Phase I/II Study of the Pharmacokinetics, Safety and Tolerability of Doravirine (MK-1439) and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (MK-1439A) in HIV-1-infected Children and Adolescents

Manual of Procedures

Version 1.2
16 September 2019
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<th>Section</th>
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| Section 1<br>Study Overview | 1.2<br>16 September 2019 | • Updated for consistency with changes made in LoA #2  
• Removed Figure 1-1, as duplicative with figure updated in LoA #2 |
| Section 2<br>Preparing for the Study | 1.2<br>16 September 2019 | • Added links to the DAIDS Delegation of Duties Log template and policy in Section 2.1  
• Removed details related to protocol registration in Section 2.2 that are now included in the Network Manual of Procedures  
• Added requirements for approvals of LoA #2 as part of site-specific study activation in Section 2.3 |
| Section 3<br>Study-Related Information and Communications | 1.2<br>16 September 2019 | • Updated data management questions contacts in Figure 3-1 |
| Section 4<br>Participant Accrual | 1.2<br>16 September 2019 | • Updated Section 4.1 for consistency with changes made in LoA #2  
• Revised Section 4.3 for consistency with clarifications made in CM #1  
• Added guidance related to obtaining screening numbers for participants enrolled in Cohort 1 who subsequently screen for Cohort 2 in Section 4.3.3; updated Figure 4-3 to indicate required correspondence with the CMC  
• Removed communication requirement for correspondence with the CMC for participants in Cohort 1  
• Updated FAQs 4-A through 4-E to include participants in Cohorts 1 or 2 with ART experience.  
• Added guidance related to maintaining screening and enrollment logs electronically in Section 4.3.6.  
• Updated Figure 4-4b to show sample SES confirmation file for participants not selected for the intensive PK subset in Cohort 2  
• Added Figure 4-4c to show sample SES confirmation file for participants selected for the intensive PK subset in Cohort 2 |
| Section 5<br>Informed Consent and Assent | 1.2<br>16 September 2019 | • Removed details related to informed consent in Sections 5.1, 5.2, 5.3, 5.4, and 5.5 and Figures 5-1 and 5-2 that are now included in the Network Manual of Procedures  
• Added sample IC comprehension checklist for Cohort 2 as Figure 5-2  
• Added row for name of study staff person to sample IC coversheet in Figures 5-3 and 5-4 |
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<td>• Modified FAQ 6-A to remove reference to Cohort 1</td>
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<td>16 September 2019</td>
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<td>Section 13</td>
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<td>• Added FAQ 13-A through FAQ 13-G</td>
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<td>16 September 2019</td>
<td>• Added scenario related to recording pre-existing conditions and adverse events</td>
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1.0 STUDY OVERVIEW

IMPAACT 2014 is a Phase I/II, multi-site, open-label, non-comparative pharmacokinetic (PK), safety, and tolerability study of doravirine (DOR) and a fixed-dose combination of doravirine, lamivudine, and tenofovir disoproxil fumarate (DOR/3TC/TDF) in HIV-1-infected children and adolescents.

The study will enroll two cohorts, Cohort 1 and Cohort 2; Cohort 1 will evaluate the PK and safety of the 100 mg DOR dose, with intensive PK evaluation completed at entry and followed through two weeks on study to assess safety. Specimens will be shipped in real time with ongoing testing, with team review of PK and safety data as available. Up to 20 participants may be enrolled to achieve at least eight evaluable participants.

As described in Letter of Amendment #2, dated 26 April 2019, on enrollment of eight evaluable participants, enrollment was paused while the Cohort 1 PK and safety data were reviewed by the protocol team and the SMC. Data were evaluated, and the decision was made to continue enrollment into Cohort 1 for participants weighing 35 to ≤45 kg, while concurrently proceeding with Cohort 2 enrollment of participants weighing greater than 45 kg (the weight group corresponding to the Cohort 1 group with sufficient data for analysis). If the 35 to ≤45 kg weight group in Cohort 1 fully enrolls and shows acceptable PK and safety, Cohort 2 will open for the 35 to ≤45 kg weight group and the study will attempt to enroll approximately five participants in this weight group. Cohort 1 will remain open until a minimum of four evaluable participants between 35 to ≤45 kg are enrolled or until Cohort 2 is fully enrolled, whichever comes first.

Cohort 2 will enroll up to 45 participants to achieve 40 evaluable participants to evaluate the safety and tolerability of a fixed-dose combination regimen, including DOR, 3TC, and TDF. Participants will be followed through 96 weeks on study to assess PK, long-term safety and tolerability, virologic efficacy, and immunologic response.
2.0 PREPARING FOR THE STUDY

2.1 Investigator Responsibilities

IMPAACT 2014 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following web site and must be followed throughout implementation of IMPAACT 2014:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

IMPAACT 2014 also must be conducted in accordance with the IMPAACT Manual of Procedures and all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all applicable regulations, policies, and guidelines should be maintained in on-site essential document files. The IMPAACT Manual of Procedures is available at:

http://impaactnetwork.org/resources/policies-procedures.htm

The Investigator of Record (IoR) at each site must sign a Form FDA 1572 to formally indicate his or her agreement to conduct the study in accordance with the protocol and all applicable regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing the Form FDA 1572 are listed on the form, which is available on the DAIDS Regulatory Support Center (RSC) web site:

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

IoRs may delegate their obligations and responsibilities for conducting IMPAACT 2014 to other study staff; however, delegation does not relieve the IoR of his or her ultimate responsibility for all study procedures performed and all study data collected. Delegation of IoR responsibilities must be formally documented throughout the period of study implementation using the DAIDS Delegation of Duties (DOD) Log template available at:


The DAIDS DOD Log Instructions and Policy is available at:

https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

Consistent with the regulations, guidelines, and policies cited above, the IoR at each site must obtain all applicable drug regulatory and ethical review approvals for IMPAACT 2014 prior to study initiation; the IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to drug regulatory authorities (DRAs), the IoR must complete initial and continuing submissions in accordance with DRA policies. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46 and the ICH GCP guidance, as well as on the web site of the US Office for Human Research Protections (OHRP):

http://www.hhs.gov/ohrp/
All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their DRAs and IRBs/ECs and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Complete documentation of all correspondence to and from all responsible DRAs and IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

2.2 Protocol Registration

Details related to the DAIDS protocol registration process for IMPAACT studies are included in the IMPAACT Network Manual of Procedures available at:

https://impaactnetwork.org/resources/policies-procedures.htm

2.3 Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals (as described above) and must complete study activation procedures with the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met in order to obtain approval to begin study implementation. These requirements are listed on the IMPAACT 2014 Site-Specific Study Activation Checklist, which is available upon request from the IMPAACT Operations Center Clinical Trial Specialists.

As included in the Information/Instructions to Study Sites from the Division of AIDS in LoA #2, dated 26 April 2019, prior to implementing LoA#2, sites must receive all IRB/EC and regulatory entity approvals and receive an Implementation Notice from the IMPAACT Operations Center confirming that all operational requirements for implementing the LoA at the network level have been completed. Registration of LoA#2 with the DAIDS Protocol Registration Office was also added as an element of activation for all sites that were not activated to initiate the study prior to issuance of the LoA.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center Clinical Trial Specialists. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a Site-Specific Study Activation Notice. At each site, no study procedures may be conducted prior to receipt of an activation notice.
3.0 STUDY-RELATED INFORMATION AND COMMUNICATIONS

All IMPAACT 2014 visits and procedures must be conducted in accordance with the study protocol. The purpose of this manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center Clinical Trial Specialists of any such inconsistencies.

The IMPAACT 2014 protocol and related protocol documents are available on the study-specific web page:


The Protocol Team has identified study-specific contacts for various types of issues and questions, as shown in Figure 3-1. For issues and questions directed to the Protocol Team, a response from the appropriate team member can generally be expected within 24 hours.

Figure 3-2 lists the study-specific email groups that have been created for IMPAACT 2014. With the exception of the protocol email group (IMPAACT.prot2014@fstrf.org), these groups are maintained by the Operations Center Clinical Trial Specialists; please contact the Clinical Trial Specialists to request changes or updates for these groups. For the protocol email group, contact user.support@fstrf.org.

Questions related to interpretation of the protocol or participant management should generally be emailed to the IMPAACT 2014 Protocol Team Group (IMPAACT.team2014@fstrf.org) or the Clinical Management Committee (CMC) (IMPAACT.2014CMC@fstrf.org). Site staff should avoid sending messages to the protocol email group (IMPAACT.prot2014@fstrf.org) as this group is used for broadcast distribution to all Protocol Team members and study sites. The group is comprised of hundreds of individuals and is not intended to receive site-specific or participant-specific queries.

As indicated in Figure 3-3, active communication is expected between site staff and the IMPAACT 2014 CMC. When submitting questions and notifications to the CMC, to help ensure that CMC members have adequate information to respond in a timely manner, please address each of the points listed in Figure 3-3. Always retain a copy of correspondence with the CMC in the relevant participant’s study chart.
### Figure 3-1
**IMPAACT 2014 Study-Related Communications**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding site staff to protocol email group (<a href="mailto:IMPAACT.prot2014@fstrf.org">IMPAACT.prot2014@fstrf.org</a>)</td>
<td>User Support <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (include the protocol number in the subject line of your email message)</td>
</tr>
<tr>
<td>Any aspect of protocol interpretation or study implementation not listed below</td>
<td>IMPAACT 2014 Team <a href="mailto:IMPAACT.team2014@fstrf.org">IMPAACT.team2014@fstrf.org</a></td>
</tr>
<tr>
<td>Clinical, adverse event, and study drug management issues</td>
<td>IMPAACT 2014 Clinical Management Committee <a href="mailto:IMPAACT.2014CMC@fstrf.org">IMPAACT.2014CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Participant eligibility, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and/or enrollment</td>
<td>IMPAACT 2014 Clinical Management Committee <a href="mailto:IMPAACT.2014CMC@fstrf.org">IMPAACT.2014CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Co-enrollment issues</td>
<td>IMPAACT 2014 Clinical Management Committee <a href="mailto:IMPAACT.2014CMC@fstrf.org">IMPAACT.2014CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Data management computer and screen problems</td>
<td>User Support <a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (or by phone: +1 716-834-0900 x7302)</td>
</tr>
<tr>
<td>Subject Enrollment System</td>
<td>DMC Randomization Support Office <a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a> (or by phone: +1 716-834-0900 x7301)</td>
</tr>
<tr>
<td>Study drug issues (other than study drug orders)</td>
<td>Protocol Pharmacist <a href="mailto:sisetk@niaid.nih.gov">sisetk@niaid.nih.gov</a> <a href="mailto:justine.beck@nih.gov">justine.beck@nih.gov</a> (or by phone: +1 240 292-4848)</td>
</tr>
<tr>
<td>Study drug orders</td>
<td>Clinical Research Products Management Center <a href="mailto:BIO.CRPMC.Ph@Thermofisher.com">BIO.CRPMC.Ph@Thermofisher.com</a> (or by phone: +1 301-294-0741)</td>
</tr>
<tr>
<td>Data management questions</td>
<td>DMC Protocol Data Managers <a href="mailto:krotje@frontierscience.org">krotje@frontierscience.org</a> <a href="mailto:woolwhine@frontierscience.org">woolwhine@frontierscience.org</a> (or by phone: +1 716-834-0900)</td>
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### Figure 3-2
**IMPAACT 2014 Email Groups**

<table>
<thead>
<tr>
<th>Email Group</th>
<th>Membership</th>
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<tbody>
<tr>
<td><a href="mailto:IMPAACT.2014CMC@fstrf.org">IMPAACT.2014CMC@fstrf.org</a></td>
<td>Subset of the Protocol Team, as listed in the protocol Section 7.1.2</td>
</tr>
<tr>
<td><a href="mailto:IMPAACT.team2014@fstrf.org">IMPAACT.team2014@fstrf.org</a></td>
<td>Individuals listed in the Protocol Team Roster of the protocol</td>
</tr>
<tr>
<td><a href="mailto:IMPAACT.team2014sitereps@fstrf.org">IMPAACT.team2014sitereps@fstrf.org</a></td>
<td>Site investigators (and designees) and site coordinators (and designees) listed in the Site Representatives Roster of the protocol</td>
</tr>
<tr>
<td><a href="mailto:IMPAACT.prot2014@fstrf.org">IMPAACT.prot2014@fstrf.org</a></td>
<td>All team and site representatives (also includes all other study-specific groups)</td>
</tr>
</tbody>
</table>
Table 3-3: Communications with IMPAACT 2014 Clinical Management Committee

<table>
<thead>
<tr>
<th>Questions and notifications for IMPAACT 2014 CMC: Copy and paste this listing into the body of your email message to <a href="mailto:impaact.2014CMC@fstrf.org">impaact.2014CMC@fstrf.org</a> to help ensure that all required information is included.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include the protocol number and PID in the subject line of your message.</td>
</tr>
<tr>
<td>1. Site number:</td>
</tr>
<tr>
<td>2. Name of person submitting query:</td>
</tr>
<tr>
<td>3. PID:</td>
</tr>
<tr>
<td>4. Study cohort: 1 or 2</td>
</tr>
<tr>
<td>5. Reason for query (choose one):</td>
</tr>
<tr>
<td>a. Consultation on eligibility, enrollment, or resumption of follow-up (describe in case description)</td>
</tr>
<tr>
<td>b. Consultation on adverse event or toxicity management, including need for prohibited or precautionary medications (describe in case description)</td>
</tr>
<tr>
<td>c. Consultation on study drug management, including formulation switches and treatment interruptions (describe in case description)</td>
</tr>
<tr>
<td>d. Other (specify in case description)</td>
</tr>
<tr>
<td>6. Age of participant:</td>
</tr>
<tr>
<td>7. Current week on study:</td>
</tr>
<tr>
<td>8. Case description and question or notification for CMC:</td>
</tr>
</tbody>
</table>

File a copy of the email exchange in the participant’s study chart.
4.0 PARTICIPANT ACCRUAL

4.1 Overview

Up to 20 participants will be enrolled in Cohort 1 to achieve at least eight evaluable participants >45 kg, with an attempt to enroll approximately four evaluable participants between 35 kg to ≤45 kg. Depending on the PK results, additional participants may be enrolled.

Accrual into Cohort 1 was expected to be completed within 3-6 months after the first participant was enrolled. However, due to challenges in identifying children in the 35-≤45 kg weight group, accrual into Cohort 1 will remain open as Cohort 2 opens to accrual for the >45 kg weight group. Enrollment into Cohort 1 will remain open until a minimum of 4 evaluable participants between 35 to ≤45 kg are enrolled or until Cohort 2 is fully enrolled, at which time both cohorts will close to enrollment. If additional participants are required based on PK results, additional time may be needed to fully meet the accrual and PK targets.

Accrual into Cohort 2 will begin following confirmation of the DOR dose in the corresponding weight group in Cohort 1. Up to 45 participants will be enrolled in Cohort 2 to achieve at least 40 evaluable participants. Based on the PK and safety evaluations in Cohort 1, if 35 kg is established as the lower weight threshold, the study will attempt to enroll approximately five participants between 35 kg and 45 kg into Cohort 2.

Accrual is expected to be completed within 6-12 months after the first participant is enrolled in Cohort 2. However, if additional participants are required (e.g., some participants considered unevaluable), additional time may be needed to fully meet the accrual targets.

4.2 Site-Specific Accrual

The study accrual plan is based on site-specific accrual projections established during the site selection process. For each site, accrual will begin after all required approvals are obtained and a site-specific study activation notice is issued by the IMPAACT Operations Center. As a condition for study activation, each site will establish SOPs for participant accrual. All sites are responsible for following these SOPs, and for updating them if needed to meet their pre-specified accrual projections, throughout the study accrual period.

Once accrual is initiated, the Statistical and Data Management Center (SDMC) will routinely report the number of participants screened and enrolled at each site — by month and cumulatively — to the Protocol Team; monthly and cumulative data on the screen-to-enroll ratio will also be reported to the team. The team will monitor these data in relation to site-specific accrual projections to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made in response to Study Monitoring Committee (SMC) reviews of the study.

4.3 Participant Recruitment, Screening, and Enrollment

Refer to protocol Section 4.4 for an overview of the participant recruitment, screening, and enrollment process for this study. Recruitment methods for this study may vary across sites and will vary based on the expected enrollment cohort. All participants must be 12 years to less than 18 years of age at the time of enrollment and must be HIV-1-infected; participants may be perinatally or behaviorally infected.
Recruitment of participants for Cohort 1 is expected to rely on current patients being seen at a study clinic or from active identification and referral of HIV-1-infected children and adolescents who are ART-experienced and virologically suppressed. Recruitment of participants for Cohort 2 is expected to rely on active identification and referral of newly diagnosed HIV-1-infected children and adolescents (i.e., Cohort 2 ART-naïve) as well as participants who are ART-experienced and virologically suppressed (i.e., Cohort 2 ART-experienced); it is expected that recruitment methods for the later participants will more closely mirror methods to recruit for Cohort 1. Participants who enrolled in Cohort 1 will be allowed to separately enroll into Cohort 2; they will need to meet the same eligibility criteria as all other participants enrolled into Cohort 2 but will be enrolled into Cohort 2 Step 2 in the Subject Enrollment System.

While recruitment methods may vary across sites, screening and enrollment methods will be more standardized across sites, consistent with the requirements of protocol Sections 6.1, 6.2, and 6.3.

A schematic overview of the recruitment, screening, and enrollment process is provided in Figure 4-1; selected operational considerations related to this process are described in the remainder of this section.

**Figure 4-1**

**IMPAACT 2014 Recruitment, Screening, and Enrollment Process**

4.3.1 Obtaining Informed Consent

Refer to Section 5 of this manual for detailed guidance on obtaining informed consent for this study. Written informed consent for study participation must be obtained before any study-specific procedures are performed.

4.3.2 Assigning Participant Identification Numbers

A participant identification (PID) number must be assigned to each potential participant for whom informed consent for study participation is obtained. The only exception to this requirement applies when a participant has previously been assigned a PID for another IMPAACT or ACTG study. In that case, the previously-assigned PID would be used for IMPAACT 2014.

Study site staff should assign PIDs from lists provided by the DMC. Contact the DMC with any questions related to use of PID lists (refer to contact information in Figure 3-1).
4.3.3 Screening for Eligibility

The study eligibility criteria are provided in protocol Sections 4.1 and 4.2; procedural eligibility screening requirements are described in protocol Section 6.1 (Screening Visit), 6.2.1 (Cohort 1 Entry Visit), and 6.3.1 (Cohort 2 Entry Visit).

As described in Section 4.3.2, a PID will be assigned to all potential participants for whom informed consent for study participation is obtained. In addition, a study-specific screening number will be obtained for each potential participant through the DMC’s Subject Enrollment System (SES) using the PS2001 IMPAACT Screening Checklist.

Note: Participants who enroll in Cohort 1 and subsequently enroll in Cohort 2 will not obtain an additional screening number from the SES for the Cohort 2 screening process (they will be tracked using the previously-assigned PID); however, all other screening procedures as indicated in protocol Section 6.1 should be followed.

Participants who meet all eligibility criteria will be enrolled in the study through the SES using the IMPAACT 2014 Eligibility Checklist. For those who are found to be ineligible, or who do not enroll in the study for any reason, the SCR10002 IMPAACT 2014 Screening Failure and Non-Enrollment Results eCRF must be entered to record the screening outcome. This form is available in the screening folder in Medidata Rave shortly after submitting the PS2001 IMPAACT Screening Log. To access, use the assigned screening number. An example of the screening SES confirmation file, which provides a screening number for the participant in screening for the study, is provided in Figure 4-2.

Figure 4-2
Screening Sample SES Confirmation File with Screening ID for IMPAACT 2014

Frontier Science SES Confirmation File with Screening ID for IMPAACT 2014

As Cohort 1 participants who later screen for Cohort 2 will not receive a new Screening Number, sites are expected to notify the IMPAACT 2014 CMC (IMPAACT.2014CMC@fstrf.org) if a Cohort 1 participant begins screening for Cohort 2 (that is, once informed consent has been obtained as described in protocol Sections 4.4 and 6.1). These emails are essential to help track potential participants in Cohort 2 and to calculate the screening to enrollment ratios, as the data available.
through the DMC’s Subject Enrollment System (SES) alone not be sufficient for these purposes. Sites should communicate with the CMC (IMPAACT.2014CMC@fstrf.org) when a potential participant who was previously enrolled in Cohort 1 is considered for screening into Cohort 2. When submitting questions and notifications to the CMC, please ensure that CMC members have adequate information to respond in a timely manner by addressing each of the points listed in Figure 4-3. Always retain a copy of correspondence with the CMC in the relevant participant’s study chart.

**Figure 4-3**
Informing IMPAACT 2014 CMC of Potential Participants in Screening for Cohort 2 Who Were Previously Enrolled in Cohort 1

<table>
<thead>
<tr>
<th>When a Cohort 1 participant has begun screening for Cohort 2 (that is, once informed consent has been obtained and a screening ID obtained from the SES, as described in protocol Sections 4.4 and 6.1), copy and paste this listing into the body of your email message to <a href="mailto:impaact.2014CMC@fstrf.org">impaact.2014CMC@fstrf.org</a>.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include the protocol number and PID in the subject line of your message.</td>
</tr>
</tbody>
</table>
1. Site number:
2. Name of person submitting query:
3. PID:
4. Date of screening:
5. Planned date of enrollment/entry:

See IMPAACT 2014 MOP Section 4.3.3 for additional details related to screening for the study.

*File a copy of the email exchange in the participant’s study chart.*

As accrual approaches the targeted number of enrollments, the team will actively communicate with sites to help inform recruitment, screening, and enrollment efforts.

It is the responsibility of the IoR and other designated study staff to ensure that all required screening procedures are performed and adequately documented, and that only participants who meet the study 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 CMC must be consulted as soon as possible and within no more than 24 hours** per the communication procedures described in Section 3 of this manual.
4.3.4 FAQs Related to Eligibility

4-A A potential participant who is ART experienced comes to your clinic for screening on 31 January 2018. Medical records show one viral load result from 6 January 2017 that was <40 copies/mL. His viral load from screening is <40 copies/mL. Is this adequate for inclusion?

Yes. Per protocol, this participant must enroll into the study within 30 days of screening (i.e., by 2 March 2018). Per protocol Section 4.1.5, this participant has one HIV RNA PCR result below the level of quantification within 15 months prior to enrollment (i.e., from 6 January 2017); the participant also has an HIV RNA PCR result less than 40 copies/mL from screening.

4-B A potential participant who is ART experienced comes to your clinic for screening on 31 January 2018. Medical records show viral load results from 6 January 2017 that was <40 copies/mL and from 7 December 2017 that was 45 copies/mL. His viral load from screening is <40 copies/mL. Is this adequate for inclusion?

No. Per protocol, this participant must enroll into the study within 30 days of screening (i.e., by 2 March 2018). Per protocol Section 4.1.5, this participant has one HIV RNA PCR result above the level of quantification within 3 months prior to enrollment (i.e., from 7 December 2017).

4-C A potential participant who is ART experienced comes to your clinic for screening on 31 January 2018. Medical records show viral load results from 6 January 2017 that was <40 copies/mL and from 2 October 2017 that was 45 copies/mL. His viral load from screening is <40 copies/mL. Is this adequate for inclusion?

Yes. Per protocol, this participant must enroll into the study within 30 days of screening (i.e., by 2 March 2018). Per protocol Section 4.1.5, this participant has one HIV RNA PCR result below the level of quantification within 15 months prior to enrollment (i.e., from 6 January 2017); the participant does not have any HIV RNA PCR results within 3 months prior to enrollment that are above the level of quantification; and the participant also has an HIV RNA PCR result less than 40 copies/mL from screening. The potential participant does have one HIV RNA PCR between 3 and 15 months prior to enrollment above the level of quantification but, this participant would qualify for the study because the result is unconfirmed and less than 500 copies/mL (per the inclusion criterion note).

4-D A potential participant who is ART experienced comes to your clinic for screening on 26 July 2018. Medical records show the following viral load results from 15 February 2018 that was <20 copies/mL, from 27 March 2018 that was 530 copies/mL, from 19 May that was <20 copies/mL, and from 7 June 2018 that was <20 copies/mL. Is this adequate for inclusion?

No. Per protocol Section 4.1.5, this participant has an HIV RNA PCR result above 500 copies/mL between 3 and 15 months prior to enrollment (i.e., from 27 March 2018), making this participant not eligible.
4-E A potential participant who is ART experienced comes to your clinic for screening on 9 July 2018. Medical records show viral load results from 6 December 2017 that was 27,600 copies/mL, which was at time of initial HIV diagnosis and prior to ART exposure. Medical records also show the following viral load results from 26 January 2018 and from 20 April 2018 that were not detected. His viral load from screening is <40 copies/mL. Is this adequate for inclusion?

Yes. Per protocol, this participant must enroll into the study within 30 days of screening (i.e., by 8 August 2018). Per protocol Section 4.1.5, this participant has one HIV RNA PCR result below the level of quantification within 15 months prior to enrollment (i.e., from 26 January 2018); the participant does not have any HIV RNA PCR results within 3 months prior to enrollment that are above the level of quantification; and the participant also has an HIV RNA PCR result less than 40 copies/mL from screening. The potential participant does have one HIV RNA PCR between 3 and 15 months prior to enrollment above the level of quantification but this participant would qualify for the study because the result was prior to ART initiation.

4.3.5 Enrolling Eligible Participants

Participants will be considered enrolled in this study upon successful entry of eligibility checklist data into the SES, which will result in generation of a Study ID Number (SID). Examples of SES confirmation files, which provide SIDs for this study, are provided in Figure 4-4 at the end of this section.

Refer to protocol Section 6.2.1 and 6.3.1 for Entry Visit requirements, including requirements related to the timing and ordering of Entry Visit procedures, which should be taken into consideration when planning for logistical and staffing needs for these visits. Further information of the timing of enrollment, vis-à-vis the study eligibility criteria, is provided in the examples below. Please contact the Clinical Management Committee (CMC) with any questions involving interpretation of these timelines for any potential participant.

4.3.6 Screening and Enrollment Logs

Per the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, study sites are required to document screening (including screening failures) and enrollment activity on screening and enrollment logs. These logs may be maintained electronically but must be 21 CFR Part 11 compliant if the log is considered a source document. Screening and enrollment logs should be updated in real time and completed once a participant provides informed consent for screening. Participants who are approached, but do not provide informed consent for screening should not be included on this log.
Figure 4-4a
Cohort 1 Sample SES Confirmation File with SID for IMPAACT 2014

Frontier Science Registration and Randomization System Result:

******************************************************************************************
SES (rando 4.0.0.0.1)
Copyright 2002 FSTRF
PRS Date & Time: [27 December 2017 15:59:14 (GMT-05:00) US Eastern Time]
Enrolling as: [goodwin.christopher]

(M0000) *** PATIENT SUCCESSFULLY ENROLLED ***
PRESCRIPTION:
Day of Entry:
- DOR (MK-1439) , 100 mg tablet , orally, single dose

[999000 9] SID Assignment: [2014 i239 a]
******************************************************************************

Figure 4-4b
Cohort 2 Sample SES Confirmation File with SIDs for IMPAACT 2014
(participant NOT selected for intensive PK subset)

Frontier Science Registration and Randomization System Result:

******************************************************************************
SES (rando 4.2.0.0.0)
Copyright 2002 FSTRF
PRS Date & Time: [03 December 2018 16:13:41 (GMT-05:00) US Eastern Time]
Enrolling as: [devans.andrew]

(M0000) *** PATIENT SUCCESSFULLY ENROLLED ***
PRESCRIPTION:
96 weeks:
- DOR/3TC/TFV (MK-1439A) , 100mg/300mg/300mg fixed dose tablet , orally, once daily

[991001 E] SID Assignment: [2014 i199 f]
******************************************************************************
Figure 4-4c
Cohort 2 Sample SES Confirmation File with SIDs for IMPAACT 2014
(participant selected for intensive PK subset)

Frontier Science Registration and Randomization System Result:

---------------------------------------------------------------

SES (rando 4.2.0.0)  
Copyright 2002 FSTRF  
PRS Date &amp; Time: [03 December 2018 16:26:50 (GMT-05:00) US Eastern Time]  
Enrolling as: [devans.andrew]  

(90000) *** PATIENT SUCCESSFULLY ENROLLED ***  

PRESCRIPTION:  
96 weeks:  
- DOR/3TC/TDF (MK-1439A) , 100mg/300mg/300mg fixed dose tablet, orally, once daily  
  - The subject has been assigned, to intensive PK at week 1 per, protocol section 10.0  
PID: [991002 C] SID Assignment: [2014 1139 1]  
Stratum string: [21] Balancing: [none]  
---------------------------------------------------------------
5.0 INFORMED CONSENT AND ASSENT

This section contains reference information and guidance for obtaining informed consent/assent in IMPAACT 2014. This study involves two different informed consent processes:

- **Informed consent for participation in the protocol**: Informed consent for participation must be obtained before any study-specific screening or on-study procedures are performed. Per local site IRB/EC policies and as applicable for each potential study participant, informed assent for participation must also be obtained before any study-specific screening or on-study procedures are performed. Each participant is expected to take part in the informed consent process with his or her parent or legal guardian and, in general, both the assent of the participant and the consent of the parent or legal guardian will be required for all consent decisions.

Note that, per protocol Section 13.3, informed consent for continued study participation must be obtained from participants who reach the legal age of consent during follow-up at their next study visit and prior to conducting any study-specific procedures.

Additional details regarding informed consent, informed assent, and considerations for these processes are provided in the protocol Section 13.3.

- **Informed consent for specimen storage and future use**: Informed consent must be requested for storage and future research of specimens that are left over after all protocol-specified testing has been performed. This informed consent process need not be conducted prior to study entry, but should ideally be conducted as soon as possible and, for participants in Cohort 2, within three months after study entry. Parents/guardians and participants may choose to either provide or decline informed consent for specimen storage and future use with no impact on other aspects of their study participation. As indicated on the sample signature page in protocol Appendix IV, this informed consent form must be signed or marked regardless of whether informed consent is provided or declined. In addition, specific notations must be recorded on the form to document consent decisions for genetic testing.

The remainder of this section provides background information and operational guidance that is applicable to all the informed consent processes noted above.

5.1 General Considerations for Obtaining Informed Consent/Assent

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in research or have their child participate in research, after having been informed of all aspects of the research that are relevant to the decision. General guidance on obtaining informed consent and assent is provided in the IMPAACT Network MOP in Section 8.6.
**IMPORTANT NOTE**

Per protocol Section 13.3, should the consenting parent (or guardian) of a participant die or no longer be available for any reason, sites should follow the guidelines and procedures as described by their IRBs/ECs. In general, if participants are doing well on the study drug, it is expected that they will stay on study drug and will have safety assessments performed per the local standard of care while continued study participation is being determined. Study sites may continue to provide care for the participant as needed and appropriate (outside of the study), consistent with local standard of care. If a guardian cannot be identified, or if the guardian does not consent to continued study participation, the participant must be withdrawn from the study. In accordance with the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research (available at the website referenced in Section 13.2), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child or adolescent, reflective of applicable IRB/EC guidance for conduct of human subjects research within the context of available local law, regulation, or government policy.

5.2 Deliver all Required Information in a Manner that is Understandable to the Consenter and Assenter

The IMPAACT Network MOP Section 8.6.1 provides guidance on delivering all required information in a manner that is understandable to the consenter and assenter.

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

The IMPAACT Network MOP Section 8.6.2 provides guidance on assuring that informed consent is obtained in a setting free of coercion and undue influence.

5.4 Confirm that the Consenter Comprehends the Information

The IMPAACT Network MOP Section 8.6.3 provides guidance on confirming the consenter comprehends the information provided. See Figures 5-1 and 5-2 for examples of informed consent comprehension checklists for Cohort 1 and Cohort 2, respectively.
## Cohort 1 Sample Informed Consent Comprehension Checklist for IMPAACT 2014

<table>
<thead>
<tr>
<th>Participant’s Identifier</th>
</tr>
</thead>
</table>

### 1. Please tell me what you understand about this study and why it is being done.
Testing an ARV medication for children and adolescents to see if it is safe and that the amount of DOR in the blood is correct.

### 2. Please tell me about who will participate in this study.
Children and adolescents who are 12 years old to less than 18 years old who have HIV.

### 3. What are participants asked to do if they join this study
Cohort 1 participants will continue to take the anti-HIV medication that controls the amount of virus in their blood.

### 4. What are the possible risks for participants in this study?
- Procedures may cause discomfort (must mention at least one; see sample ICF #12 for Cohort 1).
- DOR may cause side effects (must mention at least one; see sample ICF #13-16 for Cohort 1).
- Others may treat participants unfairly for being HIV-positive or for being in the study.

### 5. What are the possible benefits for participants in this study?
There may be no benefit (may mention one or more possible benefits; see sample ICF #18 for Cohort 1).

### 6. What happens if a potential participant chooses not to join the study?
People are free to make their own choice about joining or not joining.

*No matter what the potential participant decides about joining, there will be no effect on access to health care outside the study*

No matter what the potential participant decides about joining, it is important to take ARVs. Taking ARVs is the best-known way for people with HIV to stay healthy and avoid passing HIV to others.

### 7. How will information about participants be protected?
Every effort will be made to keep information private and confidential. *(must mention at least one method used by the site, see sample ICF #17 for Cohort 1)*.

### 8. What should participants do if they have questions or concerns about their health or what is happening in the study?
Must state how to contact study staff (see sample ICF #22 for Cohort 1).

---

**Outcome** *(mark one)*
- □ Consenter demonstrated comprehension of all required points
- □ Consenter did not demonstrate comprehension of all required points

**Study Staff Signature and Date**
**Cohort 2 Sample Informed Consent Comprehension Checklist for IMPAACT 2014**

**Participant’s Identifier**

<table>
<thead>
<tr>
<th>✓ 1. Please tell me what you understand about this study and why it is being done.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing an ARV medication for children and adolescents to see if it is safe and can control the amount of HIV so that HIV cannot be found in the blood.</td>
</tr>
<tr>
<td>DOR is a new ARV that is being tested in adults in the United States and other countries. Cohort 1 of this study was the first study of DOR in combination with TDF and 3TC in children. The study showed that DOR was safe and present in the correct amounts in blood.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 2. Please tell me about who will participate in this study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children and adolescents who are 12 years old to less than 18 years old who have HIV.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 3. What are participants asked to do if they join this study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2 participants will come to the study for about 12 visits over 2 years.</td>
</tr>
<tr>
<td>At the entry visit, participants will receive study ARVs and instructions for taking them. Participants who were taking ARVs for treatment before entering the study will stop taking them and start taking the study ARVs instead.</td>
</tr>
<tr>
<td>At each of the visits the participants have blood taken.</td>
</tr>
<tr>
<td>• At some visits, ARVs in the blood will be measured. This may involve multiple blood draws at some time points.</td>
</tr>
<tr>
<td>• For the first 10 participants, an intensive PK evaluation will be done, which requires blood collection over about 24 hours.</td>
</tr>
<tr>
<td>Visits will include a physical exam. At one of the visits this includes a genital exam to determine the stage of puberty.</td>
</tr>
<tr>
<td>Extra visits will be scheduled if HIV is not well controlled.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 4. What are the possible risks for participants in this study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures may cause discomfort (must mention at least one; see sample ICF #16 for Cohort 2).</td>
</tr>
<tr>
<td>DOR may cause side effects (must mention at least one; see sample ICF #18-20 for Cohort 2).</td>
</tr>
<tr>
<td>Others may treat participants unfairly for being HIV-positive or for being in the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 5. What are the possible benefits for participants in this study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>There may be no benefit (may mention one or more possible benefits; see sample ICF #22 for Cohort 2).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 6. What happens if a potential participant chooses not to join the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>People are free to make their own choice about joining or not joining.</td>
</tr>
</tbody>
</table>

**Outcome (mark one)**

- Consenter demonstrated comprehension of all required points
- Consenter did not demonstrate comprehension of all required points

**Study Staff Signature and Date**
For sites choosing to use informed consent comprehension checklists similar to the sample provided above, the text that follows provides guidance on its intended use. Please contact the IMPAACT Operations Center Clinical Trial Specialists with any questions.

1. The sample informed consent comprehension checklist may be adapted for use at each site.

2. The checklist should be administered after the consenter has completed the informed consent discussion, i.e., after the consenter has read the informed consent form (ICF) or had it read to her/him and discussed any issues, questions, or concerns. It is generally expected that the checklist will be administered by the same study staff member who conducted the informed consent discussion with the consenter. However, this is not required.

3. The checklist should not be presented to the consenter as a “test,” but rather as a way of double-checking that study staff have fulfilled their responsibility to provide all information needed to make an informed decision about taking part in the study. Study staff members who administer the checklist must be sufficiently knowledgeable about the study to make good judgments about consenter’s comprehension of the informed consent information. They should be thoroughly familiar with the site-specific ICFs as well as with the content of the comprehension checklists. Role-playing is strongly recommended as part of preparation and training on use of the checklists.

4. Each checklist is structured around open-ended questions that correspond to the required elements of informed consent for research. For each question, at least one “required point of comprehension” is listed on the checklist; for some questions, several required points of comprehension are listed. Each open-ended question should be read to the consenter. Then, through discussion and dialogue, the intent is for the consenter to demonstrate comprehension of all required points of comprehension listed for each question. The consenter should not be expected to state each required point of comprehension using the exact same wording that appears on the checklist. Rather, the consenter should demonstrate in her/his own words that she/he understands each required point.

5. Because the open-ended questions are to be read to consenters, these questions should be translated into local languages. Sites may also translate the required points of comprehension, but this is not as critical as translating the questions, because the required points of comprehension are not read to consenters.

6. For each question, the consenter should ideally demonstrate comprehension of all required points before proceeding to the next question. When the consenter demonstrates comprehension of one of the required points, study staff should tick that point in the designated space. If the consenter does not spontaneously address one or more of the required points in her/his response, study staff should ask another open-ended question to elicit a response about that point. For example, one of the required points in Question 3 of the sample checklist is “At most of the visits the participants have a physical exam. At one of the visits, this includes a genital exam to determine the stage of puberty.” If the consenter does not mention this in her/his initial response to Question 3, study staff may say, “You mentioned the at most visits there will be a physical exam. Can you tell me what you understand will take place in this exam?”

7. The sample comprehension checklist has been designed to include points of comprehension that address all information required to make an informed decision about study participation. As such, comprehension of all points should be demonstrated before proceeding to the final informed consent decision and signing or marking of the ICF. Sites may choose to modify the wording of the required points of comprehension to correspond with wording used in their site-specific ICFs. Sites may also add points of comprehension to the checklists. Deletions are not recommended.
8. When responding to the open-ended questions, consenters may report back more information than is included on the checklist. This is acceptable, as long as the required information is reported back. However, if any misinformation is reported back, study staff should explain the correct information before proceeding to another question.

9. Once administration of the comprehension checklist begins, it is possible that the consenter may spontaneously state many of the required points, without each open-ended question being asked. In such cases, study staff should tick the relevant points on the checklist and then ask the remaining questions or probe about the remaining points that the consenter has not yet mentioned. It is acceptable to ask a question that a consenter may have already answered in her/his response to a previous question. However, if study staff are confident that a previous response was adequate, the specific question or point does not need to be repeated.

10. It is possible that a consenter might state correct information, yet study staff may not be convinced that she/he truly understands a required point of comprehension. In such cases, the study staff member should decide if further explanation or discussion is needed before proceeding to the final informed consent decision and signing or marking of the ICF. Further explanation or discussion may take place at the same visit or at another visit. The assessment process may also take place over the course of multiple days if the consenter becomes fatigued and/or if more time is needed for any other reason.

11. Whenever additional information or explanation is needed to help ensure the consenter’s comprehension, any informed consent support materials may be used (e.g., the ICF, other visual aids) to help provide the necessary information. After additional information or explanation is provided, open-ended questions should again be asked to confirm the consenter’s comprehension of the required points. Some consenters may be more comfortable interacting with the same study staff member throughout the informed consent process and comprehension assessment. However, another staff member may be consulted, if necessary or desired, to help explain difficult concepts and/or respond to specific questions or concerns.

12. The sample comprehension checklist has been designed as a source document, which should be completed, handled, and retained in participant study records like any other source documents. Relevant consenter and participant identifiers should be recorded on the checklists and tick marks for required points of comprehension should be recorded as instructed above. The study staff member who administers the checklist should document the outcome of the assessment in the space provided and should sign and date the checklist on the date of administration. Additional comments may be recorded on the checklist or on an informed consent cover sheet or other site-specific source document per site SOPs; however, such comments are not required.

13. The study staff member who administers the checklist should carefully review it to verify that comprehension of all required points was demonstrated and that this is documented on the checklist (i.e., all required points of comprehension should be ticked). It is recommended that a second study staff member also complete this verification because failure to document comprehension of all required points could be considered an informed consent and eligibility/enrollment violation.

5.5 Document the Process

The IMPAACT Network MOP Section 8.6.4 provides guidance on documenting the informed consent process. Figures 5-3 and 5-4 provide examples of informed consent and informed assent coversheets for IMPAACT 2014.
# Figure 5-3
Sample Informed Consent Coversheet for IMPAACT 2014

<table>
<thead>
<tr>
<th>Field</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant identifier</td>
<td></td>
</tr>
<tr>
<td>Name of study staff person completing informed consent process (and this coversheet):</td>
<td></td>
</tr>
<tr>
<td>Can the consenter read?</td>
<td>☐ Yes ☐ No ⇒ A literate impartial witness should be present during the entire IC process. Record name and relationship/role of witness below.</td>
</tr>
<tr>
<td>Language of IC process</td>
<td>☐ [Language A] ☐ [Language B]</td>
</tr>
<tr>
<td>Version number and version date of informed consent form used during IC process</td>
<td></td>
</tr>
<tr>
<td>Was the IC process conducted per site SOPs?</td>
<td>☐ Yes ☐ No ⇒ Record and explain departures from site SOPs below.</td>
</tr>
<tr>
<td>Was all information required to make an informed decision provided in a language understandable to the consenter?</td>
<td>☐ Yes ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Were all of the consenter’s questions answered?</td>
<td>☐ Yes ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the consenter comprehend all information required to make an informed decision?</td>
<td>☐ Yes ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Was the consenter given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision?</td>
<td>☐ Yes ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the consenter choose to provide IC?</td>
<td>☐ Yes ☐ No ⇒ STOP.</td>
</tr>
<tr>
<td>Date and time at which the consenter signed or marked the informed consent form</td>
<td>Date:</td>
</tr>
<tr>
<td>Did the consenter accept a copy of the IC form?</td>
<td>☐ Yes ☐ No ⇒ Offer alternate form of study contact information.</td>
</tr>
<tr>
<td>Notes/Comments</td>
<td></td>
</tr>
</tbody>
</table>

Signature of study staff person completing IC process (and this coversheet)
### Sample Informed Assent Coversheet for IMPAACT 2014

<table>
<thead>
<tr>
<th>Participant identifier</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of study staff person completing informed assent process (and this coversheet):</td>
<td></td>
</tr>
<tr>
<td>Can the assenter read?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ A literate impartial witness should be present during the entire informed assent process. Record name and relationship/role of witness below.</td>
</tr>
<tr>
<td>Language of informed assent process</td>
<td></td>
</tr>
<tr>
<td>☐ [Language A]</td>
<td>☐ [Language B]</td>
</tr>
<tr>
<td>Version number and version date of informed assent form used during process</td>
<td></td>
</tr>
<tr>
<td>Was the informed assent process conducted per site SOPs?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ Record and explain departures from site SOPs below.</td>
</tr>
<tr>
<td>Was all information required to make an informed decision provided in a language understandable to the assenter?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Were all of the assenter’s questions answered?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the assenter comprehend all information required to make an informed decision?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the assenter given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td>Did the assenter choose to provide informed assent?</td>
<td></td>
</tr>
<tr>
<td>☐ Yes</td>
<td>☐ No ⇒ STOP.</td>
</tr>
<tr>
<td>Date and time at which the assenter signed or marked the informed assent form</td>
<td></td>
</tr>
<tr>
<td>☐ NA (assent declined, form not signed or marked)</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
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<tr>
<td>Time:</td>
<td></td>
</tr>
<tr>
<td>Did the assenter accept a copy of the informed assent form?</td>
<td></td>
</tr>
<tr>
<td>☐ NA (assent chose not to provide informed assent)</td>
<td>☐ Yes</td>
</tr>
<tr>
<td>Notes/Comments</td>
<td></td>
</tr>
<tr>
<td>Signature of study staff person completing informed assent process (and this coversheet)</td>
<td></td>
</tr>
</tbody>
</table>
5.6 FAQs

5-A What should we do if, during the informed consent process, an adolescent indicates that she would like to take part in the study but is not willing to undergo certain procedures, such as a genital exam for sexual maturity rating?

The protocol team would generally advise against enrolling an adolescent who refuses certain exams, especially given that the protocol and sample informed consent form does not include an “opt out” provision for any procedures.

The scenario described in this question should be distinguished from another scenario in which an adolescent indicates that she is willing to undergo all procedures as part of the study informed consent process, but then refuses a procedure later in follow-up. In this scenario, the participant’s wishes should be respected. Her refusal should be documented in her study records, and she should continue in follow-up for the full scheduled duration of study participation.
6.0 STUDY VISITS AND PROCEDURES

Protocol Section 6 and the Schedule of Evaluations (SoE) provide comprehensive information on procedural requirements for conducting study visits. FAQs related to these requirements are provided in the remainder of this section. Further detailed information on administering questionnaires for this study is provided in Section 7 of this MOP.

6-A The protocol indicates that a symptom-directed physical examination should be completed for participants at Week 2. If the participant does not note any symptoms, do we need to perform any procedures to fulfill this protocol-specified procedure?

Yes. Per protocol Section 6.8, a symptom-directed exam should include the following:

- Height and weight
- Vital signs, including heart rate, temperature and blood pressure
- Examination of body systems driven by identified signs or symptoms

This means that, regardless of the symptoms that the participant presents with, evaluation of height, weight, and vital signs should be obtained at the visits noted in the SOE; any other elements of the examination should be driven by identified signs or symptoms.

6-B The protocol indicates that PK sampling for Cohort 1 should ideally begin on the day of entry. What should we do if this is not possible for a given participant?

The protocol provides a listing of required sequencing of procedures at the Cohort 1 Entry Visit in protocol Section 6.2.1; several elements must be performed prior to enrollment and several elements must be performed in a specific order. Evaluations to inform eligibility must be confirmed (or re-confirmed) on the day of enrollment, prior to enrollment. In general, sites are expected to put procedures in place to conduct all required Entry Visit procedures in the required order, beginning on Day 0 and continuing up to approximately 72 hours post-dose.

Ideally, the single dose of DOR should be given on Day 0, with the intensive PK evaluations beginning on Day 0 as well. In the rare event that this is not possible (e.g., if the participant or guardian is urgently called away from the study site after enrollment or if the site or participant would like to begin the PK evaluations early in the morning so that the 12-hour post-dose PK is not late in the day/night), sites could consider completing as many Entry Visit procedures as possible on Day 0, with the single dose of DOR and beginning of intensive PK procedures beginning as soon as possible, thereafter; for example, on Day 1.

6-C The 8th participant enrolled in Cohort 2 comes to the clinic on Day 10, which falls within the visit windows for Week 1 and Week 2. Can study procedures for both visits be combined?

No. As this participant is one of the first 10 enrolled in Cohort 2, this participant will be selected to have intensive PK evaluations, following the procedures indicated in protocol Section 6.3.2. According to protocol Section 6.3.3, Week 1 and Week 2 visit procedures may not be combined for participants selected for intensive PK evaluations. The clinic should conduct Week 1 procedures only and schedule the participant for a separate visit within the Week 2 visit window (Day 14 ± 1 week) to complete Week 2 procedures.
At the Entry Visit, a participant enrolled in Cohort 2 who will participate in the intensive PK sampling expresses a preference for evening dosing. How will this impact the PK sampling and what advice should be given to the participant regarding dosing times?

Protocol Section 6.3.2 indicates that participants selected for intensive PK sampling should have observed dosing of study drug as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Given the required PK sampling timepoints (pre-dose and 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, and 24 hrs post-dose), observed dosing will need to take place in the morning. At a minimum, participants should be advised to take their dose in the mornings for the three days prior to their Week 1 visit. Some participants may find it easier to do morning dosing for the entire time period between Entry and Week 1, while others may prefer to switch from evening to morning dosing for only the required three days. After the intensive PK evaluation is completed, participants may choose to dose at whatever time of day works best for them.
7.0 ADMINISTERING STUDY-SPECIFIC QUESTIONNAIRES

Study-specific questionnaires will be administered in this study:

- QLW10012: IMPAACT 2014 Adherence Assessment (applicable for participants in Cohort 2 only)
- EVW10019: IMPAACT 2014 Palatability and Acceptability Assessment, Cohort 1
- EVW10020: IMPAACT 2014 Palatability and Acceptability Assessment, Cohort 2

Each questionnaire will be interviewer-administered using paper-based forms (source documents) and data collected will be entered into eCRFs. To standardize this interviewer-administered data collection from site to site, and to maximize data quality, questionnaires must be administered in a non-biased, non-judgmental manner. Study staff should help participants feel comfortable sharing their personal information and opinions while asking questions in a consistent manner from participant to participant.

Study-specific questionnaires must be administered in the preferred language of each participant. If the study staff member administering the questionnaire is not fluent in the participant’s preferred language, a translator (third party) may be used to translate questions and responses in real time; however, every effort should be made to have a staff member who is fluent in the participant’s preferred language administer the questionnaire. As a condition for site-specific study activation, each site will be required to translate the questionnaires into all applicable local languages and to submit their translations and back-translations (into English) for review and approval by the Protocol Data Managers. The exception to this is Spanish language translations, which are provided to all sites that request them by the DMC. Please contact the IMPAACT 2014 Protocol Data Managers with any questions related to this process.

For questionnaires with “other, specify” response options, participant responses should be recorded word-for-word in the language in which the response was given. After the questionnaire is completed, the response should be translated into English, for entry into eCRF screens. It is generally expected that the study staff member who administered the questionnaire will perform this translation; other study staff members are also permitted to perform this translation, provided they are fluent in both English and the language in which the response was given.

The remainder of this section provides general guidance for administering all interviewer-administered questionnaires as well as specific detailed instructions for each questionnaire.

7.1 General Guidance for Questionnaire Administration

An interviewer uses both verbal and non-verbal techniques to obtain the most honest, accurate, and thorough responses from participants. These techniques are discussed below.

7.1.1 Welcoming the Participant

When a participant decides to take part in a study, everything about the study is new. Help make her/him feel comfortable. Similarly, when a new questionnaire is introduced later in follow-up, help make the participant feel comfortable with questions that have not been asked before.

- Considering offering the participant a cup of tea or other refreshment.
- Introduce yourself and try to create rapport (connection) between yourself and the participant to help her/him feel comfortable during administration of the questionnaire.
• Speak with the participant and administer questionnaires in the participant’s preferred language. Choose the local language questionnaire that corresponds to the participant’s preferred language and read directly from that form. **Do not** use another language form and translate in real-time.

• If considered helpful, offer the participant a blank copy of the form (in the preferred language) to read along as the questionnaire is administered. It is also acceptable for the participant to see the copy of the questionnaire being completed by the interviewer, as responses are being recorded, because this can reduce anxiety and increase collaboration.

• Some questionnaires include introductory statements to help prepare the participant for sensitive questions. Read these introductions as they appear on the forms.

7.1.2 **Pacing the Questions**

Every participant is different. Some will answer questions quickly. Others may take longer to answer or may change their answers after giving more thought to the question. Always account for this variety when administering questionnaires. Read questions slowly and let the participant finish thinking before you record her/his answer and go on to the next question.

7.1.3 **Reading Items Aloud**

Read all items to the participant **word-for-word** and speak clearly. Avoid re-phrasing questions because this can change the meaning of the question, making it inconsistent with questions administered to other participants. Provide explanation or interpretation if necessary, only after reading the item word-for-word. Avoid tangential—though related—counseling and educational discussions during data collection. When applicable, acknowledge questions and concerns raised by the participant during the questionnaire and state that these can be discussed after the questionnaire is completed.

Read the questions with interest and variability, so you do not sound automated. Emphasize the important words in a question, so that the meaning of the question comes through.

For questions with multiple sub-parts, read all sub-parts to the participant and mark the appropriate response for each, based on the participant’s answers.

7.1.4 **Recording Participant Responses Verbatim**

Often, questions will have a list of response categories to capture the participant’s response. Sometimes, an “other, specify” option is included for responses that do not fit into one of the categories already listed. When “other, specify” must be used, record the participant’s verbatim response, word-for-word, in the language spoken by the participant. Once the questionnaire is completed, go back and translate the local language text into English, for entry into eCRF screens. **Do not** translate in real-time during administration of the questionnaire.

7.1.5 **Probing**

One of the objectives of the study questionnaires is to obtain accurate information on participant behaviors (e.g., adherence), feelings, and opinions. The questionnaires ask participants to recall information that participants may not have thought about or may have difficulty remembering. The technique for helping a participant remember an answer, clarify a response, decide between two similar but different answers, or report something more precisely is called **probing**.
Effective probing helps a participant think more about a question or refine an answer that is too general. However, probing must not bias or otherwise direct participant answers. As the interviewer, you cannot offer an answer to the participant. Therefore, all probes must be neutral.

The following are some probing strategies to use when a participant initially answers “don't know” to a question or cannot remember or refine her/his response enough to answer the question.

- **Repeat Probe**: The repeat probe is used by repeating the item or response categories. Although the participant might hear you the first time you ask a question, she/he may need to hear the question more than once to provide an answer. Instead of rephrasing a question, always first repeat the question as written. Sometimes hearing the question a second time is all that is needed.

- **Echo Probe**: The echo probe involves repeating the participant’s exact response. Sometimes hearing the answer with a different voice will help her/him be more precise. The echo should always be repeated in a neutral, non-judgmental style.

- **Silent Probe**: The silent probe is used by pausing briefly after a participant gives what seems to be an uncertain answer. Although silence can feel awkward, sometimes it is helpful when a participant is trying to determine the most accurate answer to a question. Use a silent probe when the participant sounds unsure of her/his answer and may need some extra time to think more carefully about the question.

- **Non-verbal Probe**: The non-verbal probe is used by giving hand or facial gestures that may help the participant to come up with an answer. All such gestures must be neutral and non-judgmental.

- **Specification Probe**: The specification probe is used by asking the participant to give a more precise answer. Although a participant may give an answer that he or she considers accurate, it may not be specific enough. For example, if an item asks how many times the participant did something, and she/he answers with a range (“5 to 10”). If a more precise answer is needed for the question, the probe, “Can you be more specific?” is often enough to help the participant choose the most accurate response.

- **Historical Probe**: The historical probe is used by asking whether the event in question occurred anytime around major holidays or personal events such as a birthday or other life event. Some items require the participant to recall dates, and initially she/he may be unable to recall a date. Referencing a calendar can also help the participant remember dates.

### 7.1.6 Watching for Non-Verbal Cues

A participant may give you one answer verbally but express something else using body language or facial expressions. Although you should not question a participant so as to make her/him feel like you don't trust the answers, be aware of non-verbal cues that indicate she/he is not feeling comfortable, not taking the questionnaire seriously, or not answering honestly.

### 7.1.7 Checking Your Work

While administering a questionnaire, follow any written form instructions and guidance. Also, make sure the participant is understanding and responding to you, and that you record all reported information on the questionnaire form.

After the questionnaire is completed, and while the participant is still at the study site, review the questionnaire form for accuracy and completeness. This review step is not intended as an active review with the participant to confirm all of her/his responses; rather, it is a check to help ensure that any items that that might have accidentally been missed or mis-marked can be completed or corrected.
before the participant leaves the study site. Thereafter, questionnaire forms may undergo additional reviews, following site SOPs for QC/QA.

7.2 Specific Guidance for Routine Adherence Assessment (QLW10012), for Cohort 2 ONLY

This questionnaire must be administered by a study staff member who is not involved in providing ARV adherence counseling to participants.

This questionnaire should be administered at all applicable follow-up visits before provision of adherence counseling at these visits.

- Read the introductory statement at the beginning of the questionnaire.

- For item “In the last 30 days, on how many days did you miss your ARV dose?”, read the question to the participant word-for-word. Allow the participant to then report the number of days (in the last 30 days) on which a dose of ARVs was missed. If needed, use probes to assist the participant in identifying her/his best estimate of the number of days.

- For items “how good a job” and “how often”, read the question to the participant word-for-word; after reading each question, read the response categories word-for-word. Further guidance related to these items is as follows:

  - The emphasis is on **how good a job** the participant feels she/he did in taking her/his ARVs in the way she/he was supposed to. There is not a single definition of what the response options for this item will mean to different participants. Different participants may understand this item and the response options differently, and that is okay. If a participant asks for clarification, study staff may offer, “How well do you think you did at taking your ARVs as instructed? It is up to you to choose one of the answers, and there is no one meaning of any answer that is the same for everyone. What one person thinks is good or fair or poor for them may be different from what you think for yourself. That is okay. You can choose the answer that feels best for you.”

  - The emphasis is on **how often** the participant feels she/he took her/his ARVs in the way she/he was supposed to. If the participant asks for clarification, study staff may offer, “The last question asked about how you did in general. This question asks about how often, or how much of the time, you took your ARVs as instructed. Of the doses you were supposed to take, how often did you take them?”

- As needed, repeat questions and/or response categories (repeat probe) to help the participant understand the question and the response categories she/he is asked to choose from. If needed, other types of probes may also be used to help the participant choose the response category that best matches her/his experience taking ARVs in the last 30 days.

- After administering all items, **retain the completed questionnaire form separate from the participant’s main study file.** The questionnaire data will need to be entered into the QLW10012 eCRF but the completed questionnaire form should not be shared with other members of the study staff team, particularly staff members who provide adherence counseling to the participant.

The reason for this approach is to promote open responding by participants. If a participant believes her/his information will be shared with the care team (clinicians, counselors, pharmacists, and others who provide care, counseling, and support), she/he may be less likely to report problems with adherence. Reporting non-adherence to care teams can be intimidating and some people avoid it. If we can help participants understand that responses to this questionnaire are kept private, we may be able to collect data about non-adherence that may not otherwise be reported.
While we will make every effort to keep these data private, there are situations in which sharing information may be warranted, as described below.

- After administering all items, review the questionnaire form (QLW10012) to determine whether the participant’s responses indicate extreme non-adherence based on any of the following:
  
  - Item “how many days did you miss your ARV dose” = more than 14 days
  - Item “how good a job did you do” = very poor
  - Item “how often did you take your ARVs in the way you were supposed to” = rarely or never

If extreme non-adherence is reported, ask the participant for permission to assist in obtaining additional support from the care team and document whether the participant accepts or declines this assistance. Suggested wording, which may be adapted for use at each site, is as follows:

“As I mentioned earlier, my job is to ask these questions and collect your answers, and to keep your answers private. You reported some trouble with taking ARVs in the last month, and maybe you are already planning to talk to the [clinician/counselor/pharmacist] about that. Many people I have worked with have said it can sometimes be difficult to talk about trouble with taking ARVs with the [clinician/counselor/pharmacist]. If the information you have given to me today is of concern to you, or if you want to share this information with the [clinician/counselor/pharmacist], I can help. If you want, I can make sure you are able to talk with the [clinician/counselor/pharmacist], who are here to help. I can join you with the [clinician/counselor/pharmacist] or I can pass on information to them, if you give me permission to do so. If you would rather this remain private (only between you and me), that is your choice, and I will respect that. What would you like to do?”

- If the participant states that she/he is concerned and/or would like to have her/his responses shared, accept her/his response and proceed based on her/his stated wishes.
- If the participant states that she/he is not concerned or otherwise does not want her/his responses shared, accept her/his response and take no further action. However, you may offer assistance should she/he change her/his mind at any time.

Record on the questionnaire form whether the participant accepted or declined the offer of assistance communication support with other study staff designated to provide adherence counseling and support.

*Note:* The suggested wording above has six key components that can be conveyed in a number of different ways, but should all be included in the follow-up discussion with participants who report extreme non-adherence:

1. You **remind** the participant that her/his answers are **private**.
2. You **acknowledge** that she/he is telling you about having **challenges** in the past month.
3. You **do not assume** that she/he is **planning to hide** this information from the care team.
4. You tell her/him it is **not uncommon** for people to get anxious or otherwise have difficulty reporting non-adherence to the care team.
5. You **offer help**.
6. You **accept her/his response**.

Even if the participant declines your offer of help, she/he will still receive client-centered ARV adherence counseling as described in Section 9.4 of this manual. As part of this counseling, participants will have opportunities to report adherence challenges to study staff members designated to provide adherence counseling. These staff members will also have access to information on the participant’s HIV viral load, which provides an objective measure of her/his adherence.
7.3 Specific Guidance for Palatability and Acceptability Assessment (EVW10019 and EVW10020)

For Cohort 1: the questionnaire (EVW10019) should be administered at the Entry Visit (Day 0) after the ingestion of the study drug.

For Cohort 2: the questionnaire (EVW10020) should be administered at the Week 2 Visit after the ingestion of the study drug. It is administered again if the formulation is changed after Entry, at the time of the switch.

The questionnaire must be administered after the drug is taken. It is preferable to be consistent across participant in the amount of time elapsed between study drug ingestion and administration of the questionnaire.

7.3.1 Cohort 1, EVW10019

- For items 1a and 2a: ask the questions as they are written in the applicable language. Read the options to the participant as they are in the questionnaire.

- For item 3: staff should document any problems experienced by the participant. Note that any adverse events will need to be source documented and captured on relevant eCRFs.

7.3.2 Cohort 2, EVW10020

- For items 1a and 2: ask the questions as they are written in the applicable language. Read the options to the participant as they are in the questionnaire.

- For item 3: staff can mark the appropriate formulation (no need to ask participant), based on source documentation.

- Items 4 and 5 apply to tablet formulation. Those taking granules can skip to item 6.
  - For item 4a: ask the question as written in the applicable language. Read the options to the participant as they are in the questionnaire.
  - For item 5: ask the question as written in the applicable language. Note that any adverse events will need to be source documented and captured on relevant eCRFs.

- Items 6 through 9 apply to the granule formulation. Those taking tablets can skip these questions.
  - For items 6a, 6b, and 6c: ask questions are written in the applicable language. Read the options to the participant as they are in the questionnaire.
  - For items 7 and 8: staff need not be asked word-for-word to the participant but should be answered in discussion with the participant and/or parent/guardian.
  - For item 9: staff should document any problems experienced by the participant. Note that any adverse events will need to be source documented and captured on relevant eCRFs.
8.0 PHARMACY CONSIDERATIONS

Refer to protocol Section 5 for detailed information regarding study drug regimens, study drug formulation and supply, study drug accountability, and study drug administration. Protocol Section 5 also provides information on concomitant medications and listings of precautionary and prohibited medications.

IMPORTANT NOTE

At this time, site teams may not offer the oral granule formulation of DOR/3TC/TDF until additional stability information can be implemented in the study. Potential participants should be counseled during the screening process that only the tablet formulation is available at this time.

FAQs related to the study drug are included below.

8-A What instructions should be provided to participants and parents/guardians if a participant in Cohort 2 vomits soon after taking a dose of DOR/3TC/TDF?

In general, if a participant vomits within 30 minutes of taking a dose of DOR/3TC/TDF, the participant should take a replacement dose. If a participant vomits more than 30 minutes after taking the dose, she or he should not take a replacement dose unless the participant (or parent/guardian) is able to identify the tablet in the vomitus.

At visits with an observed dose for a PK evaluation, additional considerations apply if the participant vomits:

- For the intensive PK evaluations (at Week 1 for the first 10 participants enrolled in Cohort 2), protocol Section 6.3.2 states that the scheduled PK visit should be rescheduled if the participant has an intercurrent illness (e.g., vomiting) that would interfere with the study drug administration or result in malabsorption of the drug.

  If the participant does not have an intercurrent illness but vomits within 60 minutes of taking a dose of DOR/3TC/TDF and the intact tablet is visible, the participant should take a replacement dose and continue with the intensive PK evaluations. If the participant vomits more than 60 minutes after taking a dose of DOR/3TC/TDF, the participant should continue with the intensive PK evaluations. For any other scenario, the intensive PK day should be rescheduled.

- For the sparse PK evaluations with an observed dose administration at Weeks 4, 24, and 48, if the participant vomits within 30 minutes of taking the dose of DOR/3TC/TDF, the participant should take a replacement dose and continue with the sparse PK evaluations.
8-B  What instructions should be provided to participants and parents/guardians if a participant misses a dose of DOR/3TC/TDF?

In general, if a participant forgets a dose of DOR/3TC/TDF, the participant should be instructed to take the dose as soon as he or she remembers. If more than 16 hours have elapsed from when the participant usually takes the ARVs, the participant should wait and take the next scheduled dose at the usual time. Double doses should not be taken after the missed dose.

When providing this guidance to participants, site staff should take into consideration when a participant usually takes the ARVs (e.g., morning, afternoon, evening, bedtime) and tailor the instructions accordingly.

If the participant misses any doses in the three days prior to the intensive PK visit, the visit should be rescheduled, as per protocol Section 6.3.2.
9.0 COUNSELING CONSIDERATIONS

This section provides guidance on the following types of counseling to be provided in IMPAACT 2014:

- HIV-related counseling
- Contraception counseling
- Study drug adherence counseling

9.1 Counseling Overview

All counseling provided in this study should be provided per site standard operating procedures (SOPs), which should reflect all national, international, and local policies and guidelines that are applicable at each site. Site SOPs should be reviewed and updated at least once annually and upon issuance of any updated policies and guidelines. SOPs should reflect the differing counseling expectations between participants enrolled in Cohort 1, in Cohort 2 as ART-naïve, and in Cohort 2 as ART-experienced. Note that many participants enrolled in Cohort 2 of this study will be newly diagnosed with HIV infection and will be starting a new antiretroviral study drug regimen upon entry into the study, while concurrently starting to cope with their new diagnosis and all its implications. As appropriate and per site SOPs, parents and guardians should be included in counseling sessions.

All study staff who provide counseling should be trained to do so in accordance with local standards of care and site training policies. Site supervisory staff are responsible for ensuring the quality of counseling provided through on-site monitoring, mentoring, and refresher training throughout the course of the study.

Counseling provided in this study may identify needs that are beyond the scope of the study to address. When such needs are identified, participants should be referred to non-study service providers and other organizations that may be able to assist them. Each site should maintain current lists of referral organizations and make these lists available to all counselors for use during all counseling sessions. At each counseling session after a referral is made, the counselor should actively follow-up on the referral to determine whether the participant sought the services to which he or she was referred, determine the outcome of the referral, and determine whether additional referrals are needed. Additional counseling may also be needed to help ensure that participants access services that may be beneficial to them.

All counseling must be documented in participant study records. Documentation should include the content of each counseling session, participant responses to the counseling provided, any concerns raised by the participant, action planned to be taken by the participant prior to the next counseling session, action to be taken by the counselor (or other study staff) prior to the next session, and issues to be reviewed or addressed at the next session. Specific to referrals, all follow-up actions, outcomes, counseling, and plans for next steps should also be documented. Study sites may choose to use checklists to document counseling sessions — particularly to document the content of each session — but it is expected that narrative notes will also be required to fully document each session. Careful attention should be paid to clearly identifying counseling issues to be addressed at the next session, given that different counselors may provide counseling at different visits.
9.2 HIV-Related Counseling

It is generally anticipated that all sites will provide HIV-related counseling to participants throughout their participation in the study. This counseling will include:

- **Counseling in relation to HIV testing:** Most participants enrolled in this study will undergo HIV testing as a study procedure, to confirm their eligibility for study participation. HIV testing must be performed in the context of pre-test and post-test counseling. Pre-test and post-test counseling should be provided per site SOPs in a client-centered manner, i.e., in a manner that is responsive to the information and counseling needs of the participant at the time of the session.

- **Counseling in relation to risk reduction:** For this study, the term risk reduction counseling refers to counseling provided to support participants in reducing their risk of re-infection and their risk of transmitting HIV to others (e.g., to sexual partners). Risk reduction counseling should be provided as part of the pre-test and post-testing counseling described above and at any time in response to client-centered needs, per site SOPs.

Condoms should be provided throughout participation in the study and risk reduction counseling should include information, education, and skills building on condom use and condom negotiation strategies as needed for each participant. Counseling should also include HIV/AIDS education, discussion of disclosure issues and emotional support, discussion of healthy living strategies, discussion of stressors and potential strategies to address these, and provision of referrals, as applicable to each participant. Counseling should include information on suppression of HIV viral load as an effective strategy to minimize the risk of transmission to others.

Sexually active participants should also be counseled on the benefits of HIV counseling and testing for couples and study sites should offer counseling and testing for partners whenever possible.

9.3 Contraception Counseling

Refer to protocol Section 8.8. All sites will provide contraceptive counseling to participants throughout their participation in the study. Counseling should be provided per site SOPs in a client-centered manner; when applicable, participants should be offered the option of having their partners attend counseling sessions with them. Study sites should ideally integrate provision of contraceptive methods with other services offered to study participants and should provide referrals to non-study sources of methods that cannot be provided at the study site.

Sites should reinforce directions related to use of effective, medically accepted contraception methods and all female participants who are engaging in sexual activity that could lead to pregnancy should be counseled about NOT becoming pregnant while in the study. For participants engaging in sexual activity that could lead to pregnancy, self-reported confirmation of contraception use should be obtained at every visit. These discussions should be source documented in research records. If participants engaging in sexual activity that could lead to pregnancy report discontinuation of contraception use, the site should consult the CMC on further management. Note that care should be taken to maintain the privacy and confidentiality of minor participants who do not wish to disclose their sexual activity to their guardians.

After the initial contraception counseling sessions, subsequent sessions should re-assess contraceptive choices over time and provide information, education, skills building, and referrals in response to current needs. At each session, issues requiring follow-up from the prior session should be reviewed and updated, and plans should be made for actions to be taken between the current session and the next session. For participants choosing to use contraception, instructions and counseling for proper use and adherence to her/his current method should be reviewed and reinforced at each session.
9.4 Study Drug Adherence Counseling

Refer to protocol Section 6.10. All sites will provide study drug adherence counseling to all participants throughout their participation in the study.

The purpose of adherence counseling is to provide information, skills building, and other guidance to support participants in taking ARVs as correctly and consistently as possible. While it is essential that participants be provided information on correct use of each ARV, once this knowledge is established, the emphasis of adherence counseling should be on supporting the participant in consistent use over time.

Adherence counseling should be provided in a client-centered manner per site SOPs. Site SOPs should designate roles and responsibilities for adherence assessment, counseling, and support and specify how clinic and pharmacy staff will share information and coordinate efforts while fulfilling their respective roles and responsibilities. It is generally anticipated that routine adherence counseling will be provided for all for participants who are generally adherent and for whom significant barriers to adherence are not identified. Enhanced adherence counseling will be provided for participants for whom significant barriers to adherence are identified (including those who do not achieve or sustain a suppressed HIV viral load).

Adherence counseling should acknowledge that consistent use of ARVs is challenging and should encourage participants to openly discuss any challenges they may face, so that study staff can assist with identifying strategies to address the challenges. Counseling should also acknowledge that adherence challenges may change over time; therefore, adherence strategies may also need to change over time. The role of the counselor is to support the participant in identifying strategies that are most likely to work for her.

Additional tips and guidance for providing adherence counseling are as follows:

- In preparation for each counseling session, review study records to:
  - Identify how long the participant has been taking ARVs; whether she/he has experienced ARV side effects; whether she/he has achieved and/or sustained a suppressed HIV viral load; and whether adherence challenges have been encountered to date.
  - Review the adherence strategies that have been identified for the participant to date and which of these have been perceived as successful or unsuccessful by the participant; pay particular attention to adherence strategies identified at the last counseling session.

- Prepare any materials that may be needed for the session.

- Greet the participant by name, establish rapport, and foster open dialogue. Reinforce confidentiality and explain that the purpose of the session is solely to assist the participant with taking her/his ARVs.

- Invite the participant to ask any questions and express any concerns she/he may have.

- As needed, address any knowledge gaps or misinformation with regard to use of ARVs. Use information sheets and/or other visual aids to help ensure the participant’s understanding of instructions for correct use of each ARV, paying particular attention to these issues as participants enter the study and when ARV regimen changes occur.

- As needed, provide skills building support to the participant (e.g., on proper storage of ARVs; on disclosure of HIV status and/or study participation to others).
• Use open-ended questions and actively listen to the participant’s responses to assess her/his experience with adherence since her/his last visit.

*Note:* Adherence questionnaire data collected as described in Section 7 of this manual may *not* be used as a basis for adherence counseling in this study. Rather, client-centered dialog should guide all counseling.

• Incorporate discussion of HIV viral load test results and trends in these results over time. If results and trends are not as expected, ask the participant for her/his thoughts on why this may be the case and build from the participant’s perceptions to guide additional counseling.

• Provide positive reinforcement for adherence successes. Ask the participant to share more information on successful strategies so that her/his approaches can be shared with other study participants. Continue successful strategies as part of the participant’s ongoing adherence plan.

• Review the adherence strategies discussed at the previous session and probe as needed to identify ongoing or new barriers to adherence. With continued dialog, assess whether the reminder and adherence strategies discussed at the previous session were perceived by the participant as useful/successful. As needed, assist the participant with identifying new strategies to try to address new or ongoing barriers.

• At each session, clearly articulate the adherence plans and strategies identified by the participant for the time period between the current session and the next session. All plans and strategies should be practical and feasible for the participant. For participants with significant adherence barriers, plans and strategies may need to be incremental. For participants whose adherence barriers change over time, plans and strategies may also need to change over time. All plans and strategies should be documented in study records with written copies given to the participant, if desired.

• Thank the participant for her/his participation in the study. Acknowledge the contributions they are making toward finding new treatments for people with HIV and improving the health of such people worldwide.

### 10.0 PARTICIPANT MANAGEMENT CONSIDERATIONS

Protocol Section 8 describes management of adverse events, drug discontinuation and pregnancy and contraception issues as relevant to the study population. FAQs related to adverse event grading and reporting, which are relevant to protocol Sections 8.1 and 8.2, as well as protocol Section 7.2, are provided below. Other FAQs and operational guidance related to participant management will be added to this section as needs for such guidance are identified.

<table>
<thead>
<tr>
<th>10-A</th>
<th>Section 8.2 of the protocol states that the CMC should be consulted regarding management of Cohort 2 participants who interrupt DOR/3TC/TDF for a period of 7 or more days. Does this refer to 7 or more consecutive days?</th>
</tr>
</thead>
</table>

Yes.
11.0 EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS

Refer to protocol Section 7.3 for detailed information on expedited adverse event (EAE) reporting requirements for this study. Other important references and resources related to EAE reporting include:

- Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0)
- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017
- Study drug Investigator’s Brochures
- DAERS Site User Instructional Guide for EAE Reporting
- DAERS Reference Guide for Site Reporters and Study Physicians
- DAIDS safety training resources

The DAERS and DAIDS resources listed above are available at:

https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-experience-reporting-system
https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources

To illustrate the EAE reporting requirements specified in protocol Section 7.3, several reporting examples are provided below. When reviewing these examples, please note that even when EAE reporting is not required, all adverse events must be source documented and selected adverse events must be entered into eCRFs, per protocol Section 7.2.

<table>
<thead>
<tr>
<th>Sample Case Description</th>
<th>Has a reportable EAE occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 14 year old girl in Cohort 2 is hospitalized after her Week 4 visit with a febrile illness; the illness is assessed as not related to study drug.</td>
<td><strong>Yes.</strong> This event is serious because it resulted in hospitalization and all SAEs must be reported as EAEs.</td>
</tr>
<tr>
<td>A 12 year old boy in Cohort 2 develops an asymptomatic Grade 4 ALT elevation.</td>
<td><strong>Yes.</strong> Any Grade 4 adverse event must be reported as an EAE, regardless of symptoms.</td>
</tr>
<tr>
<td>A 16 year old boy develops herpes zoster at study Week 8, which is suspected to be an IRIS event. He is treated as an outpatient.</td>
<td><strong>Yes.</strong> For IMPAACT 2014, an IRIS event should be reported in an expedited manner.</td>
</tr>
<tr>
<td>A 16 year old girl becomes pregnant on study. There have been no complications when she reports the pregnancy to the study team.</td>
<td><strong>No.</strong> Normal pregnancies are not reportable. However, any participant who becomes pregnant should be contacted following study discontinuation to ascertain the pregnancy outcome; if a pregnancy complication is reported during this time, the complication should be reported as an EAE. All pregnancies do need to be reported to the CMC as per protocol Section 8.8.</td>
</tr>
<tr>
<td>A 16 year old girl becomes pregnant on study and experiences a still birth at 28 weeks gestation.</td>
<td><strong>Yes.</strong> Pregnancy complications, including intrauterine fetal demise, must be reported as EAEs.</td>
</tr>
<tr>
<td>Sample Case Description</td>
<td>Has a reportable EAE occurred?</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>A 16 year old girl becomes pregnant on study and experiences a miscarriage at 8 weeks gestation.</td>
<td>Yes. Pregnancy complications, including spontaneous abortions, must be reported as EAEs.</td>
</tr>
<tr>
<td>A 14 year old girl is diagnosed with a mild basal cell carcinoma on her forearm.</td>
<td>Yes. All malignancies must be reported as EAEs.</td>
</tr>
</tbody>
</table>
12.0 LABORATORY CONSIDERATIONS

Protocol Section 6, the SoE, and Laboratory Processing Chart (LPC) are the primary sources of information on specimen collection, processing, testing, storage, and shipping for this study; both clinic and laboratory staff should routinely refer to these resources as needed.

FAQs and other operational guidance will be added to this section as needs for such guidance are identified.
13.0 DATA MANAGEMENT CONSIDERATIONS

Refer to protocol Section 11 and the eCRF completion guide developed by the DMC for this study. eLearning modules and other operational guidance on use of the Medidata Rave system for this study are available on the DMC portal.

FAQs related to eCRF completion are provided below. Also provided below is a table (Table 13-1) that maps the medical and medication history elements specified in protocol Table 17 to the eCRFs into which these elements will be entered. A scenario is also provided (following Table 13-1) to illustrate key aspects of eCRF data entry for pre-existing conditions and adverse events.

13-A Based on protocol Table 17, we believe that HIV infection should be recorded on the Medical History Log eCRF for all participants who are enrolled in the study. Is this correct?

Yes.

13-B We are not sure that we understand the instructions for entry of ARV use data into eCRFs. Could you please clarify on this?

The study drugs listed in protocol Section 5.1 — DOR for Cohort 1 and DOR/3TC/TDF for Cohort 2 — should be entered into the Treatment Log eCRF (TXW10005). All other ARVs should be entered into the Concomitant Medications Log eCRF (CMW10004). Further details are as follows.

- All ARVs received within 30 days prior to enrollment should be entered into the Concomitant Medications Log.
- The study drugs listed in protocol Section 5.1, i.e., DOR and DOR/3TC/TDF, received after enrollment, should be entered into the Treatment Log.
- All other ARVs received after enrollment should be entered into the Concomitant Medications Log. Note, as indicated in protocol Table 17, for participants in Cohort 2, DOR/3TC/TDF would be considered study drug and no other concomitant ARVs would be expected (unless the study drug is not tolerated or otherwise has to be changed).

13-C We are not sure that we understand the protocol requirement to enter into eCRFs all concomitant medications “taken at onset of” adverse events that are specified to be entered into eCRFs per Section 7.2. Could you please explain this?

The intent of this instruction is to require entry of all concomitant medications that a participant is taking at the time when an adverse event that meets criteria in protocol Section 7.2 occurs. For example:

Consider a participant who takes daily multivitamins. There is no adverse event prompting receipt of daily multivitamins. In this scenario, the multivitamins would need to be source documented, but would not need to be entered into the Concomitant Medication Log eCRF.

Now consider a different participant who take multivitamins and who receives a five-day course of an antibiotic to treat a grade 2 respiratory infection. The respiratory infection would meet criteria in protocol Section 7.2 for entry into the Adverse Event Log eCRF. In this scenario, the respiratory infection would need to be entered into the Adverse Event Log eCRF. As the antibiotics and the multivitamins were being taken when the infection occurred, both would need to be entered into the Concomitant Medication Log eCRF.
13-D We have a question about entering laboratory data into eCRFs. When we enter hematology and chemistry test results and severity grades, will Rave automatically check the severity grades in real time?

Yes. When the laboratory eCRF is saved, a custom function will check the severity grade and an automatic query will be generated if there is a discrepancy between the laboratory value and the grade. Please note, however, that this function only checks grades based on the absolute values of laboratory test results. It does not check grades based on change from baseline. Should you encounter difficulty with entering correct severity grades or resolving queries related to severity grades, please contact the Protocol Data Managers.

13-E The Adverse Events Log eCRF (ADE10000) requests a “date EAE first reported to DAERS” in item 12a and a “date of initial report” in item 13. What is the difference between these two dates?

The date requested in item 12a is the date that an adverse event was reported in the DAERS as an EAE. The date requested in item 13 is the date that a log line was added/entered into the ADE100000 eCRF for an adverse event in Rave.

13-F The Adverse Events Log eCRF (ADE10000) requests a “DAERS EAE Number” in item 12b. We have a question about this when entering log lines for a diagnosis plus associated signs and symptoms. For example, if we have a case of pneumonia that results in hospitalization. We could have one ADE10000 log line for the diagnosis of pneumonia and several other log lines for signs and symptoms such as fever, chills, shortness of breath. Assuming that one EAE report is submitted into DAERS for this event, would the same DAERS number be entered into item 12b for each of the individual ADE10000 log line entries?

Yes, the same DAERS number would be entered for each of the individual ADE10000 log line entries (this will allow the Protocol Data Managers to link all of the diagnoses, signs, and symptoms to the same adverse event in DAERS).

13-G We would like to be sure we understand some queries received for adverse events associated with abnormal laboratory values. For example, we have a participant at our site who has had grade 3 creatinine values at three consecutive visits. We entered a row in the Adverse Event Log eCRF for “increased creatinine” when the first grade 3 value was obtained. Thereafter, we considered the adverse event ongoing through the next two visits. If we understand correctly now, however, we must enter a new row in the Adverse Event Log eCRF for each grade 3 test value, even though the grade has not changed between tests. Is this correct?

Yes, this is correct. When reporting adverse events associated with abnormal laboratory test results, a new row must be entered into the Adverse Event Log eCRF associated with each individual result.
## Baseline Medical and Medication History Elements

<table>
<thead>
<tr>
<th>Assess for and Source Document</th>
<th>Enter into eCRFs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Medical and Medication History Elements</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Age and other socio-demographics | Subject Enrollment System:  
- IMPAACT 2014 Eligibility Checklist |
| HIV diagnosis, Sexual Maturity Rating (SMR), WHO clinical staging (Cohort 2), and ARV treatment history (including all ARV use within the 30 days prior to enrollment) | CMW10004: Concomitant Medications Log  
EVW10033: WHO Staging System for HIV Infection  
EVW10034: Tanner Stage/Testicular Volume  
LBW10000: HIV-1 Plasma Viral Load  
MHW10004: Medical History Log |
| History of allergy and/or hypersensitivity (including to ARVs) | MHW10004: Medical History Log |
| Ongoing or clinically relevant medical conditions (including malignancies and sleep history) occurring during the 30 days prior to enrollment | MHW10004: Medical History Log |
| Medications (other than ARVs, see above) taken within the 30 days prior to enrollment and/or ongoing at enrollment | CMW10004: Concomitant Medications Log |
| Assessment of sexual activity and contraception | Subject Enrollment System:  
- IMPAACT 2014 Eligibility Checklist  
LBW10005: Pregnancy Test |
| Any other information needed to determine eligibility for the study | Subject Enrollment System:  
- IMPAACT 2014 Eligibility Checklist  
LBW10000: HIV-1 Plasma Viral Load  
LBW10023: Chemistry/Hematology Test Results Log  
LBW10026: Reagent Strip Urinalysis Results Log  
LBW10027: Hepatitis Antigen/Antibody Test Results Log  
LBW10025: Hepatitis C Virus Quantitative RNA Results  
LDMS: Laboratory Data Management System  
VSW10000: Vital Signs |
Pre-existing Conditions and Adverse Event Recording Scenario #1
A participant enrolled with a Grade 2 AST value at screening on 16 April 2020 is found to have an asymptomatic Grade 1 AST value at Week 2 (10 May 2020).

<table>
<thead>
<tr>
<th>Medical History Log</th>
<th>First log entry for this participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHW10004 Entries for 16 April 2020</td>
<td></td>
</tr>
<tr>
<td>What is the verbatim term for the medical history condition/event?</td>
<td>Increased AST</td>
</tr>
<tr>
<td>What is the severity grade of the medical history condition/event?</td>
<td>2</td>
</tr>
<tr>
<td>What was the date medical history condition/event started?</td>
<td>16 April 2020</td>
</tr>
<tr>
<td>Is the medical history condition/event still ongoing?</td>
<td>Yes</td>
</tr>
<tr>
<td>What was the date the medical history condition/event ended?</td>
<td>[not applicable]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History Log</th>
<th>First log entry for this participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHW10004 Entries for 10 May 2020</td>
<td></td>
</tr>
<tr>
<td>What is the verbatim term for the medical history condition/event?</td>
<td>Increased AST (no change)</td>
</tr>
<tr>
<td>What is the severity grade of the medical history condition/event?</td>
<td>2 (no change)</td>
</tr>
<tr>
<td>What was the date medical history condition/event started?</td>
<td>16 April 2020 (no change)</td>
</tr>
<tr>
<td>Is the medical history condition/event still ongoing?</td>
<td>Yes (no change)</td>
</tr>
<tr>
<td>What was the date the medical history condition/event ended?</td>
<td>10 May 2020 (updated entry)</td>
</tr>
</tbody>
</table>

The participant’s AST remains at Grade 1 until the Week 64 visit; at the Week 64 visit, the participant is found to have an asymptomatic Grade 2 AST value and a normal total bilirubin (18 July 2021). Upon repeat testing one week later (25 July 2021), a confirmatory Grade 2 AST value is obtained.

<table>
<thead>
<tr>
<th>Medical History Log</th>
<th>Second log entry for this participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHW10004 Entries for 18 July 2021</td>
<td></td>
</tr>
<tr>
<td>What is the verbatim term for the medical history condition/event?</td>
<td>Increased AST</td>
</tr>
<tr>
<td>What is the severity grade of the medical history condition/event?</td>
<td>1 (no change)</td>
</tr>
<tr>
<td>What was the date medical history condition/event started?</td>
<td>10 May 2020 (no change)</td>
</tr>
<tr>
<td>Is the medical history condition/event still ongoing?</td>
<td>Yes (no change)</td>
</tr>
<tr>
<td>What was the date the medical history condition/event ended?</td>
<td>[not applicable]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events Log</th>
<th>First log entry for this participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE10000 Entries for 18 July 2021</td>
<td></td>
</tr>
<tr>
<td>What is the adverse event term?</td>
<td>Increased AST</td>
</tr>
<tr>
<td>What is the severity grade of the adverse event?</td>
<td>2</td>
</tr>
<tr>
<td>What is the date adverse event started?</td>
<td>18 July 2021</td>
</tr>
<tr>
<td>Is the adverse event still ongoing?</td>
<td>[not applicable]</td>
</tr>
<tr>
<td>On what date did the adverse event end?</td>
<td>[not applicable]</td>
</tr>
<tr>
<td>What is the outcome of the adverse event?</td>
<td>[not applicable]</td>
</tr>
</tbody>
</table>