A Multi-Center Trial of the
International Maternal Pediatric & Adolescent AIDS
Clinical Trials Group (IMPAACT)

IMPAACT P1093

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

MANUAL OF PROCEDURES (MOP)

Version 4.0
3 August 2016
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V P1093 Dosing Instructions for DTG Granules in Suspension and Dispersible Tablets
### List of Commonly Used Abbreviations and Definitions

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS</td>
</tr>
<tr>
<td>FSTRF</td>
<td>Frontier Science &amp; Technology Research Foundation</td>
</tr>
<tr>
<td>IATA</td>
<td>International Air Transport Association</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal, Pediatric &amp; Adolescent AIDS Clinical Trials Network</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LDMS</td>
<td>Laboratory Data Management System</td>
</tr>
<tr>
<td>LPC</td>
<td>Laboratory Processing Chart</td>
</tr>
<tr>
<td>OBT</td>
<td>Optimized Background Therapy</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PS</td>
<td>Patient Screening Number</td>
</tr>
<tr>
<td>PID</td>
<td>Patient Identification Number</td>
</tr>
<tr>
<td>RSC</td>
<td>Regulatory Support Center</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SES</td>
<td>Subject Enrollment System</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
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1.0 PROTOCOL OVERVIEW

1.1 Background

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

1.2 Study Overview

P1093 is a Phase I/II multi-center, open-label non-comparative study of approximately 160 HIV-1 infected infants, children and adolescents aged ≥4 weeks to <18 years, and will evaluate the pharmacokinetic parameters, safety, tolerability and efficacy of dolutegravir when administered both prior to starting, and in combination with optimized background therapy (OBT). The enrollment estimate assumes an approximate 35% dropout rate, and allows for a minimum of 120 evaluable subjects with at least 24 weeks of safety data for those treated exclusively with the selected dose. This study was first implemented with enrollment into Cohorts I and IIA, and evaluation of the tablet formulation in these cohorts. When the pediatric granule formulation became available, evaluation of this formulation was added in protocol Version 3.0; to date, this formulation has been evaluated in Cohorts IIB and III. Anticipating the availability of the dispersible tablet formulation, evaluation of this formulation will be added in protocol Version 4.0. Until this formulation is available, evaluation of the pediatric granule formulation will continue.

Each age cohort will consist of two sequential stages: Stage I and II. The objectives of Stage I are to examine pharmacokinetic parameters after intense sampling and evaluate the short term tolerability and safety of dolutegravir in approximately ten subjects allowing the selection of a dose for further study in Stage II. Those enrolled into Stage I will remain in Stage I for the duration of the study. Additional long term safety and antiviral activity of dolutegravir will be obtained by treating additional subjects in Stage II at the dose chosen from Stage I. Longer term safety and antiviral activity of dolutegravir will be assessed from data obtained from those enrolled in Stage II as well as those in Stage I who initiated treatment at the chosen dose for the cohort and remained on this dose. Those enrolled into Stage II will remain in Stage II for the duration of the study. Subjects in Stage I or Stage II will progress to the Long Term Safety Follow-up once the subject has completed 48 weeks of drug and if they are still deriving benefit from the study drug.
There are nine cohorts of HIV-1 infected children in this study:

**Cohort I:** Adolescents ≥ 12 to <18 years of age (Film-coated Tablets)

**Cohort IIA:** Children ≥ 6 to <12 years of age (Film-coated Tablets)

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

Note: Dispersible tablets may also be evaluated in this cohort if requested by regulatory authorities.

**Cohorts III:** Children ≥ 2 to < 6 years of age (Granules for suspension)

**Cohort III-DT:** Children ≥ 2 to < 6 years of age (Dispersible Tablets)

**Cohort IV:** Children ≥ 6 months to < 2 years of age (Granules for suspension)

**Cohort IV-DT:** Children ≥ 6 months to < 2 years of age (Dispersible Tablets)

**Cohort V:** Infants ≥ 4 weeks to < 6 months of age (Granules for suspension)

**Cohort V-DT:** Infants ≥ 4 weeks to < 6 months (Dispersible Tablets)

### 1.3 Target Enrollment

This study will take place at select clinical sites across the United States, South America, Asia and Africa. Across all participating sites, target enrollment is approximately 160 subjects to enroll a minimum of 120 evaluable subjects. Table 1 below describes the anticipated accrual in Stages I and II in each cohort.
Table 1: Anticipated Accrual in Stages I and II in each Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cohort Description</th>
<th>Minimum Accrual</th>
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<tbody>
<tr>
<td>I</td>
<td>Adolescents ≥ 12 to &lt;18 years of age (Film-coated Tablet formulation)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>IIA</td>
<td>Children ≥ 6 to &lt;12 years of age (Film-coated Tablet formulation)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>IIB</td>
<td>Children ≥ 6 to &lt;12 years of age (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>Children ≥ 2 to &lt; 6 years of age (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>III-DT</td>
<td>Children ≥ 2 to &lt; 6 years of age (Pediatric formulation: Dispersible Tablets)</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>Children ≥ 6 months to &lt; 2 years (Pediatric formulation Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>IV-DT</td>
<td>Children ≥ 6 months to &lt; 2 years (Pediatric formulations: Dispersible Tablets)</td>
<td>10</td>
</tr>
<tr>
<td>V</td>
<td>Infants &gt;4 weeks to &lt; 6 months (Pediatric formulation: Granules for suspension)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>V-DT</td>
<td>Infants &gt;4 weeks to &lt; 6 months (Pediatric formulation: Dispersible Tablets)</td>
<td>10</td>
</tr>
</tbody>
</table>

Note: Enrollment of children into cohorts using the granules may stop once the dispersible tablet formulation is available (see Protocol Section 3.3); therefore, the cohorts of subjects receiving granules (III, IV and V) may not reach their full enrollment targets. There will be a minimum of 10 subjects initiating the dispersible tablet formulation for each Cohort (III-DT, IV-DT, and V-DT) in Stage I and there will be a minimum of 6 subjects initiating the dispersible tablet formulation for each Cohort (III-DT, IV-DT, and V-DT) in Stage II.

*Cohort IIB will enroll a minimum of 10 subjects to dispersible tablets if required by the regulatory authorities.

2.0 PROTOCOL IMPLEMENTATION

2.1 Recruitment of Study Subjects

This is a multi-site study. Subjects will be recruited from outpatient clinics at IMPAACT sites. Each site will determine the site-specific appropriate recruitment sites and recruitment materials, to be reviewed and approved by the site IRBs/ECs and by the protocol team through the approval of the site implementation plan.
2.2 General Information Regarding Clinic Visits

2.2.1 Windows for Clinic Visits

- Entry (Day 0) must be completed within 30 days of the screening visit.
- The intensive PK visit (Stage I subjects only) must be completed within Day 5 to Day 10 after the subject starts dolutegravir.
- Study visits on weeks 4, 8, 12 and 16 should all be completed within a one (1) week window (±1 week).
- Study visits on weeks 24, 32, 40 and 48 should all be completed within a two (2) week window (±2 weeks).
- Study visits on weeks 60, 72, 96, 120, 132, 144, 156, 168, 180, and 192 should all be completed within a four (4) week window (±4 weeks).
- Viroligic Failure visit should be performed at least 1 week and within 4 weeks after the confirmatory failure specimen result was received.
- 2 week post-switch visit (for subjects switching from granules to dispersible tablets) – targeted for 2 weeks (with a window of -1 week or +4 weeks) after the date the participant switched to dispersible tablets.

2.2.2 Emergency Plan for After Hours

Study subjects should be informed of the procedures for reaching a study staff member out of normal clinic hours. Each site should have an emergency plan in place for evaluation and management of sick children for after hour’s sick visits, as per the Standard of Care at the site. The subject/caregiver should know exactly how to reach medical help in an emergency situation.

2.3 Study Discontinuation

Regardless of the reason for withdrawal, study personnel are responsible for identifying all subjects who withdraw and documenting the reason and date of termination. The criteria for study discontinuation is included in protocol Section 6.5.

3.0 SCREENING

3.1 Introduction to Informed Consent

This section contains reference information and guidance for obtaining informed consent in P1093. For this study, there are three separate consent forms, listed below.
1) Enrollment in Stage I (Protocol Appendix II),
2) Enrollment in Stage II (Protocol Appendix III) and
3) Specimen Storage and Future Use (Appendix IV).

The Specimen Storage and Future Use Consent Form (Appendix IV) was added in Protocol Version 4.0 for all participants. For NIAID sites in protocol Version 3.0, consent for long term specimen storage was included in the stage-specific forms. For NICHD sites in protocol Version 3.0 this form replaces the Fact Sheet and Template Consent Form for Specimen Storage at Repositories Funded by the NICHD. Consent for storage and future research use of blood and urine specimens may be declined, with no impact on study participation.

*Note:* For NIAID sites that participated in Version 3.0, the information in this consent form can be included in the stage-specific consent forms, as was done in Protocol Version 3.0, as long as all of the information for specimen storage and future use contained in this form is included in the stage-specific consent form.

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process is described in greater detail below. Please also refer to Section 4.8 of the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP) and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for further information.

US regulations (45 CFR 46) specify the elements of informed consent that must be conveyed to consenters through the informed consent process. It is the responsibility of the IoR, and by delegation of or to all study staff involved in the informed consent process, to deliver all required information to consenters.

Based on the reviews completed as part of the P1093 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site’s informed consent forms (ICFs) include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter comprehends the information
- Document the process

Further guidance related to each of these requirements is provided in Sections 3.2 - 3.5 below. Each site must have on file a study-specific SOP for obtaining informed consent that addresses all aspects of the informed consent process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all P1093 informed consent processes.

3.2 Deliver all Required Information in a Manner that is Understandable to the Consenter

The informed consent process should be conducted in the consenter’s preferred language and should reflect whether the consenter is determined to be literate per site SOPs.

If the consenter is literate, begin the informed consent process by providing the consenter with a copy of the ICF to read. Also provide her with any other informational materials developed to complement the ICF. If the consenter is not literate, read the materials to her. After the consenter has read the materials (or had them read to her), verbally review the information provided. A checklist or the ICF itself may serve as a useful guide for this. For example, you may note the main points described in each paragraph of the ICF and ask if the consenter has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the consenter, and discuss these thoroughly. Take as much time as needed to address each question or concern.

If the consenter is not literate, an impartial literate witness must be present during the entire informed consent process. As part of the documentation steps detailed below, the witness will be asked to sign and date the ICF to attest that the information in the ICF was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. ICH-E6 identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. The IMPAACT Operations Center has previously received guidance from the US Food and Drug Administration’s GCP office stating that the witness need not be “totally unaffiliated with the study. It may be possible, for example, to designate a "subject advocate" who would be available at each site …” Sites with questions about who may serve as an impartial witness are encouraged to consult with their IRBs/ECs on possible options.
Please see the appendix at the end of this section for a summary of considerations for obtaining informed consent from illiterate consenters.

3.3 **Assure that Informed Consent is Obtained in a Setting Free of Coercion and Undue Influence**

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consenter’s decision whether or not to take part in the study. Encourage the consenter to take as much time as she needs — and to talk about study participation with others if she chooses — before making a decision.

When a witness is present during the informed consent process, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the consenter, with emphasis on the fact that the witness is there as a protection for the consenter, not as an agent of the study per se.

3.4 **Confirm that the Consenter Comprehends the Information**

The consenter must not be asked to agree to take part in the study, or to sign or make her mark on the ICF, until she fully understands the study. Study staff are responsible for ensuring that each consenter understands all aspects of study participation before signing or marking the ICF.

A variety of approaches can be taken to assess comprehension. One approach uses a semi-structured checklist to guide a discussion in which the consenter responds to open-ended questions designed to elicit her understanding of key concepts. Sample checklists of this type are provided in the section appendix. Other approaches may include documented discussions with the consenter as well as structured knowledge quizzes administered to the consenter.

Regardless of the method used to assess comprehension, if the assessment indicates misunderstanding of aspects of the study, study staff should review those aspects again until the consenter fully understands them. If after all possible efforts are exhausted, the consenter is not able to demonstrate adequate understanding, she should not be asked to sign or make her mark on the ICF. Similarly, if the consenter has concerns about possible adverse impacts if she were to provide consent, or indicates that she may have difficulty adhering to the study requirements, she should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the consenter and the IoR (or designee).
3.5 Document the Process

US regulations require that informed consent be documented through the use of a written informed consent form approved by the IRB/EC and signed and dated by the consenter or the consenter’s legally authorized representative at the time of consent.

To fulfill this requirement, all signature and date blocks on the ICF should be completed in ink. Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a consenter’s full surname, and it is strongly recommended that initials not be used in place of a consenter’s full first name. However, if a consenter commonly signs her name using an initial for her first name, the initial may be used, provided this practice is acceptable per the policies of the study site institution(s).

If the consenter is not literate, the witness who was present during the informed consent process must sign and date the ICF to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter. The consenter’s printed name, signature, and signature date blocks on the ICF should be completed as described in the section appendix.

The DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials lists detailed requirements and suggestions for documenting the informed consent process. Study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, study staff may use informed consent coversheets similar to the examples provided in the section appendix. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent process conducted with each consenter. All informed consent documentation must be maintained on file in participant study records.
In addition to completing the documentation requirements of the ICF itself, each informed consent process should be documented in a signed and dated chart note. The note should document that informed consent was obtained before conducting any study procedures. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Informed consent will also be documented on study case report forms (CRFs). Consent decisions for storage and future research use of blood specimens will be recorded on the Specimen Consent/Deconsent Tracking for Non-Protocol Defined Testing CRF (TRK0103).

Regulations require that consenters be given a signed copy of their ICF. If a consenter opts not to receive a copy, this should be documented and the consenter should be offered an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full ICF.

### 3.6 Introduction to Screening

The study screening lab and clinical procedures are also described in the P1093 Schedule of Evaluations (Appendix IA-IG of the P1093 protocol).

#### 3.6.1 Screening and Enrollment Logs

Per the DAIDS policy for Essential Documents, study sites are required to document all screening (including screening failures) and enrollment activity on screening and enrollment logs. Screening and enrollment/randomization logs may be separate or combined. A screened subject is defined as having signed the screening or study consent.

The Screening and Enrollment Logs should be maintained in the Investigator Study Binder. Logs should include the following information:

- Initials of the subject
- PS (Patient Screening number)
- PID, if subject receives one
- Date screened
- Race
- Gender
- Status of screening, such as pass/fail
• For all screen failures, indicate why the subject is unable to participate
• Date enrolled; If not enrolled, indicate reason

For additional information, refer to the NIAID/DAIDS website

3.7 Screening/Enrolling a Subject for the Study – Using the Subject Enrollment System (SES)

The team will notify the sites in real-time the status of the open cohorts and stages (i.e. open or closed) and the dolutegravir dose. Protocol Version 4.0 Dosing Tables can be found on the P1093 Protocol-Specific Web Page at http://impaactnetwork.org/studies/P1093.asp.

1. Sites MUST receive a Site Activation E-mail correspondence from the IMPAACT Operations Center (FHI) with the subject ‘Activation of IMPAACT P1093 at Site _______’.

2. **BEFORE screening**, sites must utilize the PS2001 IMPAACT Screening System to obtain a screening number. This can be found on the DMC portal:

   - Under ‘Systems’
   - Click ‘Subject Enrollment’

<table>
<thead>
<tr>
<th>Systems (Skip)</th>
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<tbody>
<tr>
<td>Data Submission System (DSS)</td>
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<tr>
<td>Order Entry Program Resolve</td>
</tr>
<tr>
<td>Subject Enrollment eData Distributions</td>
</tr>
</tbody>
</table>

• The PS2001 IMPAACT Screening Checklist can be found in the study drop down menu (at the end of the list).
3. **BEFORE screening**, sites must email the team at impaact.teamp1093@fstrf.org to request a screening slot. In the email message, sites must include the following information:

- Cohort and Stage requested
- Participant age (DOB is optional)
- Participant weight
- Screening number (PID number is optional)
- Planned screening date
- Previous and current ARV regimens (including agents for prophylaxis as PMTCT, where applicable)
- Pre-screening Viral Load results available in medical record from the 4 – 12 weeks prior to the planned screening visit date
- Anticipated DTG dosing table (based on weight)

4. The team will review the status of the study and decide whether the subject may be screened or not. Sites MUST wait to receive permission (GRANTED SLOT) from the protocol team in order to proceed with screening evaluations. An email will be sent by the protocol data manager with the subject “P1093-Request granted to screen PS______”. IF a screening slot is not currently available for the subject, the subject will be entered onto a waiting list.
5. **BEFORE enrolling a subject**, sites MUST email the Team (impaaact.teamp1093@fstrf.org) the results of resistance testing and the proposed OBT regimen for approval. If approved, the Team will notify the site and if all other eligibility criteria are met, the site can proceed with enrollment.

**NOTE:** Individuals < 2 years of age (Cohorts IV, IV-DT, V and V-DT) can enroll with genotype results pending, but sites must still email the team and indicate that the participant belongs to this group. The site needs to timely communicate the genotype results to the team when available.

6. If any individual is consented but DOES NOT enroll for ANY reason, sites MUST notify the protocol Team of the screening failure and then complete the P1093 Screening Failure CRF (SCR0035 - IMPAACT P1093 SCREENING FAILURE AND NON-ENROLLMENT RESULTS) and submit it to the DMC database.

### 3.8 P1093 Screening Procedures

To ensure the child is in good health and eligible for the study, the procedures list below should be completed as part of screening. Screening procedures can be done over multiple days however, screening must occur ≤30 days prior to enrollment.

- **a)** Collection of medical history information including availability of viral load result for individuals on treatment and evaluation of disallowed medications Refer to protocol Section 4.3.2)

  **Note:** If an infant has received NVP as prophylaxis to prevent mother to child transmission (PMTCT), he or she must have not received ANY NVP for at least 14 days prior to enrollment into Stage I or II.

- **b)** Pregnancy test
  - Females of child bearing capacity only should be tested
  - Either blood or urine is acceptable for this test

- **c)** Confirmation of HIV infection
  **Note:** for subjects ≤18 months of age confirmatory HIV test results may be pending at the time of enrollment. Refer to protocol Section 4.1.2

- **d)** Blood draws for hematology, chemistries, lymphocyte subsets and lipid profiles
• Refer to the Schedule of Evaluations (Appendix I of the protocol) and the Lab Processing Chart for further information on specific tests and blood volumes and processing.

e) Urinalysis

f) HIV-1 RNA PCR viral load
   • ONLY the Abbott RNA PCR platform may be used for this protocol.

    Note: For individuals < 2 years of age (Cohorts IV, IV-DT, V and V-DT) the RNA test performed at screening may be pending at the time of enrollment

g) Real time genotyping for resistance testing
   • See protocol Section 6.2.1 for subjects in Cohorts IV, IV-DT, V and V-DT results may be pending at the time of enrollment.

    Note: Genotyping does not need to be repeated in the case of multiple screenings.

h) Phenotyping (if sufficient blood is collected)
   • Phenotyping will only be collected if there is sufficient blood volume drawn

Further details can be found in Section 6.2.15, Schedule of Evaluations (Appendix I of the P1093 protocol) and in the Laboratory Processing Chart.

3.9 Eligibility Determination

The eligibility criteria are specified in protocol sections 4.1 and 4.2.

It is the responsibility of the IoR and other designated study staff to ensure that all required assessments are performed and adequately documented, and that only eligible participants who meet eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. In the event that study staff identify that an ineligible participant has been enrolled, the protocol team should be consulted immediately.
3.9.1 ARV Exposure Groups at Screening

Subjects must belong to one of two ARV exposure groups (protocol Section 4.1.3.1 and 4.1.3.2). The entry criteria are copied below for your reference.

1.) ARV treatment experienced (not including ARVs as prophylaxis or PMTCT): (protocol Section 4.1.3.1).

Subjects previously took ARVs as treatment, but not currently taking ARVs:

**Must be off treatment ≥ 4 weeks**

OR

Currently taking ARVs for treatment but failing (VL > 1000 copies):

**Must be on an unchanged, failing therapeutic regimen for within the 4 to 12 weeks prior to screening (≤1 log drop in HIV-1 RNA within the 4 to 12 weeks prior to screening*)**

*Note: This criterion is intended to ensure that only individuals on ARVs who are experiencing continued virologic failure, evidenced by viremia prior to screening (outside of the study, first time point) and at the time of study screening (as part of the study-specific screening procedures, second time point), are enrolled. To meet this criterion, potential participants must have medical record documentation of HIV RNA levels at each of the following two time points: between 4 and 12 weeks prior to study screening (first time point) and at screening (second time point). The intent of requiring HIV RNA values from these two time points is to ensure that there is stable virologic failure that has persisted for at least 4-12 weeks. Requiring ≤1 log drop in HIV-1 RNA between these two time points ensures that the HIV RNA values are relatively stable and not undergoing a rapid decline due to the effects of the treatment regimen prior to study enrollment.*

OR
For individuals < 2 years of age, initiated ARVs for treatment < 4 weeks prior to screening

2.) ARV treatment naïve (no exposure to ARVs as treatment; could have received ARVs for prophylaxis or PMTCT) – for subjects < 2 years of age.

3.9.2 Baseline Genotyping

- At screening, blood should be collected for resistance testing (genotyping).

- This specimen MUST be sent in REAL time to the appropriate location (see the Laboratory Processing Chart for further instructions).

- Depending on the location of the clinical site, the closest specialty laboratory for genotyping may be in-country or specimens may need to be shipped out of the country for testing (refer to the Lab Processing Chart).

- When shipping a specimen for genotyping, please remember to include the University of Washington (UW) Requisition Form found on the P1093 website: http://impaactnetwork.org/studies/P1093.asp

- Once a site ships a genotyping specimen for testing, an email should be sent to the team informing them of the PID number, site number and shipment date so that the specimen and results can be tracked. Emails should be sent to impaact.teamp1093@fstrf.org.

- Turnaround time for the genotyping results will vary for each specialty lab, but is typically approximately 2-3 weeks from initial shipment.

3.9.3 Optimized Background Therapy (OBT):

- Subjects aged ≥2 years of age (Cohorts I, II, III, and III-DT) must have available at least one fully active drug for the OBT to enroll. Historical genotypes obtained within 1 year of screening will be considered by the Protocol Team for determination of fully active drugs if screening genotype testing is inconclusive.

- Subjects < 2 years of age (Cohorts IV, IV-DT, V, and V-DT) can enroll if genotype testing has been obtained with results pending.
Note: Subjects enrolled with genotype results pending but found to have no active drugs per genotype performed at screening should discontinue study drug, per Section 6.6 and be followed per Appendix IF. However, such subjects who have a > 1 log drop in HIV RNA by 4 weeks can continue study drug with approval by the Protocol Team.

- Please email the team with any questions: impaact.teamp1093@fstrf.org

- To allow rapid enrollment to the younger cohorts, subjects < 2 years old are not required to have the genotype testing results available at screening prior to enrollment. These subjects can enroll and if found to have no active drugs per genotype will discontinue study drug unless they have a > 1 log decrease in HIV RNA by 4 weeks post initiation of DTG (Sections 4.1.10, 6.2.1, 6.2.3.3, 6.6.8).

- Subjects < 2 years old are not required to have the HIV-1 RNA result from screening available prior to enrollment. These subjects can enroll and if found to have a screening HIV-1 RNA of ≤ 1000 c/ml the subject will discontinue study drug (Sections 4.1.5 and 6.6.7).

3.9.4 Baseline Phenotyping

- At screening, if sufficient blood is collected (see priority of blood draw volumes in Appendix IA-F, Schedule of Evaluations in the P1093 protocol), blood should be collected for resistance testing (phenotyping).

- This test will NOT be run in real time – specimens should be stored at the local site and sent in batches when requested by the team.

4.0 PROTOCOL IMPLEMENTATION – Enrollment Onwards

4.1 Putting a Subject on Study – Enrollment/Entry

- Please note there will be a waiting list for enrollment into this study if we do not have sufficient slots available in a cohort at any particular time.

- The team will notify sites in real time regarding the status of the mini-cohorts and the full cohorts (i.e., open or closed).

- Once a site has a subject that they want to screen, they must follow the screening procedures as described in Section 3.7 above. If the subject is eligible, based on the screening results, sites may enroll the subject as they would normally through the enrollment system. Sites should note that to be
able to complete enrollment, they must have the subject’s screening number available.

- Once the subject has been enrolled into the P1093 study, the following procedures should be completed:
  - Entry visit should be completed within 30 days of the screening visit
  - Refer to Schedule of Evaluations, Appendix IA-IG (P1093 protocol) for required clinical and laboratory evaluations for each specific cohort and stage
  - Study drug should also be distributed at this visit.
  - The initial dose of DTG dispersible tablets for Cohorts IV-DT and V-DT will be administered in the clinic.
  - STAGE I subjects - The subject should be scheduled to come back for the Intensive PK visit between Day 5 and Day 10.
  - Refer to protocol Section 6.2.3 for instructions on initiation of dolutegravir and Optimized Background Therapy (OBT).
  - Refer to Appendix IV of this document for instructions on dosing the granules in suspension and dispersible tablets

NOTE: Please refer to Section 4.3.2 and Table 11 in the protocol for a list of disallowed ARV Medications prior to intensive PK sampling in Stage I.

4.2 Entry Visit – Microalbumin/Creatinine (M/C) Ratio Laboratory Tests

The P1093 clinical sites MUST ship the M/C ratio urine specimens collected from all indicated time points as described in the Schedule of Evaluations (i.e. Entry, Week 12, Week 24, and Week 48) in REAL TIME. Urine specimens for this assay should be shipped as described by the Lab Processing Chart.

US Clinical Sites ONLY

- Each US clinical site MUST contact the P1093 Quest Diagnostic Lab in BALTIMORE at least 2 weeks prior to shipment of their first P1093 Real Time M/C ratio specimen, to arrange for an account to be created to allow for appropriate specimen receipt and result reporting to each clinical site. Contact the Quest Diagnostics’ Special Studies Service Representative (Larry Hirsch) at Larry.A.Hirsch@questdiagnostics.com or 1-410-536-1622.

- A custom P1093 Real Time M/C ratio requisition form will be provided to the clinical site to use with specimen submission. The P1093 custom requisition form includes the demographic data entry fields (e.g. PID/SID, Date/Time of
Specimen Collection, etc.) that must be completed by site personnel when sending the study subject’s specimen aliquots.

4.3 Preparing for the Intensive PK Visit on Day 5-10 for Stage I Subjects

What instructions should I give subjects preparing for the intensive PK visits?

- At Entry (Day 0), remind the subjects that they will undergo the intensive PK visit on Days 5-10 and they will need to come to the site for two days in a row in order to complete the 24-hour PK sampling.

- At 4 days prior to scheduled PK visit, contact the subjects to remind them of the following:
  - The visit dates and times for the two days of the PK visit
  - No missing dose(s) of dolutegravir during the 3 days prior to the scheduled PK visit; otherwise the PK visit needs to be rescheduled
  - Record the actual dose (in mg) taken, actual date and time of the dolutegravir doses on the 3 days (total of 3 doses since dolutegravir is taken once a day) prior to the scheduled PK visit. The three doses of dolutegravir taken prior to the PK visit should be taken at approximately the same time of scheduled PK visit. The actual dose taken needs to be recorded in the unit of mg, not number of tablets, number of packets, or volume of solution.
  - For subjects taking doses in the afternoon or at night, ask them to switch to take dose in the morning starting from 3 days prior to the PK visit

- At 1 day prior to the scheduled PK visit, contact the subjects for the following:
  - Confirm there was no missed dose during the 3 days prior to the PK visit. If there is any missed dose(s) of dolutegravir during the 3 days prior to the PK visit, please reschedule the PK visit for between 3-7 days later.
  - Cohorts I, II, III, and III-DT: Remind the subject of the following eating/drinking restrictions:
    - More than 6 hours PRIOR to Dosing – subjects may eat and drink without restriction
    - 4-6 hours PRIOR to Dosing – milk, apple/orange juice and water may be consumed; No food
4 hours PRIOR to Dosing – water ONLY

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

- For subjects who vomited within four hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following seven days.

- In the event the investigative site does not provide meals, remind the subject that they may consume a light meal two hours after dosing on the intensive PK visit. Avoid high fat foods.

- Check on the actual time of dose taken on this day to ensure that the dose to be taken on next day (PK visit day) is as close as 24 hours from the dose taken on this day (a window of 22-26 hours is allowed)

- Remind subject to bring their dolutegravir medicine for dosing on both days of the PK sampling visit and not to take the dose until the pre-dose PK blood sample is taken under observation at your physician’s clinic.

4.4 Intensive PK (Day 5-10) – STAGE I SUBJECTS ONLY

General Instructions

- Refer to Schedule of Evaluations, Appendix I (P1093 protocol) for required clinical and laboratory evaluations for each specific cohort and stage.

- Subjects should not have missed any of their dolutegravir doses in the 3 days prior to the intensive PK visit.

- Ensure that an Optimized Background Therapy (OBT) has been chosen for the study subject and that any drugs are available such that the subject can begin taking them AFTER the 24 hour intensive PK sample is collected.

- Food and liquids may be consumed as detailed below:
  - Cohorts I, II, III, and III-DT:
    - ≥6 hours PRIOR to dosing – subjects may eat and drink without restriction
- ≥4 to <6 hours PRIOR to dosing – milk, apple/orange juice and water may be consumed; No food
- <4 hours PRIOR to dosing – water ONLY
- From dosing to <2 hours POST dose – apple/orange juice and water may be consumed; No food
- From ≥2 to <4 hours POST dose – subjects may drink apple/orange juice and eat a snack/light meal (around 100-150 calories)
- From ≥4 hours POST dose onwards – subjects may eat and drink without restriction

Cohorts IV, IV-DT, V, and V-DT: Subjects should not ingest breastmilk, formula or any other high fat food/liquid) for 2 hours prior to and 1 hour after dosing on the intensive PK day. Water and other fluids (i.e. apple/orange juice (with the exception of grapefruit juice) and oral rehydration solution) can be taken at any time. From ≥4 hours POST dose onwards – subjects may eat and drink without restriction

- For subjects who vomited within four hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following seven days.

**What procedures are performed on the day of an intensive PK visit?**

- Review any subject documentation of prior dosing and food/drink consumption; collect undocumented information by oral interview. Example templates are available in Appendix I to assist subjects with keeping track of previous dose and meal information. Sites may print copies of these templates should they wish to provide subjects with a collection tool.
- Collect the pre-dose PK sample as close as possible to 24 hours after the subject’s last dose of dolutegravir (within a target window of 22 to 26 hours).
- Administer dolutegravir dose and record actual dose, date and time of the dose administration. The actual dose taken needs to be recorded in the mg unit, not number of tablets, number of packets, or volume of solution.
- Record whether or not the subject vomited within 4 hours after dosing:
  - For subjects who vomited within 4 hours after dosing, or who cannot complete the PK that day for any other reason, the PK should be cancelled and MUST be rescheduled AND completed within the following 3-7 days.
- Collect the remaining PK samples at time points specified in the footnotes in Appendix I of the P1093 protocol.
• Remind the subject to return to the study site on the following day for collection of the 24-hour PK sample and optimization of their background therapy; subjects should NOT take a dose prior to returning to the study site.
• Remember to complete the time unit in the LDMS (see Laboratory Processing Chart for more information).
• Record in the CRF:
  1. The dates, times, and amounts (in the unit of mg) of the three doses of dolutegravir administered prior to the PK visit and the dose administered at the PK visit; the actual dates, times, and doses should be recorded even if they are off-schedule.
  2. Whether or not the subject fasted for 6 hours prior to drug administration
  3. The actual PK sampling dates and times should be recorded even if they were off-schedule.
  4. The site should also document any food or drinks that were consumed by the subject during the 0-4 hours post dose period.

When should an intensive PK visit be rescheduled?

• If a dose was missed on any one of the 3 previous days
• The pre-dose sample would not be taken in the 20-28 hour target window
• The subject did not take the dolutegravir dose in the clinic
• The subject vomited within 4 hours after dosing
• The subject did not fast as specified above

What is the timeframe for rescheduling an intensive PK visit?

• The intensive PK visit MUST be rescheduled AND completed within 3-7 days of the original intensive PK visit. If this timeline cannot be met, sites should contact the team for guidance (impaact.teamp1093@fstrf.org)

4.5 Study Visits – Week 4, 8, 12, 16, 24, 32, 40, 48

• Refer to Schedule of Evaluations, Appendix I (P1093 protocol) for required clinical and laboratory evaluations for each specific cohort and stage.
• Please note that weight should be obtained and recorded as part of the physical exam performed at each visit. Remember that any change in the subject’s weight may require a change in medication dose. If a dose change
is required based upon weight increase/decrease, weight change is listed as a reason for change on the treatment record form.

4.6 Population PK Visits - STAGE I & STAGE II SUBJECTS

4.6.1 Objectives of Pharmacokinetic (PK) Evaluation

- Characterize the pharmacokinetics (drug concentration change over time) in subjects.
- Evaluate the effect of subject characteristics (i.e., age, gender, race, weight, liver function, concurrent medication, and disease stage) on PK.
- Assess the relationship between PK and drug effect (antiviral activity/response, and experience of AEs).
- Determine appropriate dose(s) in various subject populations or the need of dose adjustment for individual subjects.

Please note that data quality is critical

4.6.2 Before the Population PK Visit

NOTE: Subjects DO NOT need to be fasting prior to any of the population PK visits.

- Provide subjects with a diary card or discuss alternative methods to record dolutegravir dosing history at the visit before the PK sampling visit.
- Instruct the subject that he/she must record the time they took their dose of dolutegravir on each of the 3 days prior to the PK sampling visit.
- Please note that subjects must take their dolutegravir dose in the 3 days prior to the PK sampling visit at a time in the day that corresponds to the time their next visit is scheduled.
- You must call the subject on the phone 4 days, then 1 day prior to the PK visit with reminders concerning dose times. Remind them to take their dose of dolutegravir on the day of PK sampling visit under observation at the clinic.
4.6.3 **Week 4 Population PK**

- Review dolutegravir dosing prior to collecting any blood sample.

- **Blood draws for Week 4 population PK (see below for additional instructions):**

  **Pre-dose (0.5mL)**

  **2-4 hours post-dose (0.5mL)**

- The pre-dose population PK sample should be collected as close as possible to 24 hours after the subject's last dose of dolutegravir (i.e., within the target window of 20 to 26 hours). For example, if dose taken was taken at 07:00 am the day before the PK visit, the pre-dose blood sample must be taken within the target window between 03:00am-11:00am on the day of the PK visit.

- The pre-dose sample will be collected *immediately* before the clinic dose (i.e., within 15 minutes), which will be taken under observation at the clinic.

- Administer dolutegravir.

- Record whether or not the subject vomits after dosing.

- Collect the post-dose PK samples at 2 to 4 hours after the subject's witnessed dose.

4.6.4 **Week 12 Population PK**

- Review dolutegravir dosing with the subject prior to collecting any blood sample.

- **Blood draws for Week 12 population PK (see below for additional instructions):**

  **ONE blood draw: any time point post-dose (0.5mL)**

- The population PK sample at Week 12 should be collected anytime within the 24 hours following the previous dose. For example, if a subject normally takes their dose at 8am each day, the subject should come into clinic sometime between 8am (after their dose) but before 8am the following day.
4.6.5 Week 24 Population PK

- Review dolutegravir dosing history prior to collecting any blood sample.

- **Blood draws for Week 24 population PK (see below for additional instructions):**
  
  **TWO blood draws: two hours apart any time within 12 to 26 hours post dose (0.5mL each draw)**

- Collect the TWO post-dose PK samples between 12 to 26 hours following the subject's dose.

4.6.6 Re-Scheduling a Population PK

Population PK sampling should be rescheduled for the next 3-7 days if any of the following situations occur:

- If a dose was missed on any one of the 3 previous days
- The pre-dose sample would not be taken in the 20 to 28-hour target window.
- The subject did not take the dolutegravir dose in the clinic.

4.6.7 2-Week Post Switch Visit Population PK

For subjects who were receiving granules in suspension and switched to dispersible tablets and have completed 24 weeks of follow-up at the time of the switch visit, population PK specimens should be collected following the procedures below.

- Review dolutegravir dosing history prior to collecting any blood sample.

- **Blood draws for 2-Week Post Switch Visit population PK (see below for additional instructions):**
  
  **Pre-dose (0.5mL)**
  
  **2-4 hours post-dose (0.5mL)**

- The pre-dose sample will be collected immediately before the clinic dose (i.e., within 15 minutes), which will be taken under observation at the clinic.
- Administer dolutegravir.
- Record whether or not the subject vomits after dosing.
- Collect the post-dose PK samples at 2 to 4 hours after the subject's witnessed dose.
4.6.8 Next Scheduled Visit after Post Switch Visit Population PK -

For subjects who were receiving granules in suspension and switched to dispersible tablets and have completed 24 weeks of follow-up at the time of the switch visit, population PK specimens should be collected following the procedures below.

- Review dolutegravir dosing history prior to collecting any blood sample.
- **Blood draws for Next Scheduled Visit after Post Switch Visit population PK** (see below for additional instructions):
  
  TWO blood draws: two hours apart any time within 12 to 26 hours post dose (0.5mL each draw)
- Collect the TWO post-dose PK samples between 12 to 26 hours following the subject’s dose.

4.7 Virologic Failure

If a subject appears to be experiencing virologic failure (as defined in Protocol Section 6.25 of the P1093 protocol), the following procedures should be completed:

4.7.1 Consult the Subject

- Inadequate adherence is a common cause for virologic failure, and should be explored as a first step in the management of study subjects (e.g., at the first indication of inadequate virologic response or rebound).
- Upon notification that a subject’s HIV-1 RNA plasma level qualifies them as a suspected virologic failure, the investigator should query the subject regarding intercurrent illness, recent immunization, or interruption of therapy.

4.7.2 Perform Repeat VL Sampling

All cases that meet a criterion for suspected virologic failure must be confirmed by a second Viral Load measurement performed at least 1 week but not more than 4 weeks apart (if a sample cannot be obtained by 4 weeks, samples should be collected as soon as possible beyond 4 weeks) from the date of the original sample, unless one of the extenuating circumstances outlined below applies:
• Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the subject should receive full dosing of dolutegravir.

• Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the subject should receive full dosing of dolutegravir.

• If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full dosing of dolutegravir.

• The subject should have received full doses of dolutegravir for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

4.7.3 Managing Confirmed Virologic Failure/Endpoint Cases

• If this second viral load confirms the initial suspected virologic failure, the subject should have the appropriate clinical and laboratory evaluations performed (refer to Virologic Failure column in Appendix I of the P1093 protocol), as soon as possible (within 1 to 4 weeks of the confirmatory sample results).

• At virologic failure visit, blood should be collected for resistance testing (genotyping) and for phenotyping.

• The plasma specimen for genotyping MUST be sent in real time to the Seattle Children’s Research Institute (SCRI) Lab, LDMS lab 238. Please refer to the Laboratory Processing Chart for specific instructions regarding collection, processing and shipping of these specimens. [Please note US sites - Ship Real Time to LDMS LAB 238; Non-US sites ship real-time to BRI as pass through]. The P1093 Specimen Testing Requisition must be included with each shipment. This form and the Laboratory Processing Chart can be found on the Protocol Specific Web Page at the following address: http://impaactnetwork.org/studies/P1093.asp and in Appendix IV.

• If the viral load data is not available on specimen’s ship date, please send the viral load results by email to sheila.styrchak@seattlechildrens.org or ingrid.beck@seattlechildrens.org, as soon as possible. Specimens for resistance testing will not be processed until viral loads are received. Please note the viral load result should correlate with the specimen that is being sent for resistance testing; the viral load result should not be from a specimen collected at an earlier/different time point.
- Upon shipment of a specimen for genotyping testing, please e-mail the protocol team at impaact.teamp1093@fstrf.org and include the PID number, CRS number and shipment date so the team can track the specimen and the results.

- Turnaround time for the genotyping results will vary, but is typically approximately 2-3 weeks from initial shipment. Results from the genotyping will be made available to the investigator as soon as they are available.

- The plasma specimen for HIV phenotyping should be stored at the local site until requested for shipment. Please see the Laboratory Processing Chart for instructions.

- It is up to the site investigator to determine if it is in the best interests of the subject to have study drug (dolutegravir) withdrawn. Section 6.25 of the protocol explains the subject’s protocol-based treatment options if they reach virologic failure. Please email the core team with any questions – impaact.teamp1093@fstrf.org

- Every effort should be made to perform the assessments outlined for the ‘Virologic Failure’ visit before the subject is withdrawn from the study.

4.7.4 Confirmed Virologic Failure – Beyond 48 Weeks

A secondary objective of P1093 is to assess changes in HIV-1 genotype and phenotype to dolutegravir and other components of the OBT in subjects experiencing virologic failure throughout follow-up. Therefore, in addition to collection of samples for HIV genotypic and phenotypic resistance throughout the first 48 weeks of follow-up, blood sample collection for HIV genotypic and phenotypic drug resistance and plasma/PBMC should continue for participants who experience virologic failure beyond week 48. Either for the first time or in participants who experience virologic failure on multiple occasions, providing that at least 24 weeks have lapsed from the prior virologic failure drug resistance sample.

These samples should be collected according to the virologic failure column of the schedule of evaluations in appendix IE for participants and as specified above.

4.8 Premature Discontinuation of Study Drug/On Study

Dolutegravir should be discontinued early for any of the reasons described in Section 6.6 of the P1093 protocol.
If a subject meets any of the criteria for discontinuing study drug before the end of the study, the site should complete the following procedures:

- Subjects should come off study drug immediately

- If the subject is coming off of study drug due to an adverse event, the subject should remain on study until the adverse event resolves. During this time, the subject may be asked to come back to clinic as often as the site investigator feels is necessary for safe monitoring of the adverse event. Once the adverse event is resolved, the subject can come off the study entirely.

- If the subject is coming off study for any reason other than an adverse event, the subject should be asked to come back to clinic once more; 4 weeks after the subject has stopped taking study drug.

- Refer to Schedule of Evaluations, Appendix I (P1093 protocol) for required clinical and laboratory evaluations for each specific cohort and stage for “Premature Discontinuation of Study Drug/ On Study”.

- If the subject becomes pregnant, study drug should be stopped immediately. Subjects should remain in the “Off Treatment/On Study” category of visits until the birth of the baby for safety purposes. See Section 5.6 of the MOPs for additional pregnancy information.

- Subjects who are pregnant or who have an AE/SAE that has not resolved within 3 months of stopping study drug, should come back to clinic every 3 months for follow-up until the AE is resolved or the mother delivers the baby. Study required tests are an interim history and physical exam at these visits. If sites perform safety tests at these visits as a result of standard of care, sites should document all results in the case report forms.

4.9 Early Discontinuation from Study

- A subject should be discontinued early from study for any of the reasons described in Section 6.5 of the P1093 protocol.

- Every effort should be made to perform the evaluations described in the ‘Premature Discontinuation of Study Drug/On Study” visit in Appendix I (P1093 protocol) if the participant is willing before the subject comes off the study.
4.10 Long Term Follow-Up

Once the subject completes 48 weeks on study drug, and if the site investigator believes that they are gaining benefit from being on the study drug, the subject will move to the long term follow-up phase of the study. This involves less frequent visits and less lab and clinical tests at each visit, but will continue to follow the subject for several additional years.

- Sites should have subjects follow the schedule of evaluations described in Appendix IE.
- Study procedures listed in Appendix IE should be reported on the study CRFs for each visit.
- Any additional procedures should be performed as part of the local standard of care.

4.10.1 Pregnancy

Pregnancy testing, after the initial 48 weeks, should be determined as per local practice. If pregnancy occurs, this is an event that should be captured on the CRFs.

5.0 ADVERSE EVENTS (AEs)

5.1 Overview

An adverse event is any untoward, medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, regardless of the causal relationship.

This includes:
- Any clinically significant worsening of a pre-existing condition
- Any episode of overdose or abuse of a drug or investigational product

5.2 Reporting of Adverse Events for P1093

Adverse events, pregnancies and laboratory abnormalities meeting pre-defined criteria will be reported promptly by the investigator as summarized in the following table once the investigator determines that the event meets the protocol definition for that event:
<table>
<thead>
<tr>
<th>EVENT</th>
<th>TIME FRAME</th>
<th>DOCUMENTATION</th>
<th>REPORT TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>3 days</td>
<td>EAE Form</td>
<td>RSC</td>
</tr>
<tr>
<td>Grade 3 Toxicity</td>
<td>1 day</td>
<td>e-mail</td>
<td>Protocol Team</td>
</tr>
<tr>
<td>Grade 4 Toxicity</td>
<td>1 day</td>
<td>e-mail</td>
<td>Protocol Team</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>EAE Form</td>
<td>RSC</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 day</td>
<td>e-mail</td>
<td>Protocol Team</td>
</tr>
<tr>
<td></td>
<td>2 weeks</td>
<td>Pregnancy Notification CRF</td>
<td>FSTRF</td>
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<tr>
<td></td>
<td>1 week</td>
<td>Pregnancy Outcome CRF</td>
<td>FSTRF</td>
</tr>
<tr>
<td>Other Pregnancy Outcome</td>
<td>1 week</td>
<td>Pregnancy Outcome CRF</td>
<td>FSTRF</td>
</tr>
<tr>
<td>Abacavir Hypersensitivity</td>
<td>3 days</td>
<td>EAE Form</td>
<td>RSC</td>
</tr>
<tr>
<td></td>
<td>1 week</td>
<td>ABC HSR CRF</td>
<td>FSTRF</td>
</tr>
<tr>
<td>Liver Stopping Criteria Toxicity</td>
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</tr>
<tr>
<td>Hy’s Law Liver Event</td>
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<td>e-mail</td>
<td>Protocol Team</td>
</tr>
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<td>RSC</td>
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<td>Liver Event CRFs</td>
<td>FSTRF</td>
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<td>Protocol Team</td>
</tr>
<tr>
<td></td>
<td>1 week</td>
<td>Liver Event CRFs</td>
<td>FSTRF</td>
</tr>
</tbody>
</table>

5.3 Causality Assessment

All AEs and REs will have their relationship to study drug assessed using the following terms:

**Definitely related:** Clear-cut temporal association, and no other possible cause.

**Probably related:** Clear-cut temporal association and a potential alternative etiology is not apparent.

**Possibly related:** Less clear temporal association; other etiologies also possible.
Unlikely related: Temporal association between the AE and the study drug or the nature of the event is such that the study drug is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

Not related: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

5.4 Serious Adverse Events

5.4.1 Definition

A serious adverse event is an AE occurring at any time from enrollment through follow-up, whether considered related to the investigational study drug or not, that meets one of the following conditions:

- Death during the protocol-defined surveillance period
- Life threatening: defined as an event that places a subject at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death were it more severe
- Hospitalization: during the period of protocol-defined surveillance: defined as inpatient hospitalization or prolongation of existing hospitalization
- Results in a congenital anomaly or birth defect
- Results in a persistent or significant disability or incapacity; defined as a substantial disruption of the study participant’s ability to carry out normal life functions.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention.
- Life threatening refers to immediate risk of death from the event as it occurred. It does not include an experience that had it occurred in a more severe form might have caused death but as it actually occurred did not create an immediate risk of death.
- Hospitalization is to be considered a serious adverse event only in the event of an overnight admission. An elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE.

5.5 Abacavir (ABC) Hypersensitivity Reaction (HSR)

NOTE: This section applies to ALL abacavir containing products. Abacavir or abacavir containing products are also sold under the following brand names:
• Trizivir - US
• Triovir - Brazil
• Trizivar – Zimbabwe, South Africa, Namibia
• Ziagen – Brazil, South Africa, various African countries
• Ziagenavir – Thailand, various African countries
• Epzicom
• Kivexa

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity reaction (HSR). A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the Local Country Prescribing Information for each ABC-containing medication. Investigators must familiarize themselves with this information on ABC HSR in the Local Country Prescribing Information for each of these products prior to initiating subjects on ABC therapy.

Studies have shown that carriage of the *HLA-B*^*5701* allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*^*5701* and subsequently avoiding ABC in *HLA-B*^*5701* positive subjects, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) (*p*<0.0001). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*^*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

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

In any subject treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of *HLA-B*^*5701* status, it is important to permanently discontinue ABC and not re-challenge with ABC (e.g., ZIAGEN,
EPZICOM, KIVEXA or TRIZIVIR) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

5.5.1 Essential Subject Information

With reference to Local Country Prescribing Information, Investigators must ensure that subjects are fully informed regarding the following information on the hypersensitivity reaction prior to commencing ABC therapy:

Subjects must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased in individuals who are HLA-B*5701 positive.

Subjects must also be informed that HLA-B*5701 negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY subject who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

Subjects who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g., ZIAGEN, EPZICOM, KIVEXA or TRIZIVIR) again, regardless of their HLA-B*5701 status.

In order to avoid restarting abacavir, subjects who have experienced a hypersensitivity reaction should be asked to return any remaining tablets or oral solution to the Investigator or site staff.

Subjects, who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before re-starting abacavir.

Each subject should be reminded to read the Package Leaflet included in the pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

5.5.2 How to Handle Abacavir Rash

- Subjects should be instructed to contact the investigator as soon as possible if they develop a rash on ABC-containing therapy.
- Subjects who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens -
Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN, and Erythema Multiforme have been reported very rarely in subjects taking ABC-containing products. These subjects generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

- If a serious skin reaction develops, ABC (and all other concurrent medication(s) suspected in the investigators causality assessment) should be discontinued, and the subject should not be re-challenged with any ABC-containing medicinal product (i.e., ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

- As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the subject is receiving should also be reviewed and discontinued as appropriate.

### 5.5.3 Reporting of Hypersensitivity Reactions

All cases of potential ABC HSR will be reported to the RSC as EAEs. In addition to reporting the case as an EAE, the TRK0097 - IMPAACT P1093 Abacavir Hypersensitivity Reaction Record should be completed.

### 5.6 Pregnancy

- All female study subjects of child-bearing capacity (having menses) should be counseled about NOT becoming pregnant while on study.

- If a subject has a positive pregnancy test during study participation, the site should perform the following procedures:
  - The subject should immediately discontinue the study drug.
  - The pregnancy should be reported to DAIDS and to the team as an EAE within 3 business days of learning of the pregnancy. Record pregnancy using the EVW0241 - Pregnancy Notification Form and submit to FSTRF.
  - Subjects should remain “On Study / Off Treatment” and should be followed for safety concerns as per the regular visit schedule until the outcome is determined (e.g. birth, premature termination etc).
  - Once the outcome has been determined, the status of the mother and infant(s) should be recorded using the EVW0180 - Pregnancy Outcome-Revised Form and submitted to FSTRF within one week.
  - It is requested that the investigator ask the subject to return to clinic for a follow-up visit approximately 6-8 weeks later.
Pregnancy complications and elective terminations for medical reasons should be reported as an AE or SAE. Elective terminations should also be reported on the Pregnancy Outcome Form.

Spontaneous abortions MUST be reported as an SAE and reported on the Pregnancy Outcome Form.

The protocol team also encourages the sites to register the pregnancy in the Antiretroviral Pregnancy Registry (http://www.apregistry.com).

### 5.7 Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (> 0.3 mg/mg or 300 mg/g or 34 mmol/L) that represents a change from baseline and no associated increase in creatinine:

- Should have a repeat spot urine microalbumin/creatinine ratio performed within 2 to 4 weeks. See Section 4.2 of the MOP for instructions.
- If confirmed, then consideration should be made for additional evaluation after consultation with the Study medical monitor.
- Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Subjects with an abnormal urine microalbumin/creatinine ratio (> 0.3 mg/mg or 300 mg/g or 34 mmol/L) and representing a change from baseline) and a serum creatinine increase to grade 2 or above:

- Should have confirmation of both results within 2 weeks
- If confirmed, the IP should be withheld, and the Study medical monitor should be immediately contacted.
- Agreement on further management and restarting the IP should be agreed between the investigator and medical monitor.

### 5.8 Liver Toxicity Events

Liver toxicity stopping criteria are defined under Section 6.13 of the Protocol. If any of these liver toxicity stopping criteria are met, sites are instructed to complete the following procedures:

- Immediately withhold study drug
- Report the event to the study team by email within 24 hours of learning of its occurrence (impaact.teamp1093@fstrf.org)
• Report Hy’s Law liver toxicities (defined under Section 6.1.3 of the P1093 Protocol) to the RSC as an EAE

• Make every reasonable attempt to have all subjects meeting liver stopping criteria return to clinic within 24 hours to perform repeat liver chemistries

• Make every reasonable effort to schedule a follow-up visit within 72 hours of the last dose to perform the liver event follow up assessments described in Section 6.8

• Collect a blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours of last dose. (See section 5.8.1 of the MOP)

• Complete the BXW0020-Liver Events CRF, and the BXW0021-Liver Imaging and/or BXW0019-Liver Biopsy’ CRFs (if these tests are performed) and submit to FSTRF within one week of the liver stopping criteria toxicity

• Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

• A specialist or hepatology consultation is recommended

• Sites should make every attempt to carry out the following clinical and laboratory evaluations:

  ✓ Viral hepatitis serology including:
    o Hepatitis A IgM antibody
    o HBsAg and Hepatitis B Core Antibody (IgM)
    o Hepatitis C RNA; Cytomegalovirus IgM antibody
    o Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
    o Hepatitis E IgM antibody

  ✓ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);

  ✓ Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;

  ✓ Obtain complete blood count with differential to assess eosinophilia;

  ✓ Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;

  ✓ Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;
✓ Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.

✓ Record use of all concomitant medications, acetaminophen, herbal remedies, other over the counter medications, vaccinations or putative hepatotoxins, on the concomitant medications report form.

✓ Record any alcohol use on the ‘liver event alcohol intake’ case report form.

5.8.1 PK Sampling if a Liver Event Occurs

- The site personnel should try their best to schedule the subject to come back into clinic within 72 hours of the subject’s last dose of dolutegravir, in order to collect a PK sample.

- If possible, sites are requested to collect a 2mL blood specimen for PK analysis within 72 hours of the last dose of study drug taken. This is a requested (not mandated) specimen collection.
  - If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected within 72 hours, do not obtain the PK sample.
  - If the date or time of the last dose is unclear, provide the subject’s best approximation.

- Record the date and actual time of the PK blood sample draw and the date/time of the last dose of dolutegravir prior to blood sample draw on the the ‘Liver Event’ CRF.

6.0 SPECIMEN COLLECTION AND PROCESSING

6.1 Introduction

This section contains instructions related to collection and processing of P1093 specimens. For detailed information on tests and specimens required for each visit, please refer to the P1093 Schedule of Evaluations (Appendix IA-IG) of the P1093 protocol and the Laboratory Processing chart.

Regardless of where tests are performed, personnel who collect specimens and/or perform assays must be trained in proper collection, handling, testing
and associated QA/QC procedures prior to performing the tests for study purposes. Training documentation must be available for inspection at any time.

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:

http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx

As the transmission of HIV and other blood-borne diseases can occur through contact with contaminated needles, blood and blood products, appropriate precautions should be employed by all personnel when drawing blood and handling clinical specimens for this study in both the clinical and laboratory setting, as recommended by the Centers for Disease Control and Prevention (CDC). Respiratory infections may be transmitted by droplet aerosolization and fomites. All study staff should take appropriate precautions when collecting and handling biological specimens. Guidance on Universal Precautions/Body Substance Isolation is available from the US Centers for Disease Control and Prevention:

http://www.cdc.gov/ncidod/dhq/bp_universal_precautions.html
http://www.cdc.gov/ncidod/dhq/gl_isolation_standard.html

Additional laboratory reference information can be found in the joint ACTG/IMPAACT Laboratory Manual, which is available at:

http://www.hanc.info/labs/Pages/actgimpaactlabmanual.aspx

6.2 General Overview and Guidelines

Key elements of specimen management include collection, transport, storage and shipping. Also essential for clinical trials is a Chain of Custody which refers to the tracking of specimens and results.

It is essential that all staff collecting P1093 specimens have been trained in proper collection techniques, container types, and any special requirements. Specimens must be transported within predefined time limits to the laboratory under proper conditions. The remainder of this section provides information intended to standardize specimen collection and laboratory procedures across sites.
6.2.1 Specimen Chain of Custody

All IMPAACT sites must have a Standard Operating Procedure (SOP) for Chain of Custody in place. The Chain of Custody must track when specimens are transferred between clinics, processing units, and laboratories. Internal movements of specimens within the same laboratory do not need to be tracked. Laboratories with Laboratory Information Management Systems (LiMS) or the Laboratory Data Management System (LDMS) may be able to track most Chain of Custody information electronically. Tracking forms with specific information must accompany specimens. Required information includes the following: the PID/SID, collection time and date, and visit code for each specimen. Subject names or initials may NOT be used on research samples or the accompanying tracking forms.

6.2.2 Labeling Specimens

All samples collected at a study visit must be labeled at the time of collection with the PID, visit number, and collection date. PID and visit numbers may be pre-printed on these labels; however, study staff must write the specimen collection date and time on each label. Information on the specimen containers must match the information on the tracking forms. All samples must be entered into the LDMS system and aliquots must be labeled using standard LDMS-generated barcode labels.

6.2.3 Laboratory Data Management System (LDMS)

The LDMS must be used at all sites to track the collection, storage, and shipment of the laboratory specimens. Detailed instructions for use of the LDMS are available at:

[http://www.fstrf.org/ldms](http://www.fstrf.org/ldms)

All sites should upgrade to the most current version of the LDMS as soon as possible. For supported label and printer options, refer to the product listing documents located on the LDMS Client Reference Guides page on the FSTRF Portal. Contact LDMS user support for further information.

Questions about LDMS, shipping and storage for this protocol should be raised with the Laboratory Data Coordinator(s) at FSTRF:

Laura J Hovind, M.S.
Email: hovind@fstrf.org
Phone (716) 834-0900 x7468
Fax (716) 833-0655
24-Hour LDMS User Support

Technical support is also available from LDMS User Support. Usual business hours for LDMS user support are 12 AM - 6:00 PM Eastern Time in the US (ET) Monday through Friday. During business hours, please contact LDMS User support as follows:

Email: Ldmshelp@fstrf.org
Phone: (716) 834-0900, extension 7311
Fax: (716) 898-7711

Off-Hours Contact Information
If you are locked out of your LDMS or are experiencing errors that prevent you from completing your LDMS lab work during off-hours, page LDMS User Support using the LDMS Web Pager utility. Alternatively, you may e-mail the paging system directly at ldmspager1@fstrf.org. Please allow at least 15 minutes to get a response before sending another e-mail to the paging system.

Additional Resources:

LDMS website:
http://www.fstrf.org/ldms/

FSTRF portal:
http://www.fstrf.org/portal/

6.3 Specimen Collection Procedures

The Laboratory Processing Chart includes information on the type of collection tube, the amount and type of specimen to be processed and stored, and the required tests for all samples required by the P1093 protocol.

6.3.1 HIV-1 RNA Assay

For this study, only the Abbott platform may be used for the HIV-1 RNA PCR assay. If your local laboratory does not run the Abbott platform, you can visit the HANC website to obtain a list of labs that are certified to run
the Abbott platform. Sites should contact the team if they have any questions - impaact.teamp1093@fstrf.org

HANC Lab Resources site: http://www.hanc.info/labs/labresources/Pages/informationActgImpaactLabs.aspx

6.4 Specimen Processing Procedures

For laboratory processing instructions for specimens, please refer to the Laboratory Processing Chart which is located on the P1093 IMPAACT webpage (http://impaaactnetwork.org/studies/P1093.asp).

6.5 Shipping Procedures

For additional shipping instructions and addresses, please refer to the P1093 Laboratory Processing Chart available on the P1093 IMPAACT webpage (http://impaaactnetwork.org/studies/P1093.asp). If you still have questions, please contact the team at impaact.teamp1093@fstrf.org

6.5.1 Instructions for Shipments to Quest Diagnostics (Baltimore)

NOTE: The following specimens should be shipped in REAL TIME to Quest Diagnostics (Baltimore):

- M/C ratio urine specimens (US sites ONLY)

- Each US clinical site MUST contact the P1093 Quest Diagnostic Lab (BALTIMORE ONLY) at least 2 weeks prior to shipment of their first P1093 Real Time M/C ratio specimen, to arrange for an account to be created to allow for appropriate specimen receipt and result reporting to each clinical site. Contact the Quest Diagnostics’ Special Studies Service Representative (Larry Hirsch) at Larry.A.Hirsch@questdiagnostics.com or 1-410-536-1622.

- A custom P1093 Real Time M/C ratio testing requisition, as appropriate, will be provided to the clinical site/lab to use with specimen submission. The P1093 custom requisition form includes the demographic data entry fields (e.g. PID/SID, Date/Time of Specimen Collection, etc.) that must be completed by site personnel when sending the study subject’s specimen aliquots.

- Ship urine or blood specimens as appropriate, as described by the Lab Processing Chart.
• The site lab will pack and ship the box according to IATA regulations. The shipment must contain an LDSM diskette (or LDMS batch email must be sent to receiving lab), manifest, and box-map. Ship samples via priority overnight courier on a Monday through Thursday schedule. Do not ship on days that occur before a national holiday.

• The site lab must FAX or email a notification to the P1093 Quest Diagnostics Laboratory, Baltimore at 1-410-536-1474 or DGXBaltimoreSpecialStudiesDepartment@questdiagnostics.com PRIOR to shipping using the “IMPAACT Specimen Shipment Notice” from the IMPAACT website. The Quest laboratory can be contacted by telephone at 1-410-247-9100 ext. 2270.

7.0 DATA MANAGEMENT

7.1 Assignment of a Patient Identification Number (PID)
The PID is assigned at the site from a list that is generated by the DMC (FSTRF) and sent to the sites. If a subject has been on another IMPAACT or ACTG study, the same PID is carried with them for use in the new study; a new PID number would not be assigned.

7.2 Source Documents
Demographic, sample collection, clinical examination, and AE data must be collected and recorded by the Investigator’s designated personnel, directly on chart documents or investigator spreadsheets, and maintained as source documents.

Medical charts and/or subject charts, temperature cards, and any other collection tool may be used for verification of information recorded in the source documents or on Investigator spreadsheets.

All documentation must be made available to the Sponsor’s monitor at scheduled monitoring visits.

7.3 Case Report Forms
Site staff can find the schedule of case report forms for this study on the FSTRF portal website (http://www.fstrf.org/portal/).

7.4 Resources
Questions regarding data mangement, case report forms etc should be directed to the P1093 Data Managers, Stephanie Popson and Bobbie Graham, who can be reached via the contact information below:

Stephanie Popson, IMPAACT Protocol Data Manager
FSTRF
4033 Maple Rd.
Additionally, you may access the FSTRF website for additional information and resources at [www.fstrf.org](http://www.fstrf.org).
### APPENDIX I
P1093 PK Medication & Food History Logs

Subject PID: ______________________

<table>
<thead>
<tr>
<th>PK Visit Planned Date</th>
<th>Prior Dolutegravir Dosing</th>
<th>Date taken (mmm/dd/yyyy)</th>
<th>Time taken (hh:mm)</th>
<th>Single Dose Amount Taken (mg)</th>
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</thead>
<tbody>
<tr>
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<td>3 days before the PK visit</td>
<td>APR/08/2011</td>
<td>7:30</td>
<td>30</td>
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<tr>
<td></td>
<td>2 days before the PK visit</td>
<td>APR/09/2011</td>
<td>8:25</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td>APR/10/2011</td>
<td>8:10</td>
<td>30</td>
</tr>
<tr>
<td>Intensive PK</td>
<td>3 days before the PK visit</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
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</tr>
<tr>
<td>Week 4</td>
<td>3 days before the PK visit</td>
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<td></td>
</tr>
<tr>
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<td>2 days before the PK visit</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
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<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>3 days before the PK visit</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
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<td></td>
<td></td>
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<td>Week 24</td>
<td>3 days before the PK visit</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 days before the PK visit</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of most recent food intake prior to PK visit (hh:mm)</th>
<th>Type of Meal (full meal, light snack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: 18:45</td>
<td>Full meal (dinner)</td>
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APPENDIX II
Genotyping (Virologic Failure) Specimens
BRI PASS THROUGH NOTIFICATION

P1093 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Genotyping (VIROLOGIC FAILURE) specimens

Ship to **Lab 238 (UW)**:

Attn: Dr. Ingrid Beck  
University of Washington Children’s Hospital of Seattle  
1900 Ninth Ave  
Seattle WA 98101  
PHONE: 206–884-3440  
FAX NUMBER: 206-884-7311  
EMAIL: Frenkellabshipments@seattlechildrens.org
APPENDIX III
Intensive PK Specimens
BRI PASS THROUGH NOTIFICATION

P1093 Pass-Through Samples

LDMS Inventory/
BRI Storage Not Required

Intensive PK Specimens

Ship to **Lab 191 (UAB Pharmacology)**:

Attn: Kedria Walker

University of Alabama at Birmingham
Division of Pharmacology
1670 University Blvd
Volker Hall, Rm 270
Birmingham, AL 35294

PHONE: 205-975-2461
FAX NUMBER: 205-934-6201
EMAIL: kedria@uab.edu
## APPENDIX IV

**P1093 Specimen Testing Requisition - UW**

**IMPORTANT:** Please use this form when shipping specimens to Seattle Children’s Research Institute (SCRI) Lab, whether it is a direct shipment to SCRI, or if specimens will be sent to BRI first and then on to SCRI in real time. Please contact the team with any questions ([impaact.teamp1093@fstrf.org](mailto:impaact.teamp1093@fstrf.org))

Site Name & Number: __________________________________________________________

Site Contact Name & Phone Number: __________________________________________________________

<table>
<thead>
<tr>
<th>Subject PID</th>
<th>Date of Specimen Collection</th>
<th>Study Visit</th>
<th>Plasma HIV Viral Load* (c/mL)</th>
<th>Laboratory Testing Required</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genotyping (Screening)</td>
</tr>
<tr>
<td>Example:</td>
<td></td>
<td></td>
<td></td>
<td>Genotyping (Virologic failure)</td>
</tr>
<tr>
<td>123456J</td>
<td>March 1, 2011</td>
<td>Screening</td>
<td>45,000</td>
<td>X</td>
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</table>

*If viral load data is not available on specimen’s ship date, please forward viral load by email to [Frenkellabshipments@seattlechildrens.org](mailto:Frenkellabshipments@seattlechildrens.org) as soon as possible. Specimens will not be processed until viral loads are received.
Appendix V
Dosing Instructions
Directions for Parents/Legal Guardian/Caregiver

Parents/Legal Guardians/Caregivers are asked to record the date and time of doses taken 3 days prior to the scheduled intensive PK visit. The intensive PK evaluation should be scheduled to that the pre-dose PK samples and the witnessed dosing of DTG are as close to possible to 24 hours after the previous dosing. For population PK visits, subjects will need to provide a self-reported time and date of their last dose. See Section 4.4 and 4.6 for additional instructions for fasting and diet restrictions and further instructions for PK sampling doses.

Dolutegravir Granules in Suspension (Cohorts IIB, III, IV and V):

The pharmacist will dispense an initial supply of dolutegravir pediatric suspension reconstituted from granules in the same amber glass bottle in which the granules were mixed with water. Do not transfer the suspension to another container.

The pharmacist will supply all bottles of suspension already reconstituted, in which case it is important that EVERY bottle is shaken EVERY day by the parent, child or caregiver. If the participant vomits outside of PK visit (e.g. at home), then they should be re-dosed within 15 minutes.

The following instructions should be followed to administer the product.

Dosing:

You will also be supplied with dosing instructions and an oral dispenser to measure your child’s dose. Before measuring your child’s dose:

1. Shake the closed bottle well using an up and down motion, and visually check to ensure that there is no non-dispersed material adhering to the bottom or sides of the bottle. If necessary, continue shaking until all material is dispersed.
2. Remove the child resistant cap.
3. Before inserting the tip of the oral dispenser into the bottle adapter, push the plunger completely down toward the tip of the oral dispenser.
4. Insert the tip of the oral dispenser firmly into the bottle adapter, push the plunger completely down toward the tip of the oral dispenser and turn the entire unit (bottle and dispenser) upside down.

5. Ensure that the oral dispenser remains secure in the bottle adapter, pull the plunger of the oral dispenser out slowly until the desired amount of suspension is withdrawn into the oral dispenser.

6. Return the entire unit (bottle and dispenser) to an upright position and remove the oral dispenser slowly from the bottle.

7. Dispense directly into the mouth.

8. Close the bottle with the child-resistant cap after each use (do not remove the bottle 98 adapter). Disassemble the oral dispenser and remove the plunger from the oral dispenser. Rinse under running tap water and air dry prior to next use.

9. Re-shake the bottle prior to dispensing the next dose.

Dolutegravir Dispersible Tablets (Cohorts III-DT, IV-DT, and V-DT):
Subjects who switch from granules for oral suspension to dispersible tablets will have additional evaluations as indicated in the Schedules of Evaluations, Appendix I. On the day of the switch, the initial dose should be given in the study clinic and observed by study staff.

Confirm the dose to be given and select the appropriate number of dispersible tablets as directed.

Disperse the tablet in 2-5 mL water per tablet. Once dispersed, the solution should ideally be consumed immediately within 5 minutes (but no longer than within 30 minutes). If the participant vomits outside of the PK visit (e.g. at home), then they should be re-dosed within thirty minutes.

The pharmacist will dispense the dispersible tablets for suspension intact and in the original container with desiccant. Participants should be instructed to prepare only the dose needed at a particular time. Remaining study product should be stored in the original package to protect from moisture, with the bottle tightly closed. Do not remove the desiccant.

The following instructions should be followed to administer the product.

Dosing: You will need a dosing cup, and an oral dispenser to measure your child’s dose.

For older children able to drink from a dosing cup
1. For 1 or 2 tablets place 5mL of water into the dosing cup. For 3 or 4 tablets place 10mL into the supplied dosing cup.
2. Gently swirl for approximately 1 minute (until the tablet(s) have fully dispersed)
3. The child should swallow the contents of the dosing cup
4. Rinse the dosing cup 5ml of water and allow the child to swallow
5. If required, the child may drink water to wash down any taste
6. Clean and dry dosing cup to make ready for next use.

For babies and younger children who cannot drink from a dosing cup
1. Syringe 5mL of water and place in a dosing cup
2. Add the required number of tablets (1 or 2 as directed) to the dosing cup and gently swirl for approx 1 minute (until the tablet(s) have fully dispersed)
3. Using the syringe, suck the contents of the dosing cup up into the syringe
4. Syringe the contents into the cheek of the baby/child
5. Syringe a further 2mL of water into the dosing cup to rinse
6. Suck the contents back into the syringe and dose to baby/child
7. If required, the child may drink water to wash down any taste
8. Clean and dry the dosing cup and syringe to make ready for next use.