) opportunistic infection

4.2.5 Has any documented or suspected clinically significant medical condition or any other condition that, in the opinion of the site investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

4.3 Co-Enrollment Considerations

Co-enrollment in other studies is not precluded, although careful consideration must be given to study visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies. Requests for such approval should be emailed to the IMPAACT 2019 Clinical Management Committee (CMC; refer to Section 7.1.2 for more information regarding the role of the CMC for this study).

4.4 Recruitment, Screening, and Enrollment Process

Participant recruitment methods for this study may vary across sites but, for treatment-experienced participants, are expected to draw from the population of HIV-infected children currently in care at participating study sites. For treatment-naïve participants, recruitment is expected to rely on active identification and referral of children newly diagnosed with HIV-infection in study site communities.

Upon identification of a potentially eligible child, study staff will provide information about the study to the child's parent or guardian. Each parent or guardian who expresses interest in learning more about the study will be provided additional information, education, and counseling as part of the study informed consent process. The process will include detailed review of the study informed consent form and time to address any questions or concerns the parent or guardian may have, and an assessment of the parent or guardian's understanding before proceeding to the informed consent decision. In addition, children who meet local IRB/EC criteria for provision of assent will undergo an age-appropriate assent process. Informed consent and assent processes will be fully documented, consistent with the Division of AIDS (DAIDS) policies referenced in Section 11.2. Refer to Section 13.3 for further information on informed consent procedures for this study.

Eligibility screening will be initiated after written informed consent, and assent if applicable, are obtained (i.e., informed consent, and assent if applicable, must be obtained before any study-specific screening procedures are performed). Screening evaluations must be performed within 30 days prior to enrollment and may be repeated during the 30-day period, with the latest outcomes used for eligibility determination. Screening evaluations may be performed on the day of enrollment (i.e., at the Entry Visit); however, all required screening outcomes must be available prior to enrollment. In the event that the 30-day screening period is exceeded, the screening process may be repeated; in this case, most but not all screening evaluations must be repeated, as specified in Section 6.1.

Each site must establish standard operating procedures (SOPs) for eligibility determination that describe where and when screening procedures will be performed; roles and responsibilities for performing the required procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing of enrollment. For treatment-naïve children, study sites should minimize the time from screening to enrollment so that initiation of study-supplied ART is not unduly delayed. Treatment-naïve children who do not meet the study eligibility criteria should be actively referred to non-study sources of HIV care and treatment to initiate non-study ART as soon as possible.

The IMPAACT Data Management Center (DMC) Subject Enrollment System (SES) will be used to assist with tracking the screening and enrollment process, within and across weight bands and age-based quotas. When informed consent is obtained, a participant identification number (PID) will be assigned to the child and a study-specific screening number will be obtained through the SES. For children found to be eligible, enrollment will occur upon successful entry of required eligibility data into the SES. Successful entry into the SES will generate a study identification number and study drug prescribing information. For children found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into electronic case report forms (eCRFs). Refer to Section 9.5 for more information on monitoring participant accrual in this study.

4.5 Participant Retention

Once a child is enrolled in this study, study staff will make every effort to retain him or her in follow-up for the protocol-specified duration of follow-up (through Week 48), thereby minimizing potential biases and loss of statistical power associated with loss-to-follow-up. Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.6 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, children may be voluntarily withdrawn from the study by their parents or guardians. Children may also be terminated from the study by the site investigator under the following circumstances:

- Child is not exposed to ABC/DTG/3TC for any reason
- Child permanently discontinues ABC/DTG/3TC (see also Sections 5.7 and 8.2; reasons for permanent discontinuation may include but are not limited to management of an adverse event and required use of a contraindicated concomitant medication)
- Child of reproductive potential who reports sexual activity that could lead to pregnancy is not willing or able to use two methods of contraception (see also Section 8.6)
- Child re-locates away from the study site (with no options for transfer to another site) or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the child, after consultation with the CMC
- After Week 48, investigator or designee determines that child is not deriving benefit from ABC/DTG/3TC or is deriving benefit and has access to ABC/DTG/3TC from a non-study source
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs

Refer to Section 8.2 for further information on procedural expectations and timelines for termination from the study due to permanent discontinuation of ABC/DTG/3TC.

For any child who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail. If the withdrawal or termination occurs before the Week 48 Visit is conducted, study staff will make every effort to complete final evaluations as described in Section 6.15. If the circumstances that led to a child's withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator should contact the CMC to discuss the possibility of resuming of follow-up based on the child's original study entry date and follow-up schedule.

5 STUDY DRUG

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations. For this study, the term study drug refers to ABC/DTG/3TC dispersible tablets, ABC/DTG/3TC (Triumeq®) immediate release tablets, and other formulations of ABC, DTG, and 3TC listed in Section 5.2. Refer to the investigator's brochures and package inserts for further information about these drugs.

5.1 Study Drug Regimen and Administration

Abacavir/dolutegravir/lamivudine tablets (60 mg/5 mg/30 mg dispersible tablets or 600 mg/50 mg/300 mg immediate release [Triumeq®] tablets) will be taken once daily, generally with or without food, at doses specified in Table 7. For children undergoing intensive PK evaluations, food intake around the time of these evaluations will be managed as described in Section 6.3. Enrolled children will receive study drug for at least 48 weeks (through the Week 48 Visit) and up to 144 weeks.

Table 7. IMPAACT 2019 Study Drug Regimen and Administration

Weight Band		Study Drug Regimen and Administration (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	3 dispersible tablets taken orally once daily with or without food (180/15/90 mg)
#2	10 to less than 14 kg	4 dispersible tablets taken orally once daily with or without food (240/20/120 mg)
#3	14 to less than 20 kg	5 dispersible tablets taken orally once daily with or without food (300/25/150 mg)
#4	20 to less than 25 kg	6 dispersible tablets taken orally once daily with or without food (360/30/180 mg)
#5	25 kg or greater	1 immediate release tablet taken orally once daily with or without food (600/50/300 mg)

Children will initiate ABC/DTG/3TC dosing based on their weight at study entry and will remain on their initial dose through Week 4. After completing the Week 4 Visit, children will undergo individual dose adjustments when indicated based on their growth and weight gain over time. For children who grow into weight band #2, #3, or #4, increased dosing with additional dispersible tablets will be initiated at the first study visit (after Week 4) when the child has grown into the next higher weight band. For children who grow into weigh band #5, increased dosing with

immediate release tablets will be initiated at the first study visit (after Week 4) when the child has grown to 25 kg or more. For children whose weight may fluctuate over time, it is generally not expected that dosing will be decreased when weight decreases. However, if a child's weight persists in a lower weight band for two consecutive scheduled study visits, dosing should be decreased consistent with the lower weight band. All dose and formulation changes will be source documented and entered into eCRFs, along with the date of each change and measured weight on the date of each change.

There are no restrictions on the time of day at which study drug can be taken. However, to facilitate the preferred timing of study drug dosing on the day of intensive PK sampling (refer to Section 6.3), the parents or guardians of children undergoing intensive PK sampling will be counseled to administer study drug in the morning between enrollment and the Week 1 Visit. Parents or guardians will also be counseled on the co-administration of common concomitant medications as described in Section 5.7.

For children who may spit out a dose of study drug or vomit within 15 minutes after taking study drug, parents or guardians will be instructed to administer a replacement dose. If vomiting occurs more than 15 minutes after taking study drug, a replacement dose should not be administered (the next scheduled dose should be taken the next day). Refer to Section 6.3 for additional information pertaining to vomiting on the day of intensive PK sampling.

Note: In addition to the triple-agent fixed dose combination formulations of study drug noted above, single agent formulations will be available for use among children who require dose adjustments that cannot be achieved with the fixed dose combination formulations; refer to Sections 5.2 and 5.3 for more information about these formulations.

5.2 Study Drug Formulation and Preparation

5.2.1 ABC/DTG/3TC Dispersible Tablets

ABC 60 mg/DTG 5 mg/3TC 30 mg pediatric dispersible tablets are pale yellow, biconvex, oval, film-coated, debossed with 'SV WTU' on one side and plain on the opposite side. Each tablet contains 70.2 mg abacavir sulfate, which is equivalent to 60 mg of abacavir free base; 5.26 mg dolutegravir sodium, which is equivalent to 5 mg of dolutegravir free acid; and 30 mg of lamivudine. The tablets are packaged in HDPE bottles with child-resistant closures that include an induction seal and a desiccant. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. In the study site pharmacy, store up to 30°C (86°F).

ABC/DTG/3TC dispersible tablets will be dispersed in water for oral administration. From study entry through the Week 4 Visit, caregivers will be instructed to disperse the appropriate number of dispersible tablets in the volume of water shown in Table 8. For children in weight band #3 or #4 who report poor palatability and/or acceptability at the Week 4 Visit, caregivers will be provided the option of dispersing the appropriate number of dispersible tablets in the volume of water shown in Table 9. As palatability and acceptability data are accumulated in the study, if the Protocol Team determines that the dispersion volumes shown in Table 8 are not sufficiently acceptable for children in weight band #3 or #4, the volumes shown in Table 9 may be recommended for all applicable participants. Further guidance on assessing palatability and acceptability and adjusting dispersion volumes is provided in the study-specific Manual of Procedures (MOP).

Table 8. Dispersion Volumes for ABC/DTG/3TC Dispersible Tablets

Weight Band		Number of Dispersible Tablets per Dose	Dispersion Volume
#1	6 to less than 10 kg	3	15 mL
#2	10 to less than 14 kg	4	20 mL
#3	14 to less than 20 kg	5	20 mL
#4	20 to less than 25 kg	6	20 mL

Table 9. Alternate Dispersion Volumes for ABC/DTG/3TC Dispersible Tablets

Weight Band		Number of Dispersible Tablets per Dose	Dispersion Volume
#1	6 to less than 10 kg	3	15 mL
#2	10 to less than 14 kg	4	20 mL
#3	14 to less than 20 kg	5	25 mL
#4	20 to less than 25 kg	6	30 mL

The tablets disperse within three minutes. Following dispersion, the suspension should be administered from the supplied dosing cup or from an oral syringe within five minutes. The dosing cup and syringe should be rinsed with an additional 15 mL of water and the rinse administered to the child. Dispersible tablets should not be chewed or swallowed whole.

5.2.2 ABC/DTG/3TC Immediate Release (Triumeq®) Tablets

ABC/DTG/3TC immediate release (Triumeq®) tablets are purple, biconvex, oval, film-coated, debossed with "572 Tri" on one side, and plain on the opposite side. Each tablet contains 702 mg abacavir sulfate, which is equivalent to 600 mg of abacavir free base; 52.62 mg dolutegravir sodium, which is equivalent to 50 mg of dolutegravir free acid; and 300 mg of lamivudine. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. In the study site pharmacy, store at 25°C (77°F) with excursions between 15° and 30°C (59° to 86°F) permitted (See USP Controlled Room Temperature). For any child who is not able to swallow whole immediate release tablets, the tablets can be crushed and mixed with a liquid or semi-solid food such as applesauce or mashed banana (44). For children undergoing intensive PK sampling; however, swallowing of whole tablets will be required from enrollment through the day of intensive PK sampling (crushing, if needed, would be permitted thereafter). Refer to Section 10.3.3 for additional information.

5.2.3 DTG Dispersible Tablets

DTG 5 mg pediatric dispersible tablets are white, round, film-coated, and debossed with 'SV H7S' on one side and '5' on the opposite side. Each tablet contains 5.26 mg dolutegravir sodium, which is equivalent to 5 mg of dolutegravir free acid. The tablets are packaged in HDPE bottles with child-resistant closures that include an induction seal and a desiccant. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. In the study site pharmacy, store up to 30°C (86°F).

DTG dispersible tablets will be dispersed in water for oral administration (5 mL for one, two, or three tablets; 10 mL for four, five, or six tablets). Following dispersion, the suspension should be administered from the supplied dosing cup or from an oral syringe within 30 minutes. The dosing cup and syringe should be rinsed with an additional 5 mL of water and the rinse administered to the child. Dispersible tablets may also be swallowed whole with water. Dispersible tablets should not be chewed.

5.2.4 DTG (Tivicay®) Tablets

DTG 50 mg (Tivicay®) tablets are yellow, biconvex, round, film-coated, and debossed with "SV 572" on one side and "50" on the other side. Each tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir. In the study site pharmacy, store at 25°C (77°F) with excursions between 15° and 30°C (59° to 86°F) permitted (See USP Controlled Room Temperature).

5.2.5 ABC (Ziagen®) Tablets

ABC 300 mg scored (Ziagen®) tablets are yellow, biconvex, scored, capsule-shaped, film-coated, and imprinted with "GX 623" on both sides. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir, In the study site pharmacy, store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).

5.2.6 3TC (EPIVIR®) Tablets

3TC 150 mg scored (EPIVIR®) tablets are white, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7" on both sides. Each tablet contains 150 mg of 3TC. Store and dispense in the original package. In the study site pharmacy, store at controlled room temperature of 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature).

5.3 Study Drug Supply

ABC 60 mg/DTG 5 mg/3TC 30 mg dispersible tablets will be supplied by ViiV Healthcare Ltd in bottles with child-resistant closure. Dosing cups will be supplied for use with dispersible tablets. Oral syringes will be provided for administering dispersed medication.

ABC 600 mg/DTG 50 mg/3TC 300 mg immediate release (Triumeq®) tablets will be supplied by ViiV Healthcare Ltd in bottles with child resistant closure.

In addition to the triple-agent fixed dose combination formulations noted above, the following will also be supplied by ViiV Healthcare Ltd for use among children who require dose adjustments that cannot be achieved with the triple-agent fixed dose combination formulations:

- DTG 5 mg dispersible tablets
- DTG 50 mg film-coated tablets
- ABC 300 mg scored tablets
- 3TC 150 mg scored tablets

All of the above-listed formulations and dosing cups will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures (refer to Section 14.2), these supplies may be obtained by the site pharmacist following instructions provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.4 Study Drug Accountability

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

5.5 Final Disposition of Study Drug

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

5.6 Study Drug Adherence Assessment and Counseling

Study staff will provide adherence counseling to enrolled participants (and/or their parents or guardians) throughout the period of study participation. Counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills building, and support needs of each participant/parent/guardian. Information on correct storage, preparation, and administration of study drugs will be provided, particularly at the time of enrollment and in the early stages of follow-up, as well as at the time of any dose, formulation, or preparation changes. Counseling will also address challenges to consistent use of study drug over time, with the aim of supporting participants (and/or their parents or guardians) in identifying strategies to address any such challenges.

For children undergoing intensive PK sampling, adherence to daily study drug dosing will ideally be confirmed on each day prior to intensive PK sampling by texted video, video streaming, in-person directly observed therapy, or other method approved by the Protocol Team; at a minimum, dosing must be confirmed using an approved method for the four days prior to intensive PK sampling. For all children, adherence will be assessed by questionnaire administered at weeks 4, 24, and 48. After study drug dosing has been confirmed for a given weight band, results of HIV viral load testing may be used as a biologic measure of adherence to guide feedback to participants/parents/ guardians and associated adherence counseling (refer to Section 8.3 for more information on virologic monitoring and management).

5.7 Concomitant Medications

The term concomitant medication is used in this study to refer to medications other than the study drugs listed in Section 5.1.

All concomitant medications received by study participants must be source documented as part of the medical and medications histories obtained at each study visit (refer to Section 0). This includes prescription and non-prescription (over-the-counter) medications, vaccines and other preventive medications, antacids, vitamins and other nutritional supplements, and alternative, complementary, and traditional medications and preparations. Except for traditional medications and preparations, all concomitant medications must be entered into eCRFs.

Due to interactions that decrease the concentration of DTG, the following should not be co-administered with ABC/DTG/3TC: etravirine, efavirenz, nevirapine, fosamprenavir/ritonavir, tipranavir/ritonavir, dofetilide, oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort. If an enrolled participant is identified as requiring a contraindicated medication, the CMC should be consulted as soon as possible and within three business days regarding options for clinical and ART regimen management. If use of a contraindicated medication cannot be avoided, permanent discontinuation of study drug, with subsequent termination from the study, may be required.

Liquid medications containing sorbitol or other sugar alcohols (e.g., mannitol, xylitol, maltitol, isomalt) should be avoided as these excipients, which are used to sweeten pediatric liquid formulations, have been shown to reduce 3TC concentrations (45). Site investigators should carefully review all liquid concomitant medications received by enrolled participants. If any such medications are not clinically indicated, they should be discontinued. Otherwise, they should be switched to a solid dosage forms when possible or to a liquid formulation that does not contain sorbitol or other sugar alcohols. Site investigators should be particularly cognizant of liquid cotrimoxazole formulations, which tend to contain high concentrations of sorbitol and are commonly used in HIV-infected children. Liquid formulation concomitant medications should not be consumed with study drug on the day of intensive PK sampling.

Study participants who require cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications should take these medications at least six hours before or at least two hours after taking ABC/DTG/3TC. Alternatively, ABC/DTG/3TC and supplements containing calcium or iron can be taken together with food.

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

6 STUDY VISITS AND PROCEDURES

An overview of the study visit and evaluation schedule is provided in Appendix I; blood draw volumes for each visit are also detailed in Appendix I. Presented in this section is additional information on visit-specific study procedures.

In addition to the protocol-specified procedures listed in this section, study staff may complete other tasks consistent with site SOPs, including but not limited to collecting, reviewing, and updating demographic and locator information; reviewing elements of informed consent and assent; scheduling visits; providing instructions for contacting study staff between visits; providing visit reminders; and following up on missed visits. When applicable, visit reminders will include details related to study drug dosing and food intake prior to the next visit. All such tasks should be documented consistent with site SOPs. Study staff should inform parents or guardians of clinically meaningful physical exam findings and laboratory test results when available.

All visits should be conducted as close as possible to specified target visit dates and within specified allowable visit windows. For visits with specified targeted windows, every effort should be made to conduct the visit within the targeted window. Unless otherwise specified, visits may be split, with required procedures performed on more than one day within the allowable visit window if necessary.

All enrolled participants are expected to complete follow-up visits at Weeks 1, 4, 12, 24, 36, and 48 on-study. With the exception of the Week 1 Visit, the allowable windows for these visits overlap by one day; the day of overlap should be prioritized, when applicable, for completion of the earlier of the two visits. For example, there is one day of overlap between the allowable windows for the Week 4 and Week 12 Visits. If a participant were to present to the study site on this day, the Week 4 Visit should be conducted on this day, if not previously conducted; otherwise, the Week 12 Visit may be conducted on this day.

In addition to the follow-up visits noted above, some enrolled participants are expected to complete visits at Weeks 2, 6, 8, 16, and/or 20. The Week 2 and Week 6 Visits are expected for children switching to the study drug regimen from an NNRTI-containing regimen. The Week 8, Week 16, and Week 20 Visits are expected for children with a known M184V resistance mutation. The allowable windows for these visits overlap with the windows for other visits noted above. Because the purpose of these visits is to perform additional evaluations at additional time points for selected participants, these visits should be conducted as close as possible to the specified target visit dates and should not be combined with other scheduled visits.

Following completion of the Week 48 Visit, children who are deriving benefit from ABC/DTG/3TC may remain on-study for up to an additional 96 weeks if ABC/DTG/3TC is not otherwise available from a non-study source. During this time, study visits are targeted to occur every 12 weeks. For each child who remains on-study beyond Week 48, once ABC/DTG/3TC becomes available from a non-study source, or if it is determined that the child is no longer deriving benefit from ABC/DTG/3TC, study participation will be discontinued, with transition into local standard HIV care and treatment.

All visits and procedures must be documented in accordance with the DAIDS policies for source documentation; refer to Section 11 for more information on documentation requirements and entry of eCRFs. Refer to Section 7 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

6.1 Screening Visit

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

Screening procedures may be performed within 30 days prior to enrollment. Multiple visits may be conducted to complete all required screening procedures if necessary. Written informed consent, and assent if applicable, must be obtained before screening procedures are performed. For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined.

Screening Visit Procedures *(within 30 days prior to enrollment)*		
Administrative and Regulatory		• Obtain written informed consent; additionally obtain written assent if applicable per IRB/EC policies and procedures • Assign PID • Obtain screening number from SES
Clinical		• Obtain available medical records and medical and medications history (refer to Section 0) • Perform complete physical examination (refer to Section 0)
Laboratory	**Blood**	Collect blood for: • Confirmatory HIV testing *(if needed per criterion 4.1.7)* • HLA-B*5701 *(if needed per criterion 4.1.8)* • Hepatitis B surface antigen • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Total cholesterol, HDL, LDL, and triglycerides (non-fasting)
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

In the event that a potential participant is initially found to be ineligible, or that the 30-day screening period is exceeded before eligibility can be determined, the screening process may be repeated. In this case, all screening procedures listed above must be repeated, except that:

- A new PID should not be assigned
- Confirmatory HIV testing need not be repeated
- HLA-B*5701 testing need not be repeated
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

6.2 Entry Visit

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

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

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

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

Enrollment Visit Procedures *(Day 0)*		
Administrative and Regulatory		• Complete final eligibility determination and confirmation* • Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant, print and file a copy of the confirmation file
Clinical		• Update medical and medications history since last visit (refer to Section 0) • Perform complete physical exam (refer to Section 0) • Administer mood and sleep questionnaire
Study Drug		• Prescribe and dispense study drug • Provide information on potential study drug side effects and provide and explain ABC hypersensitivity alert card • Provide study drug storage and use instructions and adherence counseling • *If child is expected to undergo intensive PK sampling at Week 1,* explain and schedule procedures for daily confirmation of study drug dosing and provide instructions for study drug dosing on the day of the Week 1 Visit • *If child is expected to undergo sparse PK sampling at Week 1,* provide instructions for study drug dosing on the day of the Week 1 Visit
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Stored whole blood for possible ARV resistance testing • Stored whole blood for exploratory evaluations
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test**

*Perform prior to enrollment
**Collect specimen prior to enrollment and ideally obtain test result prior to enrollment; if result cannot be obtained prior to enrollment, it must be obtained by the day after enrollment.

For children expected to undergo intensive PK sampling at the Week 1 Visit, study drug dosing will be confirmed on each day between the Entry Visit and the day of intensive PK sampling by texted video, video streaming, in-person directly observed therapy, or other method approved by the Protocol Team. The Week 1 Visit should be scheduled to occur following confirmed dosing on at least four consecutive days prior to the visit. For each day between the Entry Visit and the day of intensive PK sampling, all of the following should be source documented and entered into eCRFs:

- Whether dosing was directly observed and, if so, by what method
- Date and time of observed dose
- Formulation and preparation of observed dose
- Observer's assessment of whether the observed dose was prepared and administered correctly
- Observer's assessment of ease of administration
- Observer's assessment of child's response to administration
- Any issues or problems with administration identified by the observer

6.3 Week 1 Visit

The Week 1 Visit is targeted to take place on Day 7, counted from the date of enrollment as Day 0, with an allowable window of -2 to +3 days (i.e., the visit may take place between Day 5 and Day 10, inclusive). Sites are encouraged to schedule this visit early in the allowable window, to accommodate re-scheduling if needed (as described below). For children undergoing intensive PK sampling, the visit may be re-scheduled up to Day 14 to permit four consecutive days of confirmed dosing prior to the visit. Contact the CMC with questions related to whether and when intensive PK sampling should be re-scheduled; this may be necessary, for example, due to issues involving missed, mis-timed, spit out, or vomited study drug doses or due to non-compliance with food intake instructions.

This visit will be conducted for all enrolled children. For each child, either intensive or sparse PK sampling will be performed.

- Intensive PK sampling will be performed among the first 5-7 children enrolled in each weight band. As described in Section 3, these children will either be ART-naïve or switching to the study drug regimen from a non-NNRTI-containing regimen. If fewer than five of the first seven children enrolled in each weight band are determined to be dose-evaluable, intensive PK sampling will be conducted among additional children in order to achieve five dose-evaluable in each weight band. Additional children may also undergo intensive PK sampling if, in the opinion of the Protocol Pharmacologists, a confident determination regarding achievement of PK targets cannot be made based on the first 5-7 dose-evaluable children in a given weight band.

  Note: The Protocol Team will provide frequent updates to all study sites via email regarding the number of dose-evaluable children enrolled in each weight band and will notify all sites when intensive PK sampling should be discontinued in each weight band. In the event that the Protocol Team determines that additional intensive PK sampling is required in a given weight band, all sites will be similarly notified.

For children undergoing intensive PK sampling:

- On each day prior to the Week 1 Visit, study drug should be administered at approximately the same time, ideally in the morning. Children receiving dispersible tablets should be administered the appropriate number of tablets for their weight band following dispersion in the appropriate volume of water. Children receiving immediate release tablets should swallow the tablet whole. Study drug administration should be confirmed as described in Section 6.2.

- If for any reason administration of study drug is not confirmed on the four days preceding the scheduled Week 1 Visit, the visit should be re-scheduled to a later date within the allowable visit window, with adherence support provided to help ensure consistent study drug administration on the four days preceding the re-scheduled visit date.

- On the day of the Week 1 Visit, the child may eat a low-fat light snack (approximately 100-150 calories) at least two hours prior to study drug dosing at the study site. Within the two hours prior to study drug dosing, and the first hour after study drug dosing, only water may be consumed. Liquid formulation concomitant medications should not be administered with study drug.

  Note: If intensive PK data from this or other pediatric DTG studies indicate a food effect, and the Protocol Team determines that further data should be collected for evaluation of PK in a non-fasted state, the team will notify all study sites and provide accrual targets, guidance for food intake, and other operational instructions for evaluation of additional participants. The Schedule of Evaluations in Appendix I and the intensive PK procedures described in this section will be followed for any additional participants enrolled for this evaluation.

- On the day of the Week 1 Visit, study drug administration should be observed at the study site in relation to intensive PK sampling, as indicated below. Study drug administration should also ideally occur 22-26 hours after the previous dose.

- If the child spits out the observed dose of study drug or vomits after observed dosing, re-dosing and intensive PK sampling should be managed as follows:

  - If the child spits out the observed dose or vomits within 15 minutes after the observed dose, study drug should be re-administered and the intensive PK sampling should be re-scheduled to occur on another day within the allowable visit window.

  - If the child vomits more than 15 minutes but within four hours after the observed dose, study drug should not be re-administered (the next scheduled dose should be taken the next day) and the intensive PK sampling should be re-scheduled to occur on another day within the allowable visit window. Intensive PK samples collected before the child vomited may be used for analysis.

  - If the child vomits more than four hours after the observed dose, study drug should not be re-administered and the intensive PK sampling should proceed based on the timing of the observed dose. All intensive PK samples may be used for analysis.

Depending on site capacity and participant preferences, children undergoing intensive PK sampling and their parents or guardians may stay at the clinical research site overnight. Alternatively, they may leave the study site after the 8-hour sampling and return the next day for the 24-hour sampling. It is generally expected that a heparin or saline lock will be used to avoid multiple needle sticks for intensive PK sampling.

- Sparse PK sampling will be performed among all children not undergoing intensive PK sampling. On the day of the Week 1 Visit, study drug administration should be observed at the study site in relation to sparse PK sampling, as indicated below.

Week 1 Visit Procedures *(Day 7 -2 to +3 days)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Review documentation of observed daily study drug dosing since the Entry Visit • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • *For children undergoing intensive PK sampling:* – Record last food intake (date and time) – Observe and record timing of study drug administration in relation to intensive PK sampling • *For children undergoing sparse PK sampling:* – If ART-experienced at study entry, record whether pre-study ART regimen was NNRTI-containing and, if so, which NNRTI was included in the regimen – Record details of last food intake (full meal or light snack, high or low fat) – Record timing of last three doses of study drug – Observe and record timing of study drug administration in relation to sparse PK sampling • *If child is expected to complete a Week 2 Visit,* provide instructions for study drug dosing on the day of the Week 2 Visit
Laboratory	**Blood**	*For children undergoing intensive PK sampling,* collect blood: • Prior to observed dosing of study drug (1 mL) • 1 hour (±30 minutes) after observed dosing of study drug (1 mL) • 2 hours (±30 minutes) after observed dosing of study drug (4 mL) • 3 hours (±30 minutes) after observed dosing of study drug (1 mL) • 4 hours (±30 minutes) after observed dosing of study drug (1 mL) • 6 hours (±60 minutes) after observed dosing of study drug (1 mL) • 8 hours (-15 to +120 minutes) after observed dosing of study drug (1 mL) • 24 hours (±120 minutes) after observed dosing of study drug (1 mL) *Note:* The 2-hour sample will also be processed for storage of plasma, DBS, and PBMC.
		For children undergoing sparse PK sampling, collect blood: • Following observed dosing of study drug (4 mL) • At least two hours after collection of the first sparse sample (1 mL) *Note:* The first sample will also be processed for storage of plasma, DBS, and PBMC.
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.4 Week 2 Visit

The Week 2 Visit will be conducted only for children who switched from a pre-study NNRTI-containing ART regimen to the study drug regimen.

The main purpose of this visit is to collect an additional sparse PK sample to enrich population PK modeling for these participants, given the potential for prior NNRTI exposure to affect observed concentrations of DTG. This visit should not be combined with any other scheduled visit.

This visit is targeted to take place on Day 14, counted from the date of enrollment as Day 0, with an allowable window of -3 to +7 days (i.e., the visit may take place between Day 11 and Day 21, inclusive).

With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit. Sparse PK sampling should ideally occur 22-26 hours after the previous dose of study drug.

Week 2 Visit Procedures *(Day 14 -3 to +7 days)*		
Clinical		*Only if clinically indicated based on medical condition at the prior or current visit:* • Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.5 Week 4 Visit

The Week 4 Visit is targeted to take place on Day 28, counted from the date of enrollment as Day 0, with an allowable window of ±14 days (i.e., the visit may take place between Day 14 and Day 42, inclusive). With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 4 Visit Procedures *(Day 28 ± 14 days)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Administer mood and sleep questionnaire • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Administer adherence questionnaire • Administer tolerability (palatability and acceptability) questionnaire • *For children in weight band #3 or #4,* determine whether a change of dispersion volume is indicated (see Section 5.2.1) • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat) • *If child is expected to complete a Week 6 Visit,* provide instructions for study drug dosing on the day of the Week 6 Visit
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.6 Week 6 Visit

The Week 6 Visit will be conducted only for children who switched from a pre-study NNRTI-containing ART regimen to the study drug regimen.

The main purpose of this visit is to collect an additional sparse PK sample to enrich population PK modeling for these participants, given the potential for prior NNRTI exposure to affect observed concentrations of DTG. This visit should not be combined with any other scheduled visit.

This visit is targeted to take place on Day 42, counted from the date of enrollment as Day 0, with an allowable window of ±7 days (i.e., the visit may take place between Day 35 and Day 49, inclusive).

With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit. Sparse PK sampling should ideally occur 22-26 hours after the previous dose of study drug.

Week 6 Visit Procedures *(Day 42 ± 7 days)*		
Clinical		*Only if clinically indicated based on medical condition at the prior or current visit:* • Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.7 Week 8 Visit

The Week 8 Visit will be conducted only for children with a documented M184V mutation.

The main purpose of this visit is to perform additional HIV-1 RNA testing to permit closer virologic monitoring for these participants. This visit should not be combined with any other scheduled visit.

This visit is targeted to take place on Day 56, counted from the date of enrollment as Day 0, with an allowable window of ±7 days (i.e., the visit may take place between Day 49 and Day 63, inclusive).

With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 8 Visit Procedures *(Day 56 ± 7 days)*		
Clinical		*Only if clinically indicated based on medical condition at the prior or current visit:* • Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.8 Week 12 Visit

The Week 12 Visit is targeted to take place on Day 84, counted from the date of enrollment as Day 0, with a targeted window of ±14 days (i.e., Day 70 to Day 98, inclusive) and an allowable window of ±42 days (i.e., Day 42 to Day 126, inclusive). Every effort should be made to conduct the visit within the targeted window; however, the visit may be conducted on any day within the allowable window. With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 12 Visit Procedures *(Day 84 ± 14 days targeted and ± 42 days allowable)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Administer adherence questionnaire • Administer tolerability (palatability and acceptability questionnaire) • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.9 Week 16 and Week 20 Visits

The Week 16 and Week 20 Visits will be conducted only for children with a documented M184V mutation.

The main purpose of these visits is to perform additional HIV-1 RNA testing to permit closer virologic monitoring for these participants. These visits should not be combined with any other scheduled visits.

The Week 16 Visit is targeted to take place on Day 112, counted from the date of enrollment as Day 0, with an allowable window of ±14 days (i.e., the visit may take place between Day 98 and Day 126, inclusive).

The Week 20 Visit is targeted to take place on Day 140, counted from the date of enrollment as Day 0, with an allowable window of ±14 days (i.e., the visit may take place between Day 126 and Day 154, inclusive).

With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at these visits.

Week 16 and Week 20 Visit Procedures *(Day 112 ± 14 days and Day 140 ± 14 days)*		
Clinical		*Only if clinically indicated based on medical condition at the prior or current visit:* • Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.10 Week 24 Visit

The Week 24 Visit is targeted to take place on Day 168, counted from the date of enrollment as Day 0, with a targeted window of ±14 days (i.e., Day 154 to Day 182, inclusive) and an allowable window of ±42 days (i.e., Day 126 to Day 210, inclusive). Every effort should be made to conduct the visit within the targeted window; however, the visit may be conducted on any day within the allowable window. With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 24 Visit Procedures *(Day 168 ± 14 days targeted and ± 42 days allowable)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Administer mood and sleep questionnaire • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Administer adherence questionnaire • Administer tolerability (palatability and acceptability) questionnaire • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Total cholesterol, HDL, LDL, and triglycerides (non-fasting) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.11 Week 36 Visit

The Week 36 Visit is targeted to take place on Day 252, counted from the date of enrollment as Day 0, with a targeted window of ±14 days (i.e., Day 238 to Day 266, inclusive) and an allowable window of ±42 days (i.e., Day 210 to Day 294, inclusive). Every effort should be made to conduct the visit within the targeted window; however, the visit may be conducted on any day within the allowable window. With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 36 Visit Procedures ***(Day 252 ± 14 days targeted and ± 42 days allowable)***		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.12 Week 48 Visit

The Week 48 Visit is targeted to take place on Day 336, counted from the date of enrollment as Day 0, with a targeted window of ±14 days (i.e., Day 322 to Day 350 inclusive) and an allowable window of ±42 days (i.e., Day 294 to Day 378, inclusive). Every effort should be made to conduct the visit within the targeted window; however, the visit may be conducted on any day within the allowable window. With the exception that study drug should be prescribed and/or dispensed (if applicable and as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Week 48 Visit Procedures *(Day 336 ± 14 days targeted and ± 42 days allowable)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer adherence questionnaire • Administer tolerability (palatability and acceptability) questionnaire • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat) • *If child is exiting the study following completion of this visit,* collect all remaining study drug supplies. • *If child is remaining on-study,* prescribe and/or dispense study drug as needed and provide study drug storage and use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Total cholesterol, HDL, LDL, and triglycerides (non-fasting) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

At this visit, the site investigator will be required to determine whether the child is deriving benefit from ABC/DTG/3TC and, if so, whether ABC/DTG/3TC is available to the child from a non-study source.

Children who are not deriving benefit from ABC/DTG/3TC, as well as children who are deriving benefit and for whom ABC/DTG/3TC is available from a non-study source, should be discontinued from study participation and transitioned into local standard HIV care and treatment. At the time of discontinuation, arrangements should be made to provide clinically meaningful test results to the parent or guardian; the parent or guardian should also be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

Children who are deriving benefit from ABC/DTG/3TC for whom ABC/DTG/3TC is not available from a non-study source may continue study participation as described in Section 6.13.

Refer to Section 13.11 for considerations related to post-study access to study drug.

6.13 Q12 Week Visits through Week 144

Refer to Section 13.11 for considerations related to post-study access to study drug.

Following completion of the Week 48 Visit, children who are deriving benefit from ABC/DTG/3TC may remain on-study for up to an additional 96 weeks if ABC/DTG/3TC is not otherwise available from a non-study source. During this time, study visits will be targeted to occur every 12 weeks (i.e., at Weeks 60, 72, 84, 96, 108, 120, 132, and 144, counted from the date of enrollment as Day 0), with a targeted window of ±14 days and an allowable window of ±42 days. Every effort should be made to conduct each visit within the targeted window; however, these visits may be conducted on any day within the allowable window.

With the exception that study drug should be prescribed and/or dispensed (if applicable and as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit.

Q12 Week Visit Procedures *(Week 60 through Week 144)*		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• *If child is exiting the study following completion of this visit,* collect all remaining study drug supplies. • *If child is remaining on-study following completion of this visit,* prescribe and/or dispense study drug as needed and provide study drug storage and use instructions, adherence counseling, and support as needed
Laboratory	**Blood**	*At Weeks 72, 96, 120, and 144,* collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula)
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

For each child who remains on-study beyond Week 48, once ABC/DTG/3TC becomes available from a non-study source, or if it is determined that the child is no longer deriving benefit from ABC/DTG/3TC, study participation should be discontinued with transition into local standard HIV care and treatment. At the time of discontinuation, arrangements should be made to provide clinically meaningful test results to the parent or guardian; the parent or guardian should also be informed of how to contact study staff with any post-study questions and how to learn about the results of the study when available.

6.14 Confirmation of Virologic Failure Visit

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

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥ 200 copies/mL:

- For participants who were ART-naïve at enrollment, the two consecutive results should be from specimens collected at or after Week 24, counted from the date of enrollment. Any ART-naïve participant with an HIV-1 RNA result ≥ 200 copies/mL at or after Week 24 should be recalled to the clinic to complete a Confirmation of Virologic Failure Visit, per the table below and the "Confirm VF" column of the Schedule of Evaluations. The visit should take place at least seven days and within 28 days after specimen collection for the initial test.

- For participants who were ART-experienced at enrollment, the two consecutive results may be from specimens collected at any time after enrollment. Any ART-experienced participant with an HIV-1 RNA result ≥ 200 copies/mL at any time after enrollment should be recalled to the clinic for a Confirmation of Virologic Failure Visit, per the table below and the "Confirm VF" column of the Schedule of Evaluations. The visit should take place at least seven days and within 28 days after specimen collection for the initial test.

With the exception that study drug should be prescribed and/or dispensed (as needed) after weight has been measured as part of the targeted physical exam, there is no required sequencing of procedures at this visit. The required procedures may be combined with regularly scheduled visit procedures if they are performed within the allowable window of a regularly scheduled visit.

Confirmation of Virologic Failure Visit Procedures		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Prescribe and/or dispense study drug as needed • Provide study drug storage and use instructions, adherence counseling, and support as needed • Administer adherence questionnaire • Administer tolerability (palatability and acceptability) questionnaire • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat)
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Genotypic and phenotypic ARV resistance testing (real-time if virologic failure is confirmed; otherwise store plasma) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

6.15 Early Discontinuation from Study Visit

Refer to Section 4.6 for criteria for withdrawal from the study. For any participant who is withdrawn from the study prior to Week 48, every effort should be made to perform a final series of evaluations, if possible, per the table below and the "Early D/C" column of the Schedule of Evaluations. However, any evaluations performed within the 28 days prior to the Early Discontinuation Visit need not be repeated at the visit.

Premature Discontinuation Visit Procedures		
Clinical		• Obtain interval medical/medications history (refer to Section 0) • Perform targeted physical exam (refer to Section 0) • Identify/review/update adverse events • Perform additional evaluations per Section 8 and/or if clinically indicated (consult CMC if indicated)
Study Drug		• Administer adherence questionnaire • Administer tolerability (palatability and acceptability) questionnaire • Record timing of last three doses of study drug and food intake prior to last dose (full meal or light snack, high or low fat) • Collect all remaining study drug supplies
Laboratory	**Blood**	Collect blood for: • HIV-1 RNA • Complete blood count with differential and platelets • CD4+ cell count and percentage • ALT, AST, total bilirubin, direct bilirubin, creatinine, and eGFR (bedside Schwartz formula) • Sparse PK sampling with storage of plasma, DBS, and PBMC
	Blood or Urine	*If female of reproductive potential*, collect blood or urine for: • Pregnancy test

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

6.16 Post Exit Visit for Children on Contraception at Last Study Visit

The Post Exit Visit will be conducted only for children who were on contraception at their last study visit.

Refer to Section 8.6.1 for study contraception and pregnancy testing requirements. Any participant who is on contraception at her last study visit will ideally undergo additional evaluations approximately four weeks after her last study visit to update her medical and medications history, including her contraceptive history, and test for pregnancy. Other clinical evaluations may be performed at the discretion of the examining clinician. There is no required sequencing of procedures at this visit. The visit should be source documented in participant study records but no eCRF data entries are expected or required.

Post Exit Visit ***(approximately four weeks after the last study visit)***		
Clinical		• Obtain interval medical/medications history, including but not limited to documentation of contraceptive method and other concomitant medications since the last study visit • Perform targeted physical exam and/or other clinical evaluations if clinical indicated as determined by the examining clinician
Laboratory	**Blood or Urine**	• Collect blood or urine for pregnancy test

6.17 Medical and Medication History

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

Documented medical conditions will be assessed for severity as described in Section 7.3.3 and new conditions occurring during follow-up will be assessed for relationship to study drug as described in Section 8.1. Relevant dates will be recorded for all conditions and medications; refer to Section 5.7 for more information on concomitant medications. Table 10 specifies the baseline and interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

Table 10. IMPAACT 2019 Documentation Requirements for Medical and Medication Histories

Assess for and Source Document	**Enter into eCRFs or SES**
Baseline Medical and Medication History Elements	
Date of birth, sex at birth, race, ethnicity	Yes
Date of HIV diagnosis and current WHO clinical stage	Yes
All documented HLA-B*5701 test results (ever)	Yes
Documented resistance to ABC, DTG, and/or 3TC (ever)	Yes

Assess for and Source Document	Enter into eCRFs or SES
All documented HIV-1 RNA test results within the six months prior to enrollment	Yes
History of allergy and/or hypersensitivity (including to ARVs)	Yes
Medical conditions ongoing or occurring within the 30 days prior to enrollment	Yes
ARVs and all other medications taken within the 30 days prior to enrollment	Yes (for liquid formulation medications, includes brand name and/or manufacturer, dose volume, and sugar alcohol content if available)
For females nine years of age and older, reproductive history as applicable: menstrual history, sexual activity, and contraceptive use	Yes
Any other information needed to determine eligibility for the study	No
Interval Medical and Medication History Elements	
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions since the last visit	All newly identified adverse events
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit	All ARVs and concomitant medications (including ARV formulation, preparation, and administration details, all ARV dose and formulation changes, the date of each change, and measured weight on the date of each change) (for liquid formulation medications, includes brand name and/or manufacturer, dose volume, and sugar alcohol content if available)
For females nine years of age and older, updates of reproductive history as applicable: menstrual history, sexual activity, and contraceptive use	Yes
For females who become pregnant: pregnancy outcome, any congenital anomalies identified in the fetus or infant	Yes
All ARV resistance test results obtained after enrollment	Transferred electronically to DMC using data submission utilities (not entered into eCRFs)

6.18 Physical Examinations

Physical examinations are required at most scheduled visits. Complete exams are required at the Screening and Entry Visits; targeted exams are required at other visits.

Complete exams should include the following:

- Height measurement
- Weight measurement
- Neurologic assessment
- Examination of:
  - General appearance
  - Head
  - Eyes
  - Ears
  - Nose
  - Neck
  - Mouth and throat
  - Lymph nodes
  - Lungs
  - Heart
  - Abdomen
  - Extremities
  - Skin
  - Other body systems driven by identified signs and symptoms

Targeted exams should include the following:

- Height measurement
- Weight measurement
- Examination of body systems driven by prior and newly identified signs and symptoms

Additional assessments may be performed at any time at the discretion of the examining clinician. Also at all visits, the measurements listed above should be used to determine weight-for-height z-scores (for children up to five years of age) or body mass index z-scores (for children greater than five years of age), which will be assessed in relation to WHO growth standards.

All exam findings should be source documented and all height and weight measurements will be entered into eCRFs. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into adverse event eCRFs.

6.19 Questionnaire Evaluations

Questionnaires will be administered at designated timepoints to collect information on adherence to study drug, tolerability (palatability and acceptability) of study drug, and participant mood and sleep patterns. All questionnaire data will be entered into eCRFs.

6.20 Additional Considerations for Laboratory Procedures

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

6.20.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the study-specific website: http://impaactnetwork.org/studies/IMPAACT2019.asp.

In accordance with US National Institutes of Health (NIH) recommendations, pediatric blood collection will not exceed 5 mL/kg in a single day or 9.5 mL/kg in any eight-week period. In the event that blood collection must be limited, available specimens should be prioritized for use in the following order: (1) chemistry, (2) hematology, (3) plasma PK, (4) HIV-1 RNA, (5) CD4+ cell count and percentage, and (5) stored plasma, DBS, and PBMCs.

6.20.2 Specimen Preparation, Testing, Storage, and Shipping

All specimens collected for this study will be labeled, transported, processed, tested, stored and/or shipped in accordance with the DAIDS policy referenced in Section 6.20, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by the Schedule of Evaluations and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in LPC.

HIV-1 RNA assays must be performed in a laboratory that is CLIA-certified (for US sites) or VQA-certified (for non-US sites) for the assay performed. At least one of the diagnostic tests to confirm HIV infection per criterion 4.1.7 must be performed in CLIA- certified (for US sites) or VQA-certified (for non-US sites) laboratory. For children who experience virologic failure, genotypic and phenotypic resistance testing will be performed in real time. Specimens collected for resistance testing at Confirmation of Virologic Failure Visits will be processed locally, with plasma retained at the site laboratory pending HIV-1 RNA testing to confirm virologic failure. If failure is confirmed, plasma from the Confirmation of Virologic Failure Visit will be shipped to a designated VQA-certified testing laboratory (residual aliquots will be stored at the site laboratory); if failure is not confirmed; all aliquots will remain stored at the site laboratory. Testing of Entry Visit samples will be directed by the Protocol Team.

Specimens collected, processed, and stored at site laboratories for intensive PK evaluations are expected to be shipped to the designated testing laboratory in real time, or as otherwise directed by the Protocol Team. Specimens collected for sparse PK evaluations will be processed for storage of plasma, DBS and PBMC consistent with a study-specific SOP that is available on the study-specific website: http://impaactnetwork.org/studies/IMPAACT2019.asp. These specimens, and all specimens collected, processed, and stored at site laboratories for exploratory evaluations, are expected to be shipped to designated central testing laboratories after all participants have completed 48 weeks of follow-up, unless otherwise directed by the Protocol Team.

After all protocol-specified laboratory testing has been performed, residual specimens may be of interest for future research use. Participants' parents or guardians will be asked to provide written informed consent for future research use of these specimens, if permitted by site IRBs/ECs and other applicable review bodies; participants will also be asked to provide assent for future research use of these specimens when applicable per IRB/EC policies and procedures. Participants/parents/guardians may choose to provide or decline this consent/assent with no impact on other aspects of study participation.

6.20.3 Biohazard Containment

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

7 SAFETY ASSESSMENT, MONITORING, AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1, 7.2, and 7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the CMC and the IMPAACT Study Monitoring Committee (SMC) are briefly referenced in Section 7.1 and described in greater detail in Section 9.5.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

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

7.1.2 Clinical Management Committee

The following Protocol Team members comprise the CMC: Co-Chairs and Vice Chair, Medical Officers, Pharmacologists, Statisticians, Data Managers, ViiV representatives, IMPAACT Laboratory Center representatives, and Clinical Trial Specialists. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility, management of adverse events, and management of study drug and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.1.

7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the composition and role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

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

The definition of the term **adverse event** provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to all participants, beginning at the time of enrollment, regardless of subsequent exposure to study drug. Any untoward medical conditions identified prior to enrollment will be considered **pre-existing conditions**. Refer to Section 4.4 for more information on defining the effective point of enrollment in the study.
Pre-existing conditions and adverse events will be entered into eCRFs as specified below.

Pre-Existing Conditions

All pre-existing conditions (i.e., all grade 1 or higher) identified during the 30 days prior to study entry will be entered into medical history eCRFs. Among other details, the severity of all such conditions will be entered into these eCRFs.

Adverse Events

All adverse events (i.e., all grade 1 or higher) identified after enrollment will be entered into adverse event eCRFs. For any event involving a hypersensitivity reaction to ABC, additional data will also be entered into other designated eCRFs.

Laboratory Test Results

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

All pregnancy test results will also be entered into laboratory eCRFs; HIV-1 RNA will be entered into laboratory eCRFs or transferred electronically to the DMC through the LDMS. ARV resistance test results will be transferred electronically to the DMC using data submission utilities.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available at:
https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available at:
https://rsc.niaid.nih.gov/clinical-research-sites/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

7.3.2 EAE Reporting Requirements for this Study

The Serious Adverse Event (SAE) reporting category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. In addition to all serious adverse events, the following must also be reported in an expedited manner (i.e., as EAEs):

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

The study drugs for which expedited reporting are required are:

- Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) dispersible tablets
- Abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) immediate release tablets
- Dolutegravir (DTG) dispersible tablets
- Dolutegravir (DTG) tablets
- Abacavir (ABC) tablets
- Lamivudine (3TC) tablets

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

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available at:
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

7.3.4 EAE Reporting Period

The EAE reporting period for this study is the protocol-specified period of follow-up, beginning at the time of enrollment and continuing through the date of the Week 48 Visit for all participants. For participants who continue in follow-up after the Week 48 Visit, the EAE reporting period will continue through the last follow-up visit (up to the Week 144 Visit).

After the above-specified period, only suspected, unexpected, serious adverse reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual will be reported if study staff become aware of such events on a passive basis (e.g., from publicly available information).

8 PARTICIPANT MANAGEMENT

8.1 Management of Adverse Events

All adverse events identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 11. Among other details, source documentation will include the severity of each event (graded as described in Section 7.3.3) and its relationship to study drug, assessed by the site investigator according to the following categories and definitions:

Related There is a reasonable possibility that the adverse event may be related to ABC/DTG/3TC

Not related There is not a reasonable possibility that the adverse event may be related to ABC/DTG/3TC

Further standardized guidance on determining whether there is a reasonable possibility of a relationship is available in the DAIDS EAE Manual (referenced in Section 7.3.1). An assessment of relationship should be documented for each component agent of the study drug and for the combination of agents. As described in greater detail below, adverse events will be managed based on their severity and assessed relationship to study drug.

All adverse events must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Grade 3 or higher laboratory tests should be repeated **as soon as possible** (within three business days) and all grade 3 or higher adverse events should be re-evaluated **at least weekly** until improvement to grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator **in consultation with the CMC**. Additional evaluations may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study drug. Clinical management of all adverse events should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

When management of an adverse event requires consultation with the CMC, the CMC should be contacted as soon as possible and within three business days of site awareness of the event. The CMC should be notified of any interruption of study drug lasting for more than three business days.

The remainder of this section provides further guidance on management of adverse events. General guidance is provided in Section 8.1.1. This guidance should be followed for all adverse events except the hepatic and renal events addressed in Sections 8.1.2 and 8.1.3. Criteria for premature discontinuation of study drug are presented in Section 8.2.

8.1.1 General Guidance for Management of Adverse Events

Adverse events other than the hepatic and renal events addressed in Sections 8.1.2 and 8.1.3 should be managed consistent with the guidelines in Table 11.

Table 11. General Guidelines for Adverse Event Management in IMPAACT 2019

Grade 1	Continue study drug with routine monitoring per the Schedule of Evaluations unless more frequent monitoring is considered clinically indicated in the opinion of the site investigator.
Grade 2	Continue study drug with routine monitoring per the Schedule of Evaluations unless more frequent monitoring is considered clinically indicated in the opinion of the site investigator. Evaluate for non-study drug explanations for the event.
Grade 3	Upon initial identification of a Grade 3 event, the CMC should be notified (as soon as possible and within three business days). Non-study drug explanations for the event should be considered. The child should be re-evaluated at least weekly until improvement to Grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC. If the initial Grade 3 event is a laboratory abnormality, the test should be repeated as soon as possible (within three business days). If an initial Grade 3 laboratory abnormality is assessed as not related to study drug, study drug may be continued while awaiting the repeat test result; otherwise study drug should be held. If the repeat test does not yield a Grade 3 result, the event should be managed according to the grade of the repeat result. For Grade 3 clinical events and confirmed Grade 3 laboratory events: • If the event is assessed as **not related** to study drug, study drug should be continued (or resumed if previously held). The CMC should be notified of the event, the assessment of relationship, and immediate management action taken; any subsequent management action should be taken in consultation with the CMC. • If the event is assessed as **related** to study drug, study drug should be held unless the site investigator feels that continuation of the study drug is in the child's best interest. The CMC should be notified of the event, the assessment of relationship, and immediate management action taken; any subsequent management action should be taken in consultation with the CMC. If study drug is held, resumption may be considered in consultation with the CMC once the event has improved to Grade 2 or lower. If study drug is resumed and the event recurs at Grade 3 or higher (confirmed), study drug must be permanently discontinued.

Grade 4	Upon initial identification of a Grade 4 event, study drug should be held unless the site investigator feels that continuation of the study drug is in the participant's best interest. The CMC should be notified as soon as possible and within three business days; notification should occur within one business day if study drug is not held. Non-study drug explanations for the event should be considered. The child should be re-evaluated at least weekly until improvement to Grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC. If the initial Grade 4 event is a laboratory abnormality, the test should be repeated as soon as possible (within three business days). If the repeat test does not yield a Grade 4 result, the event should be managed according to the grade of the repeat result. For Grade 4 clinical events and confirmed Grade 4 laboratory events: • If the event is assessed as **not related** to study drug, study drug may be resumed with approval from the CMC. If study drug is resumed and the event recurs at Grade 3 or higher (confirmed), study drug must be permanently discontinued. • If the event is assessed as **related** to study drug, study drug must be permanently discontinued.

8.1.2 Management of Hepatic Toxicity

ALT, AST, total bilirubin, and direct bilirubin will be routinely monitored in this study. If any results of severity grade 3 or higher are obtained, all four tests should be repeated as soon as possible and within three business days, and re-evaluation should continue at least weekly until improvement to grade 2 or lower or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the CMC.

Note: Treatment-experienced children on an atazanavir-containing ART regimen prior to enrollment are permitted to enter the study with a Grade 3 or higher total bilirubin level. Upon enrollment, these children will switch to the study drug regimen; any residual atazanavir should be cleared within 2-3 days after switching regimens and total bilirubin levels should normalize within two weeks after switching regimens.

Study drug must be held in the following circumstances:

- Grade 2 ALT or AST with total bilirubin greater than two times the upper limit of normal (>2xULN) and direct bilirubin greater than 35% of total bilirubin. In this case, study drug should be permanently discontinued and the CMC should be notified.

- Grade 2 or higher ALT or AST with signs or symptoms of clinical hepatitis (e.g., fatigue, nausea, vomiting, right upper quadrant pain, jaundice) or hypersensitivity (e.g., rash, fever, facial edema, eosinophilia, difficulty breathing). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug with approval from the CMC.

- Grade 3 ALT or AST for more than two weeks (with total bilirubin ≤2xULN and no signs or symptoms of clinical hepatitis or hypersensitivity). In this case, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.

- Grade 4 ALT or AST. Hold study drug upon first identification of the Grade 4 result, i.e., pending receipt of the repeat test result; inform the CMC of the initial result and the repeat result. In the case of a confirmed grade 4 result, if another cause of the ALT or AST elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.

- Grade 3 (confirmed) total or direct bilirubin (with normal or Grade 1 ALT and AST) or any occurrence of direct bilirubin greater than 35% of total bilirubin. In this case, if another cause of the bilirubin elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.

- Grade 4 total or direct bilirubin (with normal or grade 1 ALT and AST) or any occurrence of direct bilirubin greater than 35% of total bilirubin. Hold study drug upon first identification of the Grade 4 result, i.e., pending receipt of the repeat test result; inform the CMC of the initial result and the repeat result. In the case of a confirmed Grade 4 result, if another cause of the bilirubin elevation is identified, consideration may be given to resuming study drug, with approval from the CMC.

Note: Children with Hepatitis B infection will be excluded from this study. If any enrolled children are diagnosed with incident Hepatitis B infection during follow-up, the CMC should be consulted as soon as possible and within three business days regarding options for clinical and ART regimen management. A change to an ART regimen containing TDF and 3TC or FTC would generally be expected, if consistent with local HIV and Hepatitis B treatment guidelines, thereby necessitating permanent discontinuation of ABC/DTG/3TC (see also Section 8.2). However, each case will be managed individually by the site investigator in consultation with the CMC.

8.1.3 Management of Renal Toxicity

Note: DTG can inhibit the tubular secretion of creatinine and can therefore be associated with a slight increase in serum creatinine and apparent decrease in the estimated glomerular filtration rate (generally by 10% or less). This typically occurs within the first four weeks of treatment with DTG and remains stable thereafter and is not associated with renal damage or true decline in renal function.

Serum creatinine and eGFR rates will be routinely monitored in this study. At each time point when serum creatinine testing is performed, the eGFR rate should be calculated using the bedside Schwartz formula:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 0.413 * \text{height (in cm)} \div \text{serum creatinine (in mg/dL)}$$

Both the serum creatinine level and the eGFR rate should be graded for severity and assessed for change from baseline and clinical significance. When abnormal results are obtained, confounding factors and other non-study drug explanations (e.g., concomitant medications, concomitant illness, dehydration) should be considered and a nephrology consult may be obtained.

Children who experience an increase to Grade 2 from a baseline normal or Grade 1 serum creatinine level, or an increase to Grade 3 from a baseline Grade 2 creatinine level should undergo confirmatory testing within 2-4 weeks. Serum creatinine testing should be repeated and if the elevation is confirmed, the CMC should be consulted regarding further follow-up and management.

Children who experience a Grade 3 or higher eGFR rate should undergo confirmatory testing within 2-4 weeks. If the Grade 3 eGFR rate is confirmed, study drug should be held and the CMC should be consulted regarding further follow-up and management.

8.1.4 Management of Hypersensitivity Reaction to ABC

Serious and sometimes fatal hypersensitivity reactions have occurred with ABC-containing products. These reactions have been characterized by two or more of the following signs or symptoms: fever; rash; gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); constitutional symptoms (including generalized malaise, fatigue, or achiness); respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all ABC hypersensitivity reactions include fever and/or rash as part of the syndrome. Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Persons who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction. Children screened for this study will be tested for the HLA-B*5701 allele and only enrolled if HLA-B*5701-negative. However, the incidence of suspected hypersensitivity reactions in clinical trials of ABC was 1% when persons carrying the HLA-B*5701 allele were excluded. An association with ABC hypersensitivity reaction has been described with HLA-B*5701, HLA-DR7, and HLA-DQ3; if all three of these markers are present, the positive predictive value for hypersensitivity reaction is 100%, with a negative predictive value of 97%. HLA-B*5701 alone is highly predictive (46).

Children and their parents/guardians will be provided with an ABC hypersensitivity alert card and instructed to contact the study sites if they develop a rash at any time while receiving study drug. Children with rash should be evaluated for the possibility of a hypersensitivity reaction or serious skin reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme (which have been reported very rarely in persons taking ABC). If a serious skin reaction develops, ABC and all other concurrent medications suspected by the site investigator as potentially causal should be held and the CMC should be consulted. If a diagnosis of ABC hypersensitivity is made — or cannot be excluded — in consultation with the CMC, ABC must be permanently discontinued, i.e., ABC should never be re-started. The site investigator may also discontinue any other concurrent medications suspected as potentially causal.

8.2 Criteria for Premature Discontinuation of Study Drug

Administration of study drug will be permanently discontinued in the following circumstances:

- A child experiences an adverse event requiring discontinuation of study drug
- A child is diagnosed with Hepatitis B or any other condition requiring a change of ART regimen as determined by the site investigator in consultation with the CMC
- A child with confirmed virologic failure is identified with ARV resistant virus requiring a change of ART regimen as determined by the site investigator in consultation with the CMC
- A child is unable or unwilling to take study drug or a child's parent or guardian refuses further administration of study drug
- A child becomes pregnant
- The site investigator determines that further administration of study drug would be detrimental to the child's health or well-being
- New data become available indicating that study drug should be discontinued as determined by the CMC

Any child who permanently discontinues ABC/DTG/3TC will be transitioned to an alternative locally-available ART regimen obtained from non-study standard of care sources. The site investigator should make every effort to facilitate this transition and minimize gaps in ART coverage to the extent possible.

Any child who permanently discontinues ABC/DTG/3TC for reasons other than an adverse event or pregnancy should be discontinued from the study as soon as transition to non-study care and treatment is assured. If discontinuation from the study occurs before the Week 48 Visit has been conducted, an Early Discontinuation Visit should ideally be conducted as the child's final study visit.

Any child who permanently discontinues ABC/DTG/3TC due to an adverse event should remain on-study in order to follow the event to resolution or stabilization of the event at severity grade 2 or lower. Following resolution or stabilization of the event, the child should be discontinued from the study. If discontinuation from the study occurs before the Week 48 Visit has been conducted, an Early Discontinuation Visit should ideally be conducted as the child's final study visit.

Any child who permanently discontinues ABC/DTG/3TC due to pregnancy should remain on-study until delivery or other outcome of the pregnancy. Study visits and procedures should be completed per Section 6 and the Schedule of Evaluations, with the exception that no further PK sampling will be performed and no further adherence and tolerability (palatability and acceptability) questionnaires will be administered after study drug is discontinued.

8.3 Monitoring and Management of HIV Viral Load

Monitoring

HIV-1 RNA (viral load) will be monitored closely with frequent testing as specified in the Schedule of Evaluations. All HIV-1 RNA assays must be performed in CLIA-certified (US) or VQA-certified (non-US) laboratories. Site investigators should review the results of each test as well as trends over time and consult with the CMC regarding any individual test results or trends of concern. As noted in Section 5.6, viral load results should be provided to participants/parents/guardians and used to guide adherence counseling.

Definition of Virologic Failure

Virologic failure is defined as two consecutive plasma HIV-1 RNA test results ≥200 copies/mL. For participants who were ART-naïve at enrollment, the two consecutive results should be from specimens collected at or after Week 24, counted from the date of enrollment. For participants who were ART-experienced at enrollment, the two consecutive results may be from specimens collected at any time after enrollment.

Confirmation of Virologic Failure

Any ART-naïve participant with an HIV-1 RNA result ≥200 copies/mL at or after Week 24 should be recalled to the clinic for confirmatory testing at least seven days and within 28 days after specimen collection for the initial test.

Likewise, any ART-experienced participant with an HIV-1 RNA result ≥200 copies/mL at any time after enrollment should be recalled to the clinic for confirmatory testing at least seven days and within 28 days of specimen collection for the initial test.

As indicated in Section 6.14, specimen collection for genotypic and phenotypic ARV resistance testing will also be performed at the time of specimen collection for confirmatory HIV-1 RNA testing. All procedures should be performed regardless of reported adherence to study drug or any other factors that may affect HIV-1 RNA results.

Management of Confirmed Virologic Failure

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

For participants with confirmed virologic failure, upon receipt of the confirmatory HIV-1 RNA test result, specimens collected for ARV resistance testing at the Confirmation of Virologic Failure Visit should be shipped to a designated VQA-certified testing laboratory. Genotypic and phenotypic resistance test results will be provided in real time to help guide ART regimen management, as described below.

If the virologic failure is assessed as likely due to non-adherence, the current study drug regimen may be continued, with enhanced adherence support per site SOPs and continued virologic monitoring. Likewise, if the failure is assessed as due to intercurrent illness or other factors not associated with the current study drug regimen, the regimen may be continued. Otherwise, the regimen should generally be modified in consultation with the CMC. Recommendations for alternative regimens should take into consideration the participant's preferences and medical history, current regimen, current local standard guidelines for first- and second-line regimens, and resistance test results.

8.4 Management of Tuberculosis

Children who develop active tuberculosis (TB) and need rifampin-containing treatment during follow-up may have their study drug regimen modified in consultation with the CMC. It is generally expected that the frequency of DTG dosing will be increased from once daily to twice daily, using a single agent formulation of DTG for the second daily dose; doses and formulations to be provided are shown in Table 12. The CMC should be informed of each TB diagnosis and consulted on study drug regimen management on a case-by-case basis. After the period of rifampin treatment is completed, the study drug regimen corresponding to the child's current weight should be resumed.

Table 12. Second Daily Dose of DTG for Children in IMPAACT 2019 Who Require Rifampin-Containing TB Treatment

Weight Band		Second Daily Dose of DTG
#1	6 to less than 10 kg	DTG 15 mg (three 5 mg dispersible tablets)
#2	10 to less than 14 kg	DTG 20 mg (four 5 mg dispersible tablets)
#3	14 to less than 20 kg	DTG 25 mg (five 5 mg dispersible tablets)
#4	20 to less than 25 kg	DTG 30 mg (six 5 mg dispersible tablets) **OR** DTG 50 mg (one film coated tablet)
#5	25 kg or greater	DTG 50 mg (one film coated tablet)

To confirm DTG dosing in the therapeutic range, intensive PK sampling will be performed 14-21 days after initiating rifampin-containing TB treatment. In general, the operational approach to intensive PK sampling described in Section 6.3 will be followed. Samples will be collected at the following time points and will be shipped and analyzed in real time:

- Prior to observed dosing of study drug (1 mL)
- 1 hour (±30 minutes) after observed dosing of study drug (1 mL)
- 2 hours (±30 minutes) after observed dosing of study drug (4 mL)
- 3 hours (±30 minutes) after observed dosing of study drug (1 mL)
- 4 hours (±30 minutes) after observed dosing of study drug (1 mL)
- 6 hours (±60 minutes) after observed dosing of study drug (1 mL)
- 8 hours (-15 to +120 minutes) after observed dosing of study drug (1 mL)
- 12 hours (±120 minutes) after observed dosing of study drug (1 mL)

If analysis of the intensive PK samples indicates that DTG dosing in the therapeutic range has not been achieved, together with the site investigator, the CMC will review all available clinical, pharmacologic, immunologic, and virologic data for the child and determine whether another DTG dose adjustment may be indicated. If a child requires a dose adjustment, a repeat PK assessment may be performed for that child, with an appropriate sampling strategy determined by the Protocol Pharmacologists, to confirm PK targets are achieved.

8.5 Management of Participants with Intensive PK Outcomes Outside the Targeted Range

Refer to Section 10.3.4. For children undergoing intensive PK sampling, PK outcomes will be reviewed by the Protocol Team in relation to minimum and maximum tolerated exposure targets and consideration will be given to individual dose modification for children whose PK outcomes fall outside the targeted exposure range. If a child requires an individual dose adjustment, a repeat PK assessment may be performed for that child, with an appropriate sampling strategy determined by the Protocol Pharmacologists, to confirm PK targets are achieved.

8.6 Contraception and Pregnancy

8.6.1 Contraception and Pregnancy Testing Requirements

Medical history information will be collected at each scheduled visit. For female participants, starting at nine years of age, this will include reproductive history information. Date of menarche will be recorded (when applicable) and female participants will be considered "of reproductive potential" upon experiencing menarche. For female participants of reproductive potential, pregnancy testing will be routinely performed and information on sexual activity will be routinely collected at each scheduled study visit. Additional pregnancy testing may be performed at any time pregnancy is suspected. Pregnancy test results and reported sexual activity will be entered into eCRFs.

For female participants of reproductive potential who report sexual activity that could lead to pregnancy, use of two methods of contraception will be required while receiving study drug. Use of contraception is also recommended following discontinuation of study drug, until such time that a clinically insignificant amount of study drug medication is present in the participant (i.e., at least five terminal phase half-lives, which corresponds to approximately three days). One of the two methods of contraception must be highly effective (see listing in criterion 4.1.10). The second method should ideally be a barrier method; male or female condom use will be recommended with all other methods of contraception for dual protection against pregnancy and to avoid transmission of HIV and other sexually transmitted infections. All methods of contraception will be entered into eCRFs. Any female participant of reproductive potential who reports sexual activity that could lead to pregnancy who is not willing or able use two methods of contraception will be discontinued from the study.

Study staff should actively facilitate access to contraceptive services and, to the extent possible, should provide these services to participants on-site. At sites where full service provision is not possible, study staff should actively refer participants to local service providers for methods that cannot be provided on site. Access to effective contraception should be provided or facilitated for all applicable participants. Among other considerations, potential interactions with other medications, including but not limited to ARVs, should be considered when selecting an appropriate contraceptive method.

Contraceptive counseling should be routinely provided to help ensure adherence to selected methods; counseling should also include reminders to inform study staff if participants experience issues or problems in accessing or adhering to contraception and/or if they wish to stop using contraception. All counseling should be documented in participant study records.

8.6.2 Management of Pregnancy

Any participant who becomes pregnant while on-study must be discontinued from study drug and transitioned to an alternative locally-available ART regimen obtained from non-study standard of care sources as rapidly as possible. The site investigator should make every effort to facilitate this transition and minimize gaps in ART coverage to the extent possible. The site investigator should also refer the participant to standard of care antenatal services with proactive communication of clinical considerations related to conception of the pregnancy while receiving DTG.

The CMC should be informed of the pregnancy and consulted on ARV and clinical management for the participant. The participant should remain on-study through delivery or other outcome of the pregnancy. Study visits and procedures will be completed per Section 6 and the Schedule of Evaluations, with the exception that no further PK sampling will be performed and no further adherence and tolerability (palatability and acceptability) questionnaires will be administered.

Study sites are strongly encouraged to prospectively register participants who become pregnant in the APR prior to pregnancy outcome by calling the following number in the US: +1-800-258-4263. Outside the US, see the APR website (www.apregistry.com) for additional toll-free numbers.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I/II, multi-site, open-label, multiple dose non-comparative PK and safety study of ABC/DTG/3TC dispersible tablets and immediate release tablets in ART-naïve and ART-experienced HIV-1-infected children less than 12 years of age. The study will be conducted among at least 50 and up to 75 children. Children will be enrolled in weight bands and will receive ABC/DTG/3TC dispersible tablets or ABC/DTG/3TC immediate release tablets as shown in Table 6. Refer to Section 3 for a more complete description of the study design and to Section 9.4 for a description of the study accrual plan.

PK data analyses will be performed as described in Section 10; all other statistical and data analysis considerations are described in the remainder of this section. Refer to Section 9.5.1 for a description of dose confirmation analyses and to Section 3.2 for definitions of dose-evaluable, safety-evaluable, and PK-evaluable.

Children with no study drug dose adjustments, or with dose adjustments due to weight gain or decrease, will be analyzed in the original weight band in which they enrolled. For children whose study drug dose is adjusted for reasons other than weight gain or decrease, safety data up to the date of dose adjustment will be analyzed in the original 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. Children whose study drug regimen is modified due to receipt of rifampin-containing TB treatment will be described separately.

9.2 Outcome Measures

Note: The numbering of the outcome measures in this section corresponds to the numbering of the objectives in Section 2. Details of PK-related outcome measures are provided in Section 10.2.

The primary and secondary outcome measures listed in Sections 9.2.1 and 9.2.2 through Week 24 will be addressed in the study's primary statistical analysis plan, which will define the content of the primary analysis report. This report will form the basis for the primary study publication and initial result reporting to ClinicalTrials.gov. Secondary outcomes listed in Section 9.2.2 through Week 48 and Week 144 will be addressed in one or more secondary analysis reports which will form the basis for secondary publications and additional result reporting to ClinicalTrials.gov. Outcomes of interest for exploratory objectives (intended for subsequent publications) are listed in Section 9.2.3.

9.2.1	**Primary Outcome Measures**
9.2.1.1	• See Section 10.2.1
9.2.1.2	• All adverse events occurring through Week 24 • Participants with the following through Week 24: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug
9.2.2	**Secondary Outcome Measures**
9.2.2.1	• See Section 10.2.2
9.2.2.2	• All adverse events occurring through Week 48 • Participants with the following through Week 48: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug • All adverse events occurring through Week 144 • Participants with the following through Week 144: - Grade 3 or Grade 4 adverse events assessed as related to study drug - Grade 5 adverse events assessed as related to study drug - Life-threatening adverse events assessed as related to study drug - Serious adverse events assessed as related to study drug - Adverse events assessed as related to study drug that lead to permanent discontinuation of study drug

9.2.2.3	• HIV-1 RNA through Week 48 • HIV-1 RNA through Week 144 • Participants with: - HIV-1 RNA ≥200 copies/mL at Weeks 4, 24, and 48 (snapshot algorithm) - HIV-1 RNA ≥50 copies/mL at Weeks 4, 24, and 48 (snapshot algorithm) • CD4+ cell count and percentage at Weeks 4, 24, and 48 • CD4+ cell count and percentage through Week 144
9.2.2.4	• Total cholesterol, HDL, LDL, and triglycerides at Weeks 24 and 48
9.2.2.5	• Parent/guardian reported adherence to study drug at Weeks 4, 24, and 48 • Parent/guardian reported tolerability (i.e., palatability and acceptability) of study drug at Weeks 4, 12, 24, and 48
9.2.2.6	• ARV resistance mutations at time of virologic failure (and at entry for children with resistance identified at time of virologic failure)
9.2.3 Exploratory Outcome Measures	
9.2.3.1	• Parent/guardian report of child's mood and sleep habits at Weeks 4 and 24
9.2.3.2	• See Section 10.2.3
9.2.3.3	• See Section 10.2.3
9.2.3.4	• See Section 10.2.3

9.3 Randomization and Stratification

This study does not involve randomization. Enrolled participants will be stratified into weight bands based on their weight at the study Entry Visit. Enrollment will also be monitored by the Protocol Team to ensure that at least 25 participants are less than six years of age at entry and at least 25 are six to less than 12 years of age at entry.

9.4 Sample Size and Accrual

9.4.1 Sample Size

The targeted sample size of at least 50 children, with at least 25 less than six years of age and at least 25 six to less than 12 years of age, was selected based on the currently agreed PIP and PSP for ABC/DTG/3TC. Within the overall target of 50 children, at least 25 — five in each of the weight bands shown in Table 6 — must be dose-evaluable for ABC, DTG, and 3TC (defined in Section 3.2). A total sample size of up to 75 children has been specified to ensure that at least five dose-evaluable children are enrolled in each weight band, to permit additional enrollments if confident determinations regarding PK targets cannot be made based on the first 5-7 dose-evaluable children in each weight band, and to permit additional enrollments if dose adjustment and further evaluation of an adjusted dose is needed within any weight band.

Table 13 presents exact 95% confidence intervals (CIs) around potential proportions of participants experiencing grade 3 or higher adverse events that may be observed in sample sizes ranging from five to 50. The lower sample size of five corresponds to the minimum number to be enrolled in each weight band; the middle sample size of 25 corresponds to the minimum number

to be enrolled in each age group; and the upper sample size of 50 corresponds to the overall study accrual target. Other numbers between five and 50 correspond to possible sample sizes within and across weight bands. CIs will be quite wide with the minimum sample size of five participants per weight band but considerably more precise with the overall target study accrual target of 50 participants.

Table 13. Percent of Participants Experiencing Grade 3 or Higher Adverse Events with Exact 95% CIs

N*	n (%) with Grade 3 or Higher Adverse Events	95% CI
5	0 (0%)	0.0, 52.2
10	0 (0%)	0.0, 30.9
15	0 (0%)	0.0, 21.8
20	0 (0%)	0.0, 16.8
25	0 (0%)	0.0, 13.7
30	0 (0%)	0.0, 11.6
40	0 (0%)	0.0, 8.8
50	0 (0%)	0.0, 7.1
5	1 (20%)	0.5, 71.6
10	2 (20%)	2.5, 55.6
15	3 (20%)	4.3, 48.1
20	4 (20%)	5.7, 43.7
25	5 (20%)	6.8, 40.7
30	6 (20%)	7.7, 38.6
40	8 (20%)	9.1, 35.7
50	10 (20%)	10.0, 33.7

9.4.2 Accrual

To achieve the targeted sample size described above, accrual is expected to require approximately 12 months. Accrual into all weight bands will occur concurrently.

Within each weight band, accrual will initially be limited, for purposes of dose confirmation, to children who are ART-naïve or switching to the study drug regimen from a non-NNRTI-containing regimen. Accrual into weight band #1 will initially be restricted to children six months (180 days) of age and older. Once the Protocol Team has confirmed that data are available to support the specified weight band dosing for children less than six months of age, this restriction will be lifted.

A minimum of five dose-evaluable children will be enrolled in each weight band. Refer to Section 3.2 for a more detailed description of the number of children who will undergo intensive PK evaluations to achieve a minimum of five dose-evaluable in each weight band.

Guidelines for assessing safety and intensive PK outcomes for purposes of dose confirmation are provided in Section 9.5.1. Once the dose confirmation guidelines are met for a given weight band, accrual into that weight band will continue with no restriction on enrollment with respect to prior NNRTI exposure. As noted in Section 9.5.1, the Protocol Team may consider whether to permit enrollment of children switching to the study drug regimen from an NNRTI-containing regimen among the dose-evaluable in each weight band.

If the dose confirmation guidelines are not met, the Protocol Team will determine whether to adjust the dose for the weight band, as described in Section 10.3.2. If a weight band dose adjustment is deemed necessary, 5-7 additional dose-evaluable children will be enrolled to confirm the appropriateness of the adjusted dose.

The Protocol Team will closely monitor accrual into each weight band as well as progress made toward the age-based quotas, which apply across all weight bands. Accrual into the study overall will continue until study drug dosing has been confirmed for each weight band and the age-based quotas have been met. The Protocol Team may pause or close accrual into any weight band to ensure that these accrual targets are met.

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide for more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, participant safety, and PK outcomes across sites is provided below.

9.5.1 Monitoring by the Protocol Team

Study Progress and Quality of Study Conduct

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

The team will closely monitor participant accrual based on reports that will be generated at least monthly by the SDMC. The team has developed a study accrual plan that includes site-specific and total enrollment projections over the course of the accrual period, and actual accrual will be monitored relative to these projections.

The team will monitor the timing of site-specific study activation, which will determine when each site will begin accruing participants, and actual accrual following activation. The number of potential participants screened, reasons for screen failures, and the number of participants enrolled will be closely monitored. Accrual performance will be reported by the DMC — by site and across sites, within and across weight bands, and within and across age groups — and the team will review and discuss study progress at least monthly. For any site that is delayed in completing the study activation process, or that falls short of its accrual projections, the team will communicate with the site to identify the barriers the site has encountered and the operational strategies and action plans to address these.

Across sites, the team will closely monitor accrual into each weight band as well as progress made toward the age-based quotas. As needed, the team may pause or close accrual into any weight band to ensure that the accrual targets and quotas are met. For example, if accrual into one of the weight bands is initially much more rapid than accrual into other weight bands, the team may pause accrual into that weight band to ensure adequate enrollment into the other weight bands. Given that ABC/DTG/3TC immediate release tablets are being evaluated in other studies, consideration may be given to limiting accrual into weight band #5 in particular, to ensure that accrual targets for all other weight bands (in which dispersible tablets will be evaluated) are met.

The team may also consider, in consultation with the SMC, whether to permit enrollment of children switching to the study drug regimen from an NNRTI-containing regimen among the dose-evaluable in each weight band. This option would only be considered (i) six months after half of the participating study sites have been activated; (ii) if observed rates of accrual into one or more weight bands have fallen substantially short of projected rates; and (iii) if PK data from other studies (e.g., ODYSSEY) suggest that DTG PK and clinical outcomes among children switching from an NNRTI-containing regimen are not likely to differ substantially from PK and clinical outcomes among children switching from a non-NNRTI-containing regimen. Should the team determine that these conditions have been met, the team will notify the SMC and request SMC input on whether to permit enrollment of children switching from an NNRTI-containing regimen among the dose-evaluable in a given weight band. The SMC will have the option to review the team's notification, with supporting documentation, via email or to convene a teleconference review before providing a recommendation to the team.

The intent of the intensive PK evaluation in this study is to confirm dosing for use of the dispersible and immediate release tablets as directed. Consideration may be given, however, to permitting alternative preparation and administration of study drug (e.g., crushing immediate release tablets) among children undergoing intensive PK sampling if observed rates of accrual into one or more weight bands fall substantially short of projected rates, additional data from bioavailability studies are supportive of this approach, and potential differences in PK are deemed acceptable by the Protocol Team. If these conditions are met, allowances for alternative preparation and/or administration of study drug will be specified in a future protocol modification.

Additionally, if intensive PK data from this or other pediatric DTG studies indicate a food effect, and the Protocol Team determines that further data should be collected for evaluation of PK in a non-fasted state, the team will notify all study sites and provide accrual targets, guidance for food intake, and other operational instructions for evaluation of additional participants.

The Protocol Team will also monitor participant retention. On behalf of the Protocol Team, the CMC will monitor other key indicators of the quality of study conduct (e.g., adherence to study drug, specimen completeness, data completeness, data quality, protocol deviations). This monitoring will be based on reports generated by the SDMC, and team members will take action with study sites as needed to ensure high quality study conduct throughout the period of study implementation.

Participant Safety

On behalf of the Protocol Team, the CMC will closely monitor participant safety through routine review of safety data reports generated by the SDMC. These reports will be based on the safety-related data collection described in Section 7.2 and will provide listings and/or tabulations of adverse events and laboratory test results. The CMC will assess the relationship of adverse events listed in toxicity summary reports and these assessments will be recorded by the SDMC. Except in the two specific scenarios listed in this section and in Section 9.5.2, the CMC's assessments will not be used for study-related decision-making.

The CMC will review these reports via conference call or other meeting at least monthly. At the time of each call, the DAIDS Medical Officer will also review any EAEs (defined in Section 7.3) reported to the DAIDS Safety Office that are not yet reflected in the data reports. The CMC will continually evaluate the pattern and frequency of reported events and assess for any individual occurrences or trends of concern. The CMC will also monitor for the occurrence of adverse events meeting criteria to pause participant accrual and/or convene an *ad hoc* SMC review, as described in the remainder of this section and in Section 9.5.2.

Dose Confirmation for Each Weight Band

Note: Throughout this section the term "dose confirmation" is used to refer to the CMC's determination of the appropriateness of the ABC/DTG/3TC dose for each weight band.

An initial group of 5-7 children will be enrolled in each weight band and undergo intensive PK sampling at Week 1. The CMC will review intensive PK and four-week safety data for these children at least monthly until dose confirmation has been completed for each weight band. Dose confirmation will be based on dose-evaluable children as defined in Section 3.2. The CMC will take action as needed according to the PK guidelines described in Section 10.3.1 and the safety guidelines described below.

- If data from the dose-evaluable children in the weight band meet the PK and safety guidelines, and there are no safety concerns based on all available data from all weight bands, the dose will be considered appropriate for the weight band and the SMC will be notified as described in Section 9.5.2.

- If data from the dose-evaluable children in the weight band fail the PK or safety guidelines, or there are safety concerns from other weight bands, and the Protocol Team determines that an adjusted dose and/or alternative dosing strategy is needed to safely achieve targeted drug concentrations, accrual into the weight band will be paused and the SMC will be notified as described in Section 9.5.2. Following consultation with the SMC, and unless other recommendations are provided by the SMC, 5-7 additional dose-evaluable children will be enrolled into the weight band and the adjusted dose will be evaluated as described above.

- If data from other children who are evaluable for safety or PK but not both (i.e., are not dose-evaluable), are available when dose confirmation analyses are performed, these data may be included in the analyses.

- If a confident determination regarding achievement of the PK targets cannot be made, additional children enrolled in the weight band will undergo intensive PK sampling. The PK analysis for the weight band will then be repeated with data from the initial 5-7 children and the additional children.

- Unless the criteria specified below for pausing participant accrual are met, enrollment into each weight band and into the study overall will not be paused while PK and safety data are being reviewed.

Safety Guidelines for Dose Confirmation

The frequency of adverse reactions occurring among the first 5-7 participants through Week 4 will be closely monitored. Accrual into all weight bands will be paused if:

(1) Any of the first 5-7 participants in a given weight band experience a fatal or life-threatening adverse event assessed as related to study drug

OR

(2) Two or more of the first 5-7 participants in a given weight band experience a grade 3 or higher non-fatal and non-life-threatening adverse event assessed as related to study drug or an adverse event assessed as related to study drug that results in permanent discontinuation of study drug

The above-listed criteria will be applied to safety-evaluable participants. For these criteria, the site investigator's assessment of relationship to study drug will be used. If the CMC has questions about or disagrees with the site investigator's assessment, the CMC will discuss the adverse event further with the investigator and ideally come to consensus with the investigator. If consensus cannot be achieved, the CMC will request adjudication of the relationship assessment by the SMC.

If either of the above-listed criteria are met, accrual will remain paused until a safety review for the weight band is conducted by the CMC. All relevant PK and safety data from the weight band, as well as all available data from other weight bands, will be reviewed to determine whether it is safe to proceed with further evaluation of dosing for the weight band, either at the current dose or at an adjusted dose. The SMC will then review all relevant safety and PK data, along with the recommendations of the CMC, and will determine whether and under what conditions further dose evaluation for the weight band may proceed. Accrual will only be resumed if the CMC determines that it is safe to do so, and the SMC agrees. If the safety review leads to a recommendation that the dose for the weight band be decreased, the CMC and SMC will also review relevant PK data to determine whether a lower dose is likely to achieve adequate drug exposures.

If neither of the above-listed criteria are met, and there are no safety concerns from other weight bands, the dose for the weight band will be considered to have passed safety guidelines. If PK guidelines are also met, the dose will be considered appropriate for the weight band.

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

- In a group in which the true rate of toxicity is too high to warrant further exposure to the selected dose, the sample data may pass the safety guidelines.
- In a group in which the true rate of toxicity is low enough that further exposure to the selected dose is warranted, the sample data may fail the safety guidelines.

The extent to which the safety guidelines protect against these errors can be assessed by examining various hypothetical rates of "true toxicity" which could occur if the study drug were used extensively among the participant population at the dose under evaluation.

Table 14 uses a multinomial response model to assess the probability of failing the safety guidelines under each of the hypothetical situations in the table. The calculations are performed as follows: Each of the total number of participants represents a trial that may have one of three mutually exclusive outcomes: (1) a fatal or life-threatening adverse event assessed as related to study drug; (2) a grade 3 or grade 4 non-life-threatening adverse event assessed as related to study drug or an adverse event assessed as related to study drug that results in permanent discontinuation of study drug; and (3) a relatively benign outcome, satisfying neither (1) nor (2).

Table 14. Probability of Failing Dose Guidelines Under Potential Rates of True Toxicity

True Toxicity Rates		Probability of Failing Safety Guidelines
Safety Guideline (2) Grade 3 or 4 Non-Life-Threatening Related Adverse Events or Related Adverse Events that Result in Permanent Discontinuation of Study Drug	Safety Guideline (1) Life-Threatening or Fatal Related Adverse Events	
0.50	0.00	0.81
0.50	0.05	0.88
0.50	0.25	0.99
0.25	0.00	0.37
0.25	0.05	0.53
0.25	0.25	0.89
0.05	0.00	0.02
0.05	0.05	0.25
0.05	0.25	0.77
0.00	0.05	0.23
0.00	0.25	0.76

Table 14 has its sets of results under which the set of trials would pass the safety guidelines. For each of the hypothetical situations, it is assumed that a sample of five participants is drawn from the participant population and that the safety guidelines, summarized above, are followed. The probability of passing the safety guidelines represents the sum of the probabilities of these sets of results, and "1 minus the probability of passing the safety guidelines" represents the probability of failing the guidelines. The "True Toxicity Rates" presented in the table, along with the true rate of having neither of the two types of adverse events represented by the true toxicity rates (which is "1 minus the sum of the true toxicity rates"), provide the probabilities for the outcomes that are used in the multinomial calculations for each of the hypothetical situations.

As an example of how to read Table 14, the second row shows that there is an 88% chance of failing the safety guidelines at doses in which the true rate of drug related life-threatening adverse events is 5% and the true rate of drug-related non-life-threatening adverse events is 50%.

Under the conditions specified in row 2 of the table, assuming that further exposure to a dose that has these true rates of adverse events would be undesirable, the 12% chance of NOT failing the safety guidelines would represent the probability of error. As a further example, the table also shows that there is 2% chance of failing when the true rate of a drug-related grade 3 or 4 non-life-threatening adverse event is only 5% and the true rate of drug-related life-threatening or fatal adverse event is zero. Assuming that the potential benefits associated with further exposure to this dose would outweigh the risks associated with this relatively low rate of toxicity, failing the safety guidelines under these conditions would be an error.

Note that the Protocol Team may pause accrual across all weight bands if a fatal or life-threatening adverse event occurring in a given weight band is assessed as related to study drug. Thus, the probability of pausing accrual into a given weight band (pending a safety review) is somewhat higher than that of failing the safety guidelines within a given weight band (as presented in Table 14), because accrual into a given weight band may be paused due to events occurring in other weight bands.

Safety Guidelines Applicable When Additional Participants are Enrolled in a Weight Band to Attain Better Confidence in Evaluation of PK Targets

If additional participants are accrued to attain better confidence in achieving the PK targets, the number of participants evaluated for safety will be higher than the N=5 assumed in Table 14. In such cases the safety guidelines will be as follows: if any of these participants experiences a fatal or life-threatening event that is assessed as related to study drug, or if more than 25% of the participants experience a related grade 3 or higher non-fatal and non-life-threatening adverse event or a related adverse event that results in permanent discontinuation of study drug, the dose under evaluation will be considered to have failed the safety guidelines. Otherwise, and absent any safety concerns from other weight bands, the dose will be considered to have passed the safety guidelines.

9.5.2 Monitoring by the SMC

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures (MOP). The composition of the SMC will include the SMC Chair; IMPAACT Chair or Vice Chair; IMPAACT Treatment Scientific Committee Chair or Vice Chair; representatives of the IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center; and representatives of NIAID and NICHD.

Routine SMC reviews will occur at least annually and on a more frequent or *ad hoc* basis if any safety issues or concerns arise. The first routine review will take place approximately six months after the first participant is enrolled in the study, unless otherwise specified by the SMC. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

The SMC will routinely monitor study progress, quality of study conduct, and participant safety. The SMC will generally review the same types of data reports as the Protocol Team and CMC; for *ad hoc* reviews, more limited data may be reviewed, focusing on the safety issue or concern that triggered the review.

The SMC will also review safety and intensive PK outcomes and the CMC's assessment of the appropriateness of each weight band dose. For each weight band, after the CMC review described in Section 9.5.1 has occurred, the CMC will prepare a summary report for the SMC. The SMC will then have the option to review the CMC's notification via email or to convene a teleconference review before providing a recommendation with respect to confirmation of the dose for each weight band.

In addition to the above, the SMC may conduct *ad hoc* or triggered safety reviews, for which more limited data may be provided, focusing on the events that triggered the reviews. Triggered reviews will occur in the following scenarios:

(1) In the event of any adverse event that is fatal or life-threatening, the CMC will review the event as soon as possible (ideally within three business days of site awareness) and assess its relationship to study drug:

- If either the site investigator or the CMC assesses the event as related to study drug, accrual into all weight bands will immediately be paused. An ad hoc SMC review will be convened as soon as possible to discuss how the study should proceed.
- If the site investigator and the CMC assess the event as not related to study drug, participant accrual will continue. The SMC will be informed of the event along with the CMC's assessment and decision-making.

(2) If, after dose confirmation for a given weight band is completed, more than 25% of the children enrolled in that weight band experience grade 3 or higher non-fatal and non-life-threatening adverse events assessed by the site investigator as related to study drug or adverse events assessed by the site investigator as related to study drug that result in permanent discontinuation of study drug, an ad hoc SMC review will be convened. The SMC will review all relevant safety and PK data, along with the recommendations of the CMC, and determine whether and under what conditions further accrual into the study may proceed.

The CMC may also request an SMC review of any other adverse event or trend of concern. The CMC may likewise request an SMC review in the event of an unresolvable disagreement within the CMC on an issue that would impact decision-making. The CMC may choose to pause participant accrual and/or administration of study drug pending the outcome of the requested SMC review.

9.6 Analyses

9.6.1 Primary Analyses

Primary safety analyses will include safety outcomes through Week 24. To ensure that these analyses yield results that can be generalized to the overall patient population, the primary analyses will only include children who were treated with the team's final dosing recommendation. This will include children: (1) whose starting dose of ABC/DTG/3TC is the final confirmed dose for their weight band and (2) whose dose may have been increased due to weight gain putting them in a higher weight band, provided that the dose received in the higher weight band is the dose that would be recommended in the overall patient population who experience a similar weight band progression. Participants whose treatment is consistent with (1) and (2) above, but who discontinue treatment due to toxicity before Week 24 will be included and treated as safety failures in the primary safety analyses.

These primary analyses will be performed after the last participant has completed his or her Week 24 Visit. Results will be presented by weight band and in aggregate, as well by age group and study drug formulation.

All adverse events of all severity grades will be summarized.

Each participant's safety outcomes will be summarized as (1) the worst grade of adverse events, and (2) the worst grade of adverse events assessed as related to study drug. Proportions, bounded by exact 95% CIs, will be presented for participants experiencing the following:

- Grade 3 or higher adverse events
- Grade 3 or 4 adverse events assessed as related to study drug
- Grade 5 adverse events assessed as related to study drug
- Life-threatening adverse events assessed as related to study drug
- Serious adverse events assessed as related to study drug
- Adverse events assessed as related to study drug that result in permanent discontinuation of study drug

Overall proportions of participants experiencing any of these events will be presented, in addition to proportions experiencing each type of event.

Listings of all grade 3 or higher adverse events, grade 3 or grade 4 adverse events assessed as related to study drug, grade 5 adverse events assessed as related to study drug, life-threatening adverse events assessed as related to study drug, serious adverse events assessed as related to study drug, and adverse events assessed as related to study drug that result in permanent discontinuation of study drug will be provided by System Organ Class and Preferred Terms.

The proportion of participants meeting each of the criteria that trigger an SMC safety review will be presented descriptively.

Details concerning the analyses will be included in a separate statistical analysis plan.

For regulatory submission purposes, all the above analyses will be performed and will include all participants. Frequency distributions of the safety outcomes will be presented by weight band and in aggregate, as well by age group and study drug formulation.

9.6.2 Secondary Analyses

Safety

The primary safety analyses described in Section 9.6.1 will be repeated as secondary analyses for the same participants specified for the primary analyses, but including safety outcomes through Week 48, and separately through Week 144.

In addition, further analyses that include safety outcomes through Week 24, Week 48, and Week 144 for all children who received study drug will be performed. Descriptive and exposure-related analyses will present safety outcomes for children whose study drug doses were modified due to weight band dose adjustment or who otherwise received doses other than the final confirmed dose for their weight band. This will include data representing the final dose for each weight band, as well as data representing doses considered to have failed.

For each starting dose, all grade 3 or higher adverse events will be listed, along with participant demographics, the dose prescribed to the participant at the time of the event, and the site investigator's assessment of relationship to study drug.

Virologic Response

HIV-1 RNA data will be analyzed descriptively and using the FDA snapshot algorithm.

Descriptive analyses will include HIV-1 RNA data available at all timepoints and will present the number and percentage of participants with a suppressed viral load at each time point and the distribution of non-suppressed viral load values at each timepoint. Data may be presented separately for participants who were ART-naïve versus ART-experienced at study entry, as well as for participants with a documented M184V mutation, who will undergo additional HIV-1 RNA testing per the Schedule of Evaluations.

For analyses using the FDA snapshot algorithm, HIV-1 RNA values for participants who only received the final confirmed dose of ABC/DTG/3TC for their weight band will be assessed at Weeks 4, 24 and 48. At each time point, the FDA's snapshot algorithm will be used for the definition of virologic outcome, with cutoffs of 200 copies/mL or 50 copies/mL (analyses will be performed twice, once at the 200 copies/mL threshold and separately at the 50 copies/mL threshold). In addition, participants will be classified as virologic failures if they prematurely discontinued study drug prior to Week 4, Week 24, or Week 48.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on study drug within the visit of interest window (this window will be defined in the statistical analysis plan). The proportions of participants meeting the criteria

for virologic failure or success at each time point will be bounded by exact 95% CIs and will be presented both in the aggregate and by weight band.

In addition, virologic response analysis results will also be presented for all participants who received study drug.

Immunologic Response

Median and the associated interquartile range for changes in CD4+ count and percentage from baseline to Weeks 4, 24, 48, and up to Week 144, for participants who only received the final confirmed dose of ABC/DTG/3TC for their weight band will be presented by weight band and aggregated, bounded by 95% CIs. Missing CD4+ values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline CD4+ values.

In addition, immunologic response analysis results will also be presented for all participants who received study drug.

Total Cholesterol, HDL, LDL, and Triglycerides

Median and the associated interquartile range for changes in total cholesterol, HDL, LDL, and triglycerides from baseline to Weeks 24 and 48 for participants who only received the final confirmed dose of ABC/DTG/3TC for their weight band will be presented by weight band and aggregated. Missing total cholesterol, HDL, LDL, and triglyceride values for participants who discontinued study drug prior to the time point of interest due to safety or virologic failure will be replaced with their baseline values.

In addition, changes in total cholesterol, HDL, LDL, and triglycerides from baseline to Weeks 24 and 48 will also be presented for all participants who received study drug.

Adherence, Palatability and Acceptability

Adherence, palatability and acceptability measures — based on questionnaire responses — will be summarized by weight band and aggregated for all participants who received study drug.

As indicated in Section 5.2, acceptability and palatability measures will be reviewed by the Protocol Team to determine preferred dispersion volumes for children in weight bands #3 and #4. It is generally expected that these data will be reviewed after approximately 20-30 children in these weight bands have completed their Week 4 Visits; however, this determination may be made at any time in response to accumulating study data.

These data will be presented descriptively.

Antiretroviral Resistance

Participants with confirmed virologic failure (refer to Section 8.3) will be evaluated for viral resistance to the components of the study drug regimen. For these participants, resistance mutations will be presented descriptively.

9.6.3 Exploratory Analyses

Mood and sleep measures — based on questionnaire responses — will be summarized by weight band and aggregated for all participants who received study drug.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

The clinical pharmacology evaluations for this study are designed to determine the steady-state PK of DTG, ABC, and 3TC when given as a fixed dose combination dispersible or immediate release tablet to children less than 12 years of age. The pharmacology objectives reflect ViiV's currently agreed PIP and PSP and are listed below. For the primary and secondary PK objectives, drug concentrations will be quantified in plasma. For the exploratory PK objectives, drug concentrations will also be quantified in PBMCs and DBS.

All PK samples will be registered in the LDMS and shipped to the designated central pharmacology laboratory; refer to the LPC for shipping details. Intensive PK samples, collected at the Week 1 Visit, will be shipped and analyzed in real-time, with results reported to and discussed with the Protocol Team as they become available. Sparse PK samples will be analyzed in batch after follow-up of all participants has been completed unless otherwise requested by the Protocol Team.

Primary

- To determine the steady-state $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} of ABC, DTG, and 3TC and confirm the dosing of ABC/DTG/3TC dispersible and immediate release tablets that achieve protocol-defined PK targets for ABC, DTG, and 3TC in children less than 12 years of age

Secondary

- To determine the PK of ABC, DTG, and 3TC, and clinical covariates that influence PK disposition, among children less than 12 years of age using population PK analysis of intensive and sparse PK samples collected over 48 weeks of treatment with ABC/DTG/3TC dispersible and immediate release tablets

Exploratory

- To describe pharmacogenetic associations among children less than 12 years of age receiving treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets
- To determine concentrations of phosphorylated 3TC and ABC anabolites in PBMCs and DBS over 48 weeks of treatment with ABC/DTG/3TC dispersible tablets and ABC/DTG/3TC immediate release tablets among children less than 12 years of age
- To examine relationships between PK-based adherence measures and other adherence measures

10.2 Pharmacology Outcome Measures

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

10.2.1 Primary PK Outcome Measures	
10.2.1.1	• Geometric mean $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} for ABC, DTG, and 3TC based on analysis of intensive PK samples collected at Week 1 ($AUC_{0\text{-}24h}$ and C_{24h} to be compared within each weight band to the PK targets specified in Section 10.3.1)
10.2.2 Secondary PK Outcome Measures	
10.2.2.1	• $AUC_{0\text{-}24h}$, C_{0h}, C_{24h}, C_{max}, T_{max}, CL/F, and $t_{1/2}$ derived from population PK modeling with sampling through Week 48
10.2.3 Exploratory PK Outcome Measures	
10.2.3.2	• UGT1A1, CYP2B6, and other polymorphisms of interest with respect to DTG, 3TC, and/or ABC • Association of polymorphisms with PK outcomes
10.2.3.3	• Concentrations of phosphorylated ABC and 3TC anabolites in PBMCs • Concentrations of phosphorylated ABC and 3TC anabolites in DBS
10.2.3.4	• Associations between phosphorylated ABC and 3TC anabolites and directly observed dosing, participant/parent/guardian reported adherence, and drug concentrations

10.3 Pharmacology Study Design, Modeling, and Data Analysis

10.3.1 PK Criteria for Weight Band Dose Confirmation

The steady-state $AUC_{0\text{-}24h}$ of ABC, DTG, and 3TC and C_{24h} of DTG will be the primary PK parameters used to determine the appropriateness of initial selected weight band doses of ABC/DTG/3TC. These parameters will be determined based on analysis of intensive PK samples collected from the first five dose-evaluable children enrolled in each weight band (refer to Section 10.5.1 for analytic methods); if evaluable intensive PK data are also available from other children enrolled in each weight band, these data will be included in the analysis (see Section 3.2 for definitions of dose-evaluable and PK-evaluable). Children undergoing intensive PK sampling are expected to be ART-naïve or switching from a non-NNRTI-containing regimen at enrollment; however, consideration may be given to expanding intensive PK sampling to children switching from an NNRTI-containing regimen under the conditions pre-specified in Section 9.5.1.

Dose confirmation within each weight band will be based on achieving a geometric mean DTG $AUC_{0\text{-}24h}$ between 35.1 and 134 µg·h/mL and C_{24} between 0.67 and 2.97 µg/mL, and geometric mean ABC and 3TC $AUC_{0\text{-}24h}$ between 6.3 and 50.4 µg·h/mL and 6.3 and 26.5 µg·h/mL, respectively, as shown in Table 15. The rationale for these PK targets is described in Section 1.3.3.

Table 15. $AUC_{0\text{-}24h}$ and C_{24h} Targets for Each Weight Band in IMPAACT 2019

PK	DTG Targets		ABC Targets		3TC Targets	
Parameter	Lower	Upper	Lower	Upper	Lower	Upper
$AUC_{0\text{-}24h}$ (µg·h/mL)	35.1	134	6.3	50.4	6.3	26.5

C_{24h} (µg/mL)	0.67	2.97	—	—	—	—

10.3.2 Initial Dose Selection and Weight Band Dose Adjustment

The initial doses selected for evaluation in this study are based on modeling/simulations with available data from IMPAACT P1093 and published PK data for DTG, ABC, and 3TC. The selected doses of DTG are expected to achieve DTG AUC_{0-24h} similar to that observed with DTG 50 mg twice-daily in adults. The dosing for ABC and 3TC aligns with WHO weight band dosing recommendations of ~16 mg/kg and ~8 mg/kg once-daily, respectively. The selected doses of DTG are higher than those previously evaluated in IMPAACT P1093. This is because the doses for ABC and 3TC increase in sync with each other and body weight, whereas the increase is not the same for DTG. Safety data available from adults with higher DTG doses and exposures support the DTG doses selected for evaluation in this study.

For children switching to the study drug regimen from an NNRTI-containing regimen, no pre-emptive DTG dose adjustments will be made. That is, these children will receive the ABC/DTG/3TC dose selected for their respective weight band. In the SWORD 1 and 2 studies in adults, no DTG dose adjustments were made following transition from efavirenz or nevirapine to DTG with rilpivirine, and trough levels remained above the IC_{90} at all time points examined (34). If the ABC, DTG, or 3TC geometric mean AUC_{0-24h} and/or DTG C_{24h} for a given weight band fall outside the targeted range, the Protocol Team will determine whether to adjust the dose for the weight band taking into consideration the AUC_{0-24h} and C_{24h} values; clinical, virologic, and immunologic responses; and other available data from this and other ongoing and previously conducted studies. If the weight band AUC_{0-24h} or C_{24h} fall below or above the targeted PK ranges, the Protocol Team may adjust the weight band doses and/or recommend alternative dosing strategies, selecting from alternative dosing tables provided in Appendix VI.

The alternative dosing tables are based on currently available PK data and may be updated in the future as new data become available from this and other studies. If the Protocol Team deems that an adjusted dose and/or alternative dosing strategy is required to achieve the appropriate PK targets within a specific weight band, 5-7 additional dose-evaluable children will be enrolled in that weight band to confirm the appropriateness of the adjusted dose or alternative dosing strategy. Children who received the initial dose for the weight band will be managed on a case-by-case basis by the site investigator in consultation with the Protocol Pharmacologists and other Protocol Team members. Children whose PK outcomes fell outside the targeted range would generally be expected to undergo an individual dose adjustment to the same dose to be evaluated in the new group of 5-7 children. For children whose PK outcomes fell within the targeted range, the Protocol Pharmacologists will discuss options and recommendations with the site investigator, who will further discuss these with the child and/or the child's parent or guardian and determine whether to adjust the child's dose. For any child whose dose is adjusted, a repeat PK assessment may be performed in consultation with the Protocol Pharmacologists.

10.3.3 Intensive PK Evaluations

Analyses to determine the appropriateness of initial selected weight band doses of ABC/DTG/3TC will be based on a minimum of five children in each weight band. Depending on the pace of enrollment and availability of PK results, intensive PK data from additional children may also be included in these analyses. Additional children may also undergo intensive PK sampling if, in the opinion of the Protocol Pharmacologists, a confident determination regarding

achievement of PK targets cannot be made based on the first 5-7 dose-evaluable children in a given weight band. Accrual will continue while intensive PK evaluations are performed and the appropriateness of each weight band dose is determined.

Children undergoing intensive PK sampling should receive the formulation and preparation of study drug specified for their weight band between enrollment and the day of intensive PK sampling; i.e., children in weight bands #1-#4 should ingest dispersible tablets following dispersion in water and children in weight band #5 should swallow immediate release tablets whole. For weight band #5, all efforts should be made to ensure that children are able to swallow immediate release tablets whole prior to entry. If a child is enrolled and then found to be unable to swallow immediate release tablets whole prior to intensive PK sampling, he or she will be permitted to take crushed tablets and will undergo intensive PK sampling, but he or she will not be considered PK-evaluable for the weight band. If three or more participants enrolled in weight band #5 are unable to swallow the immediate release tablets whole, the Protocol Team may then decide to consider children who receive crushed tablets as PK-evaluable.

Children undergoing intensive PK sampling must have confirmed study drug dosing for at least four consecutive days leading up to the date of sampling at the Week 1 (Day 5-10) Visit. Dosing will be confirmed by texted video, video streaming, in-person directly observed therapy, or other method approved by the Protocol Team. If a child misses a dose within the four days prior to the intensive PK sampling, the sampling will be postponed (within the allowable visit window) until dosing is confirmed for at least four days leading up to the sampling.

The Week 1 Visit should be scheduled so that an observed dose of ABC/DTG/3TC is taken at the study site within 22-26 hours of the previous dose. Refer to Section 6.3 for procedures to be followed. A heparin or saline lock should be used for intensive PK sample collection if at all possible. Samples will be collected as follows:

- Prior to observed dosing of study drug (1 mL)
- 1 hour (±30 minutes) after observed dosing of study drug (1 mL)
- 2 hours (±30 minutes) after observed dosing of study drug (4 mL)
- 3 hours (±30 minutes) after observed dosing of study drug (1 mL)
- 4 hours (±30 minutes) after observed dosing of study drug (1 mL)
- 6 hours (±60 minutes) after observed dosing of study drug (1 mL)
- 8 hours (-15 to +120 minutes) after observed dosing of study drug (1 mL)
- 24 hours (±120 minutes) after observed dosing of study drug (1 mL)

10.3.4 Individual PK Evaluations and Dose Adjustments

Section 10.3.2 provides information on weight band dose adjustments that may be made based on $AUC_{0\text{-}24h}$ and C_{24h} values observed among dose-evaluable children in each weight band. For children undergoing intensive PK sampling, individual dose adjustments may also be considered based on individual $AUC_{0\text{-}24h}$ and C_{24h} values for DTG.

Consideration will be given to individual dose adjustments if a child's DTG $AUC_{0\text{-}24h}$ or the C_{24h} falls outside of the ranges described in the remainder of this section. Individual dose adjustments may be made either using ABC/DTG/3TC fixed dose combination tablets or single agent tablets, as deemed appropriate by the Protocol Team. Dose adjustments will not be made before the Week 4 Visit to permit accurate analysis of safety and virologic response to ABC/DTG/3TC.

The targeted DTG $AUC_{0\text{-}24h}$ range for individual participants is 25-134 µg·h/mL. The lower limit is based on maximum effect (E_{max}) models, where the estimated DTG $AUC_{0\text{-}24h}$ required to produce 95% of the maximum virologic response (EC_{95}) is 25 µg·h/mL. The upper limit is based on the upper bound of the 90% CI in adults receiving twice-daily DTG in the VIKING studies. The geometric mean $AUC_{0\text{-}24h}$ at steady state following 50 mg twice daily exposure was 75.1 µg·h/mL, with a 90% CI of 40-134 µg·h/mL. The minimum C_{24h} threshold for individual participants is 0.5 µg/mL. This value is based on the EC_{95} for this PK measure and is significantly above the *in vivo* EC_{90} (0.3 µg/mL). There have been no toxicities observed in association with C_{24h} values, thus no upper limit is defined for individual participants.

Based on the above-described data, the Protocol Team has determined that children undergoing intensive PK sampling with an observed DTG $AUC_{0\text{-}24h}$ value falling below 25 µg·h/mL or above 134 µg·h/mL, or C_{24h} value falling below 0.5 µg/mL, will be considered for an individual dose adjustment.

If a child requires an individual dose adjustment, a repeat PK assessment may be performed for that child, to confirm that PK targets are achieved, with an appropriate sampling strategy determined by the Protocol Pharmacologists. The Protocol Pharmacologists may also recommend that procedures for directly observed therapy (described in Section 6.2) be followed prior to the repeat PK assessment, if logistically feasible for the site and the child's parent or guardian. *Note:* Refer to Section 8.4 for a description of intensive PK evaluations to be performed for children who require rifampin-containing TB treatment.

10.3.5 Population PK Evaluations

Blood samples for population PK analysis will be collected as shown in Table 16. At most of these visits, one sparse PK sample will be collected. At Week 1, two samples will be collected, following observed administration of study drug, at least two hours apart. At Weeks 2 and 6, samples should be collected 22-26 hours after the previous dose of study drug. At all visits listed below, there is no restriction on the timing of sample collection. However, across participants, samples should be collected at different times throughout the 24-hour dosing interval (i.e., not all samples collected at the same time post-dose).

Table 16. IMPAACT 2019 Sparse PK Sampling Schedule

Study Visit	Population Sampled
Week 1	All children not undergoing intensive PK sampling at Week 1 (4 mL and 1 mL)
Week 2	Only children switching to the study drug regimen from an NNRTI-containing regimen (4 mL)
Week 4	All children (4 mL)
Week 6	Only children switching to the study drug regimen from an NNRTI-containing regimen (4 mL)
Weeks 8	Only children with a documented M184V resistance mutation (4 mL)
Week 12	All children (4 mL)
Weeks 16 and 20	Only children with a documented M184V resistance mutation (4 mL)

Weeks 24, 36, and 48	All children (4 mL)
Confirmation of Virologic Failure	All children completing these visits (4 mL)
Early Discontinuation	All children completing these visits (4 mL)

10.4 Sample Size Justification

Power calculations were performed using SAS version 9.4 (Cary, NC) for sample sizes of five participants per weight band and 25 total participants undergoing intensive PK assessments for the initial dose confirmation of the ABC/DTG/3TC fixed dose combination. Power estimates were based on comparison of the minimum and maximum $AUC_{0\text{-}24h}$ weight band targets for DTG to the geometric mean $AUC_{0\text{-}24h}$ value of 53.6 µg·h/mL (CV 26.9%) reported for once-daily DTG in adults (n=449). The lower and upper weight band targets of 35.1 and 134 µg·h/mL were log-transformed, equating to 3.558 and 4.898, respectively. The corresponding log-transformed mean (SD) for adult data was 3.982 (0.264). Using these inputs with a total sample size of 25 total participants, the study has >99.9% power to detect a change from the geometric mean values measures in adults to either the lower or upper $AUC_{0\text{-}24h}$ targets for DTG using a two-sample t-test at a significance level of 0.05. For a sample size of five participants within each weight band, the study has 94.6% and >99.9% power to detect a difference between the reference data in adults and the lower and upper PK targets, respectively.

Power calculations were also performed for comparisons of the geometric mean (%CV) C_{24h} in adults of 1.11 µg/mL (46.3%) with the minimum and maximum C_{24h} weight band targets of 0.67 and 2.97 µg/mL. These calculations were performed using the same procedures detailed for $AUC_{0\text{-}24h}$ above, results of which are detailed in Table 17 below.

Greater variability in the PK of ABC, DTG, and 3TC will likely be observed in children due to differences in formulations, preparations, and adherence in comparison to the historical data used for the power estimates above.

Table 17. Power Estimates for Total and Individual Weight Band Sample Sizes

	$AUC_{0\text{-}24h}$ (Primary)				C_{24h} (Secondary)			
	Lower Bound		Upper Bound		Lower Bound		Upper Bound	
Adult Ln-transformed mean	3.982	3.982	3.982	3.982	0.104	0.104	0.104	0.104
2019 Ln-transformed target	3.558	3.558	4.898	4.898	-0.4	-0.4	1.089	1.089
Ln-transformed SD	0.264	0.264	0.264	0.264	0.441	0.441	0.441	0.441
Adult (reference) sample size	449	449	449	449	449	449	449	449
IMPAACT 2019 sample size	25	5	25	5	25	5	25	5
Computed power	>.999	0.946	>.999	>.999	>.999	0.718	>.999	0.999

10.5 PK Analyses

10.5.1 Noncompartmental PK Analysis

Steady-state PK parameters for DTG, 3TC, and ABC will be determined using non-compartmental methods based on intensive PK samples collected at the Week 1 (Day 5-10) Visit (Phoenix WinNonlin v7.0, Pharsight Corp, Mountain View, CA). PK parameters of interest include: area-under-the-concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$), maximum

plasma concentration (C_{max}), time to C_{max} (T_{max}), plasma concentrations at the beginning (C_{0h}) and end of the 24-hour dosing interval (C_{24h}), minimum plasma concentration (C_{min}), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), elimination rate constant (k_e), and terminal half-life ($t_{1/2}$). C_{max}, T_{max}, C_{0h}, C_{24h}, and C_{min} will be determined from direct observation of the concentration versus time profiles. K_e will be determined by calculating the slope of the log-linear regression using at least three points during the elimination phase, not including C_{max}, and $t_{1/2}$ will be calculated as $0.693 \div k_e$. $AUC_{0\text{-}24h}$ will be determined using the linear up-log down trapezoidal rule. CL/F will be calculated using the equation CL/F = dose ÷ $AUC_{0\text{-}24h}$. Vz/F will be calculated using the equation $Vz/F = CL/F \div k_e$.

PK results for ABC, DTG, and 3TC will be reported on an individual basis for each participant who undergoes an intensive PK evaluation. Following the completion of PK evaluations in 5-7 dose-evaluable participants, geometric mean (%CV) $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} values will be calculated for ABC, DTG, and 3TC. Summary PK results within each weight-band will then be compared to relevant PK targets of interest for dose confirmation.

10.5.2 Population PK Analysis

The PK characteristics of ABC, DTG, and 3TC will be evaluated using non-linear mixed effects modeling (NLME). NLME uses mixed effects (random and fixed) regression to estimate population means and variances of PK parameters and to identify intrinsic and extrinsic factors, such as body weight, sex or concomitant drug that may influence these parameters. Base models will be developed using first-order conditional estimation with or without interaction. A stepwise procedure will be used to determine whether a one- or two-compartment model best fits the plasma data under the principle of parsimony. A log-normal error distribution will be assumed for the description of both interparticipant and intraparticipant (residual) PK parameter variability. If necessary, poorly identified structural parameters, such as the absorption rate constant, may be fixed. The following covariates will be collected at baseline or during follow-up visits: sex, age, weight, race, adherence, etc. The influence of each covariate on the PK characteristics of DTG will be tested sequentially. At each step, the goodness of fit plots will also be evaluated. At the end of the analysis, all covariates that show an influence on the parameters will be evaluated again by comparison of the full model (with all factors included) with a model from which each of the factors is deleted sequentially. For forward addition and backward, elimination, a decrease in objective function value by 3.84 ($p \leq 0.05$) and 6.64 ($p \leq 0.01$), respectively, would indicate influential covariates. Data from this study may be supplemented with pediatric PK data from other DTG studies (e.g., IMPAACT P1093, ODYSSEY) to support structural model and/or parameter precision if needed.

NLME uses extended least squares to calculate the objective function and the difference in the value of the objective function between models is approximately chi square distributed. A difference in objective function of greater than 6.6 is considered significant (6.6 corresponds to a chi square for $p = 0.01$ with 1 degree of freedom) when one parameter is added or the covariate (e.g., body weight) is replaced. This is analogous to the commonly used F test to select among regression models. The primary outcome of this analysis is to identify the model that best describes the plasma PK of DTG and to investigate whether any of the covariates influences the PK of DTG. The final model will include all significant covariates (if any) and the parameter estimates for all parameters together with the estimates of residual and inter-individual variability.

Another objective of this combined analysis will be to develop a linked population PK/PD model in NLME to evaluate potential relationships between these PK parameters and therapeutic outcomes (e.g., HIV viral load and adverse events).

10.5.3 Exploratory PK Analyses

In addition to plasma PK evaluations, drug concentrations will be characterized in other matrices as follows:

- Phosphorylated ABC and 3TC moieties in PBMCs
- Phosphorylated ABC and 3TC moieties in DBS

The active moieties of ABC and 3TC are found intracellularly; thus, examining intracellular levels in PBMCs may provide additional insight into exposure-response relationships at the site of action for these agents. PBMCs will be processed and stored at time points indicated in Section 6 and the Schedule of Evaluations, concurrent with sparse PK sampling. Summary statistics and graphical representations for concentrations of these active moieties will be generated for each time point of interest and may also be used to examine exposure-response relationships with therapeutic outcomes.

Drug concentrations in DBS will be quantified and compared to self-reported adherence measures. DBS collection is less invasive for quantifying drug levels and may provide improved measures of long-term adherence in comparison to plasma PK samples. DBS will be processed and stored at time points indicated in Section 6 and the Schedule of Evaluations, concurrent with sparse PK sampling. Summary statistics and graphical representations of drug levels in DBS will be generated for each time point of interest. Results will be compared to available historical data. The effect of covariates such as time post-dose, self-reported adherence leading up to the time point of interest, time on ABC/DTG/3TC, and other factors that may influence drug levels will be explored.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

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

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled children, including paper-based CRFs (if used), eCRFs, and supporting source data. In maintaining these records, sites must comply with the standards of source documentation specified in the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (available on the website referenced in Section 11.2). For participants undergoing directly observed dosing via electronic communication, study staff who receive the communication will document the date and time of the communication and the required data elements specified in Section 6.2; electronic text and/or video data will then be deleted. Electronic files will not be stored as part of participant research records.

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

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

11.2 Essential and Source Documents and Access to Source Data

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

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

Per the DAIDS policy on Storage and Retention of Clinical Research Records, study records must be stored in a manner that ensures privacy, confidentiality, security, and accessibility during the conduct of the study and after the study is completed. Records must be retained for a minimum of three years after the completion of the study. Per 21 CFR 312.62, records must be maintained for two years after the date a marketing application is approved for the study drug for the indication 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, ViiV Healthcare Ltd, the FDA, site drug regulatory authorities, site IRBs/ECs, OHRP, and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID or NICHD. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID or NICHD.

11.3 Quality Control and Quality Assurance

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

12 CLINICAL SITE MONITORING

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

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must 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 14.2).

13.2 Vulnerable Participants

The NIH is mandated by law to ensure that children be included in clinical research when appropriate (47). This study responds to that mandate and will provide clinical research data to inform study drug dosing guidelines for children. Nonetheless, the children enrolled in this study are considered vulnerable participants per 45 CFR 46 Subpart D. Site IRBs/ECs must consider the potential benefits, risks, and discomforts of the study children and assess the justification for their inclusion in this study. As part of this assessment, IRBs/ECs must determine the level of risk to children in the categories specified in 45 CFR 46.404-407. Documentation of this determination is required to complete the DAIDS protocol registration process described in Section 14.2, and the risk category assigned by the IRB/EC 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 informed consent forms as needed to accommodate the parental consent requirements associated with the IRB/EC determination.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Requirements, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations
In addition to the US regulations cited above, sites in Botswana, South Africa, and Thailand must also comply with all applicable local and national guidelines and regulations.

13.3 Informed Consent

Refer to Section 4.4 and the study-specific MOP for further information on informed consent procedures for this study. Refer to Appendices II-III for sample informed consent forms and to Appendices IV-V for sample assent forms.

Written informed consent for study participation will be obtained from each child's parent or legal guardian before any study-specific procedures are performed. It is generally expected that the consent of one parent (or legal guardian) will be sufficient for child participation in this study. However, consenting requirements at each site will depend on the IRB/EC risk determination as described in Section 13.2; all IRB/EC requirements must be followed. When applicable per site IRB/EC policies and procedures, written assent will also be obtained from each child before any study-specific procedures are performed. For participants who do not meet IRB/EC criteria for providing assent at the time of screening and enrollment, if such criteria are met during follow-up, assent should be obtained when the criteria are met.

Informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will include a description of what is currently known about the safety and efficacy of the study drug and the context of current local standards of care for HIV care and treatment. The assent process will include a similar but age-appropriate discussion. The amount of information and level of detail provided as part of the assent process should be tailored to the age and maturity of the potential participant, guided by IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, sites may remove or modify the wording included in the sample assent forms in order to provide the most appropriate information and level of detail, consistent with IRB/EC policies and procedures.

Separate from the main study informed consent and assent processes, parents, legal guardians, and/or children will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been completed. This storage and future research testing is optional and may be declined with no impact on other aspects of study participation. This informed consent and assent process should ideally be conducted at the study Screening or Entry Visit but may be completed at any time up until the Week 4 Visit.

Should the consenting parent or legal guardian of an enrolled child die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed. If the child is doing well on study drug, it is generally expected that he or she will stay on study drug with safety monitoring evaluations performed consistent with the local standard of care. Other study-specific evaluations (outside the standard of care) should not be performed until informed consent for continued study participation is obtained from the child's authorized guardian, as defined locally. If an authorized guardian cannot be identified, or if the guardian does not consent to continued study participation, the child 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 13.2), 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, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

13.4 Potential Benefits

There may or may not be direct benefit to children who take part in this study. Although direct benefit cannot be guaranteed, the fixed dose combination of ABC/DTG/3TC has been demonstrated as safe, effective, and well-tolerated in adults, and is expected to provide similar therapeutic benefits to children. The once daily ABC/DTG/3TC regimen may also facilitate correct and consistent dosing for children, compared to other currently available pediatric regimens, which often involve twice daily dosing.

Information learned in this study may be of benefit to participating children and others in the future, particularly information that may lead to more treatment options for HIV-infected children. Children may also appreciate the opportunity to contribute to HIV-related research.

13.5 Potential Risks

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

Most study procedures are routine medical procedures that are associated with minimal to no risk. Blood collection may cause pain, bruising, swelling, or fainting. There is a very small chance of infection where the needle is inserted.

Refer to Section 0, the investigator's brochures for ABC/DTG/3TC dispersible tablets, and the package insert for ABC/DTG/3TC immediate release tablets for a description of the potential risks associated with the use of these drugs. For virologically suppressed ART-experienced children switching to use of ABC/DTG/3TC, there is a potential additional risk that the ABC/DTG/3TC may not be as well-tolerated or as effective in maintaining viral suppression as the child's pre-study ART regimen.

DTG taken at the time of conception or very early pregnancy may be associated with NTDs in the fetus. There is no evidence that the risk of NTDs or other birth defects is increased when DTG is started after the early first trimester of pregnancy. Every effort will be made in this study to avoid the occurrence of new pregnancies among participants taking DTG.

Refer to Section 13.7 for further information on privacy and confidentiality. Despite efforts to maintain confidentiality, children's involvement in this study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV). For example, children could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. For children who undergo directly observed therapy with texted or streaming video, there is an additional risk of loss of confidentiality. Videos may not be encrypted and could be decoded and viewed by persons not involved in the study. Telephone numbers may also be visible to others. Every effort will be made to protect participant information, but this cannot be guaranteed.

13.6 Reimbursement/Compensation

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

13.7 Privacy and 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 as described in Section 11.2.

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

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

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

13.8 Communicable Disease Reporting

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

13.9 Management of Incidental Findings

Study staff will inform parents or guardians of all clinically meaningful physical exam findings and laboratory test results. When applicable, site investigators will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

The results of intensive PK evaluations will be provided to parents or guardians in real time with an explanation as to whether the results fall within the targeted range described in Section 10.3.4. The results of other PK evaluations are not planned to be provided to parents or guardians as these evaluations will be performed after follow-up has been completed and are not expected to be relevant to children's clinical care and management. If, however, new information becomes available during the course of the study indicating that the results of these evaluations are of clinical relevance, the results will be provided.

13.10 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.

13.11 Post-Trial Access to Study Drug

ViiV Healthcare Ltd currently plans to seek licensure of ABC/DTG/3TC for pediatric use in all countries where this study will be conducted.

Participants will be transitioned into local standard HIV care and treatment at the end of their study participation. If ABC/DTG/3TC is not locally available at that time, ABC/DTG/3TC will be provided by ViiV Healthcare Ltd through a mechanism outside of the study until one or more of the following occur:

- The age-appropriate formulation of ABC/DTG/3TC is locally available from another source
- The participant is no longer deriving benefit from ABC/DTG/3TC
- Clinical development of ABC/DTG/3TC is terminated

For children who are deriving benefit from ABC/DTG/3TC as they complete their Week 48 Visits, if ABC/DTG/3TC is not otherwise available from a non-study source, follow-up in the study — with provision of study supplies of ABC/DTG/3TC — may continue for up to 96 additional weeks, as described in Section 6.13. For these children, once ABC/DTG/3TC becomes available from a non-study source, study participation should be discontinued with transition into local standard HIV care and treatment.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

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

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

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

14.2 Protocol Registration

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

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

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

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available at:
https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US and local regulations. Study implementation will also be guided by the IMPAACT MOP, study-specific MOP, LPC, and other study implementation materials, which will be available on the study-specific website:
http://impaactnetwork.org/studies/IMPAACT2019.asp.

Study implementation at each site will also be guided site-specific SOPs. The DAIDS policy on Requirements for Manual of Operational Procedures specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials (available on the website referenced in Section 11.2). These SOPs should be updated and/or supplemented as needed to describe roles, responsibilities, and procedures for this study.

14.4 Protocol Deviation Reporting

Per the policy for *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (available at the website referenced in Section 11.2), all protocol deviations must be documented in participant research records. Reasons for the deviations and corrective and preventive actions taken in response to the deviations should also be documented.

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

14.5 Critical Event Reporting

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

14.6 ClinicalTrials.gov

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

15 PUBLICATIONS

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

16 REFERENCES

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Appendix I: Schedule of Evaluations through Week 48

	Screen	Entry	Weeks on Study											Confirm VF	Early DC	Post Exit[6]
Study Visit	*up to -30 days*	*Day 0*	1	2[1]	4	6[1]	8[2]	12	16[2]	20[2]	24	36	48			
CLINICAL EVALUATIONS																
Medical and medication history	X	X	X	[X]	X	[X]	[X]	X	[X]	[X]	X	X	X	X	X	X
Physical examination	X	X	X	[X]	X	[X]	[X]	X	[X]	[X]	X	X	X	X	X	[X]
Study drug adherence and tolerability questionnaires					X			X			X		X	X	X	
Mood and sleep questionnaire		X			X						X					
LABORATORY EVALUATIONS																
Confirmatory HIV testing (if needed)	0-6mL															
HLA-B*5701 (if needed)	0-3mL															
Hepatitis B surface antigen	2mL															
Pregnancy test[3]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	X
HIV-1 RNA	3mL	3mL			3mL		3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	3mL	
CBC with differential and platelets	1mL				1mL			1mL			1mL	1mL	1mL		1mL	
CD4+ cell count and percentage	1mL				1mL			1mL			1mL		1mL		1mL	
ALT, AST, total bilirubin, direct bilirubin, creatinine, eGFR	2mL				2mL			2mL			2mL	2mL	2mL		2mL	
Total cholesterol, HDL, LDL, and triglycerides (non-fasting)	1mL										1mL		1mL			
ARV resistance testing[4]														3mL		
Intensive PK sampling[5] (store plasma, DBS, and PBMC)			11mL													
Sparse PK sampling[5] (store plasma, DBS, and PBMC)			5mL	4mL	4mL	4ml	4mL	4ml	4mL	4mL	4mL	4mL	4mL	4mL	4mL	
Stored whole blood		4mL														
Total Blood Volume	**10-19 mL**	**7 mL**	**5 or 11 mL**	**4 mL**	**11 mL**	**4 mL**	**7 mL**	**11 mL**	**7 mL**	**7 mL**	**12 mL**	**10 mL**	**12 mL**	**10 mL**	**11 mL**	**0-1 mL**

Appendix I: Schedule of Evaluations through Week 48 Footnotes

[X] = if clinically indicated.
[1]The Week 2 and Week 6 Visits will be conducted only for participants switching to the study drug regimen from an NNRTI containing regimen.
[2]The Week 8, Week 16, and Week 20 Visits will be conducted only for children with a documented M184V mutation.
[3]Pregnancy tests are required only for female participants of reproductive potential. Urine (5 mL) or blood (1 mL) tests may be performed. At sites performing blood tests, the total blood volume would be 1 mL greater than shown in the table above.
[4]Genotypic and phenotypic ARV resistance testing of plasma collected at the Confirmation of Virologic Failure Visit will be performed in real time if virologic failure is confirmed; otherwise, the plasma sample collected for this purpose will be stored. Refer to Section 6.14 and Section 8.3 for additional detailed information.
[5]At Week 1, each participant will either undergo either intensive PK sampling or sparse PK sampling. After Week 1, all participants will undergo sparse PK sampling. Refer to Section 6.3 and Section 10 for additional detailed information on sampling volumes and time points. Refer to the LPC for sample processing, storage, and shipping instructions.
[6]The Post Exit Visit will be conducted only for participants who are on contraception at their last study visit.

Appendix I: Schedule of Evaluations after Week 48

Study Visit	Q12 Weeks[1]	Confirm VF	Post Exit[5]
CLINICAL EVALUATIONS			
Medical and medication history	X	X	X
Physical examination	X	X	[X]
Study drug adherence and tolerability questionnaires		X	
LABORATORY EVALUATIONS			
Pregnancy test[2]	[X]	[X]	X
HIV-1 RNA	3mL (Q24)	3mL	
CBC with differential and platelets	1mL (Q24)		
CD4+ cell count and percentage	1mL (Q24)		
ALT, AST, total bilirubin, direct bilirubin, creatinine, eGFR	2mL (Q24)		
ARV resistance testing[3]		3mL	
Sparse PK sampling[4] (store plasma, DBS, and PBMC)		4 mL	
Total Blood Volume	**7mL (Q24)**	**10mL**	

[1]Refer to Section 6.13. Following completion of the Week 48 Visit, children who are deriving benefit from ABC/DTG/3TC may remain on-study for up to an additional 96 weeks if ABC/DTG/3TC is not otherwise available from a non-study source. During this time, study visits will be targeted to occur every 12 weeks (i.e., at Weeks 60, 72, 84, 96, 108, 120, 132, and 144 with clinical evaluations performed every 12 weeks and laboratory performed at every 24 weeks (i.e., at Weeks 72, 96, 120, and 144).
[2]Pregnancy tests are required only for female participants of reproductive potential. Urine (5 mL) or blood (1 mL) tests may be performed. At sites performing blood tests, the total blood volume would be 1 mL greater than shown in the table above.
[3]Genotypic and phenotypic ARV resistance testing will be performed in real time if virologic failure is confirmed; otherwise, the sample collected for this purpose will be stored. Refer to Section 6.14 and Section 8.3 for additional detailed information.
[4]Refer to the LPC for sample processing, storage, and shipping instructions.
[5]The Post Exit Visit will be conducted only for participants who are on contraception at their last study visit.

Appendix II: Sample Informed Consent Form for Study Participation

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, 4 September 2019

Introduction

Your child is being asked to take part in the research study named above.

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

Here is a summary of important information about the study:

- The study is testing a new combination of anti-HIV medicines (ARVs) for children less than 12 years of age.
- The new combination is a tablet that contains 3 ARVs. The ARVs are called abacavir, dolutegravir, and lamivudine.
- The new combination is approved for older children and adults. It has not yet been tested for younger children.
- Children will be in the study for at least 1 year and up to 3 years.
- While in the study, children will have clinic visits with physical examinations and blood draws for laboratory tests. Parents will answer questions about children's health, the tablets being tested, and other medicines.
- There are possible risks for children in the study. One possible risk is that the tablets being tested could cause side effects. The most severe side effects include allergic reactions, liver problems, and mental health problems. These side effects are rare.
- There are possible benefits for children in the study. One possible benefit is that the tablets being tested will work well for children.
- Your decision on your child's participation in the study will have no effect on the medical care your child receives at this clinic. Your child's access to services, and the benefits and rights he or she normally has, will not be affected.

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

About the study

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

The study is testing a new combination of anti-HIV medicines (ARVs) for children who have HIV. The study will include about 50-75 children from Botswana, South Africa, Thailand, and the United States. The children will be less than 12 years old.

The United States National Institutes of Health and the company that makes the ARVs being tested, ViiV Healthcare Ltd, are paying for this study.

1. The study is testing a new combination of ARVs for children.

Children with HIV usually take a combination of 3 or more ARVs to stay healthy. There are not as many ARVs available for children as for adults because many ARVs have not been tested in children. This study will test a new tablet that contains 3 ARVs. The ARVs are called abacavir (ABC), dolutegravir (DTG), and lamivudine (3TC). In this form, we use "ABC/DTG/3TC" to refer to tablets that contain these ARVs.

ABC and 3TC are approved and used by adults and children throughout the world. DTG is a newer ARV that is approved for adults and children in the United States and Europe. In the United States, DTG is approved for adults and children who weigh at least 30 kg. In Europe, DTG is approved for adults and children 6 years and older who weigh at least 15 kg. *[Sites add site-specific approval information here if applicable, for example: DTG is also approved for adults in Botswana]*. The combination tablet of ABC/DTG/3TC is approved for adults and children weighing at least 40 kg in the United States and Europe. In Europe, this approval is for children 12 years and older.

This study will be the first study to test the combination tablet of ABC/DTG/3TC for younger children. The study will test different doses (amounts) of ABC/DTC/3TC to find out the correct dose for younger children. It will also look at whether ABC/DTG/3TC causes bad effects when given to younger children.

More information about the study, and the tablets being tested, is given in the rest of this form.

2. Only children who qualify can participate in the study.

If you decide to have your child join this study, we will first do some tests to find out if your child qualifies. More information about the tests is given in #4. If your child qualifies, he or she will be entered in the study. If your child does not qualify, he or she cannot be entered in the study.

3. It is your decision whether to have your child participate in the study.

Deciding to have your child to join the study is voluntary (your choice). You are free to have your child join or not join. If you decide to have your child join, you can change your mind and take your child off the study. Your decisions will have no effect on the medical care your child receives at this clinic. Your child's access to services, and the benefits and rights he or she normally has, will not be affected.

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

No matter what you decide about the study, it is important for your child to receive medical care and take ARVs. Taking ARVs is the best known way for children with HIV to stay healthy.

Finding out if your child qualifies

4. We will ask questions, examine your child, and test your child's blood.

To find out if your child qualifies for the study, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical examination.
- Draw your child's blood (up to 19 mL or about 4 teaspoons) for tests. The tests will check:
  - Your child's blood cells, liver, and kidneys. This includes checking for an infection called hepatitis B.
  - The amount of fat in your child's blood.
  - The amount of HIV in your child's blood. This is called your child's "viral load." Your child's viral load should go down and stay down when your child is taking ARVs.
  - Your child's CD4 cells. These cells help the body fight infection. HIV attacks CD4 cells. The number of CD4 cells should go up and stay up when your child is taking ARVs.
  - A gene called HLA-B*5701. People with this gene can have a serious allergic reaction to ABC. If your child has this gene, he or she cannot join the study.

  The tests will also confirm your child has HIV. Certain HIV tests are required for the study. If the required tests are not in your child's medical records, we will do the tests that are needed.

If your child can become pregnant, we will ask about her sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test. If your child is pregnant, she will not qualify for the study.

These procedures will take about 2-3 hours *[here and throughout this form, sites may modify the expected visit duration as needed]*.

Some test results will be ready quickly. Others may take about 2-3 weeks. We will schedule your child to come back when the results are ready. We may ask you to bring your child back for more tests if needed to find out if he or she qualifies for the study.

Entering the study

5. If your child qualifies, he or she will enter the study.

When you come back for your child's results, we will explain the results to you.

If your child's results do not qualify for the study, your child will not be entered in the study. We will tell you where your child can go for medical care or other services he or she may need. If your child does not enter the study, we will still use some information collected about your child (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study.

If your child's results qualify for the study, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical examination.

If your child can become pregnant, we will ask about her sexual activity and collect blood (1 mL or a few drops) or urine for a pregnancy test.

If these procedures confirm that that your child qualifies, your child will enter the study. We will:

- Ask about your child's mood, behavior, and sleep.
- Draw your child's blood (7 mL or about 1½ teaspoons). Some blood will be used to test your child's viral load. Some will be saved for later tests. The later tests may look for resistance to ARVs. Resistance means that ARVs may not work against the HIV in your child's body.
- Give you ABC/DTG/3TC tablets for your child. If your child was taking other ARVs before joining the study, he or she will stop taking those ARVs and start taking ABC/DTG/3TC tablets.

We will show you how to give ABC/DTG/3TC tablets to your child. There are two types of tablets. Each type is given once a day, every day.

- One type of tablet is dissolved in water; the child then drinks the water. This type of tablet is called a "dispersible tablet." It is given to children who weigh less than 25 kg. 3-6 tablets will be given depending on how much your child weighs.

- The other type of tablet is swallowed whole. This type of tablet is called an "immediate release" tablet. It is given to children who weigh 25 kg or more. If your child cannot swallow the tablet whole, it can be crushed and mixed with liquid or soft food.

It is very important to give your child ABC/DTG/3TC tablets as instructed. We will take as much time as needed for you to understand the instructions. We will help you come up with strategies to give the tablets to your child each day as instructed.

These procedures will take about 4 hours.

During the study

6. All children will have 6 visits over 1 year.

Your child will have visits 1 week after entering the study and 4 weeks after entering the study. After that, your child will have visits every 12 weeks (3 months).

Each visit will take about 2-3 hours. At these visits we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines. At 4 visits, this will include asking how you feel about giving ABC/DTG/3TC tablets to your child, how your child feels about taking the tablets, and how the tablets taste.
- Ask about your child's mood, behavior, and sleep. This will be done at only 2 visits.
- Give your child a physical examination.
- Draw your child's blood for tests. The amount drawn will range from 4 ml to 12 mL (about 1-3 teaspoons). At different visits, the tests will check:
  - Your child's blood cells, liver, and kidneys.
  - The amount of fat in your child's blood.
  - Your child's viral load.
  - Your child's CD4 cells.

Some blood will be saved for later tests. The later tests will check the amount of ABC, DTG, and 3TC in the blood.

- Give you ABC/DTG/3TC tablets for your child as needed. As your child grows, we may change the number or type of tablets your child takes. We may change the amount of water used to dissolve the tablets. We will keep giving you instructions on how to give the tablets to your child. For some visits, we will ask your child to take his or her tablets at the clinic (instead of at home).

In addition to the 6 visits described above, some children will have more visits. Children may have more visits if they are sick or if more tests are needed to check on their health or viral load. Children may also have more visits to check the amount of ABC, DTG, and 3TC in their blood. These visits are described in #9.

After your child has been in the study for 1 year, he or she may leave the study at that time. Or, your child may stay in the study longer. More information about this is given in #10.

7. Some children will be selected to very closely measure the amount of ABC, DTG, and 3TC in the blood.

One reason for doing this study is to find out the correct dose of ABC/DTG/3TC for children. To do this, we need to very closely measure the amount of ABC, DTG, and 3TC in the blood after children take ABC/DTG/3TC tablets. This is called a pharmacokinetic or "PK test." At least 25 children will be selected to have a PK test. For the children selected, the PK test will be done at the visit 1 week after entering the study.

We will tell you if your child is selected to have the PK test.

If your child is selected, we will ask you to bring your child to the clinic at a specified time. We will give you instructions for what your child should eat and drink before and during this visit. This may include limiting your child's food and drink for up to 3 hours.

At the clinic, your child will have blood drawn and then take his or her ABC/DTG/3TC tablets. Your child will then have blood drawn 7 more times over 24 hours (1 full day). The blood must be drawn at specified times. *[Sites may modify this wording as needed to describe local intensive PK scheduling/logistics/ procedures:]* Your child will need to stay at the clinic for 8-10 hours. Your child may then be able to go home and come back to the clinic 14-16 hours later. Or, your child may stay at the clinic for a total of 24 hours. We will explain the options for this to you.

[Sites may modify this wording as needed to describe local intensive PK procedures:] We will place a small plastic tube (like a "drip") in your child's arm to draw blood for the PK test. The tube is attached to a plastic needle. The tube and needle will stay in place until all the blood draws are done. We will not need to stick your child with a needle each time.

Most of the blood draws will collect 1 mL (a few drops) of blood. One of the blood draws will collect 4 mL (about 1 teaspoon). For all the blood draws added together, a total of 11 mL (about 2 teaspoons) will be collected.

We will give you the results of your child's PK test. If the test shows the amount of ABC, DTG, or 3TC in the blood is too high or too low, we will talk with you about changing your child's dose. If your child's dose is changed, we may ask your child to have a second PK test. The second PK test will check the amount of ABC, DTG, and 3TC in the blood after the dose is changed. For the second PK test, we might need to collect the same amount of blood as in the first test. Or, we might be able to do the test with less blood. We will explain the options to you and determine the most appropriate plan for your child.

8. We will watch children who have the PK test take ABC/DTG/3TC tablets.

For children who have the PK test, it is important to know the specific times when they take ABC/DTG/3TC tablets, from the day of entering the study to the day of the PK test. To help with this, if your child has the PK test, we will contact you every day until the day of the PK test.

[Sites may modify this wording as needed to describe local dose observation procedures:] There are different ways we can do these contacts. One way is to bring your child to the clinic to take ABC/DTG/3TC tablets in front of a study staff member. Another way is for a study staff member to go to your home or other location to watch your child take the tablets. If you have a mobile phone or computer, we may be able to watch your child take tablets (live) by video. You may also be able to send a video or text message to us. We will explain the options for this to you, and then agree on a plan with you to do these contacts.

If your child has a second PK test, we may repeat these types of contacts before the second test.

9. Some children will have additional visits.

There are 3 reasons why children may have additional visits.

Your child was taking an NNRTI.
If your child was taking ARVs before joining the study, he or she may have been taking a type of ARV called an "NNRTI." Two examples of this type of ARV are nevirapine and efavirenz. Taking this type of ARV before the study may affect the amount of ABC, DTG, and 3TC found in your child's blood during the study. Because of this, children who were taking this type of ARV before the study will have 2 additional visits during the study. The visits will be 2 weeks and 6 weeks after entering the study.

Each visit will take about 1 hour. We will draw your child's blood (4 mL or about 1 teaspoon) for later tests. The later tests will check the amount of ABC, DTG, and 3TC in the blood. If needed, we will also:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Give your child a physical examination.
- Give supplies of ABC/DTG/3TC tablets for your child.

Your child has resistance.
Children with HIV can have resistance to ARVs. One type of resistance is called "M184V." Children who have this type of resistance will have 3 extra visits during the study. The visits will be 8 weeks, 16 weeks, and 20 weeks after entering the study.

Each visit will take about 1 hour. We will draw your child's blood (7 mL or about 1½ teaspoons). Some blood will be used to check your child's viral load. Some will be saved for later tests. The later tests will check the amount of ABC, DTG, and 3TC in your child's blood. If needed, we will also:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Give your child a physical examination.
- Give supplies of ABC/DTG/3TC tablets for your child.

Your child's HIV is not controlled.
When taking ABC/DTG/3TC tablets, your child's viral load should stay controlled at a very low level. If tests show that your child's viral load is higher than expected, your child will have an additional visit. At this visit we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Ask how you feel about giving ABC/DTG/3TC tablets to your child, how your child feels about taking the tablets, and how the tablets taste.
- Give your child a physical examination.
- Draw your child's blood (up to 10 mL or about 2 teaspoons) for tests. The tests will re-check your child's viral load. If the viral load is still higher than expected, we will test for resistance.
- Save some blood for later tests. The later tests will check the amount of ABC, DTG, and 3TC in your child's blood.
- Give supplies of ABC/DTG/3TC tablets for your child as needed. If the tests show that your child has resistance, we may change your child's ARVs (see #13).

10. Some children may stay in the study for more than 1 year.

After your child has been in the study for 1 year, we will tell you about your child's options for receiving ARVs in the study and outside the study.

If your child is not gaining benefit from ABC/DTG/3TC tablets, your child will leave the study after 1 year.

If your child is gaining benefit from ABC/DTG/3TC tablets, and can get the tablets outside the study, your child will leave the study after 1 year.

If your child is gaining benefit from ABC/DTG/3TC tablets, but cannot get the tablets outside the study, your child may stay in the study for up to 2 more years. During this time, your child will have visits every 12 weeks. Each visit will take about 1 hour.

At each visit (every 12 weeks), we will:
- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines.
- Give your child a physical examination.
- Give supplies of ABC/DTG/3TC tablets for your child as needed. As your child grows, we may change the number of tablets or the type of tablets your child takes. We will keep giving you instructions on how to give the tablets to your child.

At every other visit (every 24 weeks), we will draw your child's blood (7 mL or about 1½ teaspoons) for tests. The tests will check:
- Your child's blood cells, liver, and kidneys.
- Your child's viral load.
- Your child's CD4 cells.

At each visit, we will tell you if your child is still gaining benefit from ABC/DTG/3TC tablets. We will also tell you if your child's options for getting ABC/DTG/3TC have changed. When your child can get ABC/DTG/3TC tablets from outside the study, your child will leave the study.

At the latest, your child will leave the study after a total of 3 years. After a total of 3 years, the study cannot keep giving ABC/DTG/3TC tablets for your child. The company that makes the tablets will try to provide the tablets for your child. If this is possible, the tablets will be provided until they are available locally or until your child is no longer gaining benefit. However, there is no guarantee this will be possible. If this is not possible, your child will need to switch to other ARVs that are available locally. *[Sites may modify the preceding sentence to define or explain "available locally."]*

No matter when your child leaves the study, we will talk with you about your child's options and help make sure your child can get ARVs from outside the study. We will plan for this in advance to avoid gaps in your child taking ARVs when he or she leaves the study.

11. There are additional requirements for children who can become pregnant.

Women and girls taking DTG should not become pregnant. This is because taking DTG at the time of becoming pregnant may increase the risk of serious birth defects of the baby's brain or spine.

If your child can become pregnant, we will collect blood (1 mL or a few drops) or urine for a pregnancy test at all visits. We will ask your child about sexual activity. If your child is having sex that could lead to pregnancy, she will be required to use contraception. We will talk with you and your child about the importance of avoiding pregnancy and about the contraceptive methods that can be used in this study. We will help you and your child choose the best contraceptive methods for your child. At each visit, we will talk again about contraception, to see how your child is doing with her chosen methods. We will ask you and your child to tell us if you want to stop or change methods. We will ask you and your child to tell us if your child may be pregnant at any time. If you or your child do not want your child to use contraception, your child will leave the study.

If your child becomes pregnant, she will stop taking ABC/DTG/3TC tablets. She will stay in the study until she is no longer pregnant, with the same schedule of visits as originally planned. After that, she will leave the study. We will tell you about other ARVs your child can take instead of ABC/DTG/3TC tablets. We will tell you if your child can get other ARVs here at this clinic or if you must go to another clinic. We will also tell you where you can take your child for health care related to the pregnancy. We will collect information on the outcome of the pregnancy and whether the baby has any birth defects.

If your child is using contraception at her last study visit, we will ask your child to come back one more time, about 4 weeks after her last visit. When your child comes back, we will:

- Review her medical records.
- Ask about her health, ARVs, contraception, and other medicines.
- Collect blood (1 mL or a few drops) or urine for a pregnancy test.
- If needed, give your child a physical examination.

12. Different tests will be done at different laboratories.

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

Other tests will be done in the United States or other countries. This includes tests for resistance and tests of the amount of ABC, DTG, and 3TC in your child's blood. We will give you resistance test results and explain these to you. If your child has a PK test (see #7), we will give you the results and explain these to you. Other tests of ABC, DTG, and 3TC will be done after the study is completed. The results of these tests will not be given to you.

If you agree, some of your child's blood will be used for tests of his or her genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. For this study, only genes related to HIV, ARVs, and the immune system will be tested. The immune system is the part of the body that fights infections. The results of these tests are for research purposes only and will not be given to the study staff or to you. Testing of all your child's genes, which is sometimes called whole genome sequencing, will not be done.

13. We may stop or change your child's ARVs.

Some children may need to change the tablets they are taking. This may happen if we find that the dose of ABC/DTG/3TC tablets is too high or too low. This may also happen for children with tuberculosis (see #14). If this happens for your child, we will explain the changes to you.

Some children may need to stop taking ABC/DTG/3TC tablets. This may happen for children who:

- Are not able to take the tablets
- Have bad effects from the tablets
- Need to take other medicines that cannot be taken with ABC/DTG/3TC tablets
- Have resistance to ABC, DTG, or 3TC
- Become pregnant

If your child stops taking ABC/DTG/3TC tablets, your child will leave the study. More information is given about this in #15.

14. There may be other changes if your child has tuberculosis (TB).

Children who get TB during the study will need to take medicines for TB. Some TB medicines change the effects of ARVs. Because of this, children need to take more ARVs when are they are taking TB medicines. For example, if your child gets TB during the study, he or she will need to take an extra tablet of DTG every day, in addition to taking ABC/DTG/3TC tablets every day. In this case, we would give you the extra DTG tablets and tell you how to give them to your child. When your child no longer needs TB medicines, he or she can stop taking extra DTG tablets.

Because some TB medicines change the effects of ARVs, we will do a PK test for children with TB. This will be like the test described in #7. However, all the blood draws will be done within 12 hours.

15. We may take your child off the study.

All children are expected to stay in the study for about 1 year. Some children may stay in the study for up to 3 years. However, we may take your child off the study early if:

- The study is stopped for any reason.
- Your child stops taking ABC/DTG/3TC tablets.

- We determine that your child cannot meet the study requirements.
- We determine that staying in the study might harm your child.

If your child must leave the study early, we will explain this and tell you where your child can go for the care and treatment he or she may need. It is very important for your child to keep taking ARVs after leaving the study. We will talk with you about your child's options and help make sure your child can get ARVs from outside the study.

16. Please tell us if you want your child to leave the study.

You are free to take your child off the study at any time for any reason. The care your child receives at this clinic will not be affected, but it is important that we know your decision. We will ask you to bring your child to the clinic for one last visit. At this visit, we will:

- Review your child's medical records.
- Ask about your child's health, ARVs, and other medicines. This will include asking how you feel about giving ABC/DTG/3TC tablets to your child, how your child feels about taking the tablets, and how the tablets taste.
- Give your child a physical examination.
- Draw your child's blood (11 mL or about 2 teaspoons) for tests. The tests will check:
  - Your child's blood cells, liver, and kidneys.
  - Your child's viral load.
  - Your child's CD4 cells.

  Some blood will be saved for later tests. The later tests will check the amount of ABC, DTG, and 3TC in your child's blood.

We will answer any questions you may have and tell you how to contact us in the future, if you wish.

Risks of the study

17. There is little risk from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to your child. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

18. There are risks from ARVs.

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

Some of the most common and most severe side effects of ABC/DTG/3TC tablets are listed below. This form does not list all possible side effects. At each visit, we will check on whether your child may be having side effects. If you have questions or concerns about side effects at any time, please tell us.

19. Some side effects can be severe.

First, you should know about the possible severe side effects. These effects are rare but can cause serious health problems and can result in death. Please contact us right away or go to the nearest hospital if your child has any of these side effects.

ABC can cause a severe allergic reaction.
This type of reaction is more likely in people who have the HLA-B*5701 gene. Children who have this gene cannot join the study. However, children who do not have this gene can still have the reaction.

This type of reaction can involve several organs of the body. When this type of reaction happens, it usually happens in the first 6 weeks of taking ABC. Children who have this reaction should stop taking ABC and never take ABC again. This is because the reaction can get worse if ABC is not stopped. If ABC is taken again (after stopping), the reaction can happen again. If the reaction happens again, it can be even worse, and can result in death.

If your child has an allergic reaction, he or she may have a rash; fever; poor appetite, upset stomach, vomiting (throwing up), diarrhea (loose or watery stools), or pain in the belly. He or she may feel sick or tired or weak. He or she may have aches or pains or have trouble breathing, a cough, or sore throat. We will give you a card to remind you of these signs of a reaction. If your child has 2 or more of these signs, stop giving ABC to your child and contact us right away. If you stop giving ABC to your child for any reason, always tell us and do not re-start ABC without contacting us first.

DTG can cause a severe allergic reaction.
DTG can cause a reaction that may look like the reaction described above. Children could also have blisters or sores in the mouth; blisters or peeling of the skin; redness or swelling of the eyes; swelling of the face, mouth, lips, or tongue. Contact us right away if your child has any signs of a reaction.

DTG can cause severe mental health problems.
Some people have had anxiety or depression when taking DTG. This may include feeling very sad or having thoughts or acts of hurting or killing oneself (suicide). These effects are more likely in people with a history of mental health problems. Please tell us if your child has ever had any mental health problems. Contact us right away if your child has any unusual or distressing thoughts or feelings, including any thoughts of hurting himself or herself.

DTG, ABC, and 3TC can cause severe liver problems.
The liver is an organ near the stomach. It helps digest food and keep the body healthy. Problems of the liver can be seen with abnormal blood test results. Children with liver problems may have yellowing of the skin or eyes; dark or tea colored urine; pale colored stools; upset stomach or vomiting; poor appetite; weight loss; pain, aching, or tenderness in the belly, especially on the right side below the ribs. Children may feel tired or weak or dizzy, or have difficulty breathing. When these types of problems happen, they can lead to failure of the liver and can result in death. Contact us right away if your child has any signs of liver problems.

20. There can be other side effects.

Other side effects have been seen in people taking ABC, DTG, or 3TC. These are listed below. These can be more or less common. They are not usually severe.

Very Common: expected in 1 of every 10 people taking ABC/DTG/3TC (100 of every 1000 people or 10%)
• Headache • Upset stomach • Diarrhea

Common: expected in 1 of every 100 people taking ABC/DTG/3TC (10 of every 1000 people or 1%)
• Skin rash or itching • Gas or pain in the belly • Indigestion or heartburn • Loss of appetite • Vomiting • Fever • Tiredness • Pain in the muscles or joints • Hair loss • Difficulty sleeping • Abnormal dreams • Depression • Dizziness (feeling light headed) • Increased sugar or fat in the blood • Changes in blood tests that may show problems with the muscles

Uncommon: expected in 1 of every 1000 people taking ABC/DTG/3TC (0.1%)
• Weight gain • Tingling or numbness of the arms, legs, hands, or feet • Breakdown of the muscles • Swelling of the pancreas (an organ in the belly involved in digesting food) • Decreased blood cell counts • Changes in blood tests that may show problems with the liver (an organ in the belly involved in digesting food and keeping the body healthy)

21. There may be other possible risks.

Resistance
All ARVs can cause resistance. To avoid resistance, it is important to give your child ARVs as instructed and avoid missing doses.

Switching ARVs
If your child was taking other ARVs before the study, he or she will stop taking those ARVs and start taking ABC/DTG/3TC tablets. It is possible that ABC/DTG/3TC tablets will not work as well for your child as the ARVs he or she was taking before the study.

Immune reconstitution syndrome
In some people with advanced HIV infection, symptoms of other infections or diseases may occur soon after starting ARVs. Some of these symptoms may be life threatening. If your child starts having new symptoms, or if any existing symptoms get worse after starting ABC/DTG/3TC tablets, please contact us immediately.

Hepatitis B

Children who have hepatitis B cannot join this study. However, children could get hepatitis B while in the study. If your child gets Hepatitis B, your child's ARVs may need to be changed. This is because some ARVs can be used to treat both HIV and hepatitis B, and it may be better for your child to take those ARVs. If your child needs to change ARVs, we will explain this to you. We will also explain if your child needs to leave the study (see #16).

Pregnancy

Early results from a large study in Botswana showed that DTG may increase the risk of serious birth defects of the baby's brain or spine. The increased risk was seen among babies whose mothers were taking DTG when they became pregnant. These birth defects happen during the first few weeks of pregnancy, before mothers may know they are pregnant. These birth defects have not been seen among babies whose mothers started taking DTG later in pregnancy.

22. There may be risks of disclosure of your child's information.

We will make every effort to keep your child's information private and confidential. Study records and blood samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your child's name will be written on some records. Despite our best efforts to keep your child's information private, it is possible that your child's information, could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly.

For children who have videos or text messages sent to study staff, those messages could be seen by someone who should not see them. The videos and messages may not be encrypted (scrambled), so someone with the right knowledge and equipment could see or listen to them. Telephone numbers used for these communications could also be seen.

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

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about children with HIV. Any future research done with the information from this study must be approved by the IMPAACT Network. If any future research is done, information about your child may be used. Your child's information will be labeled with a code number, and the only link between the code number and your child's name will be kept here at *[site name]*. Your child's name will not be given to other researchers.

Benefits of the study

23. There may be benefits to your child from being in the study.

By joining the study, your child will be part of the search for new treatments for children with HIV. ABC/DTG/3TC is a new treatment for young children. This treatment has been shown to be safe and effective for adults. Although there are no guarantees, we expect the same for children. Therefore, taking

ABC/DTG/3TC may be of benefit for your child. Also, ABC/DTG/3TC tablets are given once per day. This may be of benefit for children, compared to other ARVs that are given two times per day.

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

Other information about the study

24. There are no costs to you for your child being in the study.

There are no costs to you or your child for study visits or procedures or the ARVs given in the study.

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

25. Your child's records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- *[insert name of site IRB/EC]*
- *[insert name of site drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other United States, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes ABC/DTG/3TC tablets, ViiV Healthcare Ltd

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child's name or identify your child personally.

A description of this study will be available on ClinicalTrials.gov as required by United States law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

Your child's study information may be disclosed to other authorities if required by law. *[Sites may add more specific detail here describing local laws that may be applicable.]*

26. If your child gets sick or injured, contact us immediately.

Your child's health is important to us. We will make every effort to protect your child's well-being and minimize risks. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] If a study-related illness or injury occurs, we will treat your child or tell you where you can get the treatment your child needs. The cost for this treatment may be charged to you or your health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *[site name]* or the United States National Institutes of Health.

Who to contact

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

- If you have questions about the study, contact:
  [Sites insert name and telephone number of investigator or other study staff]

- If you have questions about your child's rights as a study 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]

- If your child has any health or other problems that may be related to study participation, contact:
  [Sites insert name and telephone number of investigator or other study staff]

- If you want your child to leave the study, contact:
  [Sites insert name and telephone number of investigator or other study staff]

Signatures

28. If you decide to have your child join this study, please sign or make your mark below.

Before deciding whether to have your child join this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your child.

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

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

[Sites insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing].

Please write your initials or make your mark next to your choices:

_____ I agree to have my child join this study.

For genetic testing:

_____ I agree to testing of my child's genes related to HIV, ARVs, and the immune system.

_____ I do <u>not</u> agree to testing of my child's genes.

_____
Name of Child (print)

_____	_____	_____
Name of Parent (or Legal Guardian; print)	Parent Signature	Date
_____	_____	_____
Name of Witness (if applicable, print)	Witness Signature	Date
_____	_____	_____
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date

Appendix III: Sample Informed Consent Form for Specimen Storage and Future Use

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, 4 September 2019

You have decided to have your child join the study named above. As part of the study, your child will have blood drawn. After the blood is tested, there may be some samples left over. We call these extra samples. The IMPAACT Network would like to keep these extra samples and use them for other research in the future.

This form gives information about use of extra samples. Please read it or have it read to you. 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 this form.

1. It is your decision whether to allow 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 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.

[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. If you agree to have extra samples stored, the samples will be kept in this repository. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

A repository is a secure facility that is used to store samples. The IMPAACT Network has a repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

3. Extra samples could be used for different types of research.

Extra samples may be used for research on HIV, anti-HIV medicines (ARVs), the immune system, and other diseases. The research may be done in the United States or other locations.

If you agree, extra samples could be used for research that looks at your child's genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your child's samples would only be used to look at genes related to HIV, ARVs, and the immune system. Testing of all your child's genes, which is sometimes called whole genome sequencing, will not be done.

Research done with extra samples must be 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 children whose samples will be used.

The research done with extra samples is not expected to give any information relevant to your child's health. Therefore, the results will not be given to the study staff or to you. The results will not be placed in your child's study records.

4. There is little risk to 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 the ARVs your child received and your child's response to the ARVs may also be linked to the samples. The only link between the code number and your child's name is kept here at *[site name]*. Your child's name will not be given to other researchers.

There may be some risks from tests of your child's genes. If others found out the results of these tests, they could treat your child badly or unfairly. However, this is almost impossible because the results of these tests will not be given to the study staff or to you and will not be in your child's study records.

5. There may be no benefit to your child.

By allowing your child's extra samples to be used for research, your child will be part of the search for new information that may benefit children with HIV in the future. However, the research done with the extra samples is not expected to directly benefit your child in any way.

6. You will not be paid for use of your child's extra 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
- 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 United States, local, and international regulatory entities

The people who do research with the extra samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with extra samples may be presented publicly or published. However, no presentation or publication will use your child's name or identify your child personally.

8. If you have any questions, concerns, or problems related to your child's extra samples, use these contacts.

- If you have questions about use of 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 child's extra samples, contact:
  [Sites insert name and telephone number of investigator or other study staff].

- If you have questions about your child's rights as a study 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].

Signatures

Before deciding whether to allow your child's samples to be used for research, make sure you have read this form or had it read to you. Make sure all your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

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

[Sites insert initial and signature blocks as required by site IRB/EC policies. Separate consent decisions must be documented for genetic testing]

Write your initials or make your mark next to your choice.

_____ I allow my child's extra samples to be used for research on HIV, ARVs, 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 child's extra samples to be used for research on HIV, ARVs, the immune system, and other diseases. I do <u>not</u> allow my child's samples to be used for tests of his or her genes.

_____ I do <u>not</u> allow my child's extra samples to be used for any research.

_____
Name of Child (print)

_____	_____	_____
Name of Parent (or Legal Guardian; print)	Parent Signature	Date
_____	_____	_____
Name of Witness (if applicable, print)	Witness Signature	Date
_____	_____	_____
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date

Appendix IV: Sample Informed Assent Form for Study Participation

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, 4 September 2019

[Instructions for sites: The amount of information and level of detail provided in site-specific assent forms should be tailored to the age and maturity of study participants, guided by IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, the wording included in this sample form may be modified, added to, or removed in order to provide the most appropriate information and level of detail for participants, consistent with IRB/EC policies and procedures.]

Introduction

You are being asked to take part in a research study. In order for you to take part, you must give your permission. Your parent/guardian must also give permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk with you about this, if you decide to take part in the study, you will record your decisions at the end of this form. You will be offered a copy to keep.

About the study

The study is testing new tablets for children with HIV. The tablets contain 3 medicines. The medicines are abacavir (ABC), dolutegravir (DTG), and lamivudine (3TC). The study will test different doses (amounts) of these medicines to find out the correct dose for children.

For small children, the tablets being tested are dissolved in water and swallowed as a liquid. For larger children, the tablets are swallowed whole or crushed and mixed with food.

Children in the study will take the tablets and be checked by nurses and doctors to see if the tablets cause bad effects. Children will have blood drawn to test for bad effects. Tests will also check the amount of medicine that can be found in the blood.

Your rights

It is up to you and your parent/guardian to decide if you will take part in this study. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you receive at this clinic.

What happens in the study

If you decide to take part in the study, we will first examine you (check your body), draw blood, and do some tests to see if you qualify. If you qualify, you will be in the study for at least 1 year. You may stay in the study for up to 3 years. While in the study, you will take the tablets being tested. We will remind you and your parent/guardian that you should take the tablets every day.

In the first year, you will come to this clinic for at least 8 visits. The visits will be closer together at the beginning and further apart later. In the second and third years, you will come for 4 visits per year. Most visits will take 2-3 hours.

At these visits, we will ask you and your parent/guardian about your health and the medicines you take. We will ask questions about the tablets being tested. We will examine you and draw blood for tests.

You may be asked to have a visit when you stay at the clinic for a full day and have your blood drawn 8 times. This is done to very closely measure the amount of medicine in the blood at each time. If you are asked to have this visit, we will need to know the specific time when you take the tablets being tested on each day before the visit. We will tell you more about how we will contact you and your parent/guardian to find out these times. On the day of the visit, we will place a small plastic tube (like a "drip") in your arm. The tube is attached to a plastic needle. The tube will stay in your arm until all the blood draws are done. We use the tube so we do not have to stick you with a needle each time blood is drawn.

If you agree, some of your blood could be used for tests of your genes. Genes are passed to children from their parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not.

We will tell you as much information as you want about the tablets being tested and what will happen when you come here for visits. Please ask any questions you may have. Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

What good and bad effects could happen

By taking part in this study, you will be helping test new medicines that may benefit (have good effects for) people with HIV in the future. You may also have good effects from the medicines. For example, the medicines could work well for you and help you stay healthy.

However, we do not know this for sure. The medicines may not work well for you. They could cause bad effects. For example, they could make you feel sick. We will ask you to tell your parent/guardian any time you do not feel well. You and your parent/guardian should also tell us if you do not feel well. We will ask you to come here so we can check on you and try to make you feel better.

Having your blood drawn may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm.

Another possible risk is to your privacy. For example, other people could find out that you are in the study or learn other information about you. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name). *[Sites may modify this wording as needed per local institutional policies and/or site SOPs:]* We will share information about you, including information that you tell us, with your parent or guardian. We will not share your information with other people unless you or your parent or guardian ask us to.

Who to contact

You and your parent/guardian can contact us at any time. Please talk to your parent/guardian and to us about any questions or problems you may have.

If you have questions about the study:
[Sites insert name and telephone number of investigator or other study staff].

If you have problems related to being in the study:
[Sites insert name and telephone number of investigator or other study staff].

If you have questions about your rights or how you are treated in the study:
[Sites insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

If you want to leave the study:
[Sites insert name and telephone number of investigator or other study staff].

Signatures

Before deciding whether to take part in this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered.

[Sites insert initial and signature blocks as required by site IRB/EC policies. Follow site SOPs and IRB/EC policies as to whether separate assent decisions must be documented for genetic testing among children in the age range for this study].

Please write your initials or make your mark next to your choices:

_____ I agree to take part in this study.

_____ I allow tests of my genes to be done for this study.

_____ I do <u>not</u> agree to take part in this study

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Assent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix V: Sample Assent Form for Specimen Storage and Future Use

IMPAACT 2019
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Version 2.0, 4 September 2019

[Instructions for sites: The amount of information and level of detail provided in site-specific assent forms should be tailored to the age and maturity of study participants, guided by IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, the wording included in this sample form may be modified, added to, or removed in order to provide the most appropriate information and level of detail for participants, consistent with IRB/EC policies and procedures.]

Introduction

You have joined the study named above. As part of the study, samples of your blood will be collected. After these samples are tested for the study, some may be left over. We call these extra samples.

You are being asked for permission to keep your extra samples and use them for other research in the future. Your parent/guardian will also be asked for permission.

This form gives information about extra samples. Please read it or have it read to you. Ask any questions you may have. After we talk with you about this, you will record your decisions at the end of this form. You will be offered a copy to keep.

What happens with extra samples

If you allow your extra samples to be kept, they may be used for research on HIV and the medicines used to treat HIV. They may also be used for research on other diseases and the immune system. The immune system is the part of the body that fights off infections.

There is no limit on how long extra samples will be kept or when they will be used.

If you agree, extra samples could be used for research that looks at your genes. Genes are passed to children from their parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not.

The results of research done with your samples will not be given to you or your parent/guardian.

What good or bad effect could happen

Allowing your extra samples to be used for research is not expected to have any good or bad effects for you.

By allowing your extra samples to be used, you will be helping with research that may benefit (have good effects for) people with HIV in the future. However, there is no expected benefit (good effects) for you.

By allowing your extra samples to be used, there is very little risk (chance of bad effects) for you. One possible risk is to your privacy. For example, other people could find out that you are in a study or learn other information about you. To avoid this, your extra samples will be labeled only with a code number. Your name will not be used.

Your rights

It is up to you and your parent/guardian to decide if your extra samples can be used for research. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on your being in the study. If you say no, all extra samples will be destroyed.

Who to contact

If you have questions about use of your extra samples:
[Sites insert name and telephone number of investigator or other study staff].

If you change your mind about use of your extra samples:
[Sites insert name and telephone number of investigator or other study staff].

If you have questions about your rights or how you are treated in the study:
[Sites insert name and telephone number of IRB/EC contact person or other appropriate person/organization]

Signatures

Before deciding whether to allow your extra samples to be used for research, make sure you have read this form or had it read to you. Make sure all your questions have been answered.

[Sites insert initial and signature blocks as required by site IRB/EC policies. Follow site SOPs and IRB/EC policies as to whether separate assent decisions must be documented for genetic testing among children in the age range for this study].

Please write your initials or make your mark next to your choices:

_____ I allow my extra samples to be used for research on HIV, medicines used to treat HIV, other diseases, and the immune system.

_____ I allow my extra samples to be used for tests of my genes.

_____ I do <u>not</u> allow my extra samples to be used for any research.

Name of Participant (print)	Signature of Participant	Date
Name of Study Staff Conducting Assent Process Name (print)	Signature of Study Staff	Date
Name of Witness (as appropriate; print)	Signature of Witness	Date

Appendix VI: IMPAACT 2019 Alternative Weight Band Dosing Tables

Dolutegravir dose adjustments may be required if protocol-defined $AUC_{0\text{-}24h}$ or C_{24h} targets are not met. Abacavir and lamivudine dose adjustments may be required if protocol-defined plasma $AUC_{0\text{-}24h}$ targets are not met. In the event dolutegravir, abacavir, or lamivudine targets are not achieved for a particular weight band, PK data from prior studies including IMPAACT P1093 and ODYSSEY will be used to model the doses that best achieve desired targets.

The following tables show potential dose adjustments when concentrations for all three drugs within a weight band are below target (Dosing Table 1) or above target (Dosing Table 2). Actual dose adjustments may vary once additional data are available. Other alternative dosing strategies may also include, but are not limited to, the following:

1. Dividing the dose (e.g., administering twice daily) if meeting an $AUC_{0\text{-}24h}$ or C_{24h} target would result in maximum concentrations (C_{max}) higher than those with established safety.
2. Administering with food as an alternative to increasing by an additional tablet.
3. Single agent entity adjustments (e.g., using separate doses of dolutegravir, abacavir, and/or lamivudine) if, based on modeling, the fixed dose combination tablets are unlikely to achieve target exposures for each individual drug.

Dosing Table 1. Proposed dose increases if $AUC_{0\text{-}24h}$ or C_{24h} are below the protocol-defined targets

Weight Band		Study Drug Formulation (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	4 dispersible tablets (240/20/120 mg)
#2	10 to less than 14 kg	5 dispersible tablets (300/25/150 mg)
#3	14 to less than 20 kg	6 dispersible tablets (360/30/180 mg)
#4	20 to less than 25 kg	TBD[a]
#5	25 kg or greater	TBD[a]

[a] TBD = to be determined following additional modeling and simulations.

Dosing Table 2. Proposed dose reductions if $AUC_{0\text{-}24h}$ or C_{24h} are above the protocol-defined targets

Weight Band		Study Drug Formulation (Daily Dose of ABC/DTG/3TC)
#1	6 to less than 10 kg	2 dispersible tablets (120/10/60 mg)
#2	10 to less than 14 kg	3 dispersible tablets (180/15/90 mg)
#3	14 to less than 20 kg	4 dispersible tablets (240/20/120 mg)
#4	20 to less than 25 kg	5 dispersible tablets (300/25/150 mg)
#5	25 kg or greater	TBD[a]

[a] TBD = to be determined following additional modeling and simulations.