P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study

Manual of Procedures

FINAL Version 2.1
26 May 2020
**IMPAACT P1115 Manual of Procedures**  
**Overview of Section Contents and Identification of Current Section Versions**

*This version of the MOP provides operational guidance consistent with protocol Version 2.0. Refer to previous versions for corresponding guidance applicable to protocol Version 1.0.*

<table>
<thead>
<tr>
<th>Section</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Section 1 Study Overview</td>
<td>Version 2.1</td>
<td>Updated to add a reference to protocol Section 5.1 for dosing details associated with each study regimen and to refer to extended follow-up in Step 2 during the COVID-19 pandemic per protocol Letter of Amendment (LoA) #2.</td>
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<tr>
<td>Section 2 Preparing for the Study</td>
<td>Version 2.1</td>
<td>No change from previous version.</td>
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<tr>
<td>Section 3 Study-Related Information</td>
<td>Version 2.1</td>
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<td>Section 4 Participant Accrual</td>
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<tr>
<td>Section 5 Informed Consent</td>
<td>Version 2.1</td>
<td>Updated to include “important note” related to obtaining informed consent for extended follow-up under LoA #2 and to provide guidance for eCRF entries documenting this consent.</td>
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<td>Section 6 Entry and Follow-Up in Step</td>
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<td>Section 7 Entry and Follow-Up in Step</td>
<td>Version 2.1</td>
<td>Updated to refer to extended follow-up in Step 2 during the COVID-19 pandemic per LoA #2; to refer to protocol Clarification Memorandum #2 for guidance on study implementation during the COVID-19 pandemic; to refer to obtaining informed consent for extended follow-up; and to provide listings of procedures required at extended follow-up visits.</td>
</tr>
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<td>Section 8 Counseling Considerations</td>
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<td>Section 9 Clinical Considerations</td>
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<td>Section 10 Expedited Adverse Event</td>
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This version of the MOP provides operational guidance consistent with protocol Version 2.0. Refer to previous versions for corresponding guidance applicable to protocol Version 1.0.

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<td>26 May 2020</td>
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1.0 Study Overview

IMPAACT P1115 is a Phase I/II, multi-center, exploratory, proof-of-concept study of very early intensive treatment to achieve remission in infants infected with HIV \textit{in utero}. For this study, remission is defined as having no confirmed detection of plasma HIV RNA for 48 weeks following cessation of treatment.

P1115 involves two cohorts of infants enrolled in pairs with their mothers. The study also involves four operational steps, each with its own eligibility criteria, schedule of evaluations (SoE), and participant management specifications. The two cohorts and four steps are described in detail throughout this manual. Introductory descriptions are provided in Figures 1-1 and 1-2.

Figure 1-1

IMPAACT P1115 Study Cohorts

<table>
<thead>
<tr>
<th>Cohort 1: Infants born to HIV-infected mothers who did not receive antiretrovirals during pregnancy (High-Risk Infants)</th>
</tr>
</thead>
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<tr>
<td>• These infants will enter the study in Step 1 within 48 hours of birth, at which time their HIV infection status may not be known. They will initiate early intensive treatment per protocol and undergo specimen collection for HIV testing within 48 hours of birth.</td>
</tr>
<tr>
<td>  – If HIV infection is confirmed (with two positive nucleic acid tests), the infant will enter Step 2 and continue early intensive treatment per protocol in Step 2.</td>
</tr>
<tr>
<td>  – If HIV infection is not confirmed, early intensive treatment will be switched to standard prophylaxis; the infant will remain in Step 1 for 12 weeks and then exit the study.</td>
</tr>
</tbody>
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<tr>
<th>Cohort 2: Infants with at least one positive HIV nucleic acid test from a specimen collected within 48 hours of birth who initiated a qualifying antiretroviral treatment regimen outside of the study within 48 hours of birth (Early Treated Infants)</th>
</tr>
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<tbody>
<tr>
<td>• These infants will enter the study in Step 2 within 10 days of birth and will receive intensive treatment per protocol in Step 2.</td>
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</tbody>
</table>

Figure 1-2

IMPAACT P1115 Study Steps

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Initiation of intensive treatment for high-risk infants while awaiting HIV test results (switch to standard prophylaxis if infection is not confirmed)</td>
</tr>
<tr>
<td>Step 2</td>
<td>Continued intensive treatment for confirmed HIV-infected infants with monitoring to determine eligibility for treatment cessation between two and four years of age</td>
</tr>
<tr>
<td>Step 3</td>
<td>Treatment cessation with monitoring for viral rebound for up to five years from the date of entry into Step 3</td>
</tr>
<tr>
<td>Step 4</td>
<td>Treatment re-initiation for infants who experience viral rebound after treatment cessation through five years of age or until six months after viral re-suppression on treatment, whichever is later</td>
</tr>
</tbody>
</table>

Under protocol Version 1.0, 460 mother-infant pairs were enrolled (440 in Cohort 1, 20 in Cohort 2) to identify 54 infants with \textit{in utero} HIV infection. Under protocol Version 2.0, approximately 445 additional mother-infant pairs are expected to be enrolled (430 in Cohort 1, 15 in Cohort 2) to identify approximately 45 additional infants with \textit{in utero} HIV infection.
Three early intensive treatment regimens will be assessed:

- **Regimen 1L**: Two nucleoside reverse transcriptase inhibitors plus nevirapine plus lopinavir/ritonavir (2 NRTIs + NVP + LPV/r)
- **Regimen 2R**: Two nucleoside reverse transcriptase inhibitors plus nevirapine plus raltegravir (2 NRTIs + NVP + RAL)
- **Regimen 2RV**: Two nucleoside reverse transcriptase inhibitors plus nevirapine plus raltegravir plus VRC01 monoclonal antibody (2 NRTIs + NVP + RAL + VRC01)

See Figure 1-3 for a graphical overview of the above-listed information. Regimen 1L will be provided to infants who were enrolled under protocol Version 1.0 and are continuing follow-up under protocol Version 2.0. Regimens 2R and 2RV will be provided to infants enrolled under protocol Version 2.0. Refer to protocol Section 5.1 for dosing details associated with each regimen.

Infants with confirmed *in utero* HIV infection will be followed in Step 2 for up to 192 weeks in Step 2; under Letter of Amendment (LoA) #2, follow-up in Step 2 may be extended during the COVID-19 pandemic for up to 288 weeks. Beginning at Step 2 Week 84, these infants may be evaluated for possible entry into Step 3.

Infants who enter Step 3 will be followed in Step 3 for as long as they remain in HIV remission, up to five years from the date of entry into Step 3. If confirmed viral rebound occurs in Step 3, children will enter Step 4 and be followed in Step 4 through five years of age or until six months after viral re-suppression on antiretroviral treatment (ART), whichever is later.

Mothers of enrolled infants will be followed for the same duration of time as their infants, with targeted evaluations performed at entry and every six months thereafter.

*Note*: Informed consent must be obtained separately for Steps 1 and 2, prior to entry into each step. Informed consent must also be obtained prior to entry into Step 3. A combined informed consent form is used for Steps 3 and 4; separate informed consent is not required prior to entry into Step 4.
2.0 Preparing for the Study

P1115 will be conducted at selected IMPAACT clinical research sites worldwide. Refer to previous versions of this MOP for more information on the site selection process that was conducted for protocol Version 1.0. No additional site selection is expected for protocol Version 2.0. However, Regimen 2RV will only be provided at a limited subset of selected sites. As of the date shown in the footer below, these sites are 5072, 5097, 8052, 8950, 30300, 30301, and 31890.

2.1 Investigator Responsibilities

Version 2.0 of the P1115 protocol will be conducted under Investigational New Drug (IND) application number 133,017.

Under protocol Version 2.0, P1115 must be conducted in accordance with the US Code of Federal Regulations (45 CFR 46; 21 CFR 11, 50, 54, 56, and 312) and the International Council for Harmonisation (ICH) Guideline 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 P1115:

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

P1115 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 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 Investigator of Record (IoR) at each site must sign the P1115 Protocol Signature Page to formally document his or her agreement to conduct the study in accordance with protocol Version 2.0 and all applicable protocol-related documents and in compliance with applicable US regulations; the ICH Guideline for GCP; institutional review board/ethics committee (IRB/EC) determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements and institutional policies.

The IoR at each site must also sign a Form FDA 1572 to formally indicate his or her agreement to conduct the study in accordance with protocol Version 2.0 and to personally conduct or supervise the study at his or her site. The commitments made by the IoR when signing the Form FDA 1572 are listed on the form, which is available at:

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

IoRs may delegate their responsibilities for conducting P1115 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.

Consistent with the regulations, policies, and guidelines cited above, the IoR at each site must obtain all applicable ethical and regulatory approvals to conduct P1115 and maintain these approvals in good standing throughout the period of study implementation, consistent with the DAIDS policy and associated materials available at:

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

See the protocol Version 2.0 Summary of Changes document for information and instructions to study sites on obtaining all required IRB/EC and regulatory entity approvals and completing the DAIDS protocol registration process for protocol Version 2.0. Further information on the protocol registration process can be found in the DAIDS Protocol Registration Manual, which is available at:

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

2.3  Site-Specific Transition to Protocol Version 2.0

All sites planned to implement protocol Version 2.0 were activated to initiate the study under protocol Version 1.0.

The site-specific study activation process will not be repeated for protocol Version 2.0. However, due to the extent and nature of the modifications incorporated into protocol Version 2.0, sites will be required to confirm completion of several regulatory, clinical, laboratory, data management, and other operational requirements before transitioning to implementation of protocol Version 2.0. A Transition to Version 2.0 checklist has been developed by the Protocol Team to guide sites in completing these requirements. Any questions related to the Version 2.0 transition process should be directed to the IMPAACT Operations Center Clinical Trials Specialists.

On a site-by-site basis, upon confirmation of completion of all transition requirements, the Clinical Trials Specialists will notify the Protocol Team that the site has met the Version 2.0 transition requirements. Upon receipt of this notification, the IMPAACT Data Management Center will update the Subject Enrollment System (SES) to enable the site to enroll mother-infant pairs in the study under protocol Version 2.0. Effective at this same time, the site will also transition to implementing protocol Version 2.0 with mother-infant pairs who were enrolled under protocol Version 1.0.
3.0 Study-Related Information and Communications

All P1115 visits and procedures must be conducted in accordance with the study protocol. The purpose of this MOP is to supplement the protocol, not to replace or substitute for it. In the event that this MOP is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center of any such inconsistencies.

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

https://impaactnetwork.org/studies/p1115.asp

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 members of the Protocol Team (e.g., the Clinical Management Committee (CMC) or the Questions Group), a response from the appropriate team member can generally be expected within 24 hours.

As indicated in Figure 3-1, active communication is expected between site staff and the CMC. Importantly, per protocol Section 6, the CMC must be consulted as soon as possible and within two business days on any decision to hold or permanently discontinue any antiretroviral (ARV) at any time during infant follow-up.

When submitting questions and notifications to the CMC, to ensure that CMC members have adequate information to respond in a timely manner, always address each of the points listed in Figure 3-2. Always retain a copy of correspondence with the CMC in the relevant participant’s study chart.

Site staff should avoid sending messages to the protocol email group (IMPAACT.protp1115@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. Questions related to interpretation of the protocol or participant management should generally be emailed to the P1115 Questions Group (IMPAACT.P1115Questions@fstrf.org) or CMC (IMPAACT.P1115CMC@fstrf.org).
## IMPAACT P1115 Study-Related Communications

<table>
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<tr>
<th>Topic</th>
<th>Contact</th>
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<tbody>
<tr>
<td>Adding site staff to protocol email group (<a href="mailto:IMPAACT.prot1115@fstrf.org">IMPAACT.prot1115@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 P1115 Questions Group <a href="mailto:IMPAACT.P1115Questions@fstrf.org">IMPAACT.P1115Questions@fstrf.org</a></td>
</tr>
<tr>
<td>Clinical, adverse event, and treatment regimen management issues</td>
<td>IMPAACT P1115 Clinical Management Committee <a href="mailto:IMPAACT.P1115CMC@fstrf.org">IMPAACT.P1115CMC@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 P1115 Clinical Management Committee <a href="mailto:IMPAACT.P1115CMC@fstrf.org">IMPAACT.P1115CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Co-enrollment issues</td>
<td>IMPAACT P1115 Clinical Management Committee <a href="mailto:IMPAACT.P1115CMC@fstrf.org">IMPAACT.P1115CMC@fstrf.org</a></td>
</tr>
<tr>
<td>Data management computer and screen problems</td>
<td><a href="mailto:user.support@fstrf.org">user.support@fstrf.org</a> (or by phone: +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: +716-834-0900 x7301)</td>
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<tr>
<td>Study drug issues (other than study drug orders)</td>
<td>Protocol Pharmacist <a href="mailto:lpurdue@niaid.nih.gov">lpurdue@niaid.nih.gov</a> (or by phone: +240627-3061)</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: +301-294-0741)</td>
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</table>
Copy and paste this listing into the body of your email message to IMPAACT.P1115CMC@fstrf.org to help ensure that all required information is included.

Include the protocol number and PID in the subject line of your email message.

1. Site number
2. Name of person submitting query
3. PID
4. Enrollment cohort (specify 1 or 2)
5. Sex and current age of participant
6. Currently breastfeeding (specify yes or no)
7. Current study step and week on this step
8. Current treatment regimen
9. Reason for query (choose one)
   - Consultation on eligibility or enrollment (describe in case description)
   - Consultation on adverse event or toxicity management (describe in case description)
   - Consultation on treatment regimen management (describe in case description)
   - Other (specify in case description)
10. Case description and question or notification for CMC:

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

In addition to the above, when providing updates to the CMC following an initial report or consultation, use a table format similar to the following to assist with tracking relevant details over time.

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4.0  Participant Accrual

Under protocol Version 1.0, 460 mother-infant pairs were enrolled (440 in Cohort 1, 20 in Cohort 2) to identify 54 infants with *in utero* HIV infection. As of the date shown in the footer below, 14 of these pairs remain in follow-up, receiving Regimen 1L, in Step 2.

Under protocol Version 2.0, approximately 445 additional mother-infant pairs are expected to be enrolled (430 in Cohort 1, 15 in Cohort 2) to identify approximately 45 additional infants with *in utero* HIV infection. Per protocol Section 3.2.2:

- Infants receiving Regimen 2R and infants receiving Regimen 2RV will be enrolled approximately concurrently.
- Sites will be assigned to Regimen 2R or Regimen 2RV in an effort to achieve approximately equal distribution of infants receiving each regimen. Site assignments to each regimen may be changed over time, but at no time will any site be enrolling infants receiving Regimen 2R and Regimen 2RV concurrently.
- As of the date shown in the footer below, the following sites are assigned to Regimen 2RV: 5072, 5097, 8052, 8950, 30300, 30301, and 31890. All other sites are assigned to Regimen 2R.

Accrual of 445 mother-infant pairs is expected to require up to three years (from the date of first enrollment). Throughout the accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets and/or regimen assignments should be adjusted 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 after IMPAACT Study Monitoring Committee (SMC) reviews of the study.
5.0 Informed Consent

Informed consent is a process by which an individual voluntarily expresses his or her willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the informed consent process was described in previous versions of this manual and is now described in Section 8.6 of the IMPAACT Network Manual of Procedures, which is available at:

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

Refer to the IMPAACT Manual of Procedures as needed. Also refer to protocol Section 10, Section 4.8 of the ICH Guideline for GCP, and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and the DAIDS Policy on Enrolling Children (including Adolescents) in Clinical Research as needed.

Per protocol Section 10.1, in order for infants to be enrolled in P1115, their mothers must be available, willing, and able to provide written informed consent for both maternal and infant participation in the study. That is, if a mother does not provide informed consent for her own participation in the study, her infant cannot be enrolled. However, if a mother initially provides informed consent for her own participation, and then chooses to withdraw from the study, the infant may continue his or her study participation, assuming consent for infant participation is not withdrawn.

Each study site must have on file a standing operating procedure (SOP) for obtaining informed consent that addresses all aspects of the informed consent process that are applicable to this study. All sites must follow their SOPs consistently for all P1115 informed consent processes. All site staff involved in obtaining informed consent must be designated on the study-specific delegation of duties log and listed on the Form FDA 1572 for the study. These staff must be qualified by education, experience, training, and knowledge of the study, as determined by the IoR, and appropriate training documentation must be available to support the IoR’s delegation to these staff.

5.1 Study-Specific Informed Consent Processes

P1115 involves several informed consent processes and decisions:

- **For infants enrolled under protocol Version 1.0 who will continue follow-up under protocol Version 2.0**, re-consent will be obtained for ongoing participation in Step 2 (see sample informed consent form (ICF) in protocol Appendix IV-C).

- **For mothers enrolled under protocol Version 1.0 who will continue follow-up under protocol Version 2.0**, re-consent will be obtained for ongoing participation in the study (see sample ICFs in protocol Appendices IV-F and IV-G).

- **For infants enrolled in Cohort 1 under protocol Version 2.0**, informed consent will first be obtained for participation in Step 1 (see sample Step 1 ICFs in protocol Appendices IV-A and IV-B). The final page of the Step 1 ICF provides introductory information about key aspects of Steps 2, 3, and 4. This page should be reviewed with mothers enrolled in Cohort 1 to help prepare them for the separate informed consent process for Step 2, which will be conducted if in utero HIV infection is confirmed (see sample Step 2 ICFs in protocol Appendices IV-C and IV-D).

- **For mothers enrolled in Cohort 1 under protocol Version 2.0**, informed consent will be obtained for maternal participation in the study (see sample ICF in protocol Appendix IV-F).
- **For infants enrolled in Cohort 2 under protocol Version 2.0**, informed consent will be obtained for participation in Step 2 (see sample ICFs in protocol Appendices IV-C and IV-D).

- **For mothers enrolled in Cohort 2 under protocol Version 2.0**, informed consent will be obtained for maternal participation in the study (see sample ICF in protocol Appendix IV-G).

- **For infants who enter Step 3**, informed consent will be obtained for participation in Steps 3 and 4 (see sample ICF in protocol Appendix IV-E). Any entry into Step 3 will occur after protocol Version 2.0 Letter of Amendment (LoA) #1 has been reviewed and approved by all applicable site IRBs/ECs and regulatory entities. Further detailed information on this informed consent process will be added to this manual once LoA #1 has been finalized. Mothers are not required to re-consent for their own study participation if their infants enter Step 3.

As part of each maternal and infant informed consent process, specific notations must be recorded on the ICF to document optional consent decisions (yes or no) for genetic testing as part of the study. Specific notations must also be recorded to document optional consent decisions for storage and future research use of leftover specimens and, separately, genetic testing of leftover specimens. For infants who enter Step 2 or Step 3, specific notations must also be recorded to document optional consent decisions for storage and testing of residual cerebrospinal fluid as part of the study. For each of these optional consent decisions, consent may be declined with no impact on maternal or infant study participation. All specimens specified to be collected in the SoEs should be collected, regardless of these decisions.

**IMPORTANT NOTE**

- LoA #2 permits extended follow-up in Step 2 during the COVID-19 pandemic. For children to whom extended follow-up applies, informed consent for extended follow-up should be obtained at the first in-person study visit that occurs after all required approvals of LoA #2 have been obtained (see sample ICF in LoA #2).

5.2 Assessment of Understanding

The IoR or designee is responsible for providing all information relevant to a mother’s informed consent decisions in a manner that is understandable to the mother. Mothers should not be asked to make informed consent decisions until they fully understand the study. The IoR or designee is therefore responsible for ensuring that each mother understands all aspects of study participation before signing or marking an ICF.

A variety of approaches can be taken to assess understanding. One approach uses a semi-structured checklist to guide a discussion in which the mother responds to open-ended questions designed to elicit her understanding of key concepts. Sample checklists of this type, with accompanying guidance for use, are provided in the Section Appendix at the end of this section. Other approaches may include documented discussions with mothers as well as structured knowledge quizzes administered to the mothers.

Regardless of the method used to assess understanding, if the assessment indicates misunderstanding of aspects of the study, the IoR or designee should review those aspects again until the mother fully understands them. If after additional review and discussion the mother is not able to demonstrate adequate understanding, she should not be asked to sign or mark the ICF. Similarly, if the mother has concerns about possible adverse impacts if she were to provide informed consent, or if the mother indicates that she and/or her infant may have difficulty adhering to the study requirements, she should not be asked to sign or mark the ICF unless or until such issues can be resolved to the satisfaction of the mother and the IoR or designee.
5.3 Documentation Requirements

Refer to Section 8.6 of the IMPAACT Manual of Procedures and the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials for detailed guidance on documentation requirements. The DAIDS policy includes requirements and suggestions; study sites must comply with all requirements and are encouraged to comply with all suggestions. To assist with compliance, sites may choose to use informed consent coversheets similar to the examples in the Section Appendix. Sites choosing to use coversheets should identify the coversheets as source documents in their study-specific SOPs for source documentation and should use the coversheets consistently to document each informed consent and assent process. All informed consent documentation must be maintained on file in participant study records.

In addition to completing required entries on ICFs, each informed consent process should be documented in a signed and dated chart note. The chart note should document that informed consent was obtained before any study procedures (for the relevant step) were performed. The note also should document adherence to the requirements of the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. However, if an informed consent coversheet is used, it is not necessary to transcribe information recorded on the coversheet into the chart note.

Informed consent decisions will also be entered into eCRFs as shown in the Section Appendix.
Section 5 Appendix

- Sample Informed Consent Comprehension Checklist for Mothers
- Sample Informed Consent Comprehension Checklist for Infants: Step 1
- Sample Informed Consent Comprehension Checklist for Infants: Step 2
- Guidance for Use of Sample Informed Consent Comprehension Checklists
- Sample Informed Consent Coversheet for Mothers
- Sample Informed Consent Coversheet for Infants
- eCRF Entries to Document Informed Consent Decisions
## Sample Informed Consent Comprehension Checklist for P1115 Mothers

### Mother's Identifier:

### 1. Please tell me what you understand about this study and why it is being done.
- Study is for mothers with HIV and their newborn babies.
- Study is looking at starting treatment in babies soon after birth to see if this treatment can control the amount of HIV in the baby's blood.

### 2. What are mothers asked to do in this study?
- Have blood collected for HIV-related tests.
- Have medical records reviewed and answer questions about their health every six months while their baby is in the study.
- Answer questions about their baby’s health, medicines, and feeding at clinic visits for the baby.
- AT SELECTED SITES: Take their baby’s temperature and write down how their baby is doing for 7 days after receiving VRC01. Mothers will also tell study staff the information they have written down.

### 3. What are the possible risks for mothers?
- Risks of blood collection (must mention at least one).

### 4. What are the possible benefits for mothers?
- There may be no benefit (may mention one or more possible benefits as listed in ICF).

### 5. What happens if you do not join this study?
- Free to make own choice about joining or not joining.
- If mother does not join, baby cannot join.
- No effect on access to maternal and child health care outside the study.

### 6. How will information collected in the study be protected?
- Every effort will be made to keep information private and confidential (must mention at least one method used by the site; see ICF).

### 7. What should mothers do if they have questions or concerns about themselves, their babies, or what is happening in the study?
- Must state how to contact study staff (see ICF).

### Outcome (mark one)
- □ Demonstrated comprehension of all required points
- □ Did not demonstrate comprehension of all required points

### Study Staff Signature and Date:
### Sample Informed Consent Comprehension Checklist for P1115 Infants: Step 1

**Mother’s Identifier:**

**Infant’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>Study is for mothers with HIV and their newborn babies.</td>
</tr>
<tr>
<td>Study is looking at starting treatment in babies soon after birth to see if this treatment can control the amount of HIV in the baby’s blood.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 2. This study has four steps, and you are being asked for your baby to join Step 1. What are babies asked to do in Step 1?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have 4 clinic visits within 4 weeks, then 1 more visit at 12 weeks.</td>
</tr>
<tr>
<td>Start taking ARVs within 48 hours of birth. The ARVs must be kept in the home and given to the baby every day.</td>
</tr>
<tr>
<td>AT SELECTED SITES: Receive an injection of VRC01 within 48 hours of birth.</td>
</tr>
<tr>
<td>Have physical examinations.</td>
</tr>
<tr>
<td>Have blood tests to check if the baby has HIV.</td>
</tr>
<tr>
<td>Have blood tests to check the effects of ARVs [AT SELECTED SITES: and VRC01].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 3. What happens for babies with HIV-negative test results from blood collected within 48 hours of birth?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop taking ARVs for the study, start taking ARVs that are given to all HIV-negative babies to prevent infection.</td>
</tr>
<tr>
<td>Stay in the study for 12 weeks, then leave the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 4. What happens for babies with HIV-positive test results from blood collected within 48 hours of birth?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asked to join Step 2 (Step 2 will be explained in detail separately).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 5. What are the possible risks for babies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures may cause discomfort (must mention at least one from ICF).</td>
</tr>
<tr>
<td>ARVs may cause side effects (must mention at least one from ICF).</td>
</tr>
<tr>
<td>AT SELECTED SITES: VRC01 may cause side effects (must mention at least one from ICF).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 6. What are the possible benefits for babies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>There may be no benefit.</td>
</tr>
<tr>
<td>Treatment given in the study may help control the amount of HIV in the baby’s body (may mention other possible benefits as listed in ICF).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 7. What happens if your baby does not join the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free to make own choice about baby joining or not joining.</td>
</tr>
<tr>
<td>No effect on access to maternal and child health care outside the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 8. How will information collected in the study be protected?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every effort will be made to keep information private and confidential (must mention at least one method used by the site; see ICF).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>✓ 9. What should mothers do if they have questions or concerns about their babies or what is happening in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Must state how to contact study staff (see ICF).</td>
</tr>
</tbody>
</table>

**Note:** Items 1, 7, 8, and 9 are also assessed on the mother’s comprehension checklist. If the two checklists are completed on the same day, it is not necessary to administer these items twice. Instead, entries from the mother’s checklist can be transcribed onto this checklist.

**Outcome (mark one)**

- [x] Demonstrated comprehension of all required points
- [ ] Did not demonstrate comprehension of all required points

**Study Staff Signature and Date:**
Sample Informed Consent Comprehension Checklist for P1115 Infants: Step 2

Mother’s Identifier: ____________________________
Infant’s Identifier: ____________________________

1. Please tell me what you understand about this study and why it is being done.
Study is for mothers with HIV and their newborn babies.
Study is looking at starting treatment in babies soon after birth to see if this treatment can control the amount of HIV in the baby’s blood.

2. This study has four steps, and you are being asked for your baby to join Step 2. What are babies asked to do in Step 2?
Babies take ARVs in this step. The ARVs must be kept in the home and given to the baby every day.
AT SELECTED SITES: Babies receive three injections of VRC01 in this step.

3. Please tell me what you understand about clinic visits for babies in Step 2.
Frequent visits (7-8) within the first 12 weeks. Then less frequent visits (every 4-12 weeks).
Physical examinations and blood collection at most visits.
Blood tests to check the effects of ARVs [AT SELECTED SITES: and VRC01].
Blood tests to check the amount of HIV in the blood.

4. How long do babies stay in Step 2?
Babies may stay in Step 2 for up to 4 years.
After babies are 18 months old, they have more tests to find out if they qualify for Step 3 (the step in which babies stop taking ARVs).
Babies who qualify may be asked to join Step 3 (Step 3 will be explained in detail separately).

5. What are the possible risks for babies?
Procedures may cause discomfort (must mention at least one from ICF)
ARVs may cause side effects (must mention at least one from ICF)
AT SELECTED SITES: VRC01 may cause side effects (must mention at least one from ICF)

6. What are the possible benefits for babies?
There may be no benefit.
Treatment given in the study may help control the amount of HIV in the baby’s body
(may mention other possible benefits as listed in ICF).

7. What happens if your baby does not join the study?
Free to make own choice about joining.
No effect on access to maternal and child health care outside the study.

8. How will information collected in the study be protected?
Every effort will be made to keep information private and confidential (must mention at least one method used by the site; see ICF).

9. What should mothers do if they have questions or concerns about their babies or what is happening in the study?
Must state how to contact study staff (see ICF).

Note: Items 1, 7, 8, and 9 are also assessed on the mother’s comprehension checklist. If the two checklists are completed on the same day, it is not necessary to administer these items twice. Instead, entries from the mother’s checklist can be transcribed onto this checklist.

Outcome (mark one)
- Demonstrated comprehension of all required points
- Did not demonstrate comprehension of all required points

Study Staff Signature and Date: ____________________________
For sites choosing to use comprehension checklists similar to the samples provided above, the text that follows provides guidance on their intended use. Please contact the Operations Center Clinical Trials 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 ICF or had it read to him or her 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 consenters’ 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 checklist. Role-playing is strongly recommended as part of preparation and training on use of the checklist.

4. The checklist is structured around open-ended questions that correspond to the 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 own words that she 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 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 2 of the infant Step 1 checklist is “Have physical and examinations.” If the consenter does not mention this in her initial response to Question 2, study staff may say, “You mentioned that infants will need to come to the clinic for study visits. Can you tell me what will be done at these visits?”

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 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 checklist. 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 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 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 other source documents. Relevant maternal and infant identifiers should be recorded on the checklist 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.
Sample Informed Consent Coversheet for P1115 Mothers

<table>
<thead>
<tr>
<th>Mother’s identifier</th>
</tr>
</thead>
</table>
| Mother’s Cohort     | □ Cohort 1  
|                     | □ Cohort 2  
| Can the mother read?| □ Yes  
|                     | □ No ⇒ A literate impartial witness should be present during the entire informed consent process. Record name and relationship/role of witness below.  
| Language of informed consent process | □ [Language A]  
|                     | □ [Language B]  
| Version number and version date of informed consent form used during informed consent process |  
| Was informed consent process conducted per site SOPs? | □ Yes  
|                     | □ No ⇒ Record and explain departures from site SOPs below.  
| Was all information required to make an informed decision provided in a language understandable to the mother? | □ Yes  
|                     | □ No ⇒ Explain below.  
| Were all the mother’s questions answered? | □ Yes  
|                     | □ No ⇒ Explain below.  
| Did the mother comprehend all information required to make an informed decision? | □ Yes  
|                     | □ No ⇒ Explain below.  
| Was the mother given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision? | □ Yes  
|                     | □ No ⇒ Explain below.  
| Did the mother choose to provide informed consent for study participation? | □ Yes  
|                     | □ No ⇒ STOP.  
| Did the mother choose to provide informed consent for genetic testing as part of the study? | □ Yes  
|                     | □ No  
| Did the mother choose to provide informed consent for storage and future research use of her leftover specimens? | □ Yes  
|                     | □ No  
| Did the mother choose to provide informed consent for genetic testing of her leftover specimens? | □ Yes  
|                     | □ No  
| Date and time at which the mother signed or marked the informed consent form | □ NA (consent declined, form not signed or marked)  
|                     | Date:  
|                     | Time:  
| Did the mother accept a copy of the informed consent form? | □ NA (consent declined, form not signed or marked)  
|                     | □ Yes  
|                     | □ No ⇒ Offer alternate form of study contact information.  
| Notes/Comments |  
| Signature of study staff person completing informed consent process (and this coversheet) |  

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Manual of Procedures  
26 May 2020  
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### Sample Informed Consent Coversheet for P1115 Infants
#### Step 1 and Step 2

<table>
<thead>
<tr>
<th><strong>Mother's identifier</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infant's identifier</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Infant's step</strong></td>
<td>☐ Step 1  ☐ Step 2</td>
</tr>
<tr>
<td><strong>Can the mother read?</strong></td>
<td>☐ Yes  ☐ No ⇒ A literate impartial witness should be present during the entire informed consent process. Record name and relationship/role of witness below.</td>
</tr>
<tr>
<td><strong>Language of informed consent process</strong></td>
<td>☐ [Language A]  ☐ [Language B]</td>
</tr>
<tr>
<td><strong>Version number and version date of informed consent form used during informed consent process</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Was informed consent process conducted per site SOPs?</strong></td>
<td>☐ Yes  ☐ No ⇒ Record and explain departures from site SOPs below.</td>
</tr>
<tr>
<td><strong>Was all information required to make an informed decision provided in a language understandable to the mother?</strong></td>
<td>☐ Yes  ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td><strong>Were all the mother's questions answered?</strong></td>
<td>☐ Yes  ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td><strong>Did the mother comprehend all information required to make an informed decision?</strong></td>
<td>☐ Yes  ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td><strong>Was the mother given adequate time and opportunity to consider all options, in a setting free of coercion and undue influence, before making an informed decision?</strong></td>
<td>☐ Yes  ☐ No ⇒ Explain below.</td>
</tr>
<tr>
<td><strong>Did the mother choose to provide informed consent for infant study participation?</strong></td>
<td>☐ Yes  ☐ No ⇒ STOP.</td>
</tr>
<tr>
<td><strong>Did the mother choose to provide informed consent for storage and testing of infant CSF as part of the study (applicable in Step 2)?</strong></td>
<td>☐ Yes  ☐ No</td>
</tr>
<tr>
<td><strong>Did the mother choose to provide informed consent for infant genetic testing as part of the study?</strong></td>
<td>☐ Yes  ☐ No</td>
</tr>
<tr>
<td><strong>Did the mother choose to provide informed consent for storage and future research use of infant leftover specimens?</strong></td>
<td>☐ Yes  ☐ No</td>
</tr>
<tr>
<td><strong>Did the mother choose to provide informed consent for genetic testing of infant leftover specimens?</strong></td>
<td>☐ Yes  ☐ No</td>
</tr>
</tbody>
</table>
| **Date and time at which the mother signed or marked the informed consent form** | ☐ NA (consent declined, form not signed or marked)  
Date:  
Time:  |
| **Did the mother accept a copy of the informed consent form?** | ☐ NA (consent declined, form not signed or marked)  ☐ Yes  ☐ No ⇒ Offer alternate form of study contact information. |
| **Notes/Comments** |  |
| **Signature of study staff person completing informed consent process (and this coversheet)** |  |
### Informed consent for study participation

**ADM0040, Section II**

- Item 4 = yes
- Item 4a1 = 2.0
- Item 4a2 = [date informed consent provided for participation in protocol Version 2.0]
- Item 4b = not applicable
- Item 4c = yes
- Item 4c1 = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2]
- Item 4d = not applicable
- Item 4e = not applicable

### Informed consent for genetic testing as part of study participation

**TRK0177**

- Item 1 = yes if mother provided informed consent for genetic testing to be performed as part of her study participation. Otherwise enter “no.”

### Informed consent for specimen storage and future use — research not involving genetic testing

**TRK0103**

- Item 2 = yes if mother provided informed consent for storage and testing other than genetic testing of her leftover specimens. Otherwise, enter “no.”
- Item 2a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].

### Informed consent for specimen storage and future use — research involving genetic testing

**TRK0103**

- Item 1 = yes if mother provided informed consent for genetic testing of her leftover specimens. Otherwise enter “no.”
- Item 1a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].
### eCRF Entries to Document Informed Consent Decisions

**INFANT Study Participation under Protocol Version 2.0**  
**Cohort 1, Step 1**  
*(new consent for those enrolling under Version 2.0)*

#### Informed consent for Step 1 study participation

**ADM0040, Section II**

- Item 4 = yes
- Item 4a1 = 2.0
- Item 4a2 = [date informed consent provided for participation in protocol Version 2.0]
- Item 4b = not applicable
- Item 4c = yes
- Item 4c1 = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2]
- Item 4d = not applicable
- Item 4e = not applicable

#### Informed consent for genetic testing as part of study participation

**TRK0177**

- Item 1 = yes if mother provided informed consent for genetic testing to be performed as part of infant’s participation. Otherwise enter “no.”

#### Informed consent for specimen storage and future use — research not involving genetic testing

**TRK0103**

- Item 2 = yes if mother provided informed consent for storage and testing other than genetic testing of the infant’s leftover specimens. Otherwise, enter “no.”
- Item 2a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].

#### Informed consent for specimen storage and future use — research involving genetic testing

**TRK0103**

- Item 1 = yes if mother provided informed consent for genetic testing of her infant’s leftover specimens. Otherwise enter “no.”
- Item 1a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].
**eCRF Entries to Document Informed Consent Decisions**

### INFANT Study Participation under Protocol Version 2.0
**Cohort 1 or Cohort 2, Step 2**
*(re-consent for those enrolled under Version 1.0; new consent for those enrolling under Version 2.0)*

**Informed consent for Step 2 study participation and for storage and testing of CSF as part of study participation**
**ADM0040, Section II**

- Item 4 = yes
- Item 4a1 = 2.0
- Item 4a2 = [date informed consent provided for participation in protocol Version 2.0]
- Item 4b = not applicable
- Item 4c = yes
- Item 4c1 = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2]
- Item 4d = not applicable
- Item 4e = yes if mother provided informed consent for storage and testing of CSF. Otherwise enter “no.”
- Item 4e1 = “CSF storage and testing”
- Item 4e2 = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2]

**Informed consent for genetic testing as part of study participation**
**TRK0177**

- Item 1 = yes if mother provided informed consent for genetic testing to be performed as part of infant’s participation. Otherwise enter “no.”

**Informed consent for specimen storage and future use — research not involving genetic testing**
**TRK0103**

- Item 2 = yes if mother provided informed consent for storage and testing other than genetic testing of the infant’s leftover specimens. Otherwise, enter “no.”
- Item 2a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].

**Informed consent for specimen storage and future use — research involving genetic testing**
**TRK0103**

- Item 1 = yes if mother provided informed consent for genetic testing of her infant’s leftover specimens. Otherwise enter “no.”
- Item 1a = [date this informed consent decision made; generally expected to be the same date as ADM0040 item 4a2].

### INFANT Study Participation under Protocol Version 2.0 and LoA #2
**Extended Follow-Up in Step 2**

**ADM0040, Section II**

- Item 4b = yes
- Item 4b1=2
- Item 4b2 = 2.0
- Item 4b3 = [date informed consent provided for extended follow-up in Step 2]
6.0 Entry and Follow-up in Step 1

Mother-infant pairs enrolled in Cohort 1 will enter the study in Step 1. Figure 6-1 provides a brief overview of management of infants in these pairs. Under protocol Version 2.0, approximately 430 mother-infant pairs are targeted to be enrolled in Cohort 1.

Figure 6-1
IMPAACT P1115 Cohort 1

<table>
<thead>
<tr>
<th>Cohort 1: Infants born to HIV-infected mothers who did not receive antiretrovirals during pregnancy (High-Risk Infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• These infants will enter the study in Step 1 within 48 hours of birth, at which time their HIV infection status may not be known. They will initiate early intensive treatment per protocol and undergo specimen collection for HIV testing within 48 hours of birth.</td>
</tr>
<tr>
<td>– If HIV infection is confirmed (with two positive nucleic acid tests), the infant will enter Step 2 and continue early intensive treatment per protocol in Step 2.</td>
</tr>
<tr>
<td>– If HIV infection is not confirmed, early intensive treatment will be switched to standard prophylaxis; the infant will remain in Step 1 for 12 weeks and then exit the study.</td>
</tr>
</tbody>
</table>

This section describes procedural requirements for entry and follow-up in Step 1.

6.1 Identification and Recruitment for Cohort 1

At each site, recruitment of Cohort 1 participants under protocol Version 2.0 may begin after all requirements listed on the Transition to Version 2.0 Checklist are completed.

Given the timeframe for enrollment of Cohort 1 — within 48 hours of birth — it is essential that study staff establish mechanisms to identify potential Cohort 1 participants during labor and/or immediately postpartum. For example, some sites may be able to station study staff at labor and/or postnatal wards, whereas others may rely on non-study personnel at these wards to notify them of potential study participants.

Each site must also establish operational plans for where and when eligibility determination and enrollment procedures will be performed. While some sites may be permitted to conduct these procedures in labor and/or postnatal wards, others will be required to conduct all procedures at their clinical research site facilities. Factors such as the typical length of stay in the postnatal ward and options for transport to clinical research site facilities within 48 hours of birth must be carefully considered. Regardless of the approaches taken, active communication will be needed to optimize identification of potential participants and completion of all required procedures within protocol-specified timeframes.

6.2 Eligibility Determination for Cohort 1

The eligibility criteria for Cohort 1 are specified in the following protocol sections:

Maternal Inclusion | 4.1.1.1, 4.1.1.2, 4.1.2.1, 4.1.2.2
Infant Inclusion | 4.2.1, 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6
Infant Exclusion | 4.6

Key among these criteria are requirements that mothers have presumed or confirmed HIV infection, mothers did not receive ARVs during pregnancy (receipt of ARVs during labor and within five days prior to delivery is permitted), infants are at least 36 weeks gestational age and 2 kg at birth, and enrollment occurs within 48 hours of birth.
Consistent with the inclusion and exclusion criteria referenced above, eligibility determination for Cohort 1 will be based on the following:

- Confirmation of written informed consent for maternal and infant study participation
- Review of available maternal and infant medical records
- Collection of maternal medical history information, focusing on HIV status and ARV use during the current pregnancy
- Collection of infant medical history information, focusing on date and time of birth, gestational age at birth, and weight at birth
- Assessment of infant ability to take ARVs
- Assessment of infant clinical condition, focusing on clinically significant diseases and other clinically significant findings that would interfere with study participation or interpretation

A listing of eligibility determination procedures for Cohort 1, reflective of the Cohort 1 eligibility criteria and the maternal and infant SoEs, is provided below. Procedures need not be performed in the order shown; however, written informed consent must be obtained before any study procedures are performed.

### COHORT 1 ELIGIBILITY DETERMINATION PROCEDURES

- Determine whether mother is of legal age to provide independent informed consent (*must precede informed consent process*)
- Obtain written informed consent from mother or her legal guardian (*must precede all other protocol-specified procedures*)
- Assign PIDs to mother and infant
- Review available medical records for mother and infant, collect medical and medications history information from the mother, and perform infant physical exam (*see Section 6.7 of this manual*) to determine:
  - Whether mother received ARVs during pregnancy
  - Whether mother or infant have any documented HIV testing
  - Infant gestational age at birth
  - Infant weight at birth
  - Infant ability to take ARVs by mouth, nasogastric tube, or gastrostomy tube
  - Infant clinical condition, including any clinically significant diseases or findings
- Review, confirm, and document eligibility for the mother-infant pair per site SOPs
  - If not eligible, stop
  - If eligible, continue with enrollment and Step 1 entry procedures

It is the responsibility of the site IoR and other designated study staff to ensure that all required eligibility determination procedures are performed and adequately documented, and that only participants who meet eligibility criteria are enrolled. Each site must have on file and follow an SOP for eligibility determination that describes how study staff will fulfill this responsibility. In the event that study staff identify that an ineligible participant has been enrolled, the CMC should be consulted immediately (see communication procedures in Section 3 of this manual).
6.3 Enrollment in Cohort 1 / Entry into Step 1

6.3.1 Definition of Enrollment for Cohort 1

Mother-infant pairs will be considered enrolled in Cohort 1 after study staff have entered all required eligibility checklist data into the DMC’s Subject Enrollment System (SES) and the system successfully generates confirmation files with study identification numbers (SIDs) for the mother and infant. Under protocol Version 2.0, separate eligibility checklists will be entered for mothers and infants. The mother’s checklist must be entered first, immediately followed by the infant’s checklist.

6.3.2 Enrollment Timeframe for Cohort 1

Enrollment in Cohort 1 must occur within 48 hours of infant birth. More specifically, enrollment must occur with sufficient time available to initiate the infant’s early intensive treatment regimen and collect specimens for infant HIV testing within 48 hours of birth.

6.3.3 Enrollment / Step 1 Entry Procedures for Cohort 1

A listing of Step 1 Entry procedures for Cohort 1 is provided on pages 31-32. All procedures need not be performed in the order shown; however, enrollment in the SES should precede other “on study” procedures. In addition:

- Early intensive treatment for infants — Regimen 2R or Regimen 2RV — should be initiated as soon as possible after enrollment; do not defer initiation pending collection of specimens for HIV testing or the availability of HIV test results.
  - Refer to protocol Section 5.1.1 for Step 1 regimen details.
  - The first dose of each ARV in the regimen should be administered within 48 hours of birth.
  - For infants receiving Regimen 2RV, VRC01 should also be administered within 48 hours of birth; however, if this is not possible, VRC01 may be administered within 72 hours of birth.

- Specimen collection for infant HIV nucleic acid tests (NATs) — two samples collected at least one hour apart — should be performed within 48 hours of birth; see also Section 6.4 of this manual. In addition to the two HIV NATs performed for the study, any other HIV tests performed since birth should be recorded for study purposes.

- Infant hematology and chemistry testing are required at Step 1 Entry. However, tests performed in the standard of care setting prior to study entry may be used for study purposes. If adequately documented test results are available, the tests need not be repeated at the Step 1 Entry visit.

- Two sets of infant measurements should be recorded at Step 1 Entry. Weight, length, and head circumference at birth are required as part of the infant’s medical history, with data expected to be obtained from medical records. These same measurements are also required as part of the infant physical exam that is expected to be performed by a study clinician at the Entry visit.
<table>
<thead>
<tr>
<th>STEP 1 MATERNAL ENTRY PROCEDURES</th>
<th>STEP 1 INFANT ENTRY PROCEDURES</th>
</tr>
</thead>
</table>
| **For mother-infant pair:** After confirming eligibility per site SOPs, complete paper-based Step 1 eligibility checklists, enter maternal checklist data into the SES to enroll the mother first; then enter infant checklist data to enroll the infant immediately after the mother; print and file a copy of each confirmation file.  
*Note:* To enroll eligible twins or other multiples, a separate checklist must be entered for each infant, one after the other, and after the mother. |  |
| **For mother-infant pair:** Document enrollment on Cohort 1 Screening and Enrollment Log. |  |
| Continue review of available medical records and collection of targeted medical and medications history to assess and document the following:  
• Prior HIV testing  
• Prior ARV use  
• Current WHO clinical stage  
• CD4 cell counts within the last year  
• HIV RNA results within the last year  
• Prior pregnancies, mode of delivery for the current pregnancy, and syphilis during the current pregnancy  
• Current hepatitis status  
• Other relevant pregnancy, medical, and/or medications history | Complete review of available medical records and collection of medical, medications, and feeding history to assess and document the following:  
• Sex  
• Race/ethnicity  
• Length and head circumference at birth  
  *(weight at birth and gestational age at birth should have been documented prior to enrollment as part of eligibility determination)*  
• Signs, symptoms, and diagnoses since birth  
• All HIV tests since birth  
• All ARVs since birth  
• All other concomitant medications since birth  
• All interventions for hyperbilirubinemia since birth  
• Feeding method since birth  

*Physical exam should have been performed prior to enrollment as part of eligibility determination.* |
| Review all available documentation and determine whether additional HIV testing is needed to meet study eligibility requirements | Review all available documentation and determine specimen collection requirements for HIV testing to meet study eligibility requirements (one or two specimens may be required; see Section 6.4 of this manual). |
| Collect blood per the LPC and site SOPs for:  
• HIV RNA  
• Other HIV testing if needed to meet study eligibility requirements  
• Plasma and cell storage | Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:  
• HIV NATs *(see Section 6.4 of this manual)*  
• Complete blood count with differential and platelet count  
• AST, ALT, ALP, creatinine, total bilirubin  
• Plasma and PBMC storage |
| Provide HIV-related, infant feeding, and other applicable information and counseling | Prescribe and dispense study treatment agents *(see Section 6.8 of this manual)*  
*For infants receiving Regimen 2RV:*  
• Administer VRC01 and monitor for reactogenicity per protocol Section 6.2.5.1  
• Provide instructions to mother for completing reactogenicity memory aid per protocol Section 6.2.5.2 |
|  | Provide instructions and adherence counseling to mother for administration of ARVs to infant |
|  | Provide referrals for HIV-related care and treatment |
**STEP 1 MATERNAL ENTRY PROCEDURES**

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
</tr>
<tr>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>Enter required eCRFs</td>
</tr>
</tbody>
</table>

**STEP 1 INFANT ENTRY PROCEDURES**

<table>
<thead>
<tr>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
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<tr>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>Enter required eCRFs</td>
</tr>
</tbody>
</table>

**Note:** Per protocol Section 4.1.1.1, mothers who enroll in the study with presumed HIV infection must have confirmatory testing with results available within 10 business days of enrollment. If maternal HIV infection is not confirmed within 10 business days of enrollment, mothers and their infants will be discontinued from the study.

6.3.4 **Frequently Asked Questions for Enrollment in Cohort 1 (Entry into Step 1)**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: Can mothers be enrolled in Cohort 1 prior to delivery?</td>
<td>A1: No. Mothers are enrolled in Cohort 1 in pairs with their infants. As such, mothers are enrolled</td>
</tr>
<tr>
<td>at the same time as their infants, after delivery. It is acceptable to introduce and explain the study to the</td>
<td>at the peripartum period. How should peripartum be defined for this purpose?</td>
</tr>
<tr>
<td>mother prior to delivery, but enrollment should occur after delivery.</td>
<td>A2: Based on standard obstetrical definitions, the peripartum period includes the last month of</td>
</tr>
<tr>
<td>gestation and the first few months after delivery.</td>
<td>A3: The documentation that you describe would not be adequate for eligibility confirmation per</td>
</tr>
<tr>
<td>Q2: For mothers, inclusion criterion 4.1.1.1 refers to the peripartum period. How should peripartum be defined</td>
<td>protocol, because it does not include the type of test performed, date of specimen collection and</td>
</tr>
<tr>
<td>for this purpose?</td>
<td>testing, and test result. The protocol allows for a number of different tests to be performed to</td>
</tr>
<tr>
<td>Q3: We are not clear on how to handle study-related HIV testing for mothers who do not have well documented HIV</td>
<td>document maternal infection. Given both the study eligibility requirements and the testing</td>
</tr>
<tr>
<td>testing in their medical records. For example, the labor ward record may include a notation of “rapid test positive”</td>
<td>requirements of the maternal SoE, the team recommends performing two different rapid tests and a</td>
</tr>
<tr>
<td>but not include any other specific documentation of testing performed during the intrapartum or postpartum period.</td>
<td>quantitative HIV RNA PCR on Samples 1 and 2, respectively. The rapid tests should be performed</td>
</tr>
<tr>
<td>How should we handle this?</td>
<td>for purposes of presumptive eligibility determination — prior to enrollment — and the HIV RNA</td>
</tr>
<tr>
<td>Q4: For purposes of documenting maternal eligibility, is it necessary to obtain medical records stating that the</td>
<td>PCR would be performed for both confirmation of infection and assessment of viral load. If this</td>
</tr>
<tr>
<td>mother did not take any ARVs during pregnancy, or can we use the mother’s self-report of this information?</td>
<td>approach is not possible in your setting, at least one rapid test must be performed prior to</td>
</tr>
<tr>
<td>Q5: At our recruitment locations, pregnant women who received no ARVs during pregnancy are given ARVs during</td>
<td>enrollment. Thereafter, both Sample 1 and Sample 2 would need to be collected and tested in order</td>
</tr>
<tr>
<td>labor and postpartum. Would this disqualify a woman from Cohort 1?</td>
<td>to meet protocol requirements, with at least one of these tests being a quantitative HIV RNA PCR.</td>
</tr>
<tr>
<td>A4: All available medical records should be reviewed for evidence of whether the mother took ARVs during pregnancy.</td>
<td>A5: No. Maternal receipt of ARVs during labor and/or the postpartum period is permitted. Protocol</td>
</tr>
<tr>
<td>A5: No. Maternal receipt of ARVs during labor and/or the postpartum period is permitted. Protocol Version 2.0</td>
<td>Version 2.0 also allows for receipt of ARVs within five days prior to delivery.</td>
</tr>
</tbody>
</table>
Q6: In our setting, it is not uncommon for infants to be “born before arrival” such that the mother presents to the clinic or hospital with her newborn within several hours after delivery in the home or elsewhere. In this case, we would not have any medical record to document the date and time of birth. Can we consider these mother-infant pairs for enrollment in Cohort 1?

A6: Yes, these pairs may be considered for enrollment if the mother is able to report the date and time of birth with sufficient accuracy — in the opinion of the site investigator or designee — to permit documentation that enrollment, specimen collection for infant HIV testing, and initiation of the study treatment regimen occurred within 48 hours of birth. For example, if a mother presents to the clinic at 2:00 pm stating that she delivered between 09:00 and 10:00 that morning, this would be documented and enrollment, specimen collection for HIV testing, and initiation of the study treatment regimen would need to occur within 48 hours from 09:00 that morning. As another example, if a mother presented to the clinic at 6:00 am stating that she delivered just after sunset the prior evening, study staff should work with the mother to estimate the time of birth as accurately as possible, and enrollment, specimen collection for HIV testing, and initiation of the study treatment regimen would need to occur within 48 hours from the earliest possible estimated time of birth. In all cases, the source of the infant’s date and time of birth — medical records or mother’s report — should be documented in the infant’s study chart.

Q7: We would like to ensure that we understand the correct interpretation of “within 48 hours of birth” for this study. Could you please explain?

A7: The 48 hours should be counted from the time of infant birth. For example:
- If an infant is born on a Tuesday morning at 10:25 am, the “within 48 hours” time frame would be from 10:25 am on Tuesday until 10:24 am on Thursday.
- If an infant is born on a Friday night at 11:42 pm, the “within 48 hours” time frame would be from 11:42 pm on Friday until 11:41 pm on Sunday.

Q8: What method should be used to determine infant gestational age at birth?

A8: The protocol does not specify a particular method but indicates that the “best clinical estimate” based on date of last menstrual period, antenatal ultrasound, fundal height, or Ballard score should be used.

Q9: What should we do if an infant’s gestational age at birth is not documented in his or her birth records? Must we exclude this infant from Cohort 1?

A9: If gestational age at birth is not documented in an infant’s birth records, study staff may determine his or her gestational age within 48 hours of birth. The date, time, and outcome of this assessment should be documented in the participant’s study chart and used for purposes of eligibility determination prior to enrollment in Cohort 1.

Q10: What should we do if an infant’s gestational age at birth is documented in his or her birth records, but we are not confident in the assessment? For example, estimates based on the date of the mother’s last menstrual period (LMP) may be inaccurate.

A10: The protocol allows for gestational age to be assessed based on date of LMP. However, on a case-by-case basis, if you are concerned that a documented gestational age is inaccurate, the protocol team would recommend that two clinicians from your site assess the infant and come to consensus on the most accurate assessment of his or her gestational age, prior to enrollment; when in doubt, the earliest/youngest of the two assessments should be used. The consensus assessment should be documented in the infant’s study chart and, if different from the gestational age documented in the infant’s birth records, a note explaining the difference should also be recorded. You are also encouraged to consult the CMC regarding questions of gestational age or any other aspects of eligibility.

Q11: At our site, infants who are potentially eligible for Cohort 1 may be given NVP or other ARVs on the first 1-2 days of life, before entry into the study. Is this acceptable?

A11: Yes. Infant receipt of NVP or any other ARV is permitted prior to enrollment in Cohort 1. Please be sure to document any such ARV use for study purposes.
Q12: At our site, it is very likely that high-risk infants will have blood drawn for a non-study HIV DNA PCR test within the first 12-24 hours after birth (before enrollment in the study). Can we use this test as one of the two required tests for Cohort 1? Also, does it matter if this test is performed in a certified lab?

A12: In the situation that you describe, the non-study test can be used for study purposes. It does not matter if the test is performed in a certified lab. However, if the test is not performed in a certified laboratory, the second test performed for this infant must be performed in a certified lab (CLIA-certified for US sites, VQA-certified for non-US sites). Also, when the first test done is an HIV DNA PCR, the second test must be a quantitative HIV RNA PCR.

Q13: In our setting, it is possible that a quantitative HIV RNA PCR test will be done for high-risk infants outside of the study (before enrollment in Cohort 1). Our site lab is certified to perform both RNA PCR and DNA PCR, and we are aware that the protocol indicates that DNA PCR is desirable for infant diagnosis. However, the turnaround time for DNA PCR is much longer than the turnaround time for RNA PCR (7-10 days versus 3 days). In this setting, what test should we use as the second test?

A13: You are correct that the protocol allows for both HIV RNA PCR and HIV DNA PCR to be performed as the second test for high-risk infants, and that HIV DNA PCR is specified as desirable. Assuming that HIV DNA PCR results can be obtained by the day of the infant’s Step 1 Week 2 visit, the protocol team recommends that HIV DNA PCR be performed. If HIV DNA PCR results cannot be obtained by the day of the infant’s Step 1 Week 2 visit, HIV RNA PCR should be performed.

Q14: In our setting, we commonly see physiologic jaundice in infants born to high risk mothers. We also commonly see infants who are given a course of empiric antibiotics if they are born after a prolonged period of ruptured membranes. In view of exclusion criterion 4.6 (clinically significant diseases or findings), can these infants be considered for enrollment in the study?

A14: Neither physiologic jaundice nor empiric antibiotics would, in and of themselves, be exclusionary for this study. The protocol team would encourage you to holistically assess each infant for clinically significant exclusionary conditions, but these factors alone would not be considered exclusionary. You are also encouraged to contact the CMC with any questions of eligibility for any potential participant at any time.

Q15: At the hospital where we will be identifying study participants, heel stick is routinely used for neonatal blood collection. Is this acceptable for the testing that we will be doing for P1115?

A15: Heel stick will not likely yield the full blood volumes required for P1115. Therefore, alternatives to the hospital’s standard practice should be sought, and heel stick should only be considered in the event that venipuncture is not possible. As an example of a possible alternative, some sites have identified that it will be necessary to transport study infants to the NICU for venipuncture, because the hospital does not allow venipuncture in the nursery. Please contact the P1115 team if additional information or guidance may be needed to address this type of issue at your site.

Q16: A complete blood count and several chemistry tests are specified as required for infants at entry into Step 1. If these tests are performed outside of the study, and we can obtain adequate source documentation of the results, can we use these results for study purposes, rather than drawing additional blood to perform the same tests?

A16: Yes, this is specified as acceptable — for the Entry visit only — in footnotes 4 and 5 of the Step 1 SoE.

Q17: In some cases, infants enrolled in Cohort 1 at our site will have an HIV NAT performed outside of the study from a blood specimen collected within 48 hours of birth. If this occurs, should we enter the results of the non-study tests into study eCRFs?

A17: Yes. Please enter all HIV NATs performed since infant birth into eCRFs. Quantitative HIV RNA tests should be entered into the LBW0178 eCRF. Qualitative tests, including HIV DNA tests, should be entered into the LBW0177 eCRF. One form should be entered for each test since birth.
Q18: One of our Cohort 1 mothers has provided informed consent for her own and her infant's study participation, but she has declined consent for genetic testing. Please clarify how we should approach specimen collection and testing for this mother-infant pair.

A18: For both the mother and the infant, all specimens specified in the SoE should be collected, processed, and stored as specified in the LPC, regardless of whether consent was provided for genetic testing. In the future, if the protocol team issues a specimen request for genetic testing, these participants will be excluded from that request. Please note that exclusion from the specimen request list will be based on eCRF data indicating whether informed consent for genetic testing was obtained. It is therefore essential that these entries are correct and up-to-date for all participants. See Section 5 of this manual for further guidance related to these entries.

6.4 Additional Considerations for Infant HIV Testing at Step 1 Entry

Infants should have two blood samples collected for HIV NAT at Step 1 Entry, at least one hour apart, and within 48 hours of birth. If the second sample cannot be collected within 48 hours of birth (expected to be rare), it may be collected thereafter, within 12 hours after the first sample; the first sample must be collected within 48 hours of birth. At least one of the two samples must be tested in a CLIA-certified laboratory (for US sites) or VQA-certified laboratory (for non-US sites), and at least one of the samples must be tested using an HIV RNA assay. If the two required samples are not collected within the specified timeframes, or if two valid results are not obtained for any reason, the CMC should be contacted immediately for guidance on next steps.

Infants with two positive HIV NATs, with at least one sample collected within 48 hours of birth and one positive test performed in a CLIA- or VQA-certified laboratory, will meet diagnostic criteria for in utero HIV infection.

When HIV RNA assays are used for purposes of diagnosing HIV infection, results that indicate that HIV RNA was detected at a level below the limit of detection (LOD) of the assay should be interpreted as potentially indicative of HIV infection, with further testing required to confirm or rule out infection. Examples of such results are as follows:

- Abbott RealTime result <40 copies/mL, HIV RNA target detected
- Roche Taqman result <20 copies/mL, HIV RNA target detected

In these examples, the result indicates that HIV RNA was detected by the assay at a low level that cannot be quantified by the assay. If this type of result is obtained:

- The CMC should be contacted immediately for guidance on further testing to be performed. The CMC will provide guidance on a case-by-case basis depending on the test results currently available for the infant and samples available for further testing.
- The infant should remain on the study treatment regimen until results from further testing are available and a final determination of HIV status has been made in consultation with the CMC.

If the two tests provide discordant results, the CMC should be contacted immediately for guidance on additional testing to be performed. Additional test results should be obtained as soon as possible and within 10 business days, and infants should generally remain on the study treatment regimen pending receipt of the additional results; however, the CMC will provide infant management guidance on a case-by-case basis.
HIV RNA results that are reported as below the LOD of the assay with “target detected” should be considered discordant with results that are reported as below the LOD of the assay with “target not detected.” Similarly, results that are reported as below the LOD of the assay with “target detected” should be considered discordant with results from qualitative HIV NATs (such as HIV DNA PCR) that are reported as “negative.” As such, if these combinations of results are obtained, additional testing is required to clarify the infant’s HIV status, in consultation with the CMC.

The potential need for further testing described above highlights the importance of specimen collection and storage at study entry. Every effort should be made to collect the full sample volumes specified in the SoE for HIV NATs and for storage of plasma and PBMCs. Any residual samples (whole blood, plasma, cell pellets, other) remaining after HIV NATs are performed should be stored for additional testing if needed.

6.5 Planning for Entry into Step 2

Most infants enrolled in Step 1 will be HIV-uninfected. For those found to meet diagnostic criteria for in utero HIV infection — confirmed with two positive HIV NATs — entry into Step 2 is critical to the operational success of P1115. As such, once at least one positive HIV test result is obtained, focused time and attention should be devoted to planning for entry into Step 2. Key considerations are as follows:

- HIV test results should be obtained as rapidly as possible and must be available by Step 1 Week 2 (no later than Day 16 on study; see Figure 6-2).

- Assuming informed consent is obtained, infants with confirmed in utero HIV infection will discontinue follow-up in Step 1 and enter Step 2. Under protocol Version 2.0, this transition should occur at Step 1 Week 2 (12-16 days after Step 1 Entry). Even if HIV test results that confirm in utero infection are available at the time of the Step 1 Week 1 visit, the transition to Step 2 should not take place until Step 1 Week 2. This is necessary to align the scheduling of Step 2 visits with the required timing of RAL dose increases.

![Figure 6-2 Illustration of Time Frames for Cohort 1 Infant Entry into Step 2](image)

The mothers of infants with confirmed in utero HIV infection will complete the evaluations listed under “when infant is confirmed infected (at time of Step 2 entry)” in the maternal SoE, ideally on the same day as the infant’s Step 2 Entry visit.

Figure 6-3 provides an overview of HIV testing requirements and participant management in relation to entry into Step 2 from Step 1.
**Figure 6-3**

HIV Testing Requirements and Overview of Participant Management

For Transition from Step 1 to Step 2

- **Has maternal HIV infection been confirmed per protocol Section 4.1.1?**
  - No: Discontinue mother and infant from study participation.
  - Yes: Continue with subsequent steps.

- **Has in utero HIV infection been confirmed per protocol Section 6.3.1?**
  - No: Continue with subsequent steps.
  - Yes: Stop protocol-specified treatment regimen and start standard of care prophylaxis. Complete Step 1 Week 1, Week 2, Week 4, and Week 12 visits, then exit from study. Refer to non-study sources of prophylaxis and other required care, including follow-up HIV testing and/or treatment.

- **Has informed consent been provided for Step 2?**
  - No: Continue with subsequent steps.
  - Yes: Enter Step 2 at Step 1 Week 2.

---

Positive results from sample #1 and sample #2 (collected at different time points) obtained within 10 business days of enrollment.

2 positive HIV NATs performed on separate samples collected at least one hour apart within 48 hours of birth (at least one test must be a quantitative RNA PCR and at least one must be performed in certified lab).
6.6 Follow-up in Step 1

The duration of infant follow-up in Step 1 will depend on infant HIV status. All infants enrolled in Step 1 will complete a Step 1 follow-up visit at Week 1 (±2 days). Thereafter:

- Infants with confirmed *in utero* HIV infection will enter Step 2 after completing two weeks of follow-up, on the study treatment regimen, in Step 1. These infants complete a Step 2 Entry visit instead of the Step 1 Week 2 visit and then continue study treatment and follow-up in Step 2.

- Infants without confirmed *in utero* HIV infection will complete Step 1 follow-up visits at Week 2 (±2 days), Week 4 (±7 days), and Week 12 (±14 days). Each visit should ideally be conducted on the target date but may be conducted on any day within the allowable window. The mothers of these infants will not complete any follow-up visits, and both mother and infant will exit the study upon completion of the infant’s Step 1 Week 12 visit.

To further illustrate the Step 1 infant follow-up visit schedule, Figure 6-4 provides calendar dates for visits expected for a sample HIV-uninfected infant who enters Step 1 on 1 July 2019.

### Figure 6-4
Follow-up Visit Schedule
For a Sample Infant who Enters Step 1 on 1 July 2019

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Window Opens</td>
<td>Window Closes</td>
</tr>
<tr>
<td>Week 1</td>
<td>8 JUL 2019</td>
<td>6 JUL 2019</td>
</tr>
<tr>
<td>Week 2</td>
<td>15 JUL 2019</td>
<td>13 JUL 2019</td>
</tr>
<tr>
<td>Week 4</td>
<td>29 JUL 2019</td>
<td>22 JUL 2019</td>
</tr>
<tr>
<td>Week 12</td>
<td>23 SEP 2019</td>
<td>9 SEP 2019</td>
</tr>
</tbody>
</table>

*Target visit dates are counted from the day of entry into Step 1. Day of entry = Day 0.

Listings of Step 1 follow-up visit procedures are provided on pages 39-41. There is no specified ordering or required sequence for these procedures.

For infants without confirmed *in utero* HIV infection, the study treatment regimen should be discontinued at the first visit after the infant’s HIV status is determined, with immediate transition to standard prophylaxis. The transition from study treatment to standard prophylaxis may occur at the Step 1 Week 1 visit and must occur by the date of the Step 1 Week 2 visit. To avoid gaps in ARV dosing, study sites should ideally provide prophylaxis agents for the duration specified per local standards of care. In addition, active referrals should be made to relevant non-study sources of care and treatment for mothers and infants.
### STEP 1 INFANT FOLLOW-UP PROCEDURES
#### WEEK 1

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; and feeding method
- Perform physical exam (see Section 6.7 of this manual)
- Review all available clinical and laboratory information and assess whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
  - If both HIV NAT results are available and infant is determined to be HIV-uninfected, switch from study treatment regimen to standard prophylaxis
  - If both HIV NAT results are available and infant is confirmed HIV-infected, continue study treatment regimen
  - If both HIV NAT results are available and results are discordant, continue study treatment regimen and consult the CMC
  - If both HIV NAT results are not yet available, continue study treatment regimen
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count
  - AST, ALT, ALP, creatinine, total bilirubin
  - Plasma and PBMC storage
- Prescribe and dispense ARVs (study treatment agents (see Section 6.8 of this manual) or standard prophylaxis) as needed
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable
### STEP 1 INFANT FOLLOW-UP PROCEDURES

#### WEEK 2

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; and feeding method
- Perform physical exam *(see Section 6.7 of this manual)*
- Review all available clinical and laboratory information and assess whether infant meets criteria for additional evaluations per protocol Section 6 (consult CMC if indicated)
- Both HIV NAT results should be available at this visit:
  - If infant is determined to be HIV-uninfected, switch from study treatment regimen to standard prophylaxis (if not done previously)
  - If infant is confirmed HIV-infected, conduct Step 2 Entry visit instead of Step 1 Week 2 visit
  - If results are discordant, continue study treatment regimen and consult the CMC
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - HIV NAT
  - Complete blood count with differential and platelet count
  - AST, ALT, ALP, creatinine, total bilirubin
  - Plasma and PBMC storage
  - Study agent concentrations *(only if on RAL between Week 1 and Week 2)*
- Prescribe and dispense ARVs (standard prophylaxis) as needed
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable
STEP 1 INFANT FOLLOW-UP PROCEDURES

WEEK 4

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; and feeding method
- Perform physical exam (see Section 6.7 of this manual)
- Review all available clinical and laboratory information and assess whether infant meets criteria for additional evaluations per protocol Section 6 (consult CMC if indicated)
- If applicable, review infant weight and determine maximum blood draw volume for the visit
- If any grade 1 or higher hematology results were obtained at Week 2, collect blood per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count
- If any grade 1 or higher chemistry results were obtained at Week 2, collect blood per the LPC and site SOPs for:
  - AST, ALT, ALP, creatinine, total bilirubin
- Prescribe and dispense ARVs (standard prophylaxis) as needed
- Provide instructions and adherence counseling to mother for administration of ARVs to infant as needed
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

WEEK 12

- Collect HIV testing history since the Week 4 visit
- Review all available clinical and laboratory information and assess whether infant meets criteria for additional evaluations per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - HIV NAT
  - Plasma and PBMC storage
- Prescribe and dispense ARVs (standard prophylaxis) as needed
- Provide instructions and adherence counseling to mother for administration of ARVs to infant as needed
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related prophylaxis, care, and treatment for mother and/or infant as needed
- Provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable
- Schedule visit or contact to provide infant test results to mother; if any results require further evaluation, treatment, and/or management, provide referrals as needed
6.7 Infant Physical Examinations in Step 1

A physical examination is required for infants at the Step 1 Entry, Week 1, Week 2, and Week 4 visits. At Step 1 Entry, the examination should be performed prior to enrollment, as part of eligibility determination. Examination requirements are shown below; at any visit, additional evaluations may be performed at the discretion of the examining clinician.

<table>
<thead>
<tr>
<th>Step 1 Entry</th>
<th>Step 1 Week 1, Week 2, and Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temperature</td>
<td>• Temperature</td>
</tr>
<tr>
<td>• Heart rate</td>
<td>• Heart rate</td>
</tr>
<tr>
<td>• Respiratory rate</td>
<td>• Respiratory rate</td>
</tr>
<tr>
<td>• Weight</td>
<td>• Weight</td>
</tr>
<tr>
<td>• Length</td>
<td>• Length</td>
</tr>
<tr>
<td>• Head circumference</td>
<td>• Head circumference</td>
</tr>
<tr>
<td>• Breath sounds</td>
<td>• Breath sounds</td>
</tr>
<tr>
<td>• Heart sounds</td>
<td>• Heart sounds</td>
</tr>
<tr>
<td>• Examination of skin, head, mouth, neck, abdomen, and extremities</td>
<td>• Examination of body systems driven by prior and new signs, symptoms, and diagnoses</td>
</tr>
<tr>
<td></td>
<td>• For Cohort 1 infants receiving Regimen 2RV, examination should include VRC01 injection sites when applicable (see Section 12 of this manual)</td>
</tr>
</tbody>
</table>

Note: At Step 1 Entry, two sets of infant measurements should be recorded. Weight, length, and head circumference at birth are required as part of the baseline infant history, with data generally expected to be obtained from medical records. These same measurements are also required as part of the infant physical examination expected to be performed and documented by a study clinician at the Entry visit.

6.8 Infant Study Treatment in Step 1

Refer to protocol Section 5.1.1 for comprehensive information on Step 1 study treatment regimens. Under protocol Version 2.0, all infants will receive 2 NRTIs + NVP + RAL in Step 1. Infants receiving Regimen 2RV will also receive a single administration of VRC01. See Section 12 of this manual for weight band dosing and preparation and administration instructions for VRC01.

NRTIs will be chosen by the site investigator and dosed according to World Health Organization (WHO) or individual country or local standard guidelines.

NVP will be dosed per protocol.

RAL will be dosed per protocol. RAL granules for suspension will be used. The remainder of this section provides further guidance on RAL dosing in Step 1.

6.8.1 Weight Band Dosing and Caregiver Instructions for RAL

Figure 6-5 provides weight band dosing for RAL in Step 1. Figure 6-6 provides caregiver instructions for preparing and administering RAL granules for suspension. Both figures correspond with the current package insert. Study sites are also encouraged to use the booklet entitled, ISENTRESS (raltegravir) for oral suspension instructions for use for babies and toddlers, which is posted on the study-specific web page, when providing instructions to caregivers, translating and explaining the instructions in local languages as needed to optimize caregiver understanding of correct dosing.
Figure 6-5
Weight Band Dosing for RAL in IMPAACT P1115 Step 1

<table>
<thead>
<tr>
<th>Infant Body Weight</th>
<th>Volume (Dose) of Suspension To be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1 Entry to Week 1 — Once Daily Dosing</strong> (equivalent to 1.5 mg/kg once daily)</td>
<td></td>
</tr>
<tr>
<td>2 to less than 3 kg</td>
<td>0.4 mL (4 mg) once daily</td>
</tr>
<tr>
<td>3 to less than 4 kg</td>
<td>0.5 mL (5 mg) once daily</td>
</tr>
<tr>
<td>4 to less than 5 kg</td>
<td>0.7 mL (7 mg) once daily</td>
</tr>
<tr>
<td><strong>Step 1 Week 1 to Week 2 — Twice Daily Dosing</strong> (equivalent to 3 mg/kg twice daily)</td>
<td></td>
</tr>
<tr>
<td>2 to less than 3 kg</td>
<td>0.8 mL (8 mg) twice daily</td>
</tr>
<tr>
<td>3 to less than 4 kg</td>
<td>1.0 mL (10 mg) twice daily</td>
</tr>
<tr>
<td>4 to less than 5 kg</td>
<td>1.5 mL (15 mg) twice daily</td>
</tr>
</tbody>
</table>

Source: Adapted from ISENTRESS package insert, Revised 01/2019

Figure 6-6
Caregiver Instructions for Preparing and Administering RAL Granules for Suspension

Using the provided mixing cup, combine 10 mL of water and the entire contents of one packet of ISENTRESS for oral suspension and mix. Each single-use packet for oral suspension contains 100 mg of RAL which is suspended in 10 mL of water giving a final concentration of 10 mg per mL.

Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension. Do not shake.

Once mixed, measure the prescribed dose volume of suspension with a syringe and administer the dose orally. The dose should be administered orally within 30 minutes of mixing.

Discard any remaining suspension into the trash.

Source: Adapted from ISENTRESS package insert, Revised 01/2019

6.8.2 Pharmacist Dispensing Instructions for RAL

The boxes of RAL granules supplied for this study contain sufficient supplies of granule packets, mixing cups, and syringes for two Cohort 1 infants in Step 1. Pharmacists must divide each box into two portions and dispense only one-half of a box for each infant enrolled in Step 1.

Note: Protocol Section 5.3.1 indicates that oral dispensers and push-in-bottle adapters are available from the NIAID Clinical Research Products Management Center for use with non-study-supplied ARVs. These supplies have been exhausted and are no longer available.
7.0  Entry and Follow-up in Step 2

There are two pathways to entry into Step 2:

- Mother-infant pairs enrolled in Cohort 1 may transition from Step 1 into Step 2.
- Mother-infant pairs enrolled in Cohort 2 will enter Step 2 directly.

Refer to protocol Section 3.2 and Section 4 of this manual for more detailed information on accrual into each cohort.

7.1  Cohort 1, Transition from Step 1 into Step 2

As described in Section 6.5 of this manual, Cohort 1 infants with confirmed in utero HIV infection will enter Step 2 by the date of their Step 1 Week 2 visit (i.e., by Day 16 on study). The eligibility criteria for the transition from Step 1 to Step 2 are specified in the following protocol sections:

<table>
<thead>
<tr>
<th>Infant Inclusion</th>
<th>4.3.1, 4.3.2.1, 4.3.2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Exclusion</td>
<td>4.6</td>
</tr>
</tbody>
</table>

In addition, informed consent must be obtained for participation in Step 2.

Although there are few eligibility criteria to be considered for the transition from Step 1 to Step 2, eligibility must be reviewed, confirmed, and documented prior to entry into Step 2. Eligible infants (and their mothers) will be considered entered into Step 2 after study staff have entered all required eligibility checklist data into the SES and the system successfully generates confirmation files with Step 2 SIDs for the mother and infant. Under protocol Version 2.0, separate eligibility checklists will be entered for mothers and infants. The mother’s checklist must be entered first, immediately followed by the infant’s checklist.

It is the responsibility of the site IoR and other designated study staff to ensure that all required eligibility determination procedures are performed and adequately documented, and that only participants who meet eligibility criteria enter Step 2. Each site must have on file and follow an SOP for eligibility determination that describes how study staff will fulfill this responsibility. In the event that study staff identify that an ineligible participant has been enrolled, the CMC should be consulted immediately (see communication procedures in Section 3 of this manual).

7.2  Cohort 2, Direct Entry into Step 2

Infants enrolled in Cohort 2 will enter the study in Step 2. Figure 7-1 provides a brief overview of management of these infants.

**Figure 7-1**

**IMPAACT P1115 Cohort 2**

- Cohort 2: Infants with at least one positive HIV nucleic acid test from a specimen collected within 48 hours of birth who initiated a qualifying antiretroviral treatment regimen outside of the study within 48 hours of birth (Early Treated Infants)

- These infants will enter the study in Step 2 within 10 days of birth and will receive intensive treatment per protocol in Step 2.
7.2.1 Identification and Recruitment for Cohort 2

At each site, recruitment of Cohort 2 participants under protocol Version 2.0 may begin after all requirements listed in the Transition to Version 2.0 Checklist are completed.

Given the Cohort 2 eligibility criteria, to optimize accrual into this cohort, study staff may find it beneficial to encourage and/or facilitate HIV testing and initiation of a qualifying ART regimen within 48 hours of birth, with adequate documentation thereof, outside the study. In addition, it is essential that study staff establish mechanisms to identify potential Cohort 2 participants during labor and/or immediately postpartum. For example, some sites may be able to station study staff at labor and/or postnatal wards, whereas others may rely on non-study personnel at these wards to notify them of potential study participants. Regardless of the approaches taken, active communication will be needed to optimize identification of potential participants and completion of all required procedures within protocol-specified timeframes.

7.2.2 Eligibility Determination for Cohort 2

The eligibility criteria for Cohort 2 are specified in the following protocol sections:

<table>
<thead>
<tr>
<th>Category</th>
<th>Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Inclusion</td>
<td>4.1.1.1, 4.1.1.2, 4.1.3.1</td>
</tr>
<tr>
<td>Infant Inclusion</td>
<td>4.3.1, 4.3.3.1, 4.3.3.2, 4.3.3.3, 4.3.3.4, 4.3.3.5, 4.3.3.6, 4.3.3.7</td>
</tr>
<tr>
<td>Infant Exclusion</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Key among these criteria are requirements that mothers have presumed or confirmed HIV infection, infants have at least one positive HIV NAT from a specimen collected within 48 hours of birth, and infants initiate a qualifying ART regimen within 48 hours of birth. Infants must enter the study within 10 days of birth and must take their qualifying ART regimen daily until study entry (see Figure 7-2).

---

**Figure 7-2**
Illustration of Time Frames for Cohort 2 Infant Entry into Step 2

Blood collected for HIV testing and qualifying ART regimen initiated within 48 hours of birth

Enroll in Cohort 2 (enter Step 2) within 10 days of birth

Continue qualifying ART regimen daily through study entry
Consistent with the inclusion and exclusion criteria referenced above, eligibility determination for Cohort 2 will be based on the following:

- Confirmation of written informed consent for maternal and infant study participation
- Review of available maternal and infant medical records
- Collection of maternal medical history information, focusing on HIV status
- Collection of infant medical history information, focusing on date and time of birth; gestational age and weight at birth; date, time, and results of HIV testing since birth; and ARV use since birth
- Assessment of infant ability to take ARVs
- Assessment of infant clinical condition, focusing on clinically significant diseases and other clinically significant findings that would interfere with study participation or interpretation

A listing of eligibility determination procedures for Cohort 2, reflective of the Cohort 2 eligibility criteria and the maternal and infant SoEs, is provided below. Procedures need not be performed in the order shown; however, written informed consent must be obtained before any study procedures are performed.

<table>
<thead>
<tr>
<th>COHORT 2 ELIGIBILITY DETERMINATION PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Determine whether mother is of age to provide independent informed consent <em>(must precede informed consent process)</em></td>
</tr>
<tr>
<td>• Obtain written informed consent from mother or her legal guardian <em>(must precede all other protocol-specified procedures)</em></td>
</tr>
<tr>
<td>• Assign PIDs to mother and infant</td>
</tr>
<tr>
<td>• Review available medical records for mother and infant, collect medical and medications history information from the mother, and perform infant physical exam <em>(see Section 7.5 of this manual)</em> to determine:</td>
</tr>
<tr>
<td>• Whether mother or infant have any documented HIV testing (including date and time of specimen collection for infants)</td>
</tr>
<tr>
<td>• Whether infant initiated a qualifying ARV regimen within 48 hours of birth and has taken this regimen daily since initiation</td>
</tr>
<tr>
<td>• Infant gestational age at birth</td>
</tr>
<tr>
<td>• Infant weight at birth</td>
</tr>
<tr>
<td>• Infant ability to take ARVs by mouth, nasogastric tube, or gastrostomy tube</td>
</tr>
<tr>
<td>• Infant clinical condition, including any clinically significant diseases or findings</td>
</tr>
<tr>
<td>• Review, confirm, and document eligibility per site SOPs</td>
</tr>
<tr>
<td>⇒ If not eligible, stop</td>
</tr>
<tr>
<td>⇒ If eligible, continue with enrollment and Step 2 entry procedures</td>
</tr>
</tbody>
</table>

It is the responsibility of the site IoR and other designated study staff to ensure that all required eligibility determination procedures are performed and adequately documented, and that only participants who meet eligibility criteria are enrolled. Each site must have on file and follow an SOP for eligibility determination that describes how study staff will fulfill this responsibility. In the event that study staff identify that an ineligible participant has been enrolled, the CMC should be consulted immediately (see communication procedures in Section 3 of this manual).
7.2.3 Definition of Enrollment for Cohort 2

Mother-infant pairs will be considered enrolled in Cohort 2 after study staff have entered all required eligibility checklist data into the SES and the system successfully generates confirmation files with SIDs for the mother and infant. Under protocol Version 2.0, separate eligibility checklists will be entered for mothers and infants. The mother’s checklist must be entered first, immediately followed by the infant’s checklist.

7.2.4 Enrollment Timeframe for Cohort 2

Enrollment in Cohort 2 must occur within 10 days of infant birth.

7.3 Enrollment / Step 2 Entry Procedures: Cohort 1 and Cohort 2

7.3.1 Step 2 Entry Procedures for Mothers

The mothers of all infants entering Step 2 are expected to complete study procedures on the day of infant entry into Step 2. These procedures are listed on page 48, in separate columns for mothers in Cohort 1 and Cohort 2. All procedures need not be performed in the order shown; however, enrollment in the SES should precede other “on study” procedures.

- **For mothers in Cohort 1**, who enter Step 2 from Step 1, the procedures listed in the maternal SoE under “When infant is confirmed infected (at time of infant Step 2 entry)” should be performed on the day of Step 2 entry. For these mothers, 10 mL of blood should be collected for stored plasma and cells (refer to the Laboratory Processing Chart (LPC) for tube and anticoagulant types and other associated details).

- **For mothers in Cohort 2**, who enter Step 2 directly, the procedures listed in the maternal SoE under “Entry” and under “When infant is confirmed infected (at time of infant Step 2 entry)” should be performed on the day of Step 2 entry. For these mothers, 20 mL of blood should be collected for stored plasma and cells (refer to the LPC for tube and anticoagulant types and other associated details). In the event that the full maternal blood draw volume cannot be collected on the day of Step 2 Entry, 10 mL (EDTA) should ideally be collected and processed for HIV testing if needed to confirm eligibility and plasma and cell storage. The mother should be asked to return to complete the specimen collection as soon as possible, with the expectation of completion by the date of the infant’s Step 2 Week 1 visit.

In addition for mothers in Cohort 2, per protocol Section 4.1.1.1, mothers who enroll in the study with presumed HIV infection must have confirmatory testing with results available within 10 business days of enrollment. If maternal HIV infection is not confirmed within 10 business days of enrollment, mothers and their infants will be discontinued from the study.
<table>
<thead>
<tr>
<th>COHORT 1: MATERNAL STEP 2 ENTRY PROCEDURES</th>
<th>COHORT 2: MATERNAL STEP 2 ENTRY PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>For mother-infant pair: After confirming eligibility per site SOPs, complete paper-based Step 2 eligibility checklists, enter maternal checklist data into the SES to enroll the mother first; then enter infant checklist data to enroll the infant immediately after the mother; print and file a copy of each confirmation file.</td>
<td>For mother-infant pair: After confirming eligibility per site SOPs, complete paper-based Step 2 eligibility checklists, enter maternal checklist data into the SES to enroll the mother first; then enter infant checklist data to enroll the infant immediately after the mother; print and file a copy of each confirmation file.</td>
</tr>
<tr>
<td>Collect targeted interval medical and medications history:</td>
<td>Collect targeted interval medical and medications history:</td>
</tr>
<tr>
<td>- WHO clinical stage</td>
<td>- WHO clinical stage</td>
</tr>
<tr>
<td>- ARV use</td>
<td>- ARV use</td>
</tr>
<tr>
<td>- CD4 cell counts</td>
<td>- CD4 cell counts</td>
</tr>
<tr>
<td>- HIV RNA results</td>
<td>- HIV RNA results</td>
</tr>
<tr>
<td>- Any other relevant history</td>
<td>- Any other relevant history</td>
</tr>
<tr>
<td>Continue review of available medical records and collection of targeted medical and medications history to assess and document the following:</td>
<td>Continue review of available medical records and collection of targeted medical and medications history to assess and document the following:</td>
</tr>
<tr>
<td>- Prior HIV testing</td>
<td>- Prior HIV testing</td>
</tr>
<tr>
<td>- Prior ARV use</td>
<td>- Prior ARV use</td>
</tr>
<tr>
<td>- Current WHO clinical stage</td>
<td>- Current WHO clinical stage</td>
</tr>
<tr>
<td>- CD4 cell counts within the last year</td>
<td>- CD4 cell counts within the last year</td>
</tr>
<tr>
<td>- HIV RNA results within the last year</td>
<td>- HIV RNA results within the last year</td>
</tr>
<tr>
<td>- Prior pregnancies, mode of delivery for the current pregnancy, and syphilis during the current pregnancy</td>
<td>- Prior pregnancies, mode of delivery for the current pregnancy, and syphilis during the current pregnancy</td>
</tr>
<tr>
<td>- Current hepatitis status</td>
<td>- Current hepatitis status</td>
</tr>
<tr>
<td>- Other relevant pregnancy, medical, and/or medications history</td>
<td>- Other relevant pregnancy, medical, and/or medications history</td>
</tr>
<tr>
<td>Review all available documentation and determine whether additional HIV testing is required to meet study eligibility requirements</td>
<td>Review all available documentation and determine whether additional HIV testing is required to meet study eligibility requirements</td>
</tr>
<tr>
<td>Collect blood per the LPC and site SOPs for:</td>
<td>Collect blood per the LPC and site SOPs for:</td>
</tr>
<tr>
<td>- Serum storage</td>
<td>- Serum storage</td>
</tr>
<tr>
<td>- Plasma and cell storage</td>
<td>- Plasma and cell storage</td>
</tr>
<tr>
<td>Collect blood per the LPC and site SOPs for:</td>
<td>Collect blood per the LPC and site SOPs for:</td>
</tr>
<tr>
<td>- HIV RNA</td>
<td>- HIV RNA</td>
</tr>
<tr>
<td>- Other HIV testing if needed to meet study eligibility requirements</td>
<td>- Other HIV testing if needed to meet study eligibility requirements</td>
</tr>
<tr>
<td>- Serum storage</td>
<td>- Serum storage</td>
</tr>
<tr>
<td>- Plasma and cell storage</td>
<td>- Plasma and cell storage</td>
</tr>
<tr>
<td>Provide HIV-related, infant feeding, and other applicable information and counseling</td>
<td>Provide HIV-related, infant feeding, and other applicable information and counseling</td>
</tr>
<tr>
<td>Provide or follow-up on referrals for HIV-related care and treatment</td>
<td>Provide referrals for HIV-related care and treatment</td>
</tr>
<tr>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
</tr>
<tr>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>Enter required eCRFs</td>
<td>Enter required eCRFs</td>
</tr>
</tbody>
</table>
7.3.2 Step 2 Entry Procedures for Infants

A listing of Step 2 Entry procedures for infants is provided below, in separate columns for infants in Cohort 1 and Cohort 2. All procedures need not be performed in the order shown; however, enrollment in the SES should precede other “on study” procedures.

In addition, for infants in Cohort 2:

- Per protocol Section 6.3.2.2, HIV infection must be confirmed by a second positive HIV NAT within 10 business days of enrollment. If the second NAT does not confirm the initial positive result, the CMC should be notified and a third specimen should be collected for a third test (selected in consultation with the CMC), with the result available within 10 additional business days. The infant should remain on study, and on the study treatment regimen, until the third result is available and the infant’s HIV status is confirmed in consultation with the CMC. If infection is not confirmed, infants and their mothers will be discontinued from the study. See Section 6.4 of this manual for further guidance on use of HIV RNA assays for purposes of diagnosing infant HIV infection; this same guidance is applicable in Cohort 2.

- Two sets of infant measurements should be recorded at Step 2 Entry. Weight, length, and head circumference at birth are required as part of the infant’s medical history, with data expected to be obtained from medical records. These same measurements are also required as part of the infant physical exam that is expected to be performed by a study clinician at the Entry visit.

<table>
<thead>
<tr>
<th>COHORT 1: INFANT STEP 2 ENTRY PROCEDURES</th>
<th>COHORT 2: INFANT STEP 2 ENTRY PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete eligibility checklists and entries into the SES as shown on page 48. Note: To enroll eligible twins or other multiplets, a separate checklist must be entered for each infant, one after the other, and after the mother.</td>
<td><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete eligibility checklists and entries into the SES as shown on page 48. Note: To enroll eligible twins or other multiplets, a separate checklist must be entered for each infant, one after the other, and after the mother.</td>
</tr>
</tbody>
</table>
| Collect interval medical and medications history:  
  - Signs, symptoms, and diagnoses  
  - ARVs  
  - Other concomitant medications  
  - Interventions for hyperbilirubinemia  
  - Feeding method and date of cessation of breastfeeding if applicable | Complete review of available medical records and collection of medical and medications history to assess and document the following:  
  - Sex  
  - Race/ethnicity  
  - Length and head circumference at birth (weight at birth and gestational age at birth should have been documented prior to enrollment as part of eligibility determination)  
  - Signs, symptoms, and diagnoses since birth  
  - All HIV tests since birth  
  - All ARVs since birth  
  - All other concomitant medications since birth  
  - All interventions for hyperbilirubinemia since birth  
  - Feeding method since birth |
<table>
<thead>
<tr>
<th>COHORT 1: INFANT STEP 2 ENTRY PROCEDURES</th>
<th>COHORT 2: INFANT STEP 2 ENTRY PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform physical exam (see Section 7.5 of this manual)</td>
<td>Physical exam should have been performed prior to enrollment as part of eligibility determination</td>
</tr>
<tr>
<td>Assess whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6, consulting CMC if indicated</td>
<td>Review all available documentation and determine specimen collection requirements for HIV testing to meet study eligibility requirements</td>
</tr>
<tr>
<td>Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:</td>
<td>Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:</td>
</tr>
<tr>
<td>- HIV RNA</td>
<td>- HIV RNA</td>
</tr>
<tr>
<td>- Complete blood count with differential and platelet count</td>
<td>- Other HIV NAT if needed for confirmation of HIV infection</td>
</tr>
<tr>
<td>- CD4 cell count and percentage</td>
<td>- Complete blood count with differential and platelet count</td>
</tr>
<tr>
<td>- AST, ALT, ALP, creatinine, total bilirubin</td>
<td>- CD4 cell count and percentage</td>
</tr>
<tr>
<td>- Plasma and PBMC storage (aliquots will be used for study agent concentrations at this visit)</td>
<td>- AST, ALT, ALP, creatinine, total bilirubin</td>
</tr>
<tr>
<td>- Droplet digital HIV DNA PCR (stored)</td>
<td>- Plasma and PBMC storage (aliquots will be used for study agent concentrations at this visit)</td>
</tr>
<tr>
<td>Collect and store urine per the LPC and site SOPs</td>
<td>Collect and store urine per the LPC and site SOPs</td>
</tr>
<tr>
<td>Prescribe and dispense study treatment agents (see Section 7.6 of this manual)</td>
<td>Prescribe and dispense study treatment agents (see Section 7.6 of this manual)</td>
</tr>
<tr>
<td>For infants receiving Regimen 2RV:</td>
<td></td>
</tr>
<tr>
<td>- Administer VRC01 and monitor for reactogenicity per protocol Section 6.2.5.1</td>
<td></td>
</tr>
<tr>
<td>- Provide instructions for completing reactogenicity memory aid per protocol Section 6.2.5.2 as needed</td>
<td></td>
</tr>
<tr>
<td>Provide instructions and adherence counseling to mother for administration of ARVs to infant</td>
<td>Provide instructions and adherence counseling to mother for administration of ARVs to infant</td>
</tr>
<tr>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
<td>Schedule next visit, provide reminders for next visit, and provide site contact instructions</td>
</tr>
<tr>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
<td>Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>Enter required eCRFs</td>
<td>Enter required eCRFs</td>
</tr>
<tr>
<td>Report expedited adverse events to the DAIDS Safety Office if applicable</td>
<td></td>
</tr>
</tbody>
</table>
### 7.3.3 Frequently Asked Questions for Entry into Step 2

<table>
<thead>
<tr>
<th>Q1: Maternal inclusion criterion 4.1.3.1 indicates that mothers in Cohort 2 may receive ARVs during the current pregnancy and/or the intrapartum period. Can we also enroll mothers in this cohort who did not receive any ARVs during pregnancy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: Yes. There are no eligibility criteria related to maternal ARV use for Cohort 2; therefore, mothers in this cohort may have received ARVs, or not, during pregnancy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2: For mothers, inclusion criterion 4.1.1.1 refers to the peripartum period. How should peripartum be defined for this purpose?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2: Based on standard obstetrical definitions, the peripartum period includes the last month of gestation and the first few months after delivery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3: We are not clear on how to properly interpret the columns of the maternal SoE for mothers who enroll in Cohort 2 (enter the study in Step 2). We know that the procedures listed under “Entry” should be done on the day of enrollment. When should we do the procedures listed under “When infant is confirmed infected”?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3: For mothers enrolling in Cohort 2, the procedures listed under “Entry” and the procedures listed under “When infant is confirmed infected” should be performed on the day of enrollment (day of entry into Step 2).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q4: What should we do if an infant’s gestational age at birth is not documented in his or her birth records? Must we exclude this infant from Cohort 2?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4: For Cohort 2, you have some limited options if gestational age at birth is not documented in an infant’s birth records. If a study clinician is able to assess the infant within 48 hours of birth, the clinician may determine his or her gestational age within 48 hours of birth. In this case, the date, time, and outcome of this assessment should be documented in the participant’s study chart and used for purposes of eligibility determination. If a study clinician is not able to assess the infant within 48 hours of birth, it will not be possible to enroll the infant in Cohort 2, because it will not be possible to confirm eligibility — which requires an assessment of gestational age at birth — prior to enrollment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q5: What should we do if an infant’s gestational age at birth is documented in his or her birth records, but we are not confident in the assessment? For example, estimates based on the date of the mother’s last menstrual period (LMP) may be inaccurate.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5: The protocol allows for gestational age to be assessed based on date of LMP. However, on a case-by-case basis, if you are concerned that a documented gestational age is inaccurate, the protocol team would recommend that two clinicians from your site assess the infant and come to consensus on the most accurate assessment of his or her gestational age, prior to enrollment; when in doubt, the earliest/youngest of the two assessments should be used. The consensus assessment should be documented in the infant’s study chart and, if different from the gestational age documented in the infant’s birth records, a note explaining the difference should also be recorded. You are also encouraged to consult the CMC regarding questions of gestational age or any other aspects of eligibility.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q6: In our setting, we commonly see physiologic jaundice in infants born to high risk mothers. We also commonly see infants who are given a course of empiric antibiotics if they are born after a prolonged period of ruptured membranes. In view of exclusion criterion 4.6 (clinically significant diseases or findings), can these infants be considered for enrollment in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A6: Neither physiologic jaundice or empiric antibiotics would, in and of themselves, be exclusionary for this study. The protocol team would encourage you to holistically assess each infant for clinically significant exclusionary conditions, but these factors alone would not be considered exclusionary. You are also encouraged to contact the CMC with any questions of eligibility for any potential participant at any time.</td>
</tr>
</tbody>
</table>
Q7: We have an infant at our site who qualified for Cohort 2 based on an HIV RNA PCR test performed at birth. We enrolled this infant in Cohort 2 at eight days of age, so he had been on ART for seven days at that point. Our site lab is not VQA-certified to perform HIV DNA PCR, so we performed an HIV RNA PCR on blood collected at the study entry visit, and the result came back undetectable. What should we do now? Do we need to drop this infant from the study? He will be back at the clinic tomorrow for the Step 2 Week 1 visit.

A7: Per protocol Section 6.3.2.2, please draw blood for additional HIV testing at the infant’s Step 2 Week 1 visit. It would be ideal if you could perform HIV DNA PCR or an HIV TNA test on this (third) blood sample. However, if that is not possible, you will need to perform another HIV RNA PCR and then make a final determination of HIV infection status and eligibility to remain in the study in consultation with the CMC.

Q8: We have identified our first HIV-infected infant in Step 1. When this infant enters Step 2, will he then be considered part of Cohort 2?

A8: No. Infants will always be considered part of the cohort in which they were originally enrolled. If an infant enrolls in Cohort 1, he or she will always be considered part of Cohort 1, regardless of whether he or she later enters Step 2, Step 3, or Step 4.

Q9: We have identified an HIV-infected infant in Step 1 who will be entering Step 2. Do we need to write a new prescription for this infant at the Step 2 Entry visit?

A9: Yes. A new prescription is needed upon entry into each step, using the SID generated when the infant was successfully enrolled in that step. In addition, ARV dosing is expected to change upon entry into Step 2 and the infant’s weight may have changed as well. For infants receiving Regimen 2RV, a new prescription is needed for each dose of VRC01.

Q10: We have a question about NRTI dosing at entry into Step 2. The protocol indicates that dosing for these ARVs is per WHO or country guidelines. Our country guidelines generally follow WHO guidelines, but we are unsure about NRTI dosing for infants who weigh less than 3 kg. Please advise on the recommended dosing for these infants.

A10: To assist with this question, we will refer to the 2016 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, specifically Tables 1-4 in Annex 11. The liquid formulation dosing shown in Table 4 should be followed until infants reach four weeks of age and 3 kg. Once infants reach four weeks of age and 3kg, the liquid or solid formulation dosing shown in Tables 2-4 may be followed. Please contact the CMC with any questions or concerns related to NRTI dosing or any other aspects of ARV regimen management.

Q11: In some cases, infants enrolled in Cohort 2 at our site will have more than one HIV NAT performed outside of the study prior to enrollment. If this occurs, should we enter the results of the non-study tests into eCRFs?

A11: Yes. Please enter all HIV NATs performed since infant birth into eCRFs. Quantitative HIV RNA tests should be entered into the LBW0178 eCRF. Qualitative tests, including HIV DNA tests, should be entered into the LBW0177 eCRF. One form should be completed for each test performed since birth.

Q12: One of our Cohort 2 mothers has provided informed consent for her own and her infant’s study participation, but she has declined consent for genetic testing. Please clarify how we should approach specimen collection and testing for this mother-infant pair.

A12: For both the mother and the infant, all specimens specified in the SoE should be collected, processed, and stored as specified in the LPC, regardless of whether consent was provided for genetic testing. In the future, if the protocol team issues a specimen request for genetic testing, these participants will be excluded from that request. Please note that exclusion from the specimen request list will be based on eCRF data indicating whether informed consent for genetic testing was obtained. It is therefore essential that these entries are correct and up-to-date for all participants. See Section 5 of this manual for further guidance related to these entries.
7.4 Follow-up in Step 2

After entry into Step 2, infants will complete nine or ten visits in the first six months of follow-up in Step 2 (i.e., through Step 2 Week 24). Thereafter, infants will complete monthly visits, with quarterly laboratory evaluations, over the course of the next 12 months (i.e., through Step 2 Week 72) followed by quarterly visits for the reminder of their participation in Step 2 (up to Week 192). These visits are described in Sections 7.4.1, 7.4.2, and 7.4.3. Under LoA #2, follow-up in Step 2 may be extended during the COVID-19 pandemic up to Week 288; extended follow-up visits are described in Section 7.4.4.

Beginning at Step 2 Week 84, infants who are potentially eligible for Step 3 may be further evaluated to assess eligibility for Step 3. Any such evaluation will be undertaken in close consultation with the Protocol Team, under protocol Letter of Amendment #1.

Infant HIV viral loads must be closely monitored throughout follow-up in Step 2. HIV RNA turnaround times should be agreed upon by clinic and laboratory staff and active communication should occur if HIV RNA testing cannot be performed for any reason or if results are not received within the specified turnaround time. See Section 9.5 of this manual for further guidance on virologic monitoring.

All study site laboratories should report HIV RNA results as either below the LOD of the assay or as the number of HIV RNA copies detected at or above the LOD of the assay. When results are reported as below the LOD of the assay, the result report must also indicate whether HIV RNA was detected or not detected. Any questions about this should be directed to the P1115 Questions Group, which includes representatives of the IMPAACT Laboratory Center. Each site IoR is responsible for ensuring that local laboratories report results as required for this study; each IoR is also responsible for ensuring that study clinicians and others involved in receipt, review, and/or interpretation of HIV RNA result reports are adequately trained for this critical role for this study.

Mothers of infants in Step 2 will complete follow-up visits approximately every six months. These visits are described in Section 7.4.6.

7.4.1 Follow-up Visits and Procedures for Infants: Step 2 Week 1 to Week 24

Figure 7-3 lists the visits expected to be conducted in the first six months of infant follow-up in Step 2. To further illustrate this portion of the Step 2 visit schedule, the figure also provides calendar dates for visits expected for a sample infant who enters Step 2 on 1 October 2019. Each visit should ideally be conducted on the target date but may be conducted on any day within the allowable window.

Note: The Week 8 visit is required only for infants receiving Regimen 2RV. Reactogenicity contacts will also be completed for these infants following their Step 2 Entry, Step 2 Week 4, and Step 2 Week 8 visits. Refer to protocol Section 6.2.5 and Section 12 of this manual for detailed guidance on reactogenicity monitoring.

A listing of Step 2 infant follow-up procedures through Week 9 is provided on page 55; a listing for visits thereafter through Week 24 is provided on page 56. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.
## Figure 7-3
Follow-up Visit Schedule through Week 24  
For a Sample Infant who Enters Step 2 on 1 October 2019

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Duration</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Window Opens</td>
<td>Window Closes</td>
</tr>
<tr>
<td>Week 1</td>
<td>8-OCT-2019</td>
<td>±2 days</td>
<td>6-OCT-2019</td>
</tr>
<tr>
<td>Week 4</td>
<td>29-OCT-2019</td>
<td>±7 days</td>
<td>22-OCT-2019</td>
</tr>
<tr>
<td>Week 5</td>
<td>5-NOV-2019</td>
<td>±2 days</td>
<td>3-NOV-2019</td>
</tr>
<tr>
<td>Week 8</td>
<td>26-NOV-2019</td>
<td>±7 days</td>
<td>19-NOV-2019</td>
</tr>
<tr>
<td>Week 9</td>
<td>3-DEC-2019</td>
<td>±2 days</td>
<td>1-DEC-2019</td>
</tr>
<tr>
<td>Week 12</td>
<td>24-DEC-2019</td>
<td>±14 days</td>
<td>10-DEC-2019</td>
</tr>
<tr>
<td>Week 16</td>
<td>21-JAN-2020</td>
<td>±14 days</td>
<td>7-JAN-2020</td>
</tr>
<tr>
<td>Week 20</td>
<td>18-FEB-2020</td>
<td>±14 days</td>
<td>4-FEB-2020</td>
</tr>
<tr>
<td>Week 24</td>
<td>17-MAR-2020</td>
<td>±14 days</td>
<td>3-MAR-2020</td>
</tr>
</tbody>
</table>

*Target visit dates are counted from the day of entry into Step 2. Day of entry = Day 0.
### STEP 2 INFANT FOLLOW-UP PROCEDURES
#### WEEKS 1, 2, 4, 5, 8, AND 9
- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam (see Section 7.5 of this manual)
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count (Weeks 1, 5, and 9)
  - AST, ALT, ALP, creatinine (Weeks 1, 5, and 9)
  - Total bilirubin (Week 1)
  - HIV RNA (Weeks 2, 4, and 9; see important notes)
  - Plasma and PBMC storage (Weeks 4 and 9)
  - DBS storage (Weeks 1 and 4)
  - Study agent concentrations (Weeks 1, 2, and 4 for all infants; additionally at Week 8 for infants receiving Regimen 2RV; aliquots will be obtained from plasma storage at Week 4; collect blood prior to VRC01 administration at Weeks 4 and 8)
- Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)
- For infants receiving Regimen 2RV, at Weeks 4 and 8, administer VRC01 and monitor for reactogenicity per protocol Section 6.2.5.1
- For infants receiving Regimen 2RV, at Weeks 4 and 8, provide instructions for completing reactogenicity memory aid per protocol Section 6.2.5.2 as needed
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

### IMPORTANT NOTES
- Dilution of specimens used for HIV RNA testing should be avoided whenever possible and should not occur at or after Step 2 Week 24.
  - Prior to Step 2 Week 24, when dilution is necessary, a validated diluent must be used (1:5) and the LOD of the assay must be adjusted accordingly.
STEP 2 INFANT FOLLOW-UP PROCEDURES
WEEKS 12, 16, 20, AND 24

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; feeding method and date of cessation of breastfeeding if applicable
- Perform physical exam (see Section 7.5 of this manual)
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count (Weeks 16 and 24)
  - CD4 cell count and percentage (Weeks 12 and 24)
  - AST, ALT, ALP, creatinine (Weeks 16 and 24)
  - HIV RNA (Weeks 12, 16, 20, and 24; see important notes)
  - Plasma and PBMC storage (Weeks 12, 16, 20, and 24)
  - DBS storage (Week 24)
  - Droplet digital HIV DNA PCR (stored; Weeks 12 and 24)
  - Study agent concentrations (for infants receiving Regimen 2RV, aliquots will be obtained from plasma storage at Weeks 12, 16, 20, and 24)
- Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

IMPORTANT NOTES
❖ Dilution of specimens used for HIV RNA testing should be avoided whenever possible and should not occur at or after Step 2 Week 24.
  - Prior to Step 2 Week 24, when dilution is necessary, a validated diluent must be used (1:5) and the LOD of the assay must be adjusted accordingly.
  - At and after Step 2 Week 24, if an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.
❖ Any infant with an HIV RNA value ≥200 copies/mL at Step 2 Week 24 must undergo repeat testing as soon as possible and within three weeks (specimen collection for the confirmatory test must occur within a maximum of three weeks of specimen collection for the initial test; see example in the calendar graphic on the next page).
  - If the confirmatory test confirms the initial result, or if specimen collection for the confirmatory test cannot be completed within three weeks, the infant will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.
  - If the confirmatory test result is <200 copies/mL, the infant will remain potentially eligible for Step 3.
7.4.2 Follow-up Visits and Procedures for Infants: Step 2 Week 28 to Week 72

Between Weeks 28 and 72, infant visits are expected every four weeks (±14 days). The quarterly visits during this period — at Weeks 36, 48, 60, and 72 — must be conducted in-person at the study clinic. The intervening monthly visits during this period — at Weeks 28, 32, 40, 44, 52, 56, 64, and 68 — may be conducted by phone or in-person at the study clinic if preferred by study staff. An in-person visit may be preferred if, for example, the infant’s mother does not have a phone or if an in-person visit would be beneficial to support visit compliance and/or study drug adherence. In-person visits should also be conducted when new prescriptions or changes in study drug dosing or administration are needed.

Listings of infant follow-up procedures for monthly and quarterly visits are provided below. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.

**STEP 2 INFANT FOLLOW-UP PROCEDURES (MONTHLY)**  
**WEEKS 28, 32, 40, 44, 52, 56, 64, AND 68**  
**MAY BE CONDUCTED IN-PERSON OR BY PHONE**

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; feeding method; and date of cessation of breastfeeding if applicable
- Determine whether any other evaluations or procedures are clinically indicated; if so, recall the infant to the clinic if needed and proceed per protocol Section 6 (consult CMC if indicated)
- Prescribe and dispense study treatment agents as needed (must be done at an in-person visit; see Section 7.6 of this manual)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant as needed
- Provide other information and/or counseling to mother as needed
- Schedule or re-confirm next visit, provide reminders for next visit, and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable
STEP 2 INFANT FOLLOW-UP PROCEDURES (QUARTERLY)
WEEKS 36, 48, 60, AND 72

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam (see Section 7.5 of this manual)
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count (Weeks 36, 48, 60, and 72)
  - CD4 cell count and percentage (Weeks 36, 48, 60, and 72)
  - AST, ALT, ALP, creatinine (Weeks 36, 48, 60, and 72)
  - HIV RNA (Weeks 36, 48, 60, and 72; see important notes)
  - Plasma and PBMC storage (Weeks 36, 48, 60, and 72)
  - DBS storage (Weeks 48 and 72)
  - Droplet digital HIV DNA PCR (stored; Weeks 36, 48, 60, and 72)
  - Immune responses (stored; Week 72)
- Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

IMPORTANT NOTES
❖ Dilution of specimens used for HIV RNA testing should be avoided whenever possible and should not occur at or after Step 2 Week 24.
  - At and after Step 2 Week 24, if an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.
❖ Any infant with an HIV RNA value ≥200 copies/mL at Step 2 Week 36 must undergo repeat testing as soon as possible and within three weeks (specimen collection for the confirmatory test must occur within a maximum of three weeks of specimen collection for the initial test; see example in the calendar graphic on page 57).
  - If the confirmatory test confirms the initial result, or if specimen collection for the confirmatory test cannot be completed within three weeks, the infant will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.
  - If the confirmatory test result is <200 copies/mL, the infant will remain potentially eligible for Step 3.
❖ Any infant with any HIV RNA detected at Step 2 Week 48 or thereafter, even if below the LOD of the assay, will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.
7.4.3 Follow-up Visits and Procedures for Infants: Step 2 Week 84 to Week 192

After Week 72, infant visits are expected every 12 weeks (±28 days). Per protocol Clarification Memorandum (CM) #2, during the COVID-19 pandemic, the allowable visit window for the Week 132, 144, 168, and 180 visits is expanded to ±6 weeks; the allowable window for the Week 192 visit is expanded to -6 to +24 weeks. Refer to CM #2 for further guidance on study implementation during the COVID-19 pandemic. The procedural requirements at all of these visits are very similar; however, the laboratory requirements for these visits alternate. The requirements for the Week 84, 108, 132, 156, and 180 visits are all the same. Likewise, the requirements for the Week 96, 120, 144, 168, and 192 visits are all the same.

Listings of procedures required at these visits are provided below. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.

### STEP 2 INFANT FOLLOW-UP PROCEDURES WEEKS 84, 108, 132, 156, AND 180

- *If applicable during the COVID-19 pandemic*, after obtaining all required approvals of LoA #2, obtain written informed consent for extended follow-up in Step 2.
- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam *(see Section 7.5 of this manual)*
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - Complete blood count with differential and platelet count
  - CD4 cell count and percentage
  - *If receiving Regimen 1L*: AST, ALT, lipase, glucose
  - *If receiving Regimen 2R or 2RV*: AST, ALT, ALP, creatinine
  - HIV RNA *see important notes*
  - HIV-1 antibody (ELISA or rapid test)
  - Plasma and PBMC storage
  - Droplet digital HIV DNA PCR *(stored)*
  - Immune responses *(stored; Week 180)*
- Prescribe and dispense study treatment agents as needed *(see Section 7.6 of this manual)*
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

**IMPORTANT NOTES**

- Dilution of specimens used for HIV RNA testing should be avoided whenever possible and should not occur at or after Step 2 Week 24.
  - At and after Step 2 Week 24, if an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.
- Any infant with any HIV RNA detected at Step 2 Week 48 or thereafter will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.
### STEP 2 INFANT FOLLOW-UP PROCEDURES
**WEEKS 96, 120, 144, 168, AND 192**

- If applicable during the COVID-19 pandemic, after obtaining all required approvals of LoA #2, obtain written informed consent for extended follow-up in Step 2.
- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam (see Section 7.5 of this manual)
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - CD4 cell count and percentage (with complete blood count if needed)
  - HIV RNA see important notes
  - HIV-1 antibody (ELISA or rapid test)
  - DBS storage
  - Droplet digital HIV DNA PCR (stored)
  - Replication competent virus and single copy HIV RNA (real time with overnight shipment for US sites, stored for international sites)
- Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

### IMPORTANT NOTES
- Dilution of specimens used for HIV RNA testing should be avoided whenever possible and should not occur at or after Step 2 Week 24.
  - At and after Step 2 Week 24, if an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.
- Any infant with any HIV RNA detected at Step 2 Week 48 or thereafter will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.
7.4.4 Extended Follow-up in Step 2 under LoA #2

LoA #2 permits extended follow-up in Step 2, during the COVID-19 pandemic, prior to considering treatment cessation in Step 3, with visits expected every 12 weeks (±6 weeks) up to Week 288. The procedural requirements at all of these visits are very similar; however, the laboratory requirements for these visits alternate. The requirements for the Week 204, 228, 252, and 276 visits are all the same. Likewise, the requirements for the Week 216, 240, 264, and 288 visits are all the same.

Listings of procedures required at these visits are provided below. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.

<table>
<thead>
<tr>
<th>STEP 2 INFANT EXTENDED FOLLOW-UP PROCEDURES UNDER LOA #2 WEEKS 204, 228, 252, AND 276</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Before conducting the Week 204 visit, confirm that written informed consent for extended follow-up in Step 2 has been obtained.</td>
</tr>
<tr>
<td>• Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; feeding method; and date of cessation of breastfeeding if applicable</td>
</tr>
<tr>
<td>• Perform physical exam (see Section 7.5 of this manual)</td>
</tr>
<tr>
<td>• Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)</td>
</tr>
<tr>
<td>• Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:</td>
</tr>
<tr>
<td>– Complete blood count with differential and platelet count</td>
</tr>
<tr>
<td>– CD4 cell count and percentage</td>
</tr>
<tr>
<td>– If receiving Regimen 1L: AST, ALT, lipase, glucose</td>
</tr>
<tr>
<td>– HIV RNA see important notes</td>
</tr>
<tr>
<td>– HIV-1 antibody (ELISA or rapid test)</td>
</tr>
<tr>
<td>– Plasma and PBMC storage</td>
</tr>
<tr>
<td>– Droplet digital HIV DNA PCR (stored)</td>
</tr>
<tr>
<td>– Immune responses (stored)</td>
</tr>
<tr>
<td>• Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)</td>
</tr>
<tr>
<td>• Provide instructions and adherence counseling to mother for administration of ARVs to infant</td>
</tr>
<tr>
<td>• Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed</td>
</tr>
<tr>
<td>• Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed</td>
</tr>
<tr>
<td>• Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed</td>
</tr>
<tr>
<td>• Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>• Enter required eCRFs</td>
</tr>
<tr>
<td>• Report expedited adverse events to the DAIDS Safety Office if applicable</td>
</tr>
</tbody>
</table>

**IMPORTANT NOTES**

❖ Specimens used for HIV RNA testing should not be diluted. If an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.

❖ Any infant with any HIV RNA detected during extended follow-up will be considered ineligible for Step 3 but will remain on-study until the specifications of LoA #2 are no longer applicable.
STEP 2 INFANT EXTENDED FOLLOW-UP PROCEDURES UNDER LOA #2
WEEKS 216, 240, 264, AND 288

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam (see Section 7.5 of this manual)
- Review all available clinical and laboratory information and determine whether infant meets criteria for additional evaluations and/or modification of study treatment regimen per protocol Section 6 (consult CMC if indicated)
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - CD4 cell count and percentage (with complete blood count if needed)
  - HIV RNA see important notes
  - HIV-1 antibody (ELISA or rapid test)
  - DBS storage
  - Droplet digital HIV DNA PCR (stored)
  - Replication competent virus and single copy HIV RNA (real time with overnight shipment for US sites, stored for international sites)
- Prescribe and dispense study treatment agents as needed (see Section 7.6 of this manual)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related or other care and treatment for mother and/or infant as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions as needed
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

IMPORTANT NOTES
❖ Specimens used for HIV RNA testing should not be diluted. If an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.
❖ Any infant with any HIV RNA detected during extended follow-up will be considered ineligible for Step 3 but will remain on-study until the specifications of LoA #2 are no longer applicable.
7.4.5 Premature Discontinuation Visits

For any infant who discontinues Step 2 follow-up prior to Step 2 Week 192, or prior to Week 288 under LoA #2, and does not enter Step 3, a Premature Discontinuation visit should ideally be conducted. Listings of procedures required at these visits are provided below. Critical among these is active referral to non-study HIV care and treatment for the infant. In addition, non-study ARVs should be prescribed and dispensed, along with information and counseling for the mother, to avoid gaps in treatment during the transition to non-study care. Equally important, study staff should actively follow up with the mother after the visit to provide test results from the visit and determine whether action has been taken on the referral to non-study care. If the infant has not yet been established in care at the time of this contact, additional referrals and follow-up should be continued as needed.

**STEP 2 INFANT PREMATURERE DISCONTINUATION PROCEDURES PRIOR TO WEEK 84**

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; interventions for hyperbilirubinemia; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam *(see Section 7.5 of this manual)*
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - CD4 cell count and percentage *(with complete blood count if needed)*
  - Plasma and PBMC storage
  - DBS storage
  - Droplet digital HIV DNA PCR *(stored)*
  - Immune responses *(stored)*
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related care and treatment as needed
- Prescribe and dispense non-study ARVs as needed to avoid gaps in treatment during the transition to non-study care
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

**STEP 2 INFANT PREMATURERE DISCONTINUATION PROCEDURES AFTER WEEK 84**

- Collect interval medical, medications, and feeding history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; feeding method; and date of cessation of breastfeeding if applicable
- Perform physical exam *(see Section 7.5 of this manual)*
- Review infant weight, determine maximum blood draw volume, then collect blood (up to the maximum) per the LPC and site SOPs for:
  - CD4 cell count and percentage *(with complete blood count if needed)*
  - Plasma and PBMC storage
  - Immune responses *(stored)*
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related care and treatment as needed
- Prescribe and dispense non-study ARVs as needed to avoid gaps in treatment during the transition to non-study care
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable
7.4.6 Follow-up Visits and Procedures for Mothers

Mothers of infants in Step 2 will complete follow-up visits every six months (±6 weeks) while their infants are on study.

Figure 7-4 lists visits expected to be conducted with mothers in Step 2. To further illustrate the maternal visit schedule, the figure also provides calendar dates for visits expected in the first four years for a sample mother enrolled in the study on 1 October 2019. Target dates for follow-up visits are counted from the date of study entry:

- For mothers enrolled in Cohort 1, the date of study entry is the day of enrollment in Step 1.
- For mothers enrolled in Cohort 2, the date of study entry is the day of enrollment in Step 2.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>1 APR 2020</td>
<td>19-FEB-2020 13-MAY-2020</td>
</tr>
<tr>
<td>Month 12</td>
<td>1 OCT 2020</td>
<td>20-AUG-2020 12-NOV-2020</td>
</tr>
<tr>
<td>Month 18</td>
<td>1 APR 2021</td>
<td>18-FEB-2021 13-MAY-2021</td>
</tr>
<tr>
<td>Month 24</td>
<td>1 OCT 2021</td>
<td>20-AUG-2021 12-NOV-2021</td>
</tr>
<tr>
<td>Month 36</td>
<td>1 APR 2022</td>
<td>18-FEB-2022 13-MAY-2022</td>
</tr>
<tr>
<td>Month 42</td>
<td>1 OCT 2022</td>
<td>20-AUG-2022 12-NOV-2022</td>
</tr>
<tr>
<td>Month 48</td>
<td>1 APR 2023</td>
<td>18-FEB-2023 13-MAY-2023</td>
</tr>
</tbody>
</table>

*Target visit dates are counted from the day of study entry. Day of entry = Day 0.

Each follow-up visit should ideally be conducted on the target date but may be conducted on any day within the allowable window, and study staff are encouraged to use the allowable window to schedule maternal visits on the same day as scheduled infant visits whenever possible. For example, the maternal Month 6 visit should ideally be conducted on the day of the infant Step 2 Week 24 visit.

The procedures listed below should be performed at each maternal follow-up visit. There is no specified ordering or required sequence for these procedures.

MATERNAL FOLLOW-UP PROCEDURES

- Collect targeted interval medical and medications history:
  - WHO clinical stage
  - ARV use
  - Documented CD4 cell counts
  - Documented HIV RNA results
  - Any other relevant history
- Provide HIV-related, infant feeding, and other applicable information and counseling as needed
- Provide referrals for HIV-related or other care and treatment as needed
- Schedule next visit, provide reminders for next visit, and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Enter required eCRFs
7.5 Infant Physical Examinations in Step 2

A physical examination is required for infants at the Step 2 Entry Visit and at most Step 2 follow-up visits. The only Step 2 visits at which an examination is not required are the follow-up visits permitted to be conducted by phone (i.e., at Weeks 28, 32, 40, 44, 52, 56, 64, and 68).

At Step 2 Entry, the examination should be performed prior to enrollment, as part of eligibility determination. Examination requirements are shown below; at any visit, additional evaluations may be performed at the discretion of the examining clinician.

<table>
<thead>
<tr>
<th>Step 2 Entry for Cohort 1 Infants</th>
<th>Step 2 Entry for Cohort 2 Infants and All Applicable Step 2 Follow-Up Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temperature</td>
<td>• Temperature</td>
</tr>
<tr>
<td>• Heart rate</td>
<td>• Heart rate</td>
</tr>
<tr>
<td>• Respiratory rate</td>
<td>• Respiratory rate</td>
</tr>
<tr>
<td>• Weight</td>
<td>• Weight</td>
</tr>
<tr>
<td>• Length</td>
<td>• Length</td>
</tr>
<tr>
<td>• Head circumference</td>
<td>• Head circumference</td>
</tr>
<tr>
<td>• Breath sounds</td>
<td>• Breath sounds</td>
</tr>
<tr>
<td>• Heart sounds</td>
<td>• Heart sounds</td>
</tr>
</tbody>
</table>
| • Examination of skin, head, mouth, neck, abdomen, and extremities | • Examination of body systems driven by prior and new signs, symptoms, and diagnoses  
  For Cohort 1 infants receiving Regimen 2RV, examination should include VRC01 injection sites when applicable (see Section 12 of this manual) |

Note: At Step 2 Entry for Cohort 2 infants, two sets of infant measurements should be recorded. Weight, length, and head circumference at birth are required as part of the baseline infant history, with data generally expected to be obtained from medical records. These same measurements are also required as part of the infant physical examination expected to be performed and documented by a study clinician at the Entry visit.

7.6 Infant Study Treatment in Step 2

Refer to protocol Section 5.1.2 for comprehensive information on Step 2 study treatment regimens. Under protocol Version 2.0, infants in Step 2 will receive one of three regimens:

- **Regimen 1L**: 2 NRTIs + NVP + LPV/r. This regimen will be continued under protocol Version 2.0 for Cohort 1 and Cohort 2 infants who initiated this regimen under protocol Version 1.0.

- **Regimen 2R**: 2 NRTIs + NVP + RAL. This regimen will be received by Cohort 1 and Cohort 2 infants enrolled under protocol Version 2.0.

- **Regimen 2RV**: 2 NRTIs + NVP + RAL + VRC01. This regimen will be received by Cohort 1 infants enrolled under protocol Version 2.0 at selected sites. See Section 12 of this manual for weight band dosing and preparation and administration instructions for VRC01.

NRTIs will be chosen by the site investigator and dosed according to WHO or individual country or local standard guidelines. For these agents, dosing should be adjusted based on a ≥10% increase in body weight or body surface area. For increases less than 10%, dose adjustments are permitted but not required.
LPV/r will be dosed per protocol.

NVP will be dosed per protocol. A dose of 6 mg/kg twice daily will be given from Step 2 Entry until the Step 2 Week 4 visit. Starting at the Step 2 Week 4 visit, dosing will switch to WHO weight band dosing or 200 mg/m² twice daily. Per protocol Section 6.3.2.3, use of NVP will be continued for each infant until 12 weeks after two consecutive HIV RNA results <LOD, at which time (12 weeks after the specimen collection date for the second consecutive test) NVP will be discontinued. Two examples of this are shown below.

Sample Case 1: Infant with HIV RNA levels <LOD at Step 2 Weeks 8 and 12.

This infant’s HIV RNA level would be considered confirmed <LOD upon receipt of the Week 12 test result.

Twelve weeks after Step 2 Week 12 falls at Step 2 Week 24. If the HIV RNA level remains <LOD at Weeks 16 and 20, NVP should be stopped for this infant at Step 2 Week 24.

Consultation with the CMC is not required in advance of this type of regimen change, because the change is consistent with protocol specifications. However, the CMC should be notified as soon as possible after the change occurs.

Sample Case 2: Infant with HIV RNA levels <LOD at Step 2 Weeks 12 and 16.

The infant’s HIV RNA level would be considered confirmed <LOD upon receipt of the Week 16 test result.

Twelve weeks after Step 2 Week 16 falls at Step 2 Week 28. If the HIV RNA level remains <LOD at Weeks 20 and 24, NVP should be stopped for this infant at Step 2 Week 28.

Although the SoE allows for the Step 2 Week 28 visit to be conducted as a phone contact, for this infant the visit should ideally be conducted in-person at the study clinic so that the regimen change can occur at that visit. If this is not possible, the regimen change should occur at the infant’s next in-person visit at the study clinic.

Consultation with the CMC is not required in advance of this type of regimen change, because the change is consistent with protocol specifications. However, the CMC should be notified as soon as possible after the change occurs.

RAL will be dosed per protocol. RAL granules for suspension will be used until infants reach four weeks of age and 3 kg body weight. Thereafter, RAL chewable/dispersible tablets will be used. These tablets may be chewed, swallowed whole, or dispersed in water, juice, breast milk or formula. It is generally expected that these tablets will be dispersed for infants in Step 2 until such time that they can chew and/or swallow the tablets. The remainder of this section provides further guidance on RAL dosing in Step 2.

IMPORTANT NOTES
- All study treatment agents must be provided by prescription from an authorized prescriber.
- New prescriptions are required as participants grow into the next dosing increment based on age, body weight, or body surface area.
- New prescriptions are also required for all formulation changes and for all doses of VRC01.
- All dosing changes should be implemented at an in-person visit, with provision of detailed dosing instructions and adherence counseling to the infant’s mother (or other applicable caregiver).
7.6.1 Weight Band Dosing and Caregiver Instructions for RAL

In the first four weeks of follow-up in Step 2, RAL dosing differs for Cohort 1 versus Cohort 2 and, for infants in Cohort 2, differs by age at entry into Step 2; refer to protocol Sections 5.1.2.2 and 5.1.2.3 for dosing details. Starting at Step 2 Week 4, all Step 2 infants will be receiving the same dose of RAL (6 mg/kg twice daily).

Figure 7-5 provides weight band dosing for RAL granules for suspension. This formulation should be used until infants reach four weeks of age and 3 kg body weight. Figure 7-6 provides caregiver instructions for preparing and administering RAL granules for suspension. Both figures correspond with the current package insert. Study sites are also encouraged to use the booklet entitled, ISENTRESS (raltegravir) for oral suspension instructions for use for babies and toddlers, which is posted on the study-specific web page, when providing instructions to caregivers, translating and explaining the instructions in local languages as needed to optimize caregiver understanding of correct dosing.

### Figure 7-5
Weight Band Dosing for RAL Granules for Suspension

<table>
<thead>
<tr>
<th>Infant Body Weight</th>
<th>Volume (Dose) of Suspension To be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg/kg Once Daily</td>
<td></td>
</tr>
<tr>
<td>2 to less than 3 kg</td>
<td>0.4 mL (4 mg) once daily</td>
</tr>
<tr>
<td>3 to less than 4 kg</td>
<td>0.5 mL (5 mg) once daily</td>
</tr>
<tr>
<td>4 to less than 5 kg</td>
<td>0.7 mL (7 mg) once daily</td>
</tr>
<tr>
<td>3.0 mg/kg Twice Daily</td>
<td></td>
</tr>
<tr>
<td>2 to less than 3 kg</td>
<td>0.8 mL (8 mg) twice daily</td>
</tr>
<tr>
<td>3 to less than 4 kg</td>
<td>1.0 mL (10 mg) twice daily</td>
</tr>
<tr>
<td>4 to less than 5 kg</td>
<td>1.5 mL (15 mg) twice daily</td>
</tr>
<tr>
<td>6.0 mg/kg Twice Daily</td>
<td></td>
</tr>
<tr>
<td>2 to less than 3 kg</td>
<td>1.6 mL (16 mg) twice daily</td>
</tr>
</tbody>
</table>

Source: Adapted from ISENTRESS package insert, Revised 01/2019

### Figure 7-6
Caregiver Instructions for Preparing and Administering RAL Granules for Suspension

Using the provided mixing cup, combine 10 mL of water and the entire contents of one packet of ISENTRESS for oral suspension and mix. Each single-use packet for oral suspension contains 100 mg of RAL which is suspended in 10 mL of water giving a final concentration of 10 mg per mL.

Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension. Do not shake.

Once mixed, measure the prescribed dose volume of suspension with a syringe and administer the dose orally. The dose should be administered orally within 30 minutes of mixing.

Discard any remaining suspension into the trash.

Source: Adapted from ISENTRESS package insert, Revised 01/2019
Figure 7-7 provides weight band dosing for RAL chewable/dispersible tablets. Infants may be switched to the chewable/dispersible tablet formulation once they have reached four weeks of age and 3 kg body weight. Children who have reached four weeks of age but weigh less than 3 kg should receive RAL granules for suspension at a dose of 6 mg/kg (as shown in Figure 7-5) and then switch to chewable/dispersible tablets once they weigh 3 kg.

### Figure 7-7
**Weight Band Dosing for RAL Chewable/Dispersible Tablets**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose</th>
<th>Tablets Per Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to less than 6 kg</td>
<td>25 mg</td>
<td>One 25 mg tablet</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>6 to less than 11 kg</td>
<td>50 mg</td>
<td>Two 25 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>11 to less than 14 kg</td>
<td>75 mg</td>
<td>Three 25 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>14 to less than 20 kg</td>
<td>100 mg</td>
<td>One 100 mg tablet</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>20 to less than 25 kg</td>
<td>150 mg</td>
<td>One-and-a-half 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
</tbody>
</table>

Source: Adapted from ISENTRESS package insert, Revised 01/2019

Directions for preparation and administration of the chewable/dispersible tablets are as follows:

- May be chewed or swallowed whole or dispersed
- Disperse in water, juice, breast milk, or formula
  - For 25 mg tablets: Place one, two, or three tablets in a small container for mixing and add approximately 5 mL (1 teaspoon) of liquid to the container
  - For 100 mg tablets: Place one or one-and-a-half tablets in a small container for mixing and add approximately 10 mL (2 teaspoons) of liquid to the container
- Wait for 2 minutes
- Crush the tablets in the liquid (e.g., with a spoon) if needed and stir until fully dispersed
- Within 30 minutes after dispersion, administer the liquid to the infant directly from the container or with a spoon or syringe
- Assure the infant swallows all of the liquid

When dispersing the chewable/dispersible tablets, caregivers may notice that the tablets may not dissolve completely. The mixture will usually have the appearance of a suspension that is opaque. Some particles that do not fully dissolve may be seen in the mixture. These particles typically contain inactive ingredients. Caregivers should not be concerned if the tablets do not fully dissolve, as long as the infant ingests the full dose of the mixed liquid.

### 7.6.2 Pharmacist Dispensing Instructions for RAL

The boxes of RAL granules supplied for this study contain granule packets, mixing cups, and syringes. Full boxes may be dispensed for infants in Cohort 2 until these infants switch to use of RAL chewable/dispersible tablets.

*Note:* Protocol Section 5.3.1 indicates that oral dispensers and push-in-bottle adapters are available from the NIAID Clinical Research Products Management Center for use with non-study-supplied ARVs. These supplies have been exhausted and are no longer available.
8.0 Counseling Considerations

This section provides guidance on the following types of counseling to be provided in P1115:

- HIV-related counseling
- Infant feeding counseling
- Antiretroviral adherence counseling

8.1 Counseling Overview

All counseling provided in P1115 should be provided per site SOPs, which should reflect all policies and guidelines that are applicable at each site. Site SOPs should be reviewed and updated at least once annually and following issuance of any updated policies and guidelines.

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 P1115 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 to determine whether the participant sought the services to which he or she was referred, the outcome of the referral, and 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.

8.2 HIV-Related Counseling

All sites will provide HIV-related counseling to all mothers throughout their participation in the study. This counseling will include:

- **Counseling in relation to maternal HIV testing:** Most mothers enrolled in P1115 will undergo diagnostic HIV testing as a study procedure to confirm their eligibility for study participation. All HIV testing must be performed in the context of pre-test and post-test counseling. All 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 mother at the time of the session.
• **Counseling in relation to infant HIV testing:** Most infants enrolled in P1115 will undergo diagnostic HIV testing as a study procedure. At each testing time point, pre-test counseling should be provided to the infant’s mother and test results should be provided to the mother in the context of post-test counseling. All pre-test and post-test counseling should be provided per site SOPs in a client-centered manner. When infants test positive for HIV infection, mothers may require additional post-test counseling to support their understanding and coping with the test results. All sites should offer additional counseling sessions in response to such needs.

• **Counseling in relation to risk reduction:** For this study, the term risk reduction counseling refers to counseling provided to support mothers in reducing the risk of secondary transmission of HIV to others (for themselves and their infants, if applicable). 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 to all mothers throughout their 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 mother. 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 mother. When applicable, mothers should be counseled on the benefits of HIV counseling and testing for couples and study sites should offer counseling and testing for partners whenever possible. “Treatment as prevention” and “U=U” messages should be provided when consistent with local policies and guidelines.

8.3 **Infant Feeding Counseling**

All sites will provide infant feeding counseling to all mothers throughout their participation in the study. Consistent with international guidelines, infant feeding counseling should:

• Provide mothers with information about the risks and benefits of various infant feeding options
• Guide mothers in choosing the infant feeding option that is most suitable for their situation
• Support mothers in implementing the method they choose by helping them carry it out safely and effectively

P1115 will be conducted in a variety of settings worldwide. In some settings, country-specific infant feeding guidelines encourage breastfeeding among HIV-infected mothers; in others, country-specific guidelines encourage formula feeding. All sites are expected to follow applicable policies and guidelines. All counseling should be provided per site SOPs and in a client-centered manner, responding to needs for information, guidance, and support that may change over time. Counseling should also be guided by information available from infant clinical assessments, which will monitor growth and weight gain over time.

8.4 **Antiretroviral Adherence Counseling**

All sites will provide adherence counseling to all mothers at all study visits during periods of follow-up when their infants are on ARVs.

The purpose of adherence counseling is to provide information, skills building, and other guidance to support mothers in administering ARVs to their infants, as correctly and consistently as possible. While it is essential that mothers be provided information on correct use of each medication, once this knowledge is established, the emphasis of adherence counseling should be on supporting the mother in consistent use of the medications 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.

Counseling should acknowledge that consistent use of ARVs can be challenging and should encourage mothers 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 mother 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 — clinic and pharmacy as indicated — to:
  - Identify whether the infant is on ARVs and, if so, for how long; whether the infant has experienced ARV side effects; whether the infant has achieved and/or sustained viral suppression; and whether adherence challenges have been encountered to date.
  - Review the adherence strategies that have been identified for the mother-infant pair to date and which of these have been perceived as successful or unsuccessful by the mother; pay particular attention to adherence strategies identified at the last counseling session.

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

- Greet the mother by name, establish rapport, and foster open dialogue. Reinforce confidentiality and explain that the purpose of the session is solely to assist the mother with administration of ARVs to her infant.

- Understand that the mother is likely to be concerned about HIV-related issues for herself and her infant, in the short and/or long terms. Adopt a neutral and non-judgmental but supportive approach to assist the mother in coping with these concerns in relation to adherence to the infant’s ARV regimen.

- Invite the mother to ask any questions and express any concerns she 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 mother’s understanding of instructions for correct dosing of each ARV, paying particular attention to this issue at times of formulation change and/or dose adjustment as the infant ages and grows. Ask the mother to describe or demonstrate how she administers each ARV to the infant to confirm correct dosing.

- As needed, provide reminders to not share the infant’s ARVs and to administer full doses; provide further reminders to not stop administering ARVs (e.g., if a child becomes sick) unless instructed otherwise by study clinicians.

- It is particularly important to proactively address alternative caregiver issues and the need for caregivers to provide ARVs to the infant correctly and consistently at times when the mother is not available (e.g., due to travel or work responsibilities). This may involve information, education, and counseling related to disclosure, social support, and potential stigma.
– Disclosure is strongly linked to adherence. Ask to whom the mother has disclosed her and/or her infant’s HIV status and if there are barriers to disclosure in the family or household. Discuss ways in which this can be addressed. If the mother travels, are family members aware of the need for ARVs? Can the mother safely take her own ARVs? Can the mother safely give ARVs to the child? If not, discuss strategies for the mother to consider.

– Does the mother have a treatment buddy or belong to a support group? If not, discuss how she can access a group or other similar support.

• Use open-ended questions and actively listen to the mother’s responses to assess her experience with adherence since her last visit.

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

• Provide positive reinforcement for adherence successes. Ask the mother to share more information on successful strategies so that her approaches can be shared with other study participants. Continue successful strategies as part of the mother’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 dialogue, assess whether the reminder and adherence strategies discussed at the previous session were perceived by the mother as useful/successful. As needed, assist the mother with identifying new strategies to try to address new or ongoing barriers.

• As needed, provide skills building support to the mother (e.g., on proper use of oral study drug dispensers; on disclosure of HIV status and/or study participation to others).

• At each session, clearly articulate the adherence plans and strategies identified by the mother for the time period between the current session and the next session. All plans and strategies should be practical and feasible for the mother. For mothers with significant adherence barriers, plans and strategies may need to be incremental. For mothers 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 mother, if desired. Routinely review and update locator details and consider use of interim contacts between scheduled visits to inquire about and follow-up on adherence issues (especially for mothers with adherence challenges).

• Thank the mother for her and her infant’s participation in the study and for her efforts in administering study drugs to her infant. Acknowledge the contribution she is making toward the care of her infant and determining the best approaches to treating infants who have HIV.
9.0 Clinical Considerations

This section provides information on selected clinical considerations for mothers and infants. Maternal considerations are provided in Sections 9.1 and 9.2. Infant considerations are provided in Sections 9.3-9.8.

Note: In this section, reference is made to eCRFs that may be completed at various study visits. These references are not intended to be comprehensive or all-inclusive. Always refer to the eCRF Completion Guide to determine eCRF requirements for each visit.

9.1 Maternal Medical and Medications History

Complete medical histories are not required for mothers. Rather, targeted histories are expected at study entry (baseline) and at each follow-up visit (interval).

A targeted baseline medical and medications history is required at maternal study entry. The purpose of this history is two-fold: to assess and document eligibility and to document key aspects of the mother’s clinical condition as she enters the study.

Eligibility determination will require assessment of maternal age, prior HIV testing, and ARV use during the current pregnancy. In addition, the maternal SoE requires assessment of the following as part of the baseline history:

<table>
<thead>
<tr>
<th>Baseline Maternal History Element</th>
<th>Corresponding eCRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of HIV infection</td>
<td>LBW0178</td>
</tr>
<tr>
<td>WHO clinical staging</td>
<td>PE0043</td>
</tr>
<tr>
<td>ARV use (all ARVs taken prior to study entry)</td>
<td>PE0421</td>
</tr>
<tr>
<td>CD4 cell counts within the last year*</td>
<td>HXW0187</td>
</tr>
<tr>
<td>HIV RNA results within the last year*</td>
<td>HXW0187</td>
</tr>
<tr>
<td>Obstetrical history including prior pregnancies and mode of delivery for the current pregnancy</td>
<td>EVW0326</td>
</tr>
<tr>
<td>Syphilis in the current pregnancy*</td>
<td>PE6852</td>
</tr>
<tr>
<td>Active hepatitis at the time of study entry*</td>
<td>PE6852</td>
</tr>
</tbody>
</table>

A targeted interval medical and medications history is required at each maternal follow-up visit, with assessment of the following:

<table>
<thead>
<tr>
<th>Interval Maternal History Element</th>
<th>Corresponding eCRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO clinical staging (any changes since the last visit)</td>
<td>PE0043</td>
</tr>
<tr>
<td>ARV use (all ARVs taken since the last visit)</td>
<td>PE0421</td>
</tr>
<tr>
<td>CD4 cell counts since the last visit*</td>
<td>LBW0054</td>
</tr>
<tr>
<td>HIV RNA results since the last visit*</td>
<td>LBW0178</td>
</tr>
</tbody>
</table>

At baseline and at follow-up, maternal history should be assessed and source documented based on review of available medical records and maternal report. However, the elements denoted in the tables above with an asterisk (*) should be entered into eCRFs based only on medical record documentation. All available medical records — or certified copies thereof — should be retained in participant study records, along with source documentation of self-reported maternal history. At baseline, depending on the number and type of HIV test results available to document maternal HIV infection, multiple copies of the LBW0178 eCRF may be required.
9.2 Referral to Non-Study Sources of HIV Care and Treatment

Mothers enrolled in P1115 are expected to require referrals to non-study sources of HIV-related care and treatment. As soon as possible after enrollment, active referrals should be made to establish the mother in care, consistent with local HIV treatment and prevention of perinatal transmission policies and guidelines.

All referrals should be documented in participant study charts and should be actively followed-up to determine whether the mother sought the services to which she was referred, the outcome of the referral, and whether additional referrals are needed. Follow-up should occur at scheduled maternal and infant visits, as well as by telephone or other contact between visits. Given that mothers may not have been engaged in care prior to their pregnancy, it is expected that repeated follow-up, along with additional information and counseling, may be needed to help ensure that mothers access services that may be beneficial to them and their infants.

9.3 Infant Medical and Medications History

Complete medical histories are required for infants.

9.3.1 Baseline Medical and Medications History

A **baseline** medical and medications history is required at infant study entry. The purpose of this history is two-fold: to assess and document eligibility and to document the infant’s clinical condition as he or she enters the study. The baseline history serves to document pre-existing conditions for comparison with conditions that may be identified during follow-up; as such, a detailed and comprehensive history should be obtained and documented.

Eligibility determination will require assessment of infant age (hours and/or days since birth); gestational age at birth; HIV testing since birth, ARVs taken since birth; ability to take ARVs by mouth, nasogastric tube, or gastrostomy tube; and clinical condition, including any clinically significant diseases or findings. See the FAQs in Sections 6.3.4 and 7.3.3 for operational guidance on documentation of date and time of birth and gestational age at birth for this study.

In addition, the infant SoE requires assessment of the following as part of the baseline history:

<table>
<thead>
<tr>
<th>Baseline Infant History Element</th>
<th>Corresponding eCRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex and race/ethnicity</td>
<td>Subject Enrollment System</td>
</tr>
<tr>
<td>Gestational age at birth*</td>
<td>DMW0021</td>
</tr>
<tr>
<td>Weight, length, and head circumference at birth*</td>
<td>PE0034</td>
</tr>
<tr>
<td>Clinical history since birth</td>
<td>PE6832, PE6852</td>
</tr>
<tr>
<td>ARVs taken since birth</td>
<td>TXW0312</td>
</tr>
<tr>
<td>Concomitant medications taken since birth</td>
<td>PE0412</td>
</tr>
<tr>
<td>Interventions for hyperbilirubinemia since birth</td>
<td>PE0412</td>
</tr>
<tr>
<td>Feeding method since birth</td>
<td>QLW0251</td>
</tr>
<tr>
<td>HIV NATs since birth</td>
<td>LBW0177 or LBW0178</td>
</tr>
</tbody>
</table>

*Note:* Weight, length, and head circumference at birth are required as part of the baseline infant history, with data to be entered into the PE0034 eCRF. These same measurements are also required as part of the infant physical examination performed on the day of study entry (see Sections 6.7 and 7.5 of this manual). The at entry measurements will also be entered into a PE0034 eCRF, thereby resulting in two copies of this eCRF being completed at entry (one with at birth measurements and the other with at entry measurements).
Infant baseline history should be assessed and source documented based on review of available medical records and maternal report. However, the elements denoted in the table above with an asterisk (*) should be entered into eCRFs based only on medical records documentation. All available medical records — or certified copies thereof — should be retained in participant study records, along with source documentation of maternal-reported history.

For all clinical conditions identified, source documentation should include a detailed clinical description, onset date, severity grade (per protocol Section 7.3), resolution date (if applicable), and all other relevant details. The following signs, symptoms, and diagnoses should be entered into eCRFs:

- **In Step 1**, all Grade 2 and higher signs and symptoms
- **In Steps 2, 3, and 4**, all Grade 3 and higher signs and symptoms
- All signs and symptoms — regardless of grade — that lead to any change of any ARV
- All diagnoses

All ARVs and all concomitant medications taken since birth should be recorded in source documents and on eCRFs (with associated start and stop dates). This includes all prescription and non-prescription medications; vaccinations and other preventative medications; nutritional supplements; and alternative, complementary, and traditional medications and preparations.

In addition to the above, all documented HIV NATs since birth, including tests performed outside of the study prior to study entry, should be entered into eCRFs. Quantitative HIV RNA tests should be entered into the LBW0178 eCRF. Qualitative tests, including HIV DNA tests, should be entered into the LBW0177 eCRF. One eCRF should be completed for each test since birth.

### 9.3.2 Follow-up Medical and Medications History

An **interval** medical and medications history is required at all infant follow-up visits except the Step 1 Week 12 visit, with assessment of the following:

<table>
<thead>
<tr>
<th>Interval Infant History Element</th>
<th>Corresponding eCRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history since the last visit (signs, symptoms, diagnoses)</td>
<td>PE6832</td>
</tr>
<tr>
<td>ARVs taken since the last visit</td>
<td>PE6852</td>
</tr>
<tr>
<td>Concomitant medications taken since the last visit</td>
<td>TXW0312</td>
</tr>
<tr>
<td>Interventions for hyperbilirubinemia since the last visit</td>
<td>PE0412</td>
</tr>
<tr>
<td>Feeding method since the last visit</td>
<td>QLW0251</td>
</tr>
<tr>
<td>HIV NATs since the last visit</td>
<td>LBW0177 or LBW0178</td>
</tr>
</tbody>
</table>

The interval history serves to document whether previously identified conditions remain ongoing and to determine whether any new conditions have occurred since the last history was obtained. While it is expected that interval histories will often be documented based on maternal report, study clinicians should also review all available infant medical records to supplement maternal reports. To help ensure the accuracy of medical and medications history documentation, remind mothers to bring all available medical records and all medications to all study visits.

**Note:** The CMC must be consulted as soon as possible and within two business days of any decision to hold or permanently discontinue any ARV at any time during follow-up.
At the Step 1 Week 12 visit, only HIV testing history is required. All HIV NATs performed outside of the study since the Week 4 visit should be source documented and entered into eCRFs. The HIV NAT performed at Step 1 Week 12 per protocol should also be source documented and entered into eCRFs. Quantitative HIV RNA tests should be entered into the LBW0178 eCRF. Qualitative tests, including HIV DNA tests, should be entered into the LBW0177 eCRF. One eCRF should be completed for each test.

In preparation for each interval history, study clinicians should review the infant’s prior history documentation for reference. When performing each interval history, it is not necessary to actively review or inquire about every body system. Rather, clinicians may adopt a more targeted approach of (i) asking about the current status of all conditions that were ongoing at the time of the last history, and then (ii) asking an open-ended question such as “Has the child had any other symptoms or health problems since your last visit?” to complete the interval history.

In addition to the above, all medications — ARVs and all concomitant medications — should be reviewed as part of each interval history. Study clinicians should reference the infant’s prior medications history documentation and ask whether he or she (i) is still taking each medication reported at the time of the last history, at the same dose and frequency, and (ii) has taken any new medications since the time of the last history. To further probe for updates, if the mother reports any symptoms/illnesses/conditions, ask whether the infant took any medications for those.

All new medical and medications history information should be documented:

- For previously reported conditions that have resolved at the time of the current visit, source documentation should include the date of resolution and all other relevant clinical details.
- For previously reported conditions that remain ongoing at the time of the current visit, source documentation should include the current severity grade and all other relevant clinical details.
- For newly identified conditions, source documentation should include a detailed clinical description, onset date, severity grade (per protocol Section 7.3), resolution date (if applicable), and all other relevant details. The assessed relationship to each ARV the infant is taking (or has taken previously while on study) and to VRC01, if applicable, must also be documented (per protocol Section 6.0).

Infant interval history should be assessed and source documented based on review of available medical records and maternal report. All available medical records — or certified copies thereof — should be retained in participant study records, along with source documentation of maternal-reported history. All clinical history should be recorded in source documents and the following signs, symptoms, and diagnoses should be reported on eCRFs:

- **In Step 1**, all Grade 2 and higher signs and symptoms
- **In Steps 2, 3, and 4**, all Grade 3 and higher signs and symptoms
- All signs and symptoms — regardless of grade — that lead to any change of any ARV
- All diagnoses

Event Evaluation (PE6865) eCRFs must also be completed for the following types of events:

- Grade 3 or higher chemistry and hematology results, signs, symptoms, and diagnoses
- Chemistry and hematology results, signs, symptoms, and diagnoses that lead to a change of ARV regimen, regardless of severity grade
- Chemistry and hematology results, signs, symptoms, and diagnoses that meet the ICH GCP definition of serious (see Section 10.1), regardless of severity grade
- Chemistry and hematology results, signs, symptoms, and diagnoses that meet protocol criteria for EAE reporting (see Section 10.3), regardless of severity grade
All ARVs and all concomitant medications — including vaccinations — should be recorded in source documents and on eCRFs (with associated start and stop dates). Mothers should be counseled to avoid use of traditional medications and preparations while their infants are on study. In addition, protocol Section 4.7 includes a listing of concomitant medications that should not be co-administered with study treatment agents. Refer to this listing as needed when reviewing and/or prescribing medications at each infant visit and consult the CMC as needed with respect to precautionary and prohibited medications.

9.3.3 Frequently Asked Questions Related to Infant Medications

<table>
<thead>
<tr>
<th>Q1: Protocol Section 4.7 lists corticosteroids among the medications that should not be co-administered with LPV/r. Does this include topical steroids?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: No. The P1115 CMC has confirmed that the intent of this specification in the protocol was to refer to systemic corticosteroids.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2: Protocol Section 4.7 states that the CMC should be consulted regarding any infant who requires rifampin-containing TB treatment. At our site, when a child is identified as co-infected with TB, we typically initiate TB treatment immediately, with ARV regimen modifications as needed. Are we required to obtain approval from the CMC before initiating TB treatment and/or changing ARV regimens due to TB treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2: No. The P1115 CMC has confirmed that you may initiate TB treatment and any associated ARV regimen changes immediately upon identification of the need for TB treatment. You must, however, inform the CMC as soon as possible: ideally on the same day and in all cases within two business days. The CMC will then provide any further guidance that may be applicable on a case-by-case basis. See Section 9.8 of this manual for more information on TB treatment and modification of ARV regimens due to TB treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3: At our site, the local standard of care for treatment of HIV-infected infants involves switching from zidovudine to abacavir at approximately three months of age. Can we follow this standard of care for our participants? Is consultation with the CMC required for each case?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3: Yes, you can follow this standard of care for infants in P1115 at your site. It is not necessary to consult the CMC in advance for each case. However, you must inform the CMC about the regimen change within two business days of implementing the change.</td>
</tr>
</tbody>
</table>

9.4 Infant Physical Examinations

Physical examinations are required at entry and throughout infant follow-up in P1115. See Sections 6.7 and 7.5 of this manual for examination requirements.

All exam findings should be source documented; abnormal findings should be graded for severity (per protocol Section 7.3) and assessed for relationship to each ARV the infant is taking (or has taken previously while on study) and to VRC01 if applicable (per protocol Section 6.0). Vital signs and measurements will be entered into the Detailed Pediatric Vital Signs (PE0034) eCRF. Exam findings may also be entered into other eCRFs, e.g., Signs and Symptoms (PE6832), if required per the form instructions.
9.5 Infant Virologic Monitoring: HIV RNA

For infants in Steps 2, 3, and 4, HIV RNA (viral load) testing will be performed frequently throughout follow-up. The results of this testing are the primary study endpoints and are essential for infant monitoring and management throughout follow-up. As such, all testing must be performed in a CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory.

In Steps 1, 2, and 4, standard quantitative HIV RNA assays are performed. Dilution of specimens used for these assays should be avoided whenever possible and should not occur at or after Step 2 Week 24:

- Prior to Step 2 Week 24, when dilution is necessary, a validated diluent must be used (1:5) and the LOD of the assay must be adjusted accordingly. Refer to the LPC for more information on dilution requirements.
- At and after Step 2 Week 24, if an adequate sample volume cannot be collected at a given study visit, the infant should return to the clinic on a different day within the allowable visit window for a repeat specimen collection attempt.

In Step 3, HIV RNA testing is required at all scheduled visits. A standard quantitative HIV RNA assay is performed at Step 3 Entry. At each timepoint thereafter, testing will first be performed using an on-demand assay with a 1:2 dilution. Further guidance on testing in Step 3 is provided on pages 79-80.

All sites should refer to the LPC for more information on assay and dilution requirements. US sites should also refer to Section 11.2 of this manual for information on use of a central laboratory to perform diluted HIV RNA assays if needed.

The results of all HIV RNA testing should be source documented in participant study charts. Throughout the P1115 protocol, reference is made to ideally maintaining infant HIV RNA levels below the LOD of the PCR assay. All study site laboratories should report HIV RNA results as either below the LOD of the assay or as the number of HIV RNA copies detected at or above the LOD of the assay. When results are reported as below the LOD of the assay, the result report must also indicate whether HIV RNA was detected or not detected. Any questions about this should be directed to the P1115 Questions Group, which includes representatives of the IMPAACT Laboratory Center. Each site IoR is responsible for ensuring that local laboratories report results as required for this study; each IoR is also responsible for ensuring that study clinicians and others involved in receipt, review, and/or interpretation of HIV RNA result reports are adequately trained for this critical role for this study.

At each testing time point, an HIV RNA Plasma Viral Load (LBW0178) eCRF should be completed to document specimen collection for the test. For tests performed in LDMS laboratories, items 3-7 on the LBW0178 eCRF will be skipped; test results and other applicable details will be transmitted to the DMC via LDMS. For tests performed in non-LDMS laboratories, results must be entered in item 6 of the LBW0178 eCRF as follows:

- When results are at or above the lower LOD of the assay, but below the upper LOD of the assay, the number of copies detected should be entered in the RNA Plasma Viral Load boxes and “Equal to (=)” should be selected as the Quantifier Code.
- When results are below the lower LOD of the assay, the lower LOD should be entered in the RNA Plasma Viral Load boxes and “Less than (<)” should be selected as the Quantifier Code.
- When results are above the upper LOD of the assay, the upper LOD should be entered in the RNA Plasma Viral Load boxes and “Greater than (>)” should be selected as the Quantifier Code.
Results from each test and trends over time should be reviewed by a study clinician as soon as results are available following each visit. Sites are encouraged to use flow sheets or other tools (see sample in Appendix I of this manual) to ensure that trends over time are easily discernible and available for review at any time during follow-up; the Participant Data Reports program, available on the Data Management Center portal, can also be used for this purpose.

Key considerations for virologic monitoring and associated infant management in Steps 2, 3 and 4 are as follows:

- **Following entry into Step 2, in which infants will receive ART (with VRC01 at selected sites).** up to but excluding Week 48, HIV RNA testing (standard quantitative assay) is required at Weeks 2, 4, 9, 12, 16, 20, 24, and 36. Starting at Week 24, any HIV RNA value ≥200 copies/mL must be repeated as soon as possible and within three weeks (specimen collection for the confirmatory test must occur within three weeks of specimen collection for the initial test; see example below). If the confirmatory test confirms the initial result, or if specimen collection for the confirmatory test cannot be completed within three weeks, the infant will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192. If the confirmatory test result is less than 200 copies/mL, the infant will remain potentially eligible for Step 3.

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<thead>
<tr>
<th>NOVEMBER 2019</th>
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<tbody>
<tr>
<td>3</td>
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<tr>
<td>10</td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td>24</td>
</tr>
</tbody>
</table>

At and after Week 48 in Step 2, while infants continue to receive ART. HIV RNA testing (standard quantitative assay) is required at all scheduled visits, i.e., every 12 weeks. Starting at Week 48:

- If no HIV RNA is detected, the infant will remain potentially eligible for Step 3.
- If any HIV RNA is detected, even if below the LOD of the assay, the infant will be considered ineligible for Step 3 but will remain on-study through Step 2 Week 192.

- **Following entry into Step 3, in which infants will stop ART,** HIV RNA testing is required at all scheduled visits, i.e., Weeks 1, 2, 3, 4, 6, and 8, and every four weeks thereafter. The intensive frequency of virologic monitoring in this step is critical for both infant management and for ascertainment of the primary study outcome, HIV remission, which is defined as no confirmed plasma HIV RNA at or above the LOD of the assay for 48 weeks following ART cessation.

To minimize blood draw volumes and testing turnaround time, HIV RNA testing at each timepoint will first be performed using an on-demand assay. This assay must be performed in a VQA-certified laboratory with a VQA-approved 1:2 dilution scheme. Refer to the LPC for further information on assay and dilution requirements.
If an on-demand assay yields a positive result, i.e., any detectable HIV RNA, an additional specimen must be collected as soon as possible and within 72 hours for a standard quantitative HIV RNA assay performed at the local CLIA-certified (US sites) or VQA-certified (non-US sites) laboratory. The standard quantitative HIV RNA assay should be performed such that results are available as soon as possible and within 96 hours of specimen collection (any residual samples should be stored for additional testing if needed). Clinical management will be based on the result of the standard quantitative assay; children with HIV RNA at or above the LOD of the standard quantitative assay will enter Step 4 and re-initiate ART.

- **Following entry into Step 4, in which infants will resume ART**, HIV RNA testing is required at Weeks 2, 4, 6, 8, 10, 12, and 24, and every 12 weeks thereafter. For infants whose viral load is not suppressed below the LOD of the assay by Week 12, HIV RNA testing is additionally required every four weeks until suppression below the LOD is achieved. At Weeks 10 and 12, if the viral load from the previous visit is greater than 1000 copies/mL, blood should be collected for ARV resistance testing (if done at Week 10, do not repeat at Week 12). This testing should be performed at local laboratories when possible; otherwise, the blood sample should be shipped in real time for testing at a designated regional or central laboratory.

### 9.6 Infant Immunologic Monitoring: CD4 Cell Count and Percentage

For infants in Steps 2, 3, and 4, CD4 cell counts are performed approximately every 12 weeks. The absolute value, percentage, and trend of results over time should be reviewed by a study clinician as soon as results are available following each visit. Sites are encouraged to use flow sheets or other tools (see sample in Appendix I of this manual) to ensure that trends over time are easily discernible and available for review at any time during follow-up; the Participant Data Reports program, available on the Data Management Center portal, can also be used for this purpose. Values should be assessed in relation to thresholds of clinical significance and in relation to normal ranges for infants and children. All results of concern and/or indications of unexpected downward trends should be discussed with the CMC.

In addition to the above, infant CD4 cell count and percentage must be assessed as part of eligibility determination for entry into Step 3. In order for an infant to be eligible for Step 3, his or her CD4 cell percentage must be greater than or equal to 25, and his or her CD4 cell absolute count must be greater than or equal to the lower limit of normal for age.

All CD4 count test results should be source documented in participant study records and entered into the Lymphocyte Subsets (LBW0054) eCRF.

### 9.7 Safety Monitoring and Clinical Management

Site IORs and other delegated study clinicians are responsible for monitoring participant safety and managing potential toxicities in accordance with protocol Sections 6.0, 6.1, and 6.2. These protocol sections were developed with two aims: to maximize participant safety and to minimize unnecessary interruptions of ARVs that could undermine the primary aim of the study. Consistent with this approach, **any decision to hold or permanently discontinue any ARV at any time in this study requires consultation with the CMC**. To minimize ARV interruptions, single suspect ARVs can be held for up to three days while continuing the remainder of the ARV regimen; the CMC should be contacted as soon as possible and within two business days to assist with decisions on holding the entire ARV regimen or permanent discontinuation or substitution of individual ARVs.

Protocol Section 6.1 provides general guidance on toxicity management. Protocol Section 6.2 provides specific guidance on management of anemia and neutropenia, rash, asymptomatic elevated AST or ALT, symptomatic hepatitis, and hyperbilirubinemia. Protocol Section 6.2 also provides guidance on reactogenicity monitoring for infants receiving VRC01 and guidance on managing
injection site reactions, urticaria or other hypersensitivity reaction, serum sickness, and elevated creatinine. These specifications must be followed for adverse events that:

- Occur between study entry and Step 2 Week 36 and
- Are assessed as possibly, probably, or definitely related to one or more ARVs or VRC01

All other adverse events should be managed by site IoRs and other delegated study clinicians consistent with standards of care for pediatric clinical care and ARV management. Similarly, adverse events assessed as related to concomitant medications (other than ARVs or VRC01) should be managed consistent with local standards of care. All adverse events must be followed to resolution or stabilization. See Section 10 of this manual for more information on adverse events and expedited reporting of adverse events for this study.

9.8 ARV Management for Infants with Tuberculosis

Infants who develop tuberculosis (TB) should be treated for TB consistent with local standards of care. Study sites are encouraged to prescribe and dispense anti-TB medications for study infants whenever possible; however, infants may be referred to other local sources of TB care and treatment if necessary.

Infants who develop TB may change ARV regimens to allow use of rifampin, in consultation with the CMC. Site clinicians need not consult the CMC prior to changing ARV regimens if this would delay initiation of TB treatment; however, the CMC should be consulted immediately thereafter to discuss preferred ARV and TB treatment regimens. Appendix II provides additional information on treatment of TB in P1115.

Given that anti-TB medications can cause hepatic, hematologic, and skin toxicities, the CMC should also be consulted on management of potential toxicities that occur among infants being co-treated for TB and HIV.

Infants will remain on study regardless of TB treatment or any associated change of ARV regimen. Infants who develop TB in Step 2 will remain potentially eligible for entry into Step 3. However, TB treatment should be completed before considering entry into Step 3.
10.0 Expedited Adverse Event Reporting to DAIDS

This section presents information related to expedited adverse event reporting in P1115. Also refer to Section 7 of the P1115 protocol and the following resources:

- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, January 2010

- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, July 2017
  https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

- Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events
  protocol Appendix III

- Severity grading for axillary measured fever and injection site pain/tenderness
  protocol Section 7.3

- Package inserts for RAL (Isentress), LPV/r (Kaletra), and NVP (Viramune)
  https://rsc.niaid.nih.gov/clinical-research-sites/pi-list

- Investigator’s brochure for VRC01
  available through the NIAID Clinical Research Management System

- Other safety training and resources
  https://rsc.niaid.nih.gov/clinical-research-sites/safety-training-resources

10.1 Selected Definitions

Key definitions associated with expedited adverse event reporting in P1115 are provided below. Refer to the Manual for Expedited Reporting of Adverse Events to DAIDS for additional terms and definitions.

**Adverse event (AE)**

Any untoward medical occurrence in a clinical research participant administered a study agent and which does not necessarily have a causal relationship with the study agent. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study agent, whether or not considered related to the study agent (ICH E2A).

This definition is applied to infants enrolled in P1115 beginning at entry into the study (i.e., enrollment in Cohort 1 or Cohort 2). Medical conditions, illnesses, problems, signs, symptoms, and findings identified before entry are considered pre-existing conditions. If a pre-existing condition worsens (increases in severity or frequency) after entry into the study, the worsened condition is considered an adverse event. If a pre-existing condition resolves after entry into the study, but then recurs at a later date, the recurrence is considered an adverse event.

The term study agent refers to each of the ARVs an infant receives as part of the study regimen, as well as VRC01 if applicable (i.e., if the infant received Regimen 2RV).
All adverse events occurring among infants enrolled in P1115 must be source documented in participant study charts, including the documented assessment of the IoR or designee of the severity of the event (see Section 10.2) and its relationship to each study agent (see Section 10.4).

**Serious AE (SAE)**

An adverse event that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above should usually be considered serious (ICH E6 and E2A).

In consultation with the DAIDS Safety Team, it has been determined that congenital anomalies identified in study infants should not be reported as EAEs in P1115, because any such anomalies would have occurred prior to study entry. Similarly, congenital infections (e.g., congenital syphilis), which may prolong hospitalization of a newborn infant, should not be reported as EAEs, because any such infections would have occurred prior to study entry.

Per protocol Section 7.2, the following adverse events should be considered serious should they occur among infants enrolled in P1115:

- Grade 3 or 4 rash/cutaneous toxicity
- Grade 4 asymptomatic hepatic toxicity
- Grade 3 or 4 symptomatic hepatic toxicity
- Grade 3 or higher serum sickness
- Grade 3 or higher urticarial or other hypersensitivity reactions
- Grade 4 injection site reactions
- All malignancies
- All IRIS events

**SUSAR**

Suspected unexpected serious adverse drug reaction

SUSARs are SAEs that are assessed as both suspected and unexpected:

- **Suspected** = related ⇒ there is a reasonable possibility that an adverse event may be related to a study agent
- **Unexpected** ⇒ the nature or severity of an adverse event is not consistent with a study current package insert or investigator’s brochure

As indicated in the definitions above, and as shown in Figure 10-1, SAEs are a subset of all AEs, and SUSARs are a subset of all SAEs.
**Adverse Event, Serious Adverse Event, and SUSAR Subsets**

**Expedited AE (EAE)**  
An adverse event that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office

**10.2 Adverse Event Severity**

The term severity refers to the intensity of an adverse event. All adverse events occurring among infants enrolled in P1115 must be assessed for severity per protocol Section 7.3.

**10.3 Adverse Events that Meet Protocol Criteria for Expedited Reporting (EAEs)**

No EAE reporting is required for mothers in P1115. For infants, EAE reporting is required as follows:

- **Between the date of study entry and the date of the Step 2 Week 36 visit**, all SAEs must be reported as EAEs. During this timeframe, all SAEs must be reported as EAEs regardless of assessed relationship to any study agent the infant has received.

  For infants in Step 1, under protocol Version 2.0, the EAE reporting period at the SAE Reporting Category ends on the date of the Step 1 Week 4 visit. Under Letter of Amendment #1, this reporting period is extended to the date of the Step 1 Week 12 visit.

- **After the date of the Step 2 Week 36 visit**, SUSARs must be reported as EAEs. During this timeframe, which includes subsequent follow-up in Step 2 as well as all follow-up in Step 3 and Step 4, only SAEs assessed as unexpected and related to NVP, LPV/r, RAL, and/or VRC01 must be reported as EAEs.

  See Section 10.4 of this manual for more information on relationship assessment.
10.4 **Adverse Event Relationship Assessment**

For purposes of *clinical management* — as specified in protocol Sections 6.0, 6.1, and 6.2 — the IoR or designee must assess the relationship of all adverse events to each applicable study agent according to the categories shown in Figure 10-2 (copied from protocol Section 6.0). These relationship categories are also used when recording adverse events on eCRFs.

### Figure 10-2
**Relationship Assessment Categories for Clinical Management**

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td>The event and administration of the study agent are related in time, and a direct association can be demonstrated.</td>
</tr>
<tr>
<td>Probably related</td>
<td>The event and administration of the study agent are reasonably related in time, and the event is more likely explained by the study agent than other causes.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>The event and administration of the study agent are reasonably related in time, and the event can be explained equally well by causes other than the study agent.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>A potential relationship between the event and the study agent could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the study agent.</td>
</tr>
<tr>
<td>Not related</td>
<td>The event is clearly explained by another cause not related to the study agent.</td>
</tr>
</tbody>
</table>

For purposes of *EAE reporting*, the IoR or designee must report the relationship of EAEs to each applicable study agent according to the categories shown in Figure 10-3.

### Figure 10-3
**Relationship Assessment Categories for EAE Reporting**

<table>
<thead>
<tr>
<th>Relationship Category</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Related               | There is a **reasonable possibility** that the EAE may be related to a study agent. Consistent with ICH guidance, the term “reasonable possibility” is intended to convey that there are facts, evidence, or arguments to suggest a causal relationship between the EAE and a study agent. Facts, evidence, and arguments that may support a reasonable possibility of a causal relationship include:  
  - A temporal relationship between the EAE and use of the agent  
  - A plausible biologic mechanism for the agent to cause the EAE  
  - Previous reports of similar events associated with the agent (or agents of the same class)  
  - Resolution of the event after de-challenge (hold/discontinuation of agent)  
  - Recurrence of the event after re-challenge (resumption of agent after a hold)  
  Other potential causes of the EAE (e.g., past medical history, concurrent illness, concomitant medications) should also be considered when assessing whether there is a reasonable possibility that an EAE may be related to a study agent. |
| Not related           | There is **not** a reasonable possibility that the EAE may be related to a study agent. |

Figure 10-4 presents how the five relationship categories used for clinical management should be mapped to the two relationship categories used for EAE reporting.
Figure 10-4
Mapping of Relationship Categories for Clinical Management to Relationship Categories for EAE Reporting

<table>
<thead>
<tr>
<th>Relationship Category for Clinical Management</th>
<th>Maps To</th>
<th>Relationship Category for EAE Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Possibly related</td>
<td></td>
<td>Related</td>
</tr>
<tr>
<td>Probably not related</td>
<td></td>
<td>Not related</td>
</tr>
<tr>
<td>Not related</td>
<td></td>
<td>Not related</td>
</tr>
</tbody>
</table>

10.5 EAE Reporting Procedures

All EAEs should be reported to the DAIDS RSC Safety Office using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians.

The process of EAE reporting via DAERS involves a designated “Study Reporter” creating an electronic EAE report and a designated “Study Physician” reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC Safety Office. If an EAE report is not completed and submitted within three reporting days of site awareness that an event meets EAE reporting criteria, an explanation must be entered in DAERS before the report can be submitted (see the Manual for Expedited Reporting of Adverse Events to DAIDS for the definition of reporting days).

DAERS also may be used to withdraw an EAE report that was submitted in error and to modify or update a previously submitted EAE report.

For all submitted EAE reports, updates must be submitted to report the final or stable outcome of the EAE, unless the original report provided a final or stable outcome. Updates also should be submitted if significant additional information becomes available after an EAE report is first submitted. Significant additional information may include, for example, an updated severity grade or relationship assessment, information on participant status after resumption of one or more study agents, and/or newly available information on cause of death.

Note: When updated EAE reports are submitted, it is NOT necessary to complete and submit another Event Evaluation eCRF (PE6865) to the DMC. Only one PE6865 eCRF should be completed and submitted for each event. However, the PE6865 should be updated to correspond with the EAE report form when key information (such as terminology used to describe the event, severity grade, relationship to study drug) is updated.

DAERS incorporates a report printing function that should be used to print all EAE reports — including modifications and updates — for filing in participant study records. Automated email messages confirming submission of EAE reports also should be printed and filed with the print-out of the associated EAE report.

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

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based EAE reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. The paper report form can be accessed at: https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting
10.6 EAE Reporting Examples

Several EAE reporting examples are provided below. When reviewing these examples, note that even when EAE reporting is not required, all infant adverse events must be source documented and selected adverse events must be entered into relevant eCRFs, per the P1115 SoE and eCRF instructions.

<table>
<thead>
<tr>
<th>Case Description</th>
<th>Has a reportable EAE occurred?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Following enrollment in Cohort 1/Step 1, an infant is found to have a high grade fever. Sepsis is suspected and the infant is admitted to the neonatal special care unit of the hospital where he was born.</td>
<td><strong>Yes.</strong> This event is serious because it resulted in hospitalization and it occurred between Step 1 Entry and Step 1 Week 12. Therefore, the event must be reported as an EAE regardless of relationship to study agents.</td>
</tr>
<tr>
<td>2. Following enrollment in Cohort 1/Step 1, an infant is found to have a heart defect.</td>
<td><strong>No.</strong> Congenital anomalies should not be reported as EAEs in P1115 because these events would have occurred prior to study entry.</td>
</tr>
<tr>
<td>3. For an infant in Step 1, hematology testing at Week 2 provides a Grade 3 hemoglobin result. Chart review indicates that the infant was asymptomatic and otherwise clinically well on the day of the Week 2 visit.</td>
<td><strong>No.</strong> As described, this event does not meet the ICH definition of serious and therefore does not need to be reported as an EAE.</td>
</tr>
<tr>
<td>4. For an infant in Step 1, hematology testing at Week 2 provides a Grade 4 absolute neutrophil count. Chart review indicates that the infant was asymptomatic and otherwise clinically well on the day of the Week 2 visit.</td>
<td><strong>No.</strong> As described, this event does not meet the ICH definition of serious and therefore does not need to be reported as an EAE.</td>
</tr>
<tr>
<td>5. For an infant in Step 1, chemistry testing at Week 2 provides a Grade 4 ALT result. Chart review indicates that the infant was asymptomatic and otherwise clinically well on the day of the Week 2 visit.</td>
<td><strong>Yes.</strong> As specified in protocol Section 7.2, Grade 4 asymptomatic hepatotoxicity should be considered serious and would therefore need to be reported as an EAE regardless of relationship to study agents.</td>
</tr>
<tr>
<td>6. An infant enrolled in Cohort 1/Step 1 does not return as scheduled for his Week 4 visit. The mother and infant are traced by the study site outreach team, who learn that both mother and infant have been hospitalized due to injuries sustained in a motor vehicle accident that occurred one week before the scheduled Week 4 visit.</td>
<td><strong>Yes.</strong> The mother and infant have both experienced serious events. For the infant, the event occurred between Step 1 Entry and Step 1 Week 12 and therefore must be reported as an EAE regardless of relationship to study agents. <strong>Note:</strong> No EAE reporting is required for the mother.</td>
</tr>
<tr>
<td>7. An infant in Step 2 returns to the study clinic between scheduled visits, at approximately Week 11, with the mother reporting signs and symptoms of severe gastroenteritis. The mother is reluctant to have the infant admitted to the hospital because she has other children at home to care for; the infant is therefore treated at the study clinic with antibiotic fluids and other medications.</td>
<td><strong>Yes.</strong> Although this infant was not hospitalized, the gastroenteritis is an important medical event that required intervention to prevent hospitalization and other serious outcomes. Therefore, the event should be considered serious. Because the event occurred between Step 2 Entry and Step 2 Week 36, it must be reported as an EAE regardless of relationship to study agents.</td>
</tr>
<tr>
<td>8. An infant in Step 2 is hospitalized at Step 2 Week 24 with diarrheal disease and dehydration.</td>
<td><strong>Yes.</strong> This event is serious because it resulted in hospitalization and it occurred between Step 2 Entry and Step 2 Week 36. Therefore, the event must be reported as an EAE regardless of relationship to study agents.</td>
</tr>
<tr>
<td>Case Description</td>
<td>Has a reportable EAE occurred?</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>9. An infant in Step 2 is hospitalized at Step 2 Week 48 with diarrheal disease and dehydration.</td>
<td><strong>Maybe.</strong> Because this event occurred after Step 2 Week 36, the IoR or designee must assess whether it meets criteria for reporting as a SUSAR. The event is serious, because it resulted in hospitalization, but in order to be considered a SUSAR, the event would need to be assessed as unexpected and related to one or more study agents. In this case, a reasonable possibility of a relationship appears unlikely, but the final determination would need to be made by the IoR or designee. <strong>Note:</strong> This same answer would apply if the infant was in Step 3 or Step 4.</td>
</tr>
<tr>
<td>10. A mother of an infant in Step 2 returns to the study clinic soon after the Christmas holidays to report that her infant died while the family was staying in a rural area with relatives. The mother’s description of the infant’s signs and symptoms is consistent with malaria, and the death occurred at approximately Week 27 in Step 2.</td>
<td><strong>Yes.</strong> This event is serious because it resulted in death and it occurred between Step 2 Entry and Step 2 Week 36. Therefore, the event must be reported as an EAE regardless of relationship to study agents.</td>
</tr>
<tr>
<td>11. A mother of an infant in Step 3 returns to the study clinic soon after the Christmas holidays to report that her infant died while the family was staying in a rural area with relatives. The mother’s description of the infant’s signs and symptoms is consistent with malaria, and the death occurred at approximately Week 27 in Step 3.</td>
<td><strong>Maybe.</strong> Because this event occurred in Step 3, the IoR or designee must assess whether it meets criteria for reporting as a SUSAR. The event is serious, because it resulted in death, but in order to be considered a SUSAR, the event would need to be assessed as unexpected and related to one or more study agents. In this case, a reasonable possibility of a relationship appears unlikely, but the final determination would need to be made by the IoR or designee. <strong>Note:</strong> This same answer would apply if the infant was in Step 4.</td>
</tr>
<tr>
<td>12. An infant enrolled in Step 2 does not return as scheduled for his Week 40 contact. The mother and infant are traced by the study site outreach team, who learn that the infant stopped breathing and died about two weeks after his Week 36 visit. The mother reports that the infant had been lethargic for 1-2 days and then stopped breathing; however, the cause of death is unknown.</td>
<td><strong>Yes.</strong> Because this event occurred after Step 2 Week 36, the IoR or designee must assess whether it meets criteria for reporting as a SUSAR. The event is serious, and, because the cause of death is not known, it will not be possible for the IoR or designee to rule out a reasonable possibility of a relationship between the event and study agents. Therefore, EAE reporting would be expected.</td>
</tr>
</tbody>
</table>
11.0 Specimen Collection and Laboratory Considerations

The P1115 SoEs and the LPC are the primary sources of information on specimen collection, processing, testing, and storage for this study; refer to these documents for further operational guidance as needed.

11.1 Infant Blood Collection Volumes

NIH recommendations for maximum pediatric blood draw volumes must be followed in this study. **The volume of blood drawn at any infant study visit must not exceed 5 mL/kg in a single day and 9.5 mL/kg over any eight-week period.** Both the single day limit and the eight-week limit must be considered at each infant visit; for the eight-week limit, the volume of blood drawn over the past eight weeks prior to and including the current visit must be considered. At each visit, infant weight should be measured, the total volume of blood collected over the past eight weeks should be tabulated, and the maximum blood draw for that day should be determined prior to phlebotomy. If the full blood draw volume specified in the SoE cannot be collected, refer to the notes at the end of each SoE to determine how blood collection should be prioritized. Two examples are detailed in Appendix IV of this manual.

As highlighted in the examples, it is critical that blood draw volumes are documented at each visit and are easily accessible for calculating maximum draw volumes at each visit. A sample flow sheet that may be adapted for this purpose is provided in Appendix I of this manual. At any visit when the full volume specified in the SoE cannot be collected, this should be documented in participant study charts, along with the reason for the less-than-full draw.

Based on expected infant weights, challenges with collection of full blood volumes are most likely within the first 24 weeks of follow-up. Operational tips and suggestions to address these challenges are provided below.

- Prior to study initiation, site clinic and lab staff should meet to jointly review the SoEs and LPC to:
  - Identify site-specific blood draw volumes for each type of test listed in the SoEs. For example, the SoE lists 1 mL of blood for chemistries and 1 mL of blood for CD4 counts, but a full 1 mL may not be required for each of these types of tests at all sites. If the tests can be performed with less blood at a given site, less blood should be drawn at that site.
  - Identify all opportunities for combining blood draw volumes across tests; the LPC provides detailed guidance related to this (highlighted in yellow in the specimen processing sections) and further opportunities may be identified on a site-by-site basis.

- For each enrolled infant, at each visit, site staff are encouraged to forecast forward to the next visit and estimate the blood draw volume likely to be allowed at the next visit. There will be some imprecision in these estimates, because the infant’s weight at the next visit cannot be known with certainty in advance. However, particularly for smaller infants, forecasting forward to the next visit will provide time for site clinicians to consult the CMC should there be any potential questions or concerns with respect to participant management at the next visit.
  - For example, if forecasting indicates that it may not be possible to collect blood for all safety-related tests at the next visit, site clinicians are encouraged to consult the CMC about this in advance, to help guide action to be taken at the next visit. In general, the protocol team would advise that the study regimen be continued in such cases; however, if there is a potential safety concern based on prior evaluations of the infant or an ongoing adverse event, consultation with the CMC in advance is advised.
In the event that additional blood draws are required between scheduled visits to follow adverse events to resolution (per protocol Sections 6.1 and 6.2), careful attention should be paid to blood draw volumes for repeat tests and priorities for use of available blood draw volumes should be discussed with the CMC as part of the infant’s clinical management plan.

In the event that advance consultation with the CMC is not possible, site clinicians are advised to manage infant study regimens consistent with their clinical judgment. In general, it is expected that the study regimen would be continued, even if protocol-specified safety-related tests cannot be performed, unless the site clinician identifies a potential safety concern associated with continuing the regimen. In cases such as this, in which the CMC cannot be consulted in advance, the CMC should be consulted as soon as possible after the infant visit.

At the Step 2 Week 24 visit, every effort should be made to ensure that sufficient blood can be collected to yield an adequate undiluted plasma specimen for HIV RNA (per the SoE, this is the highest priority for specimen collection at the visit). Site staff are encouraged to forecast forward to this visit and plan accordingly. Operational strategies that may be considered as needed to allow for collection of the full blood volume for the visit include utilizing the allowable visit window (±2 weeks) to shift the Week 24 visit to a date later in the window. In addition, if the full blood draw volume for the visit cannot be collected on a given date, the volume required for HIV RNA testing can be collected first and the infant can be scheduled to return to the clinic on a later date within the window to have the remainder of the blood required for the visit collected.

11.2 US Site Use of Central Laboratory for Diluted HIV RNA Assays

For US sites that do not have access to a CLIA-certified laboratory with a validated dilution plan for plasma HIV RNA PCR assays (either Abbott RealTime or Roche Taqman), the Protocol Team has designated the Lurie Children’s Hospital laboratory in Chicago (LDMS Lab #46) as a central testing facility. This laboratory has completed a VQA-approved dilution validation using the Abbott platform with Basematrix as the diluent (VQA-approved since December 2012).

Contact information for the Lurie Children’s Hospital laboratory is included in the shipping section of the LPC. US sites are responsible for establishing any necessary service agreements with this laboratory and for arranging other logistics (shipping arrangements, receipt of results, etc). All arrangements (inclusive of cost) must be settled before shipping any specimens to this laboratory for testing.

11.3 PBMC Processing

PBMCs must be processed and cryopreserved in a laboratory that is IQA-certified using methods consistent with the HIV/AIDS Network Coordination Cross-Network PBMC Processing SOP. To ensure adequate PBMC volumes, all laboratory technicians involved in processing PBMCs for this study must undergo training on SOP modifications for small sample volumes. These modifications are highlighted in an annotated copy of the SOP that is posted on the study-specific web page; this SOP must be followed for P1115 Version 2.0. A training presentation entitled, Increasing PBMC Yield from Pediatric Samples, is also posted on the study-specific web page:

https://impaactnetwork.org/studies/p1115.asp

Training must be documented at each site laboratory and will be tracked by the IMPAACT Laboratory Center (for NIAID-funded sites) and Westat (for NICHD-funded sites).
12.0 VRC01: Pharmacy, Dosing, and Reactogenicity Considerations

This section contains information related to VRC01 and administration of this study product as part of Regimen 2RV. This information is applicable only to sites assigned to provide this regimen. At these sites, infants enrolled in Cohort 1 will receive a single injection of VRC01 (40 mg/kg) at Step 1 Entry; if confirmed with in utero infection, infants will receive three additional injections of VRC01 at Step 2 Entry, Step 2 Week 4, and Step 2 Week 8.

VRC01 will be administered subcutaneously by slow push in the thigh using RMS High-Flo Subcutaneous Safety Needle Sets with 26-gauge needles. Supplies of VRC01, RMS needle sets, 4 mm needles, and 6 mm needles will be made available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). See page 97 for a copy of a technical fact sheet describing the needle sets.

BD Blunt Filter Needles (BD item number 305211; 18-gauge, 1.5 inch, with 5-micron filter) will also be made available to study sites through the CRPMC. These needles will be used when drawing VRC01 into syringes as part of preparation for subcutaneous injection.

12.1 VRC01 Dosing

Refer to Figure 12-1 below. VRC01 dose volumes are expected to range from 0.8 to 3.2 mL, corresponding to infant weights ranging from 2 to 8 kg. Per protocol Section 5.1.5.2, all dose volumes are expected to be administered as a single infusion over approximately 5-10 minutes; up to 15 minutes may be required for the largest dose volumes. However, if appropriate for an infant's size, a divided dose may be infused at two sites.

As shown in Figure 12-1, the required volume of VRC01 should be loaded into a 5 mL or 10 mL sterile syringe. For ease of handling, the loaded syringe should be no more than half-full.

In general, 4 mm needles are recommended for infants weighing less than 6 kg; 6 mm needles are recommended for infants weighing 6 kg or more. Further considerations for needle selection are as follows:

- The choice of needle length is a clinical decision and can be adjusted based on the site clinician’s assessment of the infant.
- If the needle is too short, this will result in leaking during infusion and/or infusion site reactions (itching, redness, irritation) due to administration into the dermis.
- If the needle is too long, it will enter the muscle and cause pain; the infant will usually cry. In contrast, if the needle is inserted into the correct subcutaneous location, the infant may cry at first with the needle stick and application of tape, but the infant will then calm and tolerate the infusion without further crying.
<table>
<thead>
<tr>
<th>Infant Weight Band</th>
<th>Syringe Size</th>
<th>Dose 40 mg/kg</th>
<th>Total Dose Volume</th>
<th>Additional Volume to Withdraw into Syringe</th>
<th>Total Volume to Withdraw into Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 kg to &lt; 2.2 kg</td>
<td>5 mL</td>
<td>80 mg</td>
<td>0.8 mL</td>
<td>0.1 mL</td>
<td>0.9 mL</td>
</tr>
<tr>
<td>2.2 kg to &lt; 2.4 kg</td>
<td>5 mL</td>
<td>90 mg</td>
<td>0.9 mL</td>
<td>0.1 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>2.4 kg to &lt; 2.7 kg</td>
<td>5 mL</td>
<td>100 mg</td>
<td>1.0 mL</td>
<td>0.1 mL</td>
<td>1.1 mL</td>
</tr>
<tr>
<td>2.7 kg to &lt; 3.2 kg</td>
<td>5 mL</td>
<td>120 mg</td>
<td>1.2 mL</td>
<td>0.1 mL</td>
<td>1.3 mL</td>
</tr>
<tr>
<td>3.2 kg to &lt; 3.7 kg</td>
<td>5 mL</td>
<td>140 mg</td>
<td>1.4 mL</td>
<td>0.1 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>3.7 kg to &lt; 4.3 kg</td>
<td>5 mL</td>
<td>160 mg</td>
<td>1.6 mL</td>
<td>0.1 mL</td>
<td>1.7 mL</td>
</tr>
<tr>
<td>4.3 kg to &lt; 4.8 kg</td>
<td>5 mL</td>
<td>180 mg</td>
<td>1.8 mL</td>
<td>0.1 mL</td>
<td>1.9 mL</td>
</tr>
<tr>
<td>4.8 kg to &lt; 5.3 kg</td>
<td>5 mL</td>
<td>200 mg</td>
<td>2.0 mL</td>
<td>0.1 mL</td>
<td>2.1 mL</td>
</tr>
<tr>
<td>5.3 kg to &lt; 5.8 kg</td>
<td>5 mL</td>
<td>220 mg</td>
<td>2.2 mL</td>
<td>0.1 mL</td>
<td>2.3 mL</td>
</tr>
<tr>
<td>5.8 kg to &lt; 6.3 kg</td>
<td>10 mL</td>
<td>240 mg</td>
<td>2.4 mL</td>
<td>0.1 mL</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>6.3 kg to &lt; 6.8 kg</td>
<td>10 mL</td>
<td>260 mg</td>
<td>2.6 mL</td>
<td>0.1 mL</td>
<td>2.7 mL</td>
</tr>
<tr>
<td>6.8 kg to &lt; 7.3 kg</td>
<td>10 mL</td>
<td>280 mg</td>
<td>2.8 mL</td>
<td>0.1 mL</td>
<td>2.9 mL</td>
</tr>
<tr>
<td>7.3 kg to &lt; 7.8 kg</td>
<td>10 mL</td>
<td>300 mg</td>
<td>3.0 mL</td>
<td>0.1 mL</td>
<td>3.1 mL</td>
</tr>
<tr>
<td>7.8 kg to &lt; 8.3 kg</td>
<td>10 mL</td>
<td>320 mg</td>
<td>3.2 mL</td>
<td>0.1 mL</td>
<td>3.3 mL</td>
</tr>
<tr>
<td>8.3 kg to &lt; 8.8 kg</td>
<td>10 mL</td>
<td>340 mg</td>
<td>3.4 mL</td>
<td>0.1 mL</td>
<td>3.5 mL</td>
</tr>
<tr>
<td>8.8 kg to &lt; 9.3 kg</td>
<td>10 mL</td>
<td>360 mg</td>
<td>3.6 mL</td>
<td>0.1 mL</td>
<td>3.7 mL</td>
</tr>
<tr>
<td>9.3 kg to &lt; 9.8 kg</td>
<td>10 mL</td>
<td>380 mg</td>
<td>3.8 mL</td>
<td>0.1 mL</td>
<td>3.9 mL</td>
</tr>
<tr>
<td>9.8 kg to &lt; 10.3 kg</td>
<td>10 mL</td>
<td>400 mg</td>
<td>4.0 mL</td>
<td>0.1 mL</td>
<td>4.1 mL</td>
</tr>
</tbody>
</table>
12.2 VRC01 Thawing Instructions

VRC01 will be thawed by the site Pharmacist of Record (PoR) or appropriate pharmacy personnel designated by the PoR.

Thaw vial(s) of VRC01 at controlled room temperature 15°C to 27°C (59°F to 80°F) for a minimum of one hour and up to a maximum of 24 hours. Continue to thaw the vial(s) until the fluid is a clear, colorless to yellow liquid and no particles are observed (see next paragraph for further guidance regarding particles). Thawed VRC01 vials must either be used to prepare a syringe for subcutaneous injection or placed in a refrigerator at 2°C to 8°C (36°F to 46°F) before reaching the maximum storage of 24 hours at controlled room temperature. VRC01 in a vial may be stored up to 4 weeks at 2°C to 8°C. After storage at 2°C to 8°C, vials may be held at controlled room temperature for a maximum of 8 hours prior to product preparation.

VRC01 is a highly-concentrated protein solution and may develop white-to-translucent particles after thawing. Vial(s) of VRC01 containing particles at 24 or fewer hours after being thawed should be placed in the refrigerator for possible future use, because particles may continue to dissipate at 2°C to 8°C. Vials of VRC01 that previously contained particles but subsequently become clear of particles may be used. Vials that continue to have visible particles after a maximum of 24 hours at controlled room temperature or up to 4 weeks at 2°C to 8°C should not be used; these vials should be disposed of as described in protocol Section 5.3.2.

VRC01 in a syringe for subcutaneous injection may be stored at 2°C to 8°C for up to 24 hours or at controlled room temperature (maximum 30°C) for up to 4 hours, starting at the time when the syringe is prepared. If the syringe is stored at 2°C to 8°C, the syringe must be equilibrated to room temperature for a minimum of 30 minutes prior to and during product administration. Do not store in direct sunlight.

Note: If individual institutional policies specify shorter timeframes for expiry than specified above, site institutional policies must be followed.

12.3 VRC01 Preparation Instructions

VRC01 will be prepared by the site PoR or appropriate pharmacy personnel designated by the PoR using aseptic technique in a laminar flow biosafety cabinet. It is generally expected that the VRC01 dose volumes required for this study will be administered as a single infusion. However, if appropriate for an infant’s size, a divided dose may be infused at two sites. Procedures for preparing VRC01 as a single dose infusion (in one syringe) are provided in steps #1-5 below. Further information for preparing a divided dose infusion (in two syringes) is then provided at the end of this section.

For single dose infusion (in one syringe)

1. Refer to Figure 12-1 to determine (i) the volume of VRC01 required based on the infant’s weight and (ii) number of vials needed assuming a 2-mL withdrawal volume of per vial. For example:

- For a 3.0 kg infant, 1.3 mL of VRC01 would be required and therefore one vial would be needed
- For a 6.0 kg infant, 2.5 mL of VRC01 would be required and therefore two vials would be needed
2. After thawing as described in Section 12.2 of this manual, gently swirl the vial(s) for 30 seconds to avoid foaming. **DO NOT SHAKE THE VIAL(S).** Keep the vial(s) upright at all times until ready to withdraw the contents. **DO NOT INVERT THE VIAL(S) DURING INSPECTION.**

3. Inspect the vial(s) for particles. If upon inspection particles are observed, follow the instructions in Section 12.2 of this manual.

4. Using a BD Blunt Filter Needle (BD item number 305211), withdraw the required volume (determined from Figure 12-1) from the vial(s) into a sterile syringe using aseptic technique:
   - Secure the hub of the filter needle to the syringe by twisting clockwise.
   - With the cap still on the filter needle, pull back on the plunger of the syringe to draw a volume of air into the syringe approximately equal to the volume of VRC01 to be administered.
   - Place the vial on a flat surface.
   - Remove the cap from the filter needle.
   - Holding the vial with one hand, insert the filter needle into the stopper of the vial at a 90° angle with the other hand.
   - Push the plunger of the syringe to inject air into the vial prior to withdrawing VRC01.
   - Withdraw the required volume of VRC01 into the syringe (through the filter needle).
   - Remove the filter needle from the vial once the required volume of VRC01 has been filtered into the syringe.
   - Recap the filter needle using passive, one-handed recapping technique.
   - Detach the filter needle from the syringe by twisting counterclockwise.
   - Discard the filter needle in an approved sharps container.
   - Place a cap on the syringe containing VRC01.

5. Label the syringe with expiration times for storage at controlled room temperature (maximum 30°C) or refrigerated at 2°C to 8°C (see Section 12.2 of this manual for expiry requirements). Dispense each prepared and labeled syringe with one RMS High-Flo Subcutaneous Safety Needle Set infusion set with a 26-gauge needle (4 mm or 6 mm).

**For divided dose infusion (in two syringes)**

When a divided dose infusion is needed, the instructions provided in #1-5 above should generally be followed. However, an additional **0.1 mL** of VRC01 is required to prime the tubing in the second needle set. For example, to prepare a 3.2 mL dose for an 8.0 kg infant in two syringes, a total dose volume of 3.4 mL would be required (rather than 3.3 mL as shown in Figure 12-1). Once the total dose volume is determined, approximately half of the total volume should be withdrawn into each of the two syringes, following the instructions in #4 above.

### 12.4 Subcutaneous Injection of VRC01

VRC01 will be administered by designated site clinical staff subcutaneously by slow push in the thigh using an RMS High-Flo Subcutaneous Safety Needle Set with a 26-gauge needle. Refer as needed to the technical fact sheet on page 97 and see Section 12.1 of this manual for more information on choosing the most appropriate needle length (4 mm or 6 mm) for each injection.
The site clinician will assemble the following materials for subcutaneous injection:

- Alcohol wipes
- Sterile gauze
- Transparent dressing (provided with each needle set)

a. After confirming eligibility and successful enrollment into the study, with assignment to Regimen 2RV, provide a study product prescription, signed by an investigator listed on the FDA Form 1572, to the study site pharmacy. A new prescription is required for each dose of VRC01 to be administered. Prescriptions must include:

- The infant’s PID, SID, date of birth, and current weight
- The number of syringes (one or two) requested for administration
- The needle length (4 mm or 6 mm) requested for administration

In addition to the signed prescription, documentation that the infant’s parent or legal guardian has provided written informed consent for infant participation in the study must be provided to the pharmacy (study product cannot be dispensed prior to receipt of this documentation).

b. Obtain prepared study product and needle set from the pharmacy. As indicated in Section 12.3 of this manual, the prepared product will be dispensed in capped syringes labeled with expiration times for storage at controlled room temperature (maximum 30°C) or at 2°C to 8°C. The prepared product (VRC01 in a syringe) must be administered within the expiry time specified on the label. If stored at 2°C to 8°C, the prepared product must be equilibrated to room temperature (maximum 30°C) for a minimum of 30 minutes prior to and during administration.

c. Wash hands per institutional policy.

d. Remove the needle set from the package; remove the cap from the prepared syringe.

e. Aseptically remove the end cap from the female luer at the end of the needle set tubing and connect the luer to the syringe. Do not remove the cap from the needle attached to the tubing.

f. Lay out the tubing so that fluid moving through the tubing can be visualized. Gently push the plunger of the syringe to prime the tubing until you see fluid near the end of the tubing. Do not prime to the tip of the tubing — the needle should be dry. Inserting a dry needle helps avoid local injection site reactions. Clamp the tubing with the slide clamp to prevent leakage.

g. Place the infant on his or her back on a clean surface and expose the legs.

h. Select the appropriate site on the thigh where the skin and subcutaneous tissue can be pinched. Avoid sites where the skin or tissue is irritated. Whenever possible, avoid sites in which immunizations or other injectable medications have been administered within the past two weeks. When VRC01 must be administered in the same thigh as a recent immunization or other injection, select a site at least 2.4 cm away from the prior immunization/injection site and mark each site as needed so that each can be clearly identified for purposes of assessment of injection site reactions.
i. Use alcohol wipes to clean the selected site on the thigh where the injection will be administered.

j. Open the winged safety closure that encloses the needle and remove the needle shield.

k. Grasp (pinch) the infant’s skin and subcutaneous tissue (at the selected site on the thigh) between your thumb and forefinger. Insert the needle into the pinched skin at a 90° angle (right angle). After the needle is inserted, release the pinched skin and secure the needle with tape.

l. Pull back on the syringe to check for blood return. If blood return occurs, remove the needle, select another site, and repeat steps h-l.

m. Cover the site with the transparent dressing. Manually push the study product slowly over approximately 5-10 minutes to complete the infusion; up to 15 minutes may be required for the largest dose volumes. In practice, the rate of infusion will be limited by the amount of back-pressure experienced, the strength of the person administering the product, and the occurrence of leaking. Slower rates of infusion prevent leaking at the site.

   Note: Calculations for the volume of study product to be administered account for the volume that remains in the tubing. DO NOT attempt to flush tubing at the end of the infusion.

n. When the infusion is complete, remove the transparent dressing and the needle from the infant’s thigh, and close the wings of the safety closure around the needle (apply even pressure at the safety closure circles, located at the tips of the wings, to snap closed).

o. Place a 2x2 gauze over the injection site and apply pressure over the site for approximately one minute. A few drops of fluid may appear at the site (this is normal) but there should not be a lot of leaking.

p. Apply a new 2x2 gauze over the injection site and tape the gauze down applying pressure.

q. Source document the infusion consistent with site SOPs. The following will be required for entry into the VCW0082: IMPAACT P1115 Study Product Record eCRF: date of infusion, site of infusion (e.g., right or left thigh), start time of infusion, end time of infusion, volume and dose of VRC01 infused, and lot number of VRC01 infused.

   Note: The volume of VRC01 entered into the VCW0082 eCRF should be the infusion volume. DO NOT include the volume of product included in the total dispensed volume to prime the tubing.

r. Observe the infant after the infusion as specified in protocol Section 6.2.5 (see also Section 12.5 of this manual).
**Indications For Use:** RMS HlgH-Flo Subcutaneous Safety Needle Sets™ are intended for the delivery of medication to the subcutaneous tissue.

**How to use HlgH-Flo needle sets:**

1. **Remove Cap**
   - Remove the end cap from the female luer and connect the luer to the source of infusion.

2. **Remove Closure**
   - Remove the wings closure band to separate each wing.

3. **Bend Back Wings**
   - Bring the wings together and hold them between two fingers so that the needle guard is exposed.

4. **Insert Needle**
   - Remove the needle guard and insert needle into the subcutaneous tissue; cover with adhesive dressing.

5. **Remove Needle**
   - When infusion is complete, remove adhesive and pull needle out by bringing the wings together. Snap closed to enclose needle and discard.
12.5 Reactogenicity Assessment

Refer to protocol Section 6.2.5 and the infant Step 1 and Step 2 SoEs for a detailed description of reactogenicity monitoring requirements for this study. These requirements are also depicted in Figure 12-2. As shown below, both local reactogenicity parameters (i.e., at the site of VRC01 injection) and systemic reactogenicity parameters will be assessed. All reactogenicity assessments will be source documented by study staff and all findings will be entered into eCRFs.

<table>
<thead>
<tr>
<th>Local Reactogenicity Parameters</th>
<th>Systemic Reactogenicity Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>Temperature</td>
</tr>
<tr>
<td>Warmth</td>
<td>Alertness</td>
</tr>
<tr>
<td>Swelling</td>
<td>Rash</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Swelling of joints</td>
</tr>
<tr>
<td></td>
<td>Feeding</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

Reactogenicity will be monitored by study staff in close collaboration with infant caregivers. Study staff will directly monitor reactogenicity on the day of each injection, as indicated in the top panel of Figure 12-2. Monitoring then will continue for seven days, based on assessments completed by infant caregivers and reported to study staff, as indicted in the bottom panel of Figure 12-2.

To support caregiver recall and reporting, caregivers will be given a memory aid to be completed following the Step 1 Entry, Step 2 Entry, Step 2 Week 4, and Step 2 Week 8 visits. Caregivers will first complete the memory aid in the evening of these visits. Caregivers will then complete additional entries at approximately the same time on the next six days (each entry will record observations from one day). In Step 2, study staff will contact caregivers on the third day after each injection visit to solicit information based on caregiver assessments. These +3-day contacts may be performed by telephone or in person — in the home or in the study clinic — as preferred by study staff or caregivers. If any grade 1 or higher signs or symptoms are identified, caregivers will be instructed to return to the study clinic with their infants as soon as possible — and within 48 hours — for further evaluation by a study clinician. The same type of data collection, based on caregiver assessments performed after the +3-day contact, will occur at the in-person study visit scheduled seven days after each injection visit.

A snapshot of the caregiver memory aid is shown in Figure 12-3. Sites must translate the memory aid into applicable local languages and are permitted to adapt the formatting for local use. Following any re-formatting that may occur, sites are responsible for ensuring that the graphic intended to demonstrate a measurement of 2.5 cm is actually 2.5 cm in length on the re-formatted document.

The page shown in Figure 12-3 is intended to be completed on each date of caregiver assessment. Therefore, a total of seven pages would need to be provided to the caregiver at each Step 1 Entry, Step 2 Entry, Step 2 Week 4, and Step 2 Week 8 visit. Sites are encouraged to staple multiple pages together or compile them into a booklet for ease of use and to avoid loss of one or more pages.

Instructions, tips, and examples are provided below to assist study staff in preparing memory aids, instructing caregivers, and communicating with caregivers to assess reactogenicity parameters. Corresponding to this guidance, each site should develop sample scripts for study staff to follow when performing these tasks on a day-to-day basis.
**Figure 12-2**

**Overview of Reactogenicity Monitoring for IMPAACT P1115**

<table>
<thead>
<tr>
<th>AT INJECTION VISIT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior to injection:</strong></td>
<td>Perform physical exam with vital signs (temp, HR, RR, BP if possible) and visually inspect injection site. Confirm eligibility to receive injection.</td>
</tr>
<tr>
<td><strong>15 (±5) minutes after injection:</strong></td>
<td>Assess HR and RR and visually inspect injection site. If local or systemic reaction is suggested, assess temp and BP, examine relevant body systems, and perform any other clinically indicated procedures.</td>
</tr>
<tr>
<td><strong>30 (±5) minutes after injection:</strong></td>
<td>Assess HR and RR and visually inspect injection site. If local or systemic reaction is suggested, assess temp and BP, examine relevant body systems, and perform any other clinically indicated procedures.</td>
</tr>
<tr>
<td><strong>60 (±15) minutes after injection:</strong></td>
<td>Assess vital signs (temp, HR, RR, BP if possible), visually inspect injection site, and palpate injection site for induration and tenderness. If local or systemic reaction is suggested, examine relevant body systems and perform any other clinically indicated procedures.</td>
</tr>
</tbody>
</table>

**At first injection visit, 120 (±15) minutes after injection:** Repeat 60-minute assessment. If local or systemic reaction is suggested, examine relevant body systems and perform any other clinically indicated procedures.

<table>
<thead>
<tr>
<th>ON THE SEVEN DAYS FOLLOWING INJECTION VISIT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On evening of injection visit:</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On first day after injection visit (+1d):</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On second day after injection visit (+2d):</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On third day after injection visit (+3d):</strong></td>
<td>Caregiver completes reactogenicity memory aid. In Step 2, study staff complete contact with caregiver and document reactogenicity outcomes from all caregiver assessments thus far.</td>
</tr>
<tr>
<td><strong>On fourth day after injection visit (+4d):</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On fifth day after injection visit (+5d):</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On sixth day after injection visit (+6d):</strong></td>
<td>Caregiver completes reactogenicity memory aid.</td>
</tr>
<tr>
<td><strong>On seventh day after injection visit (+7d):</strong></td>
<td>At scheduled study visit, study staff document reactogenicity outcomes from caregiver assessments since the injection (in Step 1) or since the +3d contact (in Step 2).</td>
</tr>
</tbody>
</table>
**How is your baby doing today?**

<table>
<thead>
<tr>
<th>PID:</th>
<th>Date:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Time Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**When checking where the injection was given, was there any ...**

<table>
<thead>
<tr>
<th>Leg injected:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Swelling where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Warmth where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Crying when area of injection is touched</td>
<td>No</td>
</tr>
<tr>
<td>Less movement of the leg than usual</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leg injected:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Swelling where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Warmth where injection was given</td>
<td>No</td>
</tr>
<tr>
<td>Crying when area of injection is touched</td>
<td>No</td>
</tr>
<tr>
<td>Less movement of the leg than usual</td>
<td>No</td>
</tr>
</tbody>
</table>

**Did your baby have ...**

| Any rash on body | No | Yes |
| Any swollen joints | No | Yes |
| Any vomiting | No | Yes |
| Any diarrhea | No | Yes |

**Has your baby been ...**

| Less alert/awake than usual | No | Yes |
| Feeding less than usual | No | Yes |
| Sleeping less than usual | No | Yes |
| Sleeping more than usual | No | Yes |
| Crying more often than usual | No | Yes |
| Crying for more than one hour | No | Yes |
Preparing Memory Aids

1. Record the infant’s PID in the designated box on each of the seven pages.

2. Record the expected date of completion in the designated box on each of the seven pages.

3. Record the leg injected — left or right — in the designated grey box on each of the seven pages.

4. Ensure that written instructions for contacting the study site are provided on the memory aid or are otherwise provided to the caregiver (e.g., on a separate contact card).

Instructing Caregivers on How to Complete Memory Aids

Complete instructions should be provided at the Step 1 Entry Visit; depending on the information and skills-building needs of the caregiver, complete or abbreviated instructions may be provided at the Step 2 Entry, Step 2 Week 4, and Step 2 Week 8 visits.

Operational Tip: Consider providing these instructions during the required post-administration observation period at the clinic, demonstrating how to perform the required evaluations as needed.

1. Review the purpose of the memory aid with the caregiver. Remind the caregiver that study staff are available to answer any questions about use of the memory aid and that the caregiver should feel free to contact the study staff with any questions or concerns about the infant’s health or well-being.

2. Instruct the caregiver that the first page of the memory aid should first be completed on the evening of the visit. A new page should then be completed at approximately the same time on the next six days. Point out the dates recorded at the top of each page.

3. Review each item on the memory aid with the caregiver. Take as much time as needed to ensure caregiver understanding of the meaning and intent of each item and how information should be recorded in each item. As needed, reassure the caregiver that it will only take a few minutes to complete the memory aid each evening.

4. When reviewing the temperature item, provide the caregiver with a thermometer and demonstrate how to use it to take the infant’s temperature. Ask the caregiver to practice taking the infant’s temperature at least once before leaving the study site.

5. When explaining the items for redness and swelling at the injection site, demonstrate how to measure the largest dimension of the area to be measured, using visual aids. Point out the 2.5 cm marker on the memory aid and instruct the caregiver to mark the relevant box if the area of redness or swelling is larger than 2.5 cm.

6. When explaining the items for rash, swollen joints, vomiting, and diarrhea, use appropriate lay language to explain these terms. With respect to vomiting, differentiate between spitting out breastmilk or formula versus regurgitation (in lay language). Point out the additional lines for writing the number of episodes of vomiting and diarrhea each day.

7. Advise the caregiver that she may use any white space or the back of the page to write any information she thinks is important to remember and report to study staff.
8. In Step 2 (Step 2 Entry, Week 4, and Week 8 visits), remind the caregiver of the +3-day contact scheduled on the third day after the visit. Designate a time for these contacts so the caregiver can plan accordingly. Instruct the caregiver that, during these contacts, the study staff member will ask questions about the information recorded on each page of the memory aid so far. The questions will follow the order of the memory aid and the caregiver will be asked to report the information he or she recorded on the page. The study staff may ask other questions to clarify the caregiver report, such as:

- At what time did a recorded sign or symptom start or stop?
- At what time were ARVs or other medications given to the infant that day?
- Did you notice anything else different about the infant when the recorded sign or symptom occurred?
- Was the recorded sign or symptom the same, better or worse than the day before?
- Did you do anything to help the infant feel better? Did this help?

*Note:* The above-listed types of questions are expected to be needed to estimate the severity grade of reported signs and symptoms. Because infants with presumptive grade 1 or higher symptoms must be recalled to the clinic for in-person evaluation, all study staff involved in completing +3-day contacts with caregivers must be familiar with the severity grading guidelines for reactogenicity parameters. Refer to protocol Section 7.3 and Corrected Version 2.1 of the DAIDS Adverse Event Grading Table for grading guidance.

Explain to the caregiver that, after the +3-day contact, she will continue to complete memory aid pages for a total of seven days, and that pages completed after the +3-day contact will be reviewed at the +7 day visit at the study clinic.

**Conducting Reactogenicity Assessment Contacts with Caregivers**

1. In preparation for the contact, retrieve the infant’s study chart and review relevant details from prior study visits. Prepare source documents needed to record information reported by the caregiver.

   *Note:* Documentation recorded by study staff based on caregiver report serves as source documentation for reactogenicity data to be entered into eCRFs. Caregiver memory aids should not be collected for this purpose.

2. Contact the caregiver on the designated day. Remind the caregiver of the purpose of the contact and ask her to refer to the memory aid during the contact.

3. Ask questions to obtain the caregiver’s assessments of all applicable reactogenicity parameters on each day since the last contact. Initial questions should follow the structure of the memory aid; follow-up questions should probe as needed to clarify each sign and symptom reported by the caregiver. Query for onset and resolution dates and times and for details needed to estimate severity grade (as illustrated in #8 under *Instructing Caregivers on How to Complete Memory Aids*). Also query for other potential causes of reported signs and symptoms (e.g., concomitant illnesses and/or medications).

4. Source document all reported signs and symptoms and all relevant supplemental details. If any presumptive grade 1 or higher signs or symptoms are reported, arrange for the infant to return to the clinic as soon as possible (within 48 hours) for further evaluation.
12.6 Immediate Management of Infusion Reactions

Protocol Sections 6.2.6 and 6.2.7 provide guidance on management of injection site reactions and urticaria or other hypersensitivity reactions, which in some circumstances require site investigators and/or their designees to “provide immediate clinical management” of these types of reactions, followed by further management as needed in consultation with the CMC.

As shown on the next three pages, the Protocol Team has developed guidelines for immediate management of infusion reactions with cutaneous involvement (localized or diffuse urticaria or hives; no airway involvement) and infusion reactions with systemic anaphylaxis-like symptoms (such as mouth swelling, stridor, wheezing, bronchospasm, hypotension, vomiting). Site investigators should apply their best clinical judgment when managing any reactions, including decisions to transfer participants to other medical facilities and selection of medications and doses to be prescribed. The guidelines shown below do not supersede local clinical judgement and use of appropriate locally-available treatment options.
Guidelines for Management of Infusion Reactions with Cutaneous Involvement
(localized or diffuse urticaria or hives; no airway involvement)

**Note:** Site investigators should apply their best clinical judgment when managing any reactions, including decisions to transfer participants to other medical facilities and selection of medications and doses to be prescribed. The guidelines shown below do not supersede local clinical judgement and use of appropriate locally-available treatment options.

1. Stop infusion immediately.

2. Assess vital signs and perform targeted physical examination.

3. If hives are localized, may choose to observe or immediately administer antihistamine. If hives are diffuse, or if localized hives progress or do not resolve after stopping the infusion, administer antihistamine STAT:
   - Diphenhydramine, 1 mg/kg IM or IV over 10-15 minutes
   - Chlorpheniramine, 0.2 mg/kg orally (maximum 4 mg)

4. Administer corticosteroids STAT:
   - Prednisolone 1mg/kg orally up to every 6 hours
   - Hydrocortisone 1-2mg/kg IM or IV
   - Methylprednisolone succinate, 2 mg/kg IM or IV over two minutes
   (not compatible with IV diphenhydramine — do not give in same infusion)

5. Assess vital signs every 15 minutes or more often if indicated.

6. Photograph the reaction following standard precautions to protect participant confidentiality.

7. Observe the participant for at least 2 hours unless transfer for inpatient observation and/or treatment is clinically indicated. Otherwise, after at least 2 hours of observation, if medically stable and no new skin lesions, discharge home.

8. Prescribe oral antihistamine for 2-3 days:
   - Diphenhydramine, 0.5 to 1 mg/kg orally PRN every 6 hours
   - Chlorpheniramine, 0.2 mg/kg orally every 12 hours

9. Maintain daily telephonic contact with the participant’s mother or caregiver for at least two days or until resolution, whichever is later.
### Guidelines for Management of Infusion Reactions with Systemic Anaphylaxis-Like Symptoms (such as mouth swelling, stridor, wheezing, bronchospasm, hypotension, vomiting)

*Note: Site investigators should apply their best clinical judgment when managing any reactions, including decisions to transfer participants to other medical facilities and selection of medications and doses to be prescribed. The guidelines shown below do not supersede local clinical judgement and use of appropriate locally-available treatment options.*

1. Stop infusion immediately.

2. **Administer epinephrine/adrenaline STAT**
   - Administer epinephrine/adrenaline 0.01 mg/kg (max 0.5 mg) of 1mg/ml (1:1000) solution intramuscularly (IM) in the lateral thigh.
   - Repeat every 5-15 minutes if no improvement.

3. **Call institutional emergency response team (if available).**

4. **Assess vital signs and perform targeted physical examination.**

5. **Administer antihistamine STAT:**
   - Diphenhydramine 1mg/kg IM or IV over 10-15 minutes OR
   - Promethazine 1 mg/kg IV OR
   - Chlorpheniramine 0.2 mg/kg orally (maximum 4 mg)

6. **For wheeze or bronchospasm unresponsive to adrenaline:**
   - Albuterol 0.15 mg/kg nebulized x 1, repeat every 20 minutes as needed OR
   - Salbuterol 2.5 mg nebulized every 20 minutes or continuous

7. **Administer corticosteroids STAT:**
   - Prednisolone 1mg/kg orally up to every 6 hours OR
   - Hydrocortisone 1-2mg/kg IM or IV OR
   - Methylprednisolone succinate, 2 mg/kg IM or IV over two minutes (not compatible with IV diphenhydramine – do not give in same infusion)

8. **Assess vital signs every 15 minutes or more often if indicated.**

9. **Photograph the reaction following standard precautions to protect participant confidentiality.**

10. **Transfer to emergency department/casualty facility/intensive or high care unit by ambulance or other appropriate urgent transport is usually indicated as anaphylaxis can be biphasic. Observe the participant closely while awaiting transfer in case more epinephrine/adrenaline or other interventions are needed. If not transferred, observe the participant for at least 4 hours.**
<table>
<thead>
<tr>
<th>Guidelines for Management of Infusion Reactions with Systemic Anaphylaxis-Like Symptoms (such as mouth swelling, stridor, wheezing, bronchospasm, hypotension, vomiting)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11.</strong> Maintain daily telephonic contact with the emergency or admitting clinical team until the participant is discharged. Discharge on oral antihistamine for 2-3 days.</td>
</tr>
</tbody>
</table>
|   | **•** Diphenhydramine 0.5 to 1 mg/kg orally PRN every 6 hours  
   | **OR**  
   | **•** Chlorpheniramine 0.2 mg/kg orally every 12 hours |
| **12.** Maintain daily telephone contact with the participant’s mother or caregiver for at least two days after discharge or until resolution, whichever is later. |
Appendix I
Sample Flow Sheet for IMPAACT P1115 Infants

<table>
<thead>
<tr>
<th>Visit</th>
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<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Length/height (cm)</th>
<th>Body surface area (m²)</th>
<th>Blood draw volume (mL)</th>
<th>HIV RNA (viral load)</th>
<th>CD4 cells (count/percentage)</th>
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<tr>
<th>Weight (kg)</th>
<th>Length/height (cm)</th>
<th>Body surface area (m²)</th>
<th>Blood draw volume (mL)</th>
<th>HIV RNA (viral load)</th>
<th>CD4 cells (count/percentage)</th>
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Appendix II
Considerations for Tuberculosis Prophylaxis and Treatment in IMPAACT P1115

A. Tuberculosis (TB) exposure and post-exposure prophylaxis

Maternal TB occurs commonly in sub-Saharan Africa. In women, TB occurs most commonly in the childbearing years. Also, HIV co-infection varies from 30% in Mozambique to 54% in South Africa and 70% in Malawi for co-infected women. (1) In P1115, the majority of infants born to HIV and TB co-infected mothers will require isoniazid preventive therapy (IPT) at a dosage of 10mg/kg/day, once active TB has been excluded. (2) For children born to mothers with multidrug-resistant TB (MDR-TB), preventive therapy should be individualized according to the drug susceptibility pattern of the mother’s *M. tuberculosis* isolate, where possible. (3, 4) Similarly, for infants and children exposed to either drug-susceptible or MDR-TB source cases, the same principles apply.

Before proceeding to post-exposure preventive therapy, TB disease should be sought and excluded. Each episode of exposure to a source case requires the same procedures. Care should be taken to monitor for toxicity, especially when study participants are still receiving nevirapine (NVP) as both are potentially hepatotoxic.

B. Isoniazid preventive therapy (IPT) in programs

Many countries are implementing IPT for six months in HIV-infected children over 12 months of age and without TB disease. (5) This may apply to P1115 participants and should proceed according to national guidelines. Again, study personnel should be alert for potential hepatotoxicity. Symptoms and signs include vomiting, abdominal pain and jaundice (the latter is a late sign).

C. TB co-treatment requiring rifampicin (RMP)

**Adjustment of ARV regimen for rifampicin (RMP) co-treatment (drug-susceptible TB)**

*Note: The P1115 Clinical Management Committee (CMC) must be consulted and approve any change of ART regimen for children who develop TB.*

**Super-boosting lopinavir/ritonavir (LPV/r) with additional ritonavir (RTV)**

For infants and children receiving LPV/r (LPV - 80mg, RTV - 20mg per mL) super-boosting with RTV to achieve mg for mg parity is standard of care in South Africa. For this recommendation, 15 children median age 16 months receiving co-treatment were compared to an older group (median age 29 months) without RMP co-treatment. (6) For LPV/r solid formulation (Aluvia®: LPV - 100mg; RTV - 25mg), the same RTV super-boosting strategy is required. Liquid RTV has a short shelf life (6 months) and requires storage below 25°C (package insert). A RTV solid formulation with better storage characteristics has been developed. (7) Because of lack of availability of liquid RTV, many advocate doubling the dosage of LPV/r solution. However, this strategy gives poor exposure to LPV and should not be used in children. (8)

**Nevirapine (NVP)**

NVP as a component of a fixed drug combination at a dosage between 120 and 200mg/m² twice daily gave good NVP exposures with RMP dosed at 8 to 12 mg/kg/day in 8 children from Thailand between 4.4 and 11.7 years of age. (9) Of note, currently a higher dosage of RMP is recommended. (10) We do not know whether NVP exposure will be affected. However, in 21 African children of median age 1.6 years, a median dosage of 174 mg/kg/m² twice daily gave a 41% lower exposure than children not receiving RMP. Eleven children (51%) had baseline values below 3mg/L, the target...
trough for therapeutic efficacy. (11) NVP is one of the alternatives advocated by the WHO for RMP co-treatment. (5) NVP is part of the four-drug regimen in P1115 until plasma HIV RNA is durably suppressed for 12 or more weeks (refer to protocol Section 6.322), expected at about 6 months of age. If RMP is required in this period, please discuss with the CMC.

Efavirenz (EFV)
EFV is less affected by RMP than NVP. Until recently, EFV had no dosage for children <3 years of age and weighing <10kg. More recently, dosing for children ≥ 3 months of age and weighing ≥3.5kg was approved by the FDA (package insert). However, the results of IMPAACT P1070, a Phase I, dose-finding study of EFV among HIV-infected and HIV/TB co-infected infants and children (https://impaacctnetwork.org/studies/P1070.asp), indicate that CYP2B6 516 genotype-directed dosing improves EFV exposures in this age group. CYP2B6 516 genotype was used to classify children into extensive metabolizers [(EMs), 516 GG/GT genotype] and poor metabolizers [(PMs), CYP2B6 516 TT]. For EM participants with HIV, higher doses of EFV than endorsed by the FDA were required to achieve therapeutic EFV levels. In addition, EFV clearance was found to be significantly reduced in PMs with or without TB and in children 24-36 months of age receiving anti-TB therapy, such that significantly lower doses of EFV were needed to reach therapeutic levels (see dosing table). (12, 13) Based on the results of IMPAACT P1070, genotype-directed dosing is recommended for children with HIV/TB co-infection <24 months of age to safely achieve therapeutic EFV concentrations; however, but further study is needed to confirm appropriate dosing for children 24–36 months of age.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>CYP 2B6 516 GG and GT Genotypes (EM)</th>
<th>CYP 2B6 516 TT Genotype (PM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4.99</td>
<td>200 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>5-6.99</td>
<td>300 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>7-9.99</td>
<td>400 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>10-13.99</td>
<td>400 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>14-16.99</td>
<td>500 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>≥ 17</td>
<td>600 mg</td>
<td>150 mg</td>
</tr>
</tbody>
</table>

Triple NRTI
The WHO also advocates this option for RMP co-treatment. (5) In a recent randomized ART strategy trial in Africa investigating clinical versus laboratory monitoring with subsequent randomization at Week 36 to triple NRTI or NVP plus 2 NRTIs showed no difference between the latter two strategies at week 144. (14) In P1115, assuming no TB co-infection early on, the triple NRTI regimen may be effective in an already suppressed infant or child but viral suppression must be carefully monitored. A triple NRTI regimen plus NVP gives better viral suppression than triple NRTI alone, but has not been used with RMP co-treatment. (15) This may be an option, however, for consideration if the infant is too young for LPV/r (below 42 weeks postmenstrual age) or unable to tolerate LPV/r.

Raltegravir (RAL)
The safety and pharmacokinetics of RAL-containing ART in HIV/TB co-infected children as young as five months of age has been studied in IMPAACT P1101 (https://impaacctnetwork.org/studies/P1101.asp). A RAL dose of approximately 12 mg/kg twice daily, given in weight band doses, was found to be safe and achieve target RAL exposures in children receiving RMP-based TB co-treatment. (16) Note that this is double the dose of RAL for infants who are not being co-treated for TB. Based on these findings, P1115 participants receiving RAL who require RMP-based TB co-treatment should receive RAL as shown in the table below, using chewable/ dispersible tablets. Refer to protocol Section 5.2.2 and Section 7.6.1 of this manual for detailed dispersion instructions. Note also that the weight bands in the table below differ from those in Section 7.6.1 of this manual.
### Weight Band Dosing for RAL Chewable/Dispersible Tablets for or P1115 Participant Receiving RMP-based TB Co-Treatment

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Dose</th>
<th>Tablets Per Dose</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>3 to less than 6 kg</td>
<td>50 mg</td>
<td>Two 25 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>6 to less than 10 kg</td>
<td>100 mg</td>
<td>One 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>10 to less than 14 kg</td>
<td>150 mg</td>
<td>One-and-a-half 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>14 to less than 20 kg</td>
<td>200 mg</td>
<td>Two 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>20 to less than 28 kg</td>
<td>300 mg</td>
<td>Three 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>28 to less than 40 kg</td>
<td>400 mg</td>
<td>Four 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>40 kg or higher</td>
<td>500 mg</td>
<td>Five 100 mg tablets</td>
<td>Twice Daily</td>
</tr>
</tbody>
</table>

### MDR and RMP-mono-resistant TB

Children with MDR-TB or RMP-resistant TB will not receive RMP. They will, however, be given between 5 and 8 anti-TB medications, requiring careful monitoring for tolerability and toxicity. (17)

### References

7. Salem AH, Chiu YL, Valdes JM, Nilius AM, Klein CE. A novel ritonavir paediatric powder formulation is bioequivalent to ritonavir oral solution with a similar food effect. Antivir Ther. 2015.


## Appendix III
### Off-Treatment, Off-Step, and Off-Study Codes for ADM0030, PE4005, and F1601 Case Report Forms

<table>
<thead>
<tr>
<th>Case Description*</th>
<th>ADM0030</th>
<th>PE4005</th>
<th>F1601</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a. Infant</strong> enrolled in Step 1 who is not confirmed to be infected and who exits the study after completing follow-up through Step 1 Week 12</td>
<td>WHEN DISCONTINUING STEP 1</td>
<td>When DISCONTINUING STEP 1 REGIMEN</td>
<td>In item 2, enter “Infant not infected, completed follow-up in Step 1.” In item 3, select “Completion of protocol defined period of study evaluation. No further follow-up required.”</td>
</tr>
<tr>
<td><strong>1b. Mother</strong> of infant enrolled in Step 1 who is not confirmed to be infected</td>
<td>When DISCONTINUING STEP 1</td>
<td>(form not required)</td>
<td>In item 2, enter “Infant not infected, completed follow-up in Step 1.” In item 3, select “Completion of protocol defined period of study evaluation. No further follow-up required.”</td>
</tr>
<tr>
<td><strong>2a. Infant</strong> enrolled in Step 1 who is confirmed infected and enters Step 2</td>
<td>When DISCONTINUING STEP 1</td>
<td>NA (form not required)</td>
<td>NA (form not required)</td>
</tr>
<tr>
<td><strong>2b. Mother</strong> of infant enrolled in Step 1 who is confirmed infected and enters Step 2</td>
<td>When DISCONTINUING STEP 1</td>
<td>NA (form not required)</td>
<td>NA (form not required)</td>
</tr>
<tr>
<td>Case Description*</td>
<td>ADM0030</td>
<td>PE4005</td>
<td>F1601</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>3a. Infant</strong> enrolled in Step 1 whose mother is not confirmed to be HIV-infected</td>
<td>WHEN DISCONTINUING STEP 1 In item 2, select “Other, specify.” In item 3, enter “Maternal HIV infection not confirmed.”</td>
<td>In item 3, enter “Maternal HIV infection not confirmed.” In item 3, select “Pending results at randomization did not confirm eligibility.”</td>
<td>In item 2, enter “Maternal HIV infection not confirmed.” In item 3, select “Test results which were pending at the time of randomization subsequently did not meet the eligibility requirements for the study.”</td>
</tr>
<tr>
<td><strong>3b. Mother</strong> enrolled in Step 1 who is not confirmed to be HIV-infected</td>
<td>WHEN DISCONTINUING STEP 1 In item 2, select “Other, specify.” In item 3, enter “Maternal HIV infection not confirmed.”</td>
<td>NA (form not required)</td>
<td>In item 2, enter “Maternal HIV infection not confirmed.” In item 3, select “Test results which were pending at the time of randomization subsequently did not meet the eligibility requirements for the study.”</td>
</tr>
</tbody>
</table>

*None of the scenarios described in this table represent enrollment violations or any other type of protocol deviation.*
Appendix IV
Infant Blood Draw Volume Examples

*handout version of presentation slides numbered 1-32 on the following 16 pages*
Infant Blood Draw Volumes

EXAMPLES FOR IMPAACT P1115 VERSION 2.0

Blood draw volumes

- IMPAACT P1115 follows US National Institutes of Health recommendations for maximum pediatric blood draw volumes
  - 5 mL/kg in a single day
  - 9.5 mL/kg over any eight-week period
**Blood draw volumes**

- At each visit:
  - Infant weight should be measured,
  - The total volume of blood collected over the last 8 weeks should be determined, and
  - The maximum blood draw volume for that day should be calculated *before phlebotomy*

---

**Example 1:** Cohort 1 infant on Regimen 2R with weight measurements as follows:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Entry</td>
<td>04 SEP 2019</td>
<td>3.2</td>
</tr>
<tr>
<td>Step 1 Week 1</td>
<td>11 SEP 2019</td>
<td>3.0</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>3.0</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>3.2</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
</tr>
</tbody>
</table>
Example 1: Step 1 Entry

- At Step 1 Entry, the infant weighs 3.2 kg
- The single day limit is $3.2 \times 5 = 16$ mL
- The targeted blood draw volume per the SoE is 10.5 mL (assuming 3.0 mL is needed for each HIV NAT)
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected

Blood Draw Volumes Over Time

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Weight (kg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Entry</td>
<td>04 SEP 2019</td>
<td>3.2</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 1 Week 1</td>
<td>11 SEP 2019</td>
<td>3.0</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>3.0</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>3.2</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>?</td>
</tr>
</tbody>
</table>
Example 1: Step 1 Week 1

- At Step 1 Week 1, the infant weighs 3.0 kg
- The single day limit is 3.0*5 = 15 mL
- The eight-week limit is (3.0*9.5) – 10.5 = 18 mL
- The targeted blood draw volume per the SoE is 3.5 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected

Blood Draw Volumes Over Time

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Weight (kg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Entry</td>
<td>04 SEP 2019</td>
<td>3.2</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 1 Week 1</td>
<td>11 SEP 2019</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
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<td>?</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
<td>?</td>
</tr>
<tr>
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<td>3.2</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>?</td>
</tr>
</tbody>
</table>
Example 1: Step 2 Entry

- At Step 2 Entry, the infant weighs 3.0 kg
- The single day limit is $3.0 \times 5 = 15$ mL
- The eight-week limit is $(3.0 \times 9.5) - 10.5 - 3.5 = 14.5$ mL
- The targeted blood draw volume per the SoE is 10.5 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected

<table>
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<td>10.5</td>
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<td>25 SEP 2019</td>
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<td>?</td>
</tr>
<tr>
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<td>02 OCT 2019</td>
<td>3.2</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>?</td>
</tr>
</tbody>
</table>
Example 1: Step 2 Week 1

- At Step 2 Week 1, the infant weighs 3.1 kg
- The single day limit is $3.1 \times 5 = 15.5$ mL
- The eight-week limit is $(3.1 \times 9.5) - 10.5 - 3.5 - 10.5 = 4.95$ mL
- The targeted blood draw volume per the SoE is 1.9 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected

Blood Draw Volumes Over Time

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<th>Volume (mL)</th>
</tr>
</thead>
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<tr>
<td>Step 1 Week 1</td>
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<td>3.5</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>3.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>3.2</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>?</td>
</tr>
</tbody>
</table>
Example 1: Step 2 Week 2

- At Step 2 Week 2, the infant weighs 3.2 kg
- The single day limit is $3.2 \times 5 = 16$ mL
- The eight-week limit is $(3.2 \times 9.5) - 10.5 - 3.5 - 10.5 - 1.9 = 4.0$ mL
- The targeted blood draw volume per the SoE is 3.15 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected

Blood Draw Volumes Over Time

<table>
<thead>
<tr>
<th>Visit</th>
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<th>Weight (kg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Entry</td>
<td>04 SEP 2019</td>
<td>3.2</td>
<td>10.5</td>
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<tr>
<td>Step 1 Week 1</td>
<td>11 SEP 2019</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>3.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>3.2</td>
<td>3.15</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>?</td>
</tr>
</tbody>
</table>
Example 1: Step 2 Week 4

- At Step 2 Week 4, the infant weighs 3.4 kg
- The single day limit is $3.4 \times 5 = 17$ mL
- The eight-week limit is $(3.4 \times 9.5) - 10.5 - 3.5 - 10.5 - 1.9 - 3.15 = 2.75$ mL
- The targeted blood draw volume per the SoE is 5.25 mL
- The targeted blood draw volume is more than the limit so the full targeted volume cannot be collected
- Only 2.75 mL can be collected at this visit

Blood Draw Volumes Over Time

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Weight (kg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Entry</td>
<td>04 SEP 2019</td>
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<td>10.5</td>
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<tr>
<td>Step 1 Week 1</td>
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<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>3.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>3.2</td>
<td>3.15</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>3.4</td>
<td>2.75</td>
</tr>
</tbody>
</table>
Blood Volume Priorities in Step 2

- Per the SoE, if blood collection must be limited at Step 2 visits through Week 20, available volumes should be prioritized for use in the following order:
  - Virology (except stored samples)
  - Hematology
  - Chemistries
  - CD4
  - Study agent concentrations
  - Stored samples

Example 1: Step 2 Week 4

- At Step 2 Week 4, the infant weighs 3.4 kg and the maximum allowed blood draw volume is 2.75 mL.
- Per the SoE, the 2.75 mL that can be collected should be prioritized for virology, i.e., HIV RNA PCR.
- If the 2.75 mL collected does not yield adequate plasma for HIV RNA testing, the sample should be diluted (1:5) using the site laboratory’s validated dilution method.
- *Dilution should be avoided whenever possible but is permitted prior to Step 2 Week 24.*
**Example 2:** Cohort 2 infant on Regimen 2R with weight measurements as follows:

<table>
<thead>
<tr>
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<th>Date</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>2.20</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
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<td>Step 2 Week 2</td>
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<td>2.10</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>2.15</td>
</tr>
</tbody>
</table>

**Example 2: Step 2 Entry**

- At Step 2 Entry, the infant weighs 2.20 kg
- The single day limit is $2.2 \times 5 = 11$ mL
- The targeted blood draw volume per the SoE is 10.5 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected
### Blood Draw Volumes Over Time

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Weight (kg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2 Entry</td>
<td>18 SEP 2019</td>
<td>2.20</td>
<td>10.5</td>
</tr>
<tr>
<td>Step 2 Week 1</td>
<td>25 SEP 2019</td>
<td>2.20</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>2.10</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>2.15</td>
<td>?</td>
</tr>
</tbody>
</table>

### Example 2: Step 2 Week 1

- At Step 2 Week 1, the infant weighs 2.20 kg
- The single day limit is $2.2 \times 5 = 11$ mL
- The eight-week limit is $(2.2 \times 9.5) - 10.5 = 10.4$ mL
- The targeted blood draw volume per the SoE is 1.9 mL
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected
Blood Draw Volumes Over Time

<table>
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<tr>
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<th>Weight (kg)</th>
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<td>02 OCT 2019</td>
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<td>2.15</td>
<td>?</td>
</tr>
</tbody>
</table>

Example 2: Interim Visit

- Following Step 2 Week 1, a grade 3 ANC value is obtained from the local laboratory.
- The infant returns to the clinic two days after the Step 2 Week 1 visit for a repeat test and 0.5 mL is collected for the repeat test (weight at this visit is 2.19 kg).
- The repeat test result is grade 3.
- The study clinician places a reminder in the infant’s study chart to perform continue to follow this event to resolution at subsequent visits (in consultation with the CMC).
### Blood Draw Volumes Over Time

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<td>Step 2 Week 1</td>
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<td>2.20</td>
<td>1.9</td>
</tr>
<tr>
<td>Step 2 Interim</td>
<td>27 SEP 2019</td>
<td>2.19</td>
<td>0.5</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>02 OCT 2019</td>
<td>2.10</td>
<td>?</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>2.15</td>
<td>?</td>
</tr>
</tbody>
</table>

### Example 2: Step 2 Week 2

- At Step 2 Week 1, the infant weighs 2.10 kg
- The single day limit is $2.1 \times 5 = 10.5$ mL
- The eight-week limit is $(2.1 \times 9.5) - 10.5 - 1.9 - 0.5 = 7.05$ mL
- The targeted blood draw volume per the SoE is 3.15 mL and an additional 0.5 mL is needed for another ANC (total 3.65 mL for this visit)
- The targeted blood draw volume is less than the limit so the full targeted volume can be collected
Blood Draw Volumes Over Time

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<td>Step 2 Interim</td>
<td>27 SEP 2019</td>
<td>2.19</td>
<td>0.5</td>
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<td>2.10</td>
<td>3.65</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>09 OCT 2019</td>
<td>2.15</td>
<td>?</td>
</tr>
</tbody>
</table>

Example 2: Post Step 2 Week 2

- Following the Step 2 Week 2 Visit, a grade 1 ANC value is obtained from the local laboratory
- The study clinician notes this value and confirms that ANC monitoring should revert to the frequency specified in the SoE (in consultation with the CMC)
Example 2: Step 2 Week 4

- At Step 2 Week 1, the infant weighs 2.15 kg
- The single day limit is $2.15 \times 5 = 10.75$ mL
- The eight-week limit is $(2.15 \times 9.5) - 10.5 - 1.9 - 0.5 - 3.65 = 3.875$ mL
- The targeted blood draw volume per the SoE is 5.25 mL
- The targeted blood draw volume is more than the limit so the full targeted volume cannot be collected
- Only 3.875 mL can be collected at this visit

Blood Draw Volumes Over Time

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<td>1.9</td>
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<td>Step 2 Interim</td>
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Blood Volume Priorities in Step 2

- Per the SoE, if blood collection must be limited at Step 2 visits through Week 20, available volumes should be prioritized for use in the following order:
  - Virology (except stored samples)
  - Hematology
  - Chemistries
  - CD4
  - Study agent concentrations
  - Stored samples

Example 2: Step 2 Week 4

- At Step 2 Week 4, the infant weighs 2.15 kg and the maximum allowed blood draw volume is 3.875 mL
- Per the SoE, 3 mL should be collected for virology, i.e., HIV RNA PCR
- 0.875 mL could also be collected for stored samples