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

Manual of Procedures

Version 1.6
3 November 2017
## IMPAACT P1115 Manual of Procedures
### Overview of Section Contents and Identification of Current Section Versions

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<tr>
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<th>Comments</th>
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<td>Section 1 Study Overview</td>
<td>Version 1.6</td>
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<td>Section 2 Preparing for the Study</td>
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<td>Section 5 Informed Consent</td>
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<td>Section 6 Entry and Follow-Up in Step 1</td>
<td>Version 1.6</td>
<td>No change from prior version</td>
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</table>
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| Section 9 Clinical Considerations | Version 1.6     | No change from prior version                                             |
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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 antiretroviral therapy (ART) to achieve remission in infants infected with HIV in utero. For this study, remission is defined as having no confirmed detection of plasma HIV RNA for 48 weeks following cessation of ART.

P1115 involves two cohorts of infants who will be enrolled in the study in pairs with their mothers. Some pairs will breastfeed while others will formula feed. 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 (ARVs) 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 be unknown. They will initiate intensive ART per protocol and undergo specimen collection for HIV testing within 48 hours of birth.</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Cohort 2: Infants with at least one positive HIV nucleic acid test from a specimen collected within 48 hours of birth and initiate a qualifying ART regimen outside of the study within 48 hours of birth (Early Treated Infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• These infants will enter the study in Step 2 within 10 days of birth and will receive intensive ART per protocol in Step 2.</td>
</tr>
</tbody>
</table>

Figure 1-2
IMPAACT P1115 Study Steps

| Step 1 | Initiation of intensive ART for high-risk infants while awaiting HIV test results (switch to standard prophylaxis if infection is not confirmed) |
| Step 2 | Continued intensive ART for confirmed HIV-infected infants with monitoring to determine eligibility for cessation of ART between two and four years of age |
| Step 3 | ART cessation with monitoring for viral rebound for up to five years from the date of entry into Step 3 |
| Step 4 | ART re-initiation for infants who experience viral rebound after ART cessation through five years of age or until six months after viral re-suppression on ART, whichever is later |
Under LoA #4, up to 472 mother-infant pairs — 440 in Cohort 1 and up to 32 in Cohort 2 — are targeted to be enrolled in the study to identify 54 infants with *in utero* HIV infection who enter Step 2. Infants with confirmed infection will be followed for at least 24 weeks and up to 192 weeks in Step 2.

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 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.
2.0 Preparing for the Study

P1115 will be conducted at selected IMPAACT clinical research sites worldwide. To take part in this study, clinical research sites must submit a Site Implementation Plan (SIP) for review and approval by the Protocol Team. Following review of all submitted SIPs, the team will prepare a site selection and participant accrual plan for review and approval by the IMPAACT Management Oversight Group (MOG). Upon obtaining MOG approval, selected sites will be notified and designated as permitted to complete the protocol registration process (described in Section 2.2) for this study. Selected sites should maintain a copy of their approved SIPs in their study-specific essential document files.

2.1 Investigator Responsibilities

P1115 must be conducted in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice (GCP). The Division of AIDS (DAIDS) policies on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials are useful for interpreting and operationalizing the regulations and guidelines in accordance with DAIDS expectations. These policies are available at the following web site and must be followed throughout implementation of P1115:

http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Pages/ClinicalSite.aspx

P1115 also must be conducted in accordance with all site-specific regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular. Copies of all of the above-listed regulations, policies, and guidelines should be maintained in on-site essential document files.

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

http://rsc.tech-res.com/protocolregistration/

IoRs may delegate their obligations and 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, guidelines, and policies cited above, the IoR at each site must obtain all applicable drug regulatory and ethical review approvals for P1115 prior to study initiation; the IoR must also maintain these approvals in good standing throughout the period of study implementation. With regard to drug regulatory authorities (DRAs), the IoR must complete initial and continuing submissions in accordance with DRA policies. With regard to institutional review boards and ethics committees (IRBs/ECs), further guidance on initial and continuing review requirements is available in 45 CFR 46 and the ICH GCP guidance, as well as on the web site of the US Office for Human Research Protections (OHRP):

http://www.hhs.gov/ohrp/
All sites are encouraged to request an acknowledgement of receipt for all documents submitted to their DRAs and IRBs/ECs and to request that DRAs and IRBs/ECs note the effective and expiry dates of all approvals. Because P1115 involves pediatric participants, IRBs/ECs must consider the potential benefits, risks, and discomforts of the study to children and assess the justification for their inclusion in the study. As part of this assessment, IRB/ECs must assess the level of risk to children in the following categories:

§46.404 Research not involving greater than minimal risk

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

The risk category assessed by the IRBs/ECs then determines the informed consent requirements for participation of children in the study. Specifically, per 45 CFR 46.408 (b), “the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §46.406 and §46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.”

IRBs/ECs should document their risk determination and study sites should adapt the signature pages of their informed consent forms as needed to accommodate the parental consent requirements associated with the IRBs/ECs determination. In the absence of a clearly documented determination from the IRBs/ECs, the most conservative approach specified in the regulations should be followed.

Complete documentation of all correspondence to and from all responsible DRAs and IRBs/ECs (i.e., complete copies of all submissions, responses, and approvals) must be maintained in on-site essential document files. All submission letters should list the date of the submission, the contents of the submission, and the version number and/or version date of each document submitted.

2.2 Protocol Registration

Each site’s SIP must be approved by the Protocol Team prior to the site’s submission for protocol registration; following team approval of the SIP, the IMPAACT Operations Center will notify the DAIDS Protocol Registration Office (PRO) that the site is permitted to register for the study. After all required DRA and IRB/EC approvals are obtained, site staff are then responsible for submitting documentation of the approvals, and other required documentation, to the PRO.

Per protocol Section 10.1, sites conducting P1115 should have on record at the site a plan that detects and addresses any changes in guardianship for pediatric participants and determines when a participant must have a consent process that involves a legally authorized representative other than a family member with guardianship. The plan should follow all applicable IRB/EC, local, state, and/or national guidelines, and confirmation that such a plan is on record at the site should be submitted with protocol registration materials.
Further information on the protocol registration process can be found in the *DAIDS Protocol Registration Manual*. Upon confirming receipt of all required documentation, the PRO will issue an Initial Registration Notification that indicates successful completion of the process. Site staff are responsible for maintaining documentation of all submissions for the study, along with all associated approvals/notifications and other correspondence from the PRO. *For this study, sites must obtain both an Initial Registration Notification for protocol Version 1.0 and a Registration Notification for protocol Letter of Amendment #1 prior to study initiation.*

2.3  Site-Specific Study Activation

Prior to conducting any study procedures, each site must obtain all required approvals as described in Section 2.2 above. Each site must also complete study-specific activation procedures with the Protocol Team. To help ensure site readiness for study initiation, the Protocol Team has specified a set of study activation requirements that must be met in order to obtain approval to begin study implementation. These requirements are listed on the P1115 Site-Specific Study Activation Checklist, which is available from the IMPAACT Operations Center.

Any questions related to the study activation process should be directed to the IMPAACT Operations Center. On a site-by-site basis, when all activation requirements have been met, the Operations Center will issue a Site-Specific Study Activation Notice. At each site, no study procedures may be conducted prior to receipt of the activation notice.
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 manual is to supplement the protocol, not to replace or substitute for it. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please notify the IMPAACT Operations Center of any such inconsistencies.

The P1115 Protocol Team has developed study-specific procedures for addressing various types of study-related questions, as follows:

- **Study implementation questions** may include questions related to protocol interpretation as well as administrative, ethical, regulatory, clinical, counseling, data, and laboratory operations. Any such questions that are not answered by the protocol, this manual, or the FAQs should be emailed to the P1115 Questions Email Group as listed in Figure 3-1. Also notify this group of protocol deviations.

- **Clinical management questions and notifications** should be emailed to the P1115 Clinical Management Committee (CMC) as listed in Figure 3-1. Questions related to participant eligibility, co-enrollment, potential enrollment of an ineligible participant, and/or deviation from protocol requirements for eligibility determination and enrollment should also be directed to the CMC. When emailing the CMC, to help ensure that CMC members have adequate information to respond to your question in a timely manner, please structure your message as shown in Figure 3-2.

  ![The CMC must be consulted as soon as possible and within two business days on any decision to hold or permanently discontinue any ARV at any time during infant follow-up.]

- **Other types of questions** should be managed as listed in Figure 3-1.
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<thead>
<tr>
<th>Topic</th>
<th>Contact for Questions</th>
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</thead>
<tbody>
<tr>
<td>Adding site staff to protocol email group (<a href="mailto:IMPAACT.protot1115@fstrf.org">IMPAACT.protot1115@fstrf.org</a>)</td>
<td><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 including administrative, ethical, regulatory, clinical, counseling, data, and laboratory operations</td>
<td><a href="mailto:IMPAACT.P1115Questions@fstrf.org">IMPAACT.P1115Questions@fstrf.org</a></td>
</tr>
<tr>
<td>Clinical and ART management issues</td>
<td><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><a href="mailto:IMPAACT.P1115CMC@fstrf.org">IMPAACT.P1115CMC@fstrf.org</a></td>
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<td><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><a href="mailto:rando.support@fstrf.org">rando.support@fstrf.org</a> (or by phone: +716-834-0900 x7301)</td>
</tr>
<tr>
<td>Study drug (other than study drug orders)</td>
<td><a href="mailto:wildmanmm@niaid.nih.gov">wildmanmm@niaid.nih.gov</a> (or by phone: +301-496-5213)</td>
</tr>
<tr>
<td>Study drug orders</td>
<td><a href="mailto:BIO.CRPMC.Ph@Thermofisher.com">BIO.CRPMC.Ph@Thermofisher.com</a> (or by phone: +301-294-0741)</td>
</tr>
<tr>
<td>DAIDS Adverse Experience Reporting System (DAERS)</td>
<td><a href="mailto:DAIDS-ESSSupport@niaid.nih.gov">DAIDS-ESSSupport@niaid.nih.gov</a> (questions also may be submitted from within the DAERS application)</td>
</tr>
</tbody>
</table>
Communications with the P1115 Clinical Management Committee

Please 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:

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

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Step/Week</th>
<th>AE Description or Lab Value with Grade</th>
<th>ARVs</th>
<th>Actions Taken/Comments</th>
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</table>


4.0 Participant Accrual

**IMPORTANT NOTE:** This section of the MOP provides operational guidance consistent with LoA #4. Please refer to previous versions of this section for corresponding guidance applicable prior to LoA #4.

Up to 472 mother-infant pairs are targeted to be enrolled in this study, 440 in Cohort 1 and up to 32 in Cohort 2, to identify 54 infants with *in utero* HIV infection who enter Step 2. While maternal participation in this study is limited, mothers must provide informed consent to take part in the study themselves and also provide informed consent for infant participation. Please see Section 5 of this manual for more information on obtaining informed consent for this study.

Prior to the issuance of LoA #4, accrual targets were specified by infant feeding method — breastfeeding or formula feeding — and accrual of breastfeeding participants was limited by a cap on the number of breastfed participants entering Step 2 (n=22). On 26 October 2016, all sites were informed that this cap had been reached and accrual of breastfeeding participants was paused. On 16 December 2016, LoA #4 was issued to eliminate the cap on breastfeeding participants. At each site, once all required approvals of LoA #4 have been obtained, accrual of breastfeeding participants may be resumed.

Under LoA #4:

- Accrual into Cohort 1 will remain open until 440 mother infant pairs have been enrolled in this cohort.

- If, by the time 440 mother-infant pairs have been enrolled in Cohort 1, fewer than 54 infants with *in utero* HIV infection have been enrolled in Step 2, accrual into Cohort 1 will close but accrual into Cohort 2 will remain open. Accrual into Cohort 2 will then close when 54 infants with *in utero* HIV infection have been enrolled in Step 2.

As of 31 December 2016, 223 mother-infant pairs had been enrolled in Cohort 1 (176 breastfeeding, 47 formula feeding) and 11 mother-infant pairs had been enrolled in Cohort 2 (7 breastfeeding, 4 formula feeding). During the three months prior to the pause of accrual for breastfeeding participants, an average of 32 mother-infant pairs were enrolled per month in Cohort 1. If this same rate of accrual is achieved under LoA #4, accrual into Cohort 1 is expected to be completed within calendar year 2017.

Throughout the study accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after IMPAACT Study Monitoring Committee (SMC) reviews of the study; SMC reviews are expected every six months or as specified by the SMC.
5.0 Informed Consent

This section contains reference information and guidance for obtaining informed consent in P1115. For this study, several consent processes are required:

- **For infants enrolled in Cohort 1**, informed consent will first be obtained for participation in Step 1 (reference sample informed consent form in protocol Appendix IV-A, Infant, Cohort 1/Step 1). If these infants are found to be eligible for Step 2, informed consent will be obtained separately for participation in Steps 2, 3, and 4 (reference sample informed consent form in protocol Appendix IV-B, Infant, Cohorts 1 and 2/Steps 2, 3, and 4). As part of these informed consent processes, specific notations must be recorded on the informed consent form to document consent decisions (yes or no) for genetic testing of infant blood specimens.

The final page of the sample informed consent forms for Cohort 1/Step 1 (reference protocol Appendix IV-A) provides introductory information about key aspects of Steps 2, 3, and 4. This information sheet should be reviewed with mothers enrolled in Cohort 1 to help prepare them for the separate informed consent process for Steps 2, 3, and 4, which will be conducted if infant HIV infection is confirmed.

- **For infants enrolled in Cohort 2**, informed consent will be obtained for participation in Steps 2, 3, and 4 (reference sample informed consent form in protocol Appendix IV-B, Infant, Cohorts 1 and 2/Steps 2, 3, and 4). As part of this informed consent process, specific notations must be recorded on the informed consent form to document consent decisions (yes or no) for genetic testing of infant blood specimens.

Also as part of this process, mothers will be informed that, if their child meets criteria to enter Step 3 and stop taking ARVs, the site investigator will meet with them to discuss the child’s health status and laboratory test results. Using materials provided by the protocol team, the investigator will also provide informational updates from the fields of HIV remission, reservoirs, and cure to provide current context for the child’s potential entry into Step 3. All of the mother’s questions will be answered and the discussion will be documented in detail in the child’s study chart. If the mother requests additional time to consider the child’s entry into Step 3, this will be accommodated and follow-up discussions will be scheduled accordingly. If the mother remains supportive of the child entering Step 3 and stopping use of ART (as indicated by her initial consent decision), the child will enter Step 3. If the mother is not supportive, the child will remain in Step 2 (on ART) through Week 192 and then exit the study. If the mother changes her mind while the child is still on study, and the child continues to meet criteria for Step 3, the child may then enter Step 3.

*For infants enrolled in either Cohort 1 or Cohort 2, if informed consent for genetic testing is not obtained, do not collect blood specimens specified in the SoEs for “pharmacogenetics sampling.”*

- **For all mothers**, informed consent will be obtained for maternal participation in the study (reference sample informed consent form in protocol Appendix IV-C, Mother). As part of this informed consent process, specific notations must be recorded on the informed consent form to document consent decisions (yes or no) for genetic testing of maternal blood specimens.
• **For all mothers and infants**, informed consent is requested for storage and future research use of blood specimens collected during the study. At NICHD-funded sites, separate informed consent forms are used to document these informed consent processes for mothers and infants *(reference protocol Appendix V, Fact Sheet and Template Consent Form for Specimen Storage at Repositories Funded by the NICHD, as clarified in protocol Clarification Memorandum #1, dated 27 May 2014).* At NIAID-funded sites, specific notations must be recorded on the main study informed consent forms to document this informed consent process. Consent for storage and future research use of blood specimens may be declined, with no impact on study participation.

As specified in protocol Section 10.1, in order for infants to take part in this study, 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).

Throughout this section, the term “consenter” is used to refer to the person taking part in the informed consent process with study staff. Mothers will serve as consenters for each mother-infant pair enrolled. If site IRBs/ECs determine that fathers must also provide informed consent for infant participation (per Section 2.1 above), fathers may serve also as consenters.

### 5.1 General Considerations for Obtaining Informed Consent

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

P1115 involves several different informed consent processes. For each process, however, the same ethical principles, regulations, policies, and guidelines apply.

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

Based on the reviews completed as part of the P1115 protocol development and study activation processes, there is adequate assurance that once a site-specific study activation notice has been issued, a site’s informed consent forms (ICFs) include all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate ICF. It also is the responsibility of the IoR and designated study staff to:

- Deliver all required information in a manner that is understandable to the consenter
- Assure that informed consent is obtained in a setting free of coercion and undue influence
- Confirm that the consenter comprehends the information
- Document the process
Further guidance related to each of these requirements is provided in Sections 5.2-5.5 below. Each site must have on file a study-specific SOP for obtaining informed consent that addresses all aspects of the informed consent process consistent with all applicable regulations, DAIDS policies and procedures, and protocol specifications. All sites must follow their SOPs consistently for all P1115 informed consent processes.

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

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

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

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

Please see the appendix at the end of this section for a summary of considerations for obtaining informed consent from illiterate consentees.

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

During informed consent discussions, take care to not overstate the possible benefits of the study, nor to understate the risks. Also describe the alternatives to study participation and emphasize that the availability of medical care and other services routinely obtained from the study site institution will not be affected by the consentee’s decision whether or not to take part in the study. Encourage the consentee to take as much time as she needs — and to talk about study participation with others if she chooses — before making a decision. This may be challenging in P1115, given protocol-specified time frames for enrollment. However, given the potential vulnerabilities of postpartum women and their newborn infants, sufficient time must be provided for an adequate informed consent process to be conducted.

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

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

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

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

The informed consent process for Steps 2, 3, and 4 must clearly identify that participants are asked to take part in the study long-term, with frequent infant study visits. Mothers must also be willing and able to store infant ARVs in the home and administer ARVs daily to their infants. Potential participants who may not be able to adhere to these requirements should not be enrolled.

5.5 Document the Process

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

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

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

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

Informed consent will also be documented on study case report forms (CRFs). Main study consent decisions will be recorded on the Visit Status Report CRF (ADM0040), and consent decisions for storage and future research use of blood specimens will be recorded on the Specimen Consent/Deconsent Tracking for Non-Protocol Defined Testing CRF (TRK0103).

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

- Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters
- Example of Completion of Informed Consent Form for Illiterate Consenters
- Sample Informed Consent Comprehension Checklist for Mothers
- Sample Informed Consent Comprehension Checklist for Infants: Step 1
- Sample Informed Consent Comprehension Checklist for Infants: Steps 2, 3, and 4
- Sample Informed Consent Coversheet for Mothers
- Sample Informed Consent Coversheet for Infants
Summary of Considerations for Obtaining Informed Consent from Illiterate Consenters

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials and must be followed each time informed consent is obtained from an illiterate consenter. It is recommended that each site seek IRB/EC review and approval of these procedures.

- An impartial witness must be present during the entire informed consent process with an illiterate consenter. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the consenter, and that informed consent was freely given by the consenter.

- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.

- Take care to minimize the perception of coercion due to the presence of the witness.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should print the consenter’s name below the consenter’s printed name line on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- The consenter should make her mark on the consenter’s signature line.

- Unless other conventions that have been endorsed by DAIDS are specified in site SOPs, the study staff member who completes the informed consent process with the consenter should enter the date upon which the consenter made her mark on the informed consent form below the consenter’s signature date line, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry (see figure below).

- For more information, see Section 4.8 of the ICH GCP guidance and the informed consent section of the DAIDS policy on Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials.
### Example of Completion of Informed Consent Form for Illiterate Consenters

<table>
<thead>
<tr>
<th>SIGNATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Name</td>
</tr>
<tr>
<td>Mary Phiri</td>
</tr>
</tbody>
</table>

*Participant name and date written by Martha Moore. MM 25 NOV 2014*

<table>
<thead>
<tr>
<th>Martha Moore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Staff Person Conducting Consent Discussion</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Debra Ross</th>
</tr>
</thead>
<tbody>
<tr>
<td>Witness Name</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
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 ARVs in babies soon after birth to see if this can control HIV so well that HIV cannot be detected in the baby’s blood. If HIV is well controlled, it may be possible for babies to later stop taking ARVs for a prolonged period of time and still stay healthy. |

| ✓ 2. What are mothers asked to do in this study? |
| Have blood collected for HIV-related tests when they join the study. |
| 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. |

| ✓ 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, but information learned in the study may help people who have HIV. |

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

| ✓ 6. How will information collected in the study be protected? |
| Every effort will be made to keep information private and confidential |

| ✓ 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 |

**Outcome (mark one)**

- [ ] Mother demonstrated comprehension of all required points
- [ ] Mother 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:**

### 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 ARVs in babies soon after birth to see if this can control HIV so well that HIV cannot be detected in the baby’s blood. If HIV is well controlled, it may be possible for babies to later stop taking ARVs for a prolonged period of time and still stay healthy.

### 2. This study has 4 steps, and you are being asked for your baby to join Step 1 at this time. What are babies asked to do in Step 1?

- Have 4 clinic visits within 4 weeks.
- Start taking ARVs within 48 hours of birth. The ARVs must be kept in the home and given to the baby every day.
- Have physical examinations.
- Have blood tests to check if the baby has HIV.
- Have blood tests to check the effects of ARVs.

### 3. What happens for babies that have HIV-negative test results?

- Stop taking ARVs for the study, start taking other medicines that are given to all HIV-negative babies.
- Stay in the study for 4 weeks, then leave the study.

### 4. What happens for babies that have HIV-positive test results?

- Asked to join Step 2 of the study (this will be explained in detail separately).

### 5. What are the possible risks for babies?

- Procedures may cause discomfort *(must mention at least one)*
- ARVs may cause side effects *(must mention at least one)*

### 6. What are the possible benefits for babies?

- There may be no benefit, but information learned in the study may help people who have HIV.

### 7. What happens if your baby does not join the study?

- Free to make own choice about joining.
- No change in access to maternal and child health care outside of the study.

### 8. How will information collected in the study be protected?

- Every effort will be made to keep information private and confidential.

### 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

---

**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)

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

**Study Staff Signature and Date:**

---

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**Manual of Procedures**

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### Sample Informed Consent Comprehension Checklist for P1115 Infants: Steps 2, 3, and 4

| 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 ARVs in babies soon after birth to see if this can control HIV so well that HIV cannot be detected in the baby’s blood. If HIV is well controlled, it may be possible for babies to later stop taking ARVs for a prolonged period of time and still stay healthy.

#### 2. This study has 4 steps, and you are being asked for your baby to join Step 2 at this time. Your baby may also qualify later for Step 3 or Step 4. For how long will babies be in this study, In Steps 2, 3, and 4?
- All babies will be in Step 2 for at least 6 months.
- Babies may stay in Step 2 until 4 years of age.
- Babies who enter Step 3 will stay in Step 3 for as long as tests show no HIV in the blood, up to 5 years after entering Step 3.
- Babies who enter Step 4 will stay in Step 4 until 5 years of age or until 6 months after tests show no HIV in the blood (after re-starting ART), whichever is later.

#### 3. Please tell me what you understand about clinic visits for babies.
- Frequent visits in the first 6 months of each step (every 1-4 weeks); then less frequent (every 8-12 weeks).
- Physical examinations and blood collection at most visits.
- Blood tests check the amount of HIV in the blood and other effects of ARVs.

#### 4. What happens in Step 2?
- Babies take ARVs. The ARVs must be kept in the home and given to the baby every day.
- If tests show no HIV in the blood, babies may qualify for Step 3.

#### 5. What happens in Step 3?
- Babies stop taking ARVs.
- If tests show HIV in the blood, babies enter Step 4 and start taking ARVs again.

#### 6. What happens in Step 4?
- Babies take ARVs.

#### 7. What are the possible risks for babies?
- Procedures may cause discomfort (must mention at least one)
- ARVs may cause side effects (must mention at least one)
- Stopping ARVs (in Step 3) may cause the amount of HIV in the blood to rise and lead to ARV resistance.

#### 8. What are the possible benefits for babies?
- There may be no benefit, but information learned in the study may help people who have HIV.
- ARVs given in the study may help control the amount of HIV in the baby’s body.

#### 9. What happens if your baby does not join the study?
- Free to make own choice about joining.
- No change in access to maternal and child health care outside of the study.

#### 10. How will information collected in the study be protected?
- Every effort will be made to keep information private and confidential.

#### 11. 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

**Note:** Items 7, 9, 10, and 11 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)
- ☐ Mother demonstrated comprehension of all required points
- ☐ Mother did not demonstrate comprehension of all required points

### Study Staff Signature and Date:  

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**3 November 2017**  
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**Page 23**
Sample Informed Consent Coversheet for P1115 Mothers

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s identifier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can the mother read?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>A literate impartial witness should be present during the entire IC process. Record name and relationship/role of witness below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language of IC process</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>[Language A]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Language B]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Version number and version date of informed consent form used during IC process</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Was the IC process conducted per site SOPs?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Record and explain departures from site SOPs below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was all information required to make an informed decision provided in a language understandable to the mother?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Explain below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were all of the mother’s questions answered?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Explain below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother comprehend all information required to make an informed decision?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Explain below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Explain below.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother choose to provide IC?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>STOP.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date and time at which the mother signed or marked the informed consent form</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>NA (consent declined, form not signed or marked)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother accept a copy of the IC form?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>NA (mother chose not to provide informed consent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer alternate form of study contact information.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes/Comments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signature of study staff person completing informed consent process (and this coversheet)
## Sample Informed Consent Coversheet for P1115 Infants

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes/Opt</th>
<th>Notes/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s identifier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant’s identifier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant participation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can the mother read?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language of IC process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Version number and version date of informed consent form used during IC process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the IC process conducted per site SOPs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was all information required to make an informed decision provided in a language understandable to the mother?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were all of the mother’s questions answered?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother comprehend all information required to make an informed decision?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother choose to provide IC?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date and time at which the mother signed or marked the informed consent form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the mother accept a copy of the IC form?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes/Comments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Signature of study staff person completing informed consent process (and this coversheet)**
6.0 Entry and Follow-up in Step 1

**IMPORTANT NOTE: This section of the MOP provides operational guidance consistent with LoA #4. Please refer to previous versions of this section for corresponding guidance applicable prior to LoA #4.**

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. A total of 440 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 ARVs 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 be unknown. They will initiate intensive ART 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 intensive ART per protocol in Step 2.</td>
</tr>
<tr>
<td>- If HIV infection is not confirmed, intensive ART will be discontinued and standard ARV prophylaxis will be initiated; the infant will remain in Step 1 for four weeks and then exit the study.</td>
</tr>
</tbody>
</table>

This section describes procedural requirements for entry and follow-up in Step 1. Section 7.0 provides similar information for Step 2. Subsequent sections address Steps 3 and 4, and study drug and clinical considerations in all steps.

6.1 Identification and Recruitment for Cohort 1

At each site, recruitment of Cohort 1 participants may begin after all required approvals have been obtained and a site-specific study activation notice has been issued.

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 study staff 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 the labor and/or postnatal wards, others will be required to conduct all procedures at their clinical research site facilities. As such, 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.

For both of the above-mentioned issues, study sites are required to specify their operational approaches in their SIPs. 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:

<table>
<thead>
<tr>
<th>Maternal Inclusion</th>
<th>4.111, 4.112, 4.121, 4.122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Inclusion</td>
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</tr>
<tr>
<td>Infant Exclusion</td>
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</tbody>
</table>

Key among these criteria are the requirements that mothers have presumed or confirmed HIV infection, mothers did not receive ARVs during pregnancy (receipt of ARVs during labor and delivery is permitted), infants are at least 34 weeks gestation age at birth, and enrollment occurs within 48 hours of birth.

**IMPORTANT NOTE:** On 20 April 2015, the P1115 Protocol Team notified study sites of new information related to gestational age and nevirapine (NVP) dosing for Cohort 1 infants. Based on review of available data on the pharmacokinetics of NVP in preterm infants, the team determined that the protocol-specified dose of NVP should be reduced for Cohort 1 infants born before 37 weeks of gestational age. The team also determined that an LoA was needed to specify this dosing change, and LoA #2 (dated 11 May 2015) was issued on 17 May 2015. On a site-by-site basis, until LoA #2 is approved, infants born before 37 weeks of gestational age are not permitted to be enrolled in Cohort 1 (Step 1). Please refer to the LoA document for more information as needed.

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 pregnancy
- Collection of infant medical history information, focusing on date and time of birth and gestational age 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 both the Cohort 1 eligibility criteria and the Step 1 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 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 to determine:
  - Whether mother received ARVs during pregnancy
  - Whether mother and/or infant have any documented HIV testing
  - Infant gestational age 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 per site SOPs
  ⇒ If not eligible, stop
  ⇒ If eligible, continue with enrollment and Step 1 entry procedures

It is the responsibility of the IoR and other designated study staff to ensure that all required assessments are performed and adequately documented, and that only mother-infant pairs who meet eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. In the event that study staff identify that an ineligible mother-infant pair has been enrolled, the CMC should be consulted immediately, per the communication procedures described 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

Eligible 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 and the system successfully generates a confirmation file with study identification (SID) numbers assigned for mother and infant.

6.3.2 Enrollment Timeframe for Cohort 1

Enrollment in Cohort 1 must occur within 48 hours of infant birth.

6.3.3 Enrollment Procedures for Cohort 1

A listing of enrollment (Step 1 Entry) procedures for Cohort 1 is provided on page 31. All procedures need not be performed in the order shown; however, enrollment in the Subject Enrollment System should precede other “on study” procedures. In addition:

- Infants should initiate protocol-specified intensive ART as soon as possible after enrollment.
- Initiation of ART and specimen collection for infant HIV testing must occur within 48 hours of birth.
  - The ART regimen initiated in Step 1 must include two nucleoside reverse transcriptase inhibitors (NRTIs) administered at standard doses and nevirapine (NVP) administered twice daily as specified in LoA #2:
For infants who are at least 37 weeks gestational age at birth: 6 mg/kg per dose orally twice daily from entry through the end of Step 1 dosing

For infants who are less than 37 weeks gestational age at birth (permitted to be enrolled in Cohort 1 after approval of LoA #2): 4 mg/kg per dose orally twice daily from entry to the Step 1 Week 1 visit, then 6 mg/kg per dose orally twice daily through the end of Step 1 dosing

– Specimen collection for HIV testing must include two samples collected at least one hour apart, and each sample must be tested using a nucleic acid testing method. At least one of the two tests must be a quantitative RNA PCR, and at least one must be performed in a certified laboratory (CLIA-certified for US sites, VQA-certified for non-US sites). Refer to Section 6.4 below for more information on infant HIV testing.

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 HIV care and treatment, consistent with local policies and guidelines.
### STEP 1 MATERNAL ENTRY PROCEDURES

For mother-infant pair: After confirming eligibility per site SOPs, complete paper-based Step 1 Eligibility Checklist, enter checklist data into the Subject Enrollment System to enroll the mother-infant pair, and print and file a copy of the confirmation file.

**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 PCR viral load results within the past 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 and medications history to assess and document the following:
- Sex
- Race/ethnicity
- Apgar scores, weight, length, head circumference, and gestational age at birth
- Signs, symptoms, and diagnoses since birth
- All HIV tests since birth
- All ARVs since birth
- Other concomitant medications since birth
- Feeding method since birth

Review all available documentation and determine whether additional HIV testing is required to meet study eligibility requirements.

Review all available documentation and determine specimen collection requirements for HIV testing to meet study eligibility requirements. If collection of two samples is required, collect the first sample per the LPC and site SOPs and defer collection of the second sample for at least one hour.

Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments.

Collect blood per LPC and site SOPs for:
- HIV RNA PCR
- Other HIV testing if needed to meet study eligibility requirements

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
- AST and ALT
- HIV nucleic acid testing
- Plasma and PBMC storage

Prescribe and dispense ARVs: 2 NRTIs plus NVP dosed as specified in LoA #2.

Provide HIV-related, infant feeding, and other applicable information and counseling.

Prescribe and dispense ARVs: 2 NRTIs plus NVP dosed as specified in LoA #2.

Provide referrals for HIV-related care and treatment.

Provide instructions and adherence counseling to mother for administration of ARVs to infant.

Schedule next visit, provide reminders for next visit, and provide site contact instructions.

Schedule next visit, provide reminders for next visit, and provide site contact instructions.

Document visit per site SOPs and DAIDS policies for source documentation.

Document visit per site SOPs and DAIDS policies for source documentation.

Complete and submit all required CRFs.

Complete and submit all required CRFs.
### 6.3.4 Frequently Asked Questions for Enrollment in Cohort 1 (Entry into Step 1)

<table>
<thead>
<tr>
<th>Q1: Can mothers be enrolled in Cohort 1 prior to delivery?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: No. Mothers are enrolled in Cohort 1 in pairs with their infants. As such, mothers are enrolled at the same time as their infants, after delivery. It is acceptable to introduce and explain the study to the mother prior to delivery, but enrollment should occur after delivery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2: For mothers, inclusion criterion 4.111 makes reference to the peripartum period in the definition of presumed HIV infection. 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 handle study-related HIV testing for mothers who do not have well documented HIV testing in their medical records. For example, the labor ward record may include a notation of “rapid test positive” but not include any other specific documentation of testing performed during the intrapartum or postpartum period. How should we handle this?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3: The documentation that you describe would not be adequate for eligibility confirmation per protocol, because it does not include the type of test performed, date of specimen collection and testing, and test result. The protocol allows for a number of different tests to be performed to document maternal infection. Given both the study eligibility requirements and the testing requirements of the maternal SoE, the team recommends performing two different rapid tests and a qualitative HIV RNA PCR on Samples 1 and 2, respectively. The rapid tests should be performed for purposes of presumptive eligibility determination — prior to enrollment — and the HIV RNA PCR would be performed for both confirmation of infection and assessment of viral load. If this approach is not possible in your setting, at least one rapid test must be performed prior to enrollment. Thereafter, both Sample 1 and Sample 2 would need to be collected and tested in order to meet protocol requirements, with at least one of these tests being a quantitative HIV RNA PCR.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q4: For purposes of documenting maternal eligibility, is it necessary to obtain medical records stating that the mother did not take any ARVs during pregnancy, or can we use the mother’s self-report of this information?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4: All available medical records should be reviewed for evidence of whether the mother took ARVs during pregnancy. If there is any documented evidence that the mother took ARVs during pregnancy, the mother-infant pair should be excluded from Cohort 1 (but may be considered for Cohort 2). If there is no documented evidence that the mother took ARVs during pregnancy, the mother should still be asked about ARV use, and her responses recorded in study source documents. In this case, assuming the mother reports no ARV use, she may be considered for Cohort 1.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q5: At our recruitment locations, pregnant women who received no ARVs during pregnancy are given ARVs during labor and postpartum. Would this disqualify a woman from Cohort 1?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5: No. Maternal receipt of ARVs during labor and/or the postpartum period is permitted.</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 ART 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 ART 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 ART 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, and we are concerned about this both with respect to eligibility determination and with respect to initiation of LPV/r in Step 2.

A10: As noted above, 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 with 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.

### 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 a DNA PCR, the second test must be a quantitative 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 RNA PCR and DNA PCR to be performed as the second test for high-risk infants, and that DNA PCR is specified as desirable. Assuming that DNA PCR results can be obtained by the day of the infant’s Step 1 Week 2 visit, the protocol team recommends that DNA PCR be performed. If DNA PCR results cannot be obtained by the day of the infant’s Step 1 Week 2 visit, 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 be not 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: The Step 1 SoE for infants requires a complete blood count and ALT and AST testing at entry. 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: The protocol team encourages efforts to minimize infant blood draw volumes whenever possible. The test results that you describe can be used under certain circumstances:

- For US sites, the results can be used if the tests were performed in a CAP- or CLIA-certified laboratory.
- For non-US sites, the results can be used if the tests were performed in a local laboratory that has been approved to perform these tests for P1115.
Q17: We have a question about NRTI dosing at entry into Step 1. The protocol indicates that dosing for these ARVs is per WHO or country guidelines. We follow WHO guidelines, which are weight-based beginning at weights of 3 kg. We would like to request guidance on dosing for infants who weigh less than 3 kg.

A17: As recently highlighted in protocol LoA #2, current WHO guidelines for weight-based dosing are not intended for neonates and should not be followed for infants who are less than six weeks of age or weigh less than 3 kg. For these infants, in the absence of other local guidelines for neonates, NRTI dosing should be guided by US guidelines, which are available at: http://aidsinfo.nih.gov/guidelines. Once infants reach six weeks of age and weigh at least 3 kg, WHO guidelines for weight-band dosing may be followed. Please contact the CMC with any questions or concerns related to NRTI dosing or any other aspects of ARV regimen management.

Q18: 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 record the results of the non-study tests on study CRFs?

A18: Yes. Please record the results of all HIV NATs performed after infant birth on study CRFs. Quantitative HIV RNA PCR tests should be recorded on the F3109 CRF. Qualitative tests, including HIV DNA PCR tests, should be recorded on the LBW0082 CRF. One form should be completed for each test.

Q19: 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.

A19: For the mother, all specimens specified in the maternal SoE should be collected. For the infant, all specimens except the 0.12 mL of blood specified for “pharmacogenetics sampling” at Step 1 Week 1 should be collected.

6.4 Additional Considerations for Infant HIV Testing in Step 1

Infants must have two blood samples collected for HIV nucleic acid testing at Step 1 Entry, at least one hour apart, and within 48 hours of birth. At least one of the 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-1 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 operational guidance on next steps.

When HIV-1 RNA assays are used for purposes of diagnosing HIV infection, results that indicate that HIV-1 RNA was detected at a level below the lower limit of quantitation 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-1 RNA target detected
- Roche Taqman result <20 copies/mL, HIV-1 RNA target detected

In these examples, the result indicates that HIV-1 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 (impaaact.p1115cmc@fstrf.org) 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 protocol-specified ART regimen until results from further testing are available and a final determination of HIV infection status has been made in consultation with the CMC.
HIV-1 RNA results that are reported as below the lower limit of quantitation of the assay with “target detected” should be considered discordant with results that are reported as below the lower limit of quantitation of the assay with “target not detected.” Similarly, results that are reported as below the lower limit of quantitation of the assay with “target detected” should be considered discordant with results from qualitative tests (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 CMC should be contacted immediately so that appropriate guidance can be provided within the limited amount of time available for clarification of infant HIV infection status.

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 nucleic acid testing and for storage of plasma and PBMCs. As indicated in footnote 7 of the Step 1 SoE, leftover blood samples (i.e., frozen whole blood, plasma, or cell pellets) remaining after HIV nucleic acid testing is performed should be stored for confirmatory testing if needed.

6.5 Planning for Entry into Step 2

Most infants enrolled in Cohort 1 will be HIV-uninfected. For those found to be HIV-infected (confirmed with two positive nucleic acid tests), 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 in Step 2. Key considerations are as follows:

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

- Assuming informed consent is obtained, infants with confirmed infection will discontinue follow-up in Step 1 and enter Step 2. The timing of this transition will depend on when HIV test results are obtained and when the mother and infant return to the study clinic following receipt of these results.
  - If confirmatory HIV test results are obtained before the Step 1 Week 1 visit, the infant will complete a Step 2 Entry visit instead of the Step 1 Week 1 visit. In this case, the infant will not complete any Step 1 follow-up visits (i.e., the Step 1 Week 1, Week 2, and Week 4 visits will not be done).
  - If confirmatory HIV test results are not obtained before the Step 1 Week 1 visit, they must be obtained before the Step 1 Week 2 visit. In this case, the infant will complete a Step 1 Week 1 visit (while the HIV test results are pending) and then complete a Step 2 Entry visit instead of the Step 1 Week 2 visit; the infant will not complete a Step 1 Week 4 visit.
  - In addition to the above, the mothers of infants with confirmed HIV infection will complete the evaluations listed under “when infant is confirmed infected” in the maternal SoE, ideally on the same day as the infant’s Step 2 entry visit.

Also refer to Figure 6-3 which provides an overview of HIV testing requirements and participant management in relation to entry into Step 2 from Step 1.
Figure 6-2
Illustration of Time Frames for Cohort 1 Infant Entry into Step 2

Initiate ART and collect blood for HIV testing within 48 hours of birth

Enter Step 2 by the date of the Step 1 Week 2 visit
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 4.111?

no
Discontinue mother and infant from study participation.

Positive results from sample #1 and sample #2 (collected at different time points) obtained within 7 business days of enrollment

yes

Has in utero HIV infection been confirmed per protocol Section 6.31?

no

Stop protocol-specified ART and start standard of care prophylaxis. Complete Step 1 Week 1, Week 2, and Week 4 visits, then exit from study. Refer to non-study sources of prophylaxis and other required care, including follow-up HIV testing and/or treatment.

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)

yes

Has informed consent been provided for Steps 2-4?

no

yes

Enter Step 2 must occur by the date of the Step 1 Week 2 visit
6.5 Follow-up in Step 1

Conduct of infant follow-up visits in Step 1 will depend on when infant HIV test results are received and whether HIV-infection is confirmed. For infants in whom HIV infection is not confirmed, Step 1 follow-up visits will be conducted at Week 1 (±2 days), Week 2 (±2 days), and Week 4 (±7 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 4 visit.

To further illustrate the Step 1 infant follow-up visit schedule, Figure 6-5 provides calendar dates for visits expected for a sample HIV-uninfected infant who enters Step 1 on 1 July 2014.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Visit Window</th>
<th></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 July 2014</td>
<td>6 July 2014</td>
<td>10 July 2014</td>
</tr>
<tr>
<td>Week 2</td>
<td>15 July 2014</td>
<td>13 July 2014</td>
<td>17 July 2014</td>
</tr>
<tr>
<td>Week 4</td>
<td>29 July 2014</td>
<td>22 July 2014</td>
<td>5 August 2014</td>
</tr>
</tbody>
</table>

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

A listing of Step 1 follow-up procedures is provided on page 40. There is no specified ordering or required sequence for these procedures, with the exception that blood specimens for NVP dose evaluation — stored plasma and DBS — must be collected at the same time (see also the operational note on the bottom of page 40). Unless otherwise specified, all procedures should be performed at all visits (i.e., at Week 1, Week 2, and Week 4).

Per protocol Section 6.31, infants with Grade 2 or higher toxicities at the Step 1 Week 4 visit will continue to be followed until the toxicity has resolved or stabilized; see page 41 for further guidance on this protocol requirement.

Upon entry into Step 1, infants will initiate protocol-specified intensive ART. For infants in whom in utero HIV infection is not confirmed based on testing of samples collected within 48 hours of birth, protocol-specified ART should be discontinued at the first visit after the infant’s HIV infection status is determined, with immediate transition to standard of care prophylaxis. The transition from protocol-specified ART to standard of care prophylaxis must occur by the date of the Step 1 Week 2 visit. To avoid gaps in ARV dosing, study staff should ideally provide standard of care prophylaxis to study infants through Step 1 Week 4. In addition, active referrals should be made to non-study sources of prophylaxis and other required infant care, including follow-up HIV testing, which is indicated at six weeks of age.

The P1115 protocol allows for mother-infant pairs to be enrolled based on presumptive evidence of maternal HIV infection (at least one positive rapid test result obtained in the peripartum period), with additional testing required to confirm infection, and results available within seven business days of enrollment. If additional testing does not confirm maternal infection, both mother and infant must be discontinued from follow-up.
### STEP 1 INFANT FOLLOW-UP PROCEDURES
#### WEEKS 1, 2, AND 4

- Collect interval (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Administer adherence questionnaire to mother (*Weeks 1 and 2*)
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments
- Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting 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 (*Week 2, also at Week 4 if Week 2 result is Grade 1 or higher*)
  - AST and ALT (*Week 2, also at Week 4 if Week 2 result is Grade 1 or higher*)
  - HIV nucleic acid test (*Week 2*)
  - Plasma and PBMC storage (*Week 1*)
  - Pharmacokinetics sampling (*DBS; Week 1, also at Week 2 only if infant was taking NVP at the protocol-specified treatment dose between Week 1 and Week 2*)
  - Pharmacogenetics sampling (*DBS; Week 1*)
- Prescribe and dispense ARVs as needed (*Week 1; adjust doses when indicated based on ≥10% increase in weight*)
- Provide instructions and adherence counseling to mother for administration of ARVs to infant (ART or prophylaxis)
- 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
- Schedule next visit, provide reminders for next visit, and provide site contact instructions (*Weeks 1 and 2*)
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

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**Per protocol Clarification Memorandum #1, DNA PCR, RNA PCR, and TNA tests may be performed at Step 1 Week 2.**

**On 14 June 2016, study sites were notified that the NVP dose evaluation described in protocol Section 9.2 had been completed and that the protocol-specified dose of NVP was accepted. Effective immediately thereafter for infants in Step 1:**

- The 1 mL of blood specified for “Stored Plasma and PBMC” at Step 1 Week 2 should no longer be collected.
- The 2.5 mL of blood specified for “Stored Plasma and PBMC” at Step 1 Week 1 should still be collected per the SoE (all infants).
- The 0.12 mL of blood specified “PK Sampling” at Step 1 Week 1 and Step 1 Week 2 should still be collected per the SoE (infants “still taking NVP in study treatment doses”).

At Week 1, samples collected for stored plasma must be collected at the same time as samples collected for pharmacology (PK sampling). It is generally expected that these samples will be collected during a single phlebotomy session, i.e., from the same needle stick. However, if both samples cannot be collected from the same needle stick, the second sample may be collected from a second needle stick later in the visit. The two samples should be collected within the shortest possible time period, and the time of collection of each sample must be documented.

Refer to Appendix III for guidance on assigning off-treatment, off-step, and off-study codes to be recorded on the ADM0030, PE4005, and F1601 CRFs.
Per protocol Section 6.31, infants with Grade 2 or higher toxicities at the Step 1 Week 4 visit will continue to be followed until the toxicity has resolved or stabilized. Further guidance to operationalize this protocol requirement is as follows:

• **Any infant with a Grade 2 or higher adverse event (sign, symptom, diagnosis, or lab value) assessed as possibly, probably, or definitely related to study drug (any ARV in the study drug regimen) should continue to be followed until the condition improves to Grade 1 or lower.** The frequency of follow-up and re-evaluation should be guided by the severity of the event and relevant portions of protocol Section 6:
  
  – Grade 2 events should be re-evaluated within 1-2 weeks.

  – Grade 3 or 4 events should be re-evaluated consistent with the relevant guidelines provided in protocol Sections 6.1 and 6.2.

  – For all events, guidance on the frequency of re-evaluation may also be requested from the CMC.

• Once the event has improved to Grade 1 or lower, the infant should then be discontinued from follow-up. For events that have been re-evaluated and determined to have stabilized at Grade 2 or higher, consult the CMC for further guidance on when further follow-up may be discontinued.

With respect to data collection:

• The infant should be considered on-study until the event has improved to Grade 1 or lower (or the CMC has advised that follow-up may be discontinued). Do not complete the Study Step Discontinuation (ADM0030) or Off Study (F1601) CRFs before improvement of the event to Grade 1 or lower (or the CMC has advised that follow-up may be discontinued).

• At the time of follow-up evaluation (after Week 4), complete relevant CRFs to document the follow-up evaluation and the current status of the event.

• Once the infant has been discontinued from follow-up, complete the Study Step Discontinuation (ADM0030) and Off Study (F1601) CRFs.
7.0 Entry and Follow-up in Step 2

**IMPORTANT NOTE:** This section of the MOP provides operational guidance consistent with LoA #4. Please refer to previous versions of this section for corresponding guidance applicable prior to LoA #4.

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.

See Section 4 of this manual and protocol Section 8.3 for more detailed information on accrual into each cohort.

7.1 Cohort 1, Transition from Step 1 into Step 2

As described in Section 6.4, infants enrolled in Cohort 1 who are found to be HIV-infected (confirmed with two positive nucleic acid tests) will enter Step 2 by the date of their Step 1 Week 2 visit (i.e., by Day 16 on study). The Step 2 eligibility criteria for these infants are specified in the following protocol sections:

<table>
<thead>
<tr>
<th>Infant Inclusion</th>
<th>4.31, 4.311, 4.312</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Exclusion</td>
<td>4.6</td>
</tr>
</tbody>
</table>

In addition, informed consent must be obtained for infant participation in Steps 2, 3, and 4.

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 DMC’s Subject Enrollment System and the system successfully generates a confirmation file with Step 2 SID numbers assigned for mother and infant.

It is the responsibility of the IoR and other designated study staff to ensure that only infants who meet eligibility criteria for Step 2 enter this step, per study-specific SOPs that should be followed for all infants. In the event that study staff identify that an ineligible infant has been entered into Step 2, the CMC should be consulted immediately, per the communication procedures described 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 and initiate a qualifying ART 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 ART per protocol in Step 2.
7.2.1 Identification and Recruitment for Cohort 2

At each site, recruitment of Cohort 2 participants may begin after all required approvals have been obtained and a site-specific study activation notice has been issued.

Given the Cohort 2 eligibility criteria, to optimize accrual into this cohort, study staff may be required 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 study staff of potential study participants. For both of the above-mentioned issues, study sites are required to specify their operational approaches in their SIPs. 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>Maternal Inclusion</th>
<th>4.111, 4.112, 4.131</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant Inclusion</td>
<td>4.31, 4.331, 4.332, 4.333, 4.334, 4.335, 4.336</td>
</tr>
<tr>
<td>Infant Exclusion</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Key among these criteria are the requirements that infants have at least one positive HIV nucleic acid test from a specimen collected within 48 hours of birth and initiate a qualifying ART regimen outside of the study within 48 hours of birth. These infants must enter the study within 10 days of birth and must take their qualifying ART regimen daily prior to study entry (see Figure 7-2).

Qualifying ART regimens include two NRTIs plus NVP and/or lopinavir/ritonavir (LPV/r). The dose of NVP provided must be at least 8 mg per day for infants with birth weights up to 2 kg or 12 mg per day for infants with birth weights greater than 2 kg.

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

Days of age
0 1 2 10
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 at birth; date, time, and results of HIV testing; and ARV use
- 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 both the Cohort 2 eligibility criteria and the Step 2 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 2 ELIGIBILITY DETERMINATION PROCEDURES

- Determine whether mother is of 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 to determine:
  - Whether mother and/or infant have any documented HIV testing (including date and time of specimen collection for infants)
  - Whether infant initiated a qualifying ARV regimen within 48 hours of birth and has taken this regimen daily since initiation
  - Infant gestational age 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 per site SOPs
  ⇒ If not eligible, stop
  ⇒ If eligible, continue with enrollment and Step 2 entry procedures

It is the responsibility of the IoR and other designated study staff to ensure that all required assessments are performed and adequately documented, and that only mother-infant pairs who meet eligibility criteria are enrolled. Each site must have on file a study-specific SOP for eligibility determination that describes how study staff will fulfill this responsibility; all sites must follow their SOPs when assessing eligibility for all potential participants. Should study staff identify that an ineligible mother-infant pair has been enrolled, the CMC should be consulted immediately, per the communication procedures described in Section 3 of this manual.

#### 7.2.3 Definition of Enrollment for Cohort 2

Eligible mother-infant pairs will be considered enrolled in Cohort 2 after study staff have entered all required eligibility checklist data into the DMC’s Subject Enrollment System and the system successfully generates a confirmation file with SID numbers assigned for mother and infant.

#### 7.2.4 Enrollment Timeframe for Cohort 2

Enrollment in Cohort 2 must occur within 10 days of infant birth.
7.3 Step 2 Entry Procedures: Cohort 1 and Cohort 2

7.3.1 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 46, in separate columns for mothers in Cohort 1 and Cohort 2.

- **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” should be performed on the day of Step 2 entry.

- **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” should be performed on the day of Step 2 entry.

All procedures need not be performed in the order shown on page 46; however, for mothers in Cohort 2, enrollment in the Subject Enrollment System should precede other “on study” procedures.

*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 and treatment, consistent with local policies and guidelines.*

7.3.2 Procedures for Infants

A listing of Step 2 Entry procedures for infants is provided on page 47, 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 Subject Enrollment System should precede other “on study” procedures.

*The P1115 protocol allows for mother-infant pairs to be enrolled based on presumptive evidence of both maternal and infant HIV infection, with additional testing required to confirm infection and results available within seven business days of enrollment. If additional testing does not confirm both maternal and infant infection, both mother and infant must be discontinued from follow-up (with referral to non-study sources of care and treatment). For infants enrolled in Cohort 2, if a second nucleic acid test does not confirm the initial positive result, the CMC should be notified and a third specimen should be collected for additional testing, with results available within seven additional business days. In this scenario, the mother and infant may remain on study pending receipt of the third test result. Refer to Section 6.4 for further guidance on use of HIV-1 RNA assays for purposes of diagnosing infant HIV infection; this same guidance is applicable in Cohort 2 as well as in Cohort 1.*
<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><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete paper-based Step 2 Eligibility Checklist, enter checklist data into the Subject Enrollment System to enter the mother-infant pair into Step 2, and print and file a copy of the confirmation file</td>
<td><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete paper-based Step 2 Eligibility Checklist, enter checklist data into the Subject Enrollment System to enroll the mother-infant pair, and print and file a copy of the confirmation file</td>
</tr>
</tbody>
</table>
| Collect targeted interval (since the last visit) medical and medications history:  
  • WHO clinical stage  
  • ARV use  
  • CD4 cell counts  
  • HIV RNA PCR viral load results  
  • Any other relevant history | 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 PCR viral load results within the past 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 |
| Collect blood per LPC and site SOPs for:  
  • Stored serum  
  • Stored plasma and cells | Collect blood per LPC and site SOPs for:  
  • HIV RNA PCR  
  • Other HIV testing if needed to meet study eligibility requirements  
  • Stored serum  
  • Stored plasma and cells |
| Provide HIV-related, infant feeding, and other applicable information and counseling | Provide HIV-related, infant feeding, and other applicable information and counseling |
| Provide or follow up on referrals for HIV-related care and treatment | Provide referrals for HIV-related care and treatment |
| Schedule next visit, provide reminders for next visit, and provide site contact instructions | Schedule next visit, provide reminders for next visit, and provide site contact instructions |
| Document visit per site SOPs and DAIDS policies for source documentation | Document visit per site SOPs and DAIDS policies for source documentation |
| Complete and submit all required CRFs | Complete and submit all required CRFs |

**In the event that the full maternal blood draw volume cannot be collect on the day of Step 2 Entry, 10 mL should ideally be collected in an EDTA tube and processed for (i) HIV testing if needed to confirm eligibility per protocol Section 4.111 and (ii) plasma and PBMC storage. The mother should also 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.**
<table>
<thead>
<tr>
<th><strong>COHORT 1: INFANT STEP 2 ENTRY PROCEDURES</strong></th>
<th><strong>COHORT 2: INFANT STEP 2 ENTRY PROCEDURES</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete paper-based Step 2 Eligibility Checklist, enter checklist data into the Subject Enrollment System to enter the mother-infant pair into Step 2, and print and file a copy of the confirmation file</td>
<td><strong>For mother-infant pair:</strong> After confirming eligibility per site SOPs, complete paper-based Step 2 Eligibility Checklist, enter checklist data into the Subject Enrollment System to enroll the mother-infant pair, and print and file a copy of the confirmation file</td>
</tr>
</tbody>
</table>
| Collect interval medical and medications history:  
- Signs, symptoms, and diagnoses  
- ARVs  
- Other concomitant medications  
- Feeding method | Complete review of available medical records and collection of medical and medications history to assess and document the following:  
- Sex  
- Race/ethnicity  
- Apgar scores, weight, length, head circumference, and gestational age at birth  
- Signs, symptoms, and diagnoses since birth  
- All HIV tests since birth  
- All ARVs since birth  
- Other concomitant medications since birth  
- Feeding method since birth |
| Determine and document postmenstrual age | Determine and document postmenstrual age |
| Administer adherence questionnaire to mother | Administer adherence questionnaire to mother |
| Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments | Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments |
| Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting CMC if indicated | Review all available documentation and determine specimen collection requirements for HIV testing to meet study eligibility requirements. |
| 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  
- AST, ALT, and lipase  
- CD4 cell count  
- HIV RNA PCR  
- Plasma and PBMC storage  
- Digital droplet DNA PCR (stored)  
- Pharmacokinetics sampling (DBS) | 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  
- AST, ALT, lipase  
- CD4 cell count  
- HIV RNA PCR  
- Other HIV nucleic acid test if needed for confirmation of HIV infection  
- Plasma and PBMC storage  
- Digital droplet DNA PCR (stored)  
- Pharmacokinetics sampling (DBS) |
| Prescribe and dispense ARVs: 2 NRTIs plus NVP dosed at 6 mg/kg twice daily plus LPV/r if ≥14 days of age and ≥42 weeks postmenstrual age | Prescribe and dispense ARVs: 2 NRTIs plus NVP dosed at 6 mg/kg twice daily |
| Provide instructions and adherence counseling to mother for administration of ARVs to infant | Provide instructions and adherence counseling to mother for administration of ARVs to infant |
| Schedule next visit, provide reminders for next visit, and provide site contact instructions | Schedule next visit, provide reminders for next visit, and provide site contact instructions |
| Document visit per site SOPs and DAIDS policies for source documentation | Document visit per site SOPs and DAIDS policies for source documentation |
| Complete and submit all required CRFs | Complete and submit all required CRFs |
| Report expedited adverse events to the DAIDS Safety Office if applicable | |
### 7.3.3 Frequently Asked Questions for Entry into Step 2

<table>
<thead>
<tr>
<th>Q1: Maternal inclusion criterion 4.131 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 4.111 makes reference to the peripartum period in the definition of presumed HIV infection. 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 done on the day of enrollment (day of entry into Step 2).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q4: The Eligibility Checklist for Step 2 asks “Does the infant have confirmed evidence of in utero HIV infection as defined in protocol Section 6.31?” For our infants in Cohort 2, we understand that we must have at least one positive HIV NAT test from a specimen collected within 48 hours of birth, and we expect that we will need to perform the second confirmatory test upon enrollment in the study. We are not clear, however, on which CRFs should be completed to record the relevant data from these tests. Could you please advise?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4: All nucleic acid tests performed prior to and following study entry should be recorded on the F3109 CRF (for quantitative RNA PCR tests) or on the LBW0082 CRF (for DNA PCR and other qualitative tests). Please complete and enter the relevant form for each test performed since infant birth.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q5: 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>A5: 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>Q6: 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, and we are concerned about this both with respect to eligibility determination and with respect to initiation of LPV/r in Step 2.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A6: The protocol allows for gestational age to be assessed based on date of LMP and, unless study staff are able to assess the infant within 48 hours of birth, the documented gestational assessment should be used. However, if study staff are able to assess the infant within 48 hours of birth, 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; 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 with the CMC regarding questions of gestational age or any other aspects of eligibility.</td>
</tr>
</tbody>
</table>
Q7. 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?

A7: 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 be not considered exclusionary. You are also encouraged to contact the Clinical Management Committee with any questions of eligibility for any potential participant at any time.

Q8: We have an infant at our site who qualified for Cohort 2 based on an 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 DNA PCR, so we performed an 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.

A8: Per protocol Section 6.32.2, please draw blood for additional HIV testing at the infant’s Step 2 Week 1 visit. It would be ideal if you could perform DNA PCR or a TNA test on this (third) blood sample, with results available within seven business days. However, if that is not possible, you will need to perform another RNA PCR and then make a final determination of HIV infection status and eligibility to remain in the study in consultation with the CMC.

Q9: 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?

A9: No. Infants will always be considered part of the cohort in which they were originally enrolled. So 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.

Q10: We have identified an HIV-infected infant in Step 1 who will be entering Step 2. When he enters Step 2, he will be taking the same ARV regimen that he was taking in Step 1, because he has not yet reached the age required to start LPV/r. Do we need to write a new prescription for this infant at the Step 2 Entry visit, or can the prescription from the Step 1 entry visit still apply?

A10: Yes. A new prescription is needed at Step 2 Entry, using the SID number generated when the infant was successfully entered into Step 2 using the Subject Enrollment System.

Q11: 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. We follow WHO guidelines, which are weight-based beginning at weights of 3 kg. We would like to request guidance on dosing for infants who weigh less than 3 kg.

A11: As recently highlighted in protocol LoA #2, current WHO guidelines for weight-based dosing are not intended for neonates and should not be followed for infants who are less than six weeks of age or weigh less than 3 kg. For these infants, in the absence of other local guidelines for neonates, NRTI dosing should be guided by US guidelines, which are available at: http://aidsinfo.nih.gov/guidelines. Once infants reach six weeks of age and weigh at least 3 kg, WHO guidelines for weight-band dosing may be followed. Please contact the CMC with any questions or concerns related to NRTI dosing or any other aspects of ARV regimen management.

Q12: We enrolled an infant in Cohort 2 at 10 days of age and would like to clarify expectations for his ART management. Do we need to bring this infant back to the clinic in four days to add LPV/r to his ART regimen?

A12: No, the infant does not need to return to the clinic in four days to add LPV/r to his ART regimen. The protocol specifies that LPV/r should be added to the ART regimen as infants reach 14 days of age and 42 weeks of postmenstrual age. However, the addition of LPV/r to the ART regimen does not need to happen on the exact day when an infant reaches 14 days of age and 42 weeks of postmenstrual age. Rather, you can wait until the scheduled date of the Step 2 Week 1 visit and add LPV/r at that time.
Q13: 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 record the results of the non-study tests on study CRFs?

A13: Yes. Please record the results of all HIV NATs performed after infant birth on study CRFs. Quantitative HIV RNA PCR tests should be recorded on the F3109 CRF. Qualitative tests, including HIV DNA PCR tests, should be recorded on the LBW0082 CRF. One form should be completed for each test.

Q14: 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.

A14: For the mother, all specimens specified in the maternal SoE should be collected. For the infant, all specimens except the 0.12 mL of blood specified for “pharmacogenetics sampling” at Step 2 Week 1 should not be collected.

7.4 Follow-up in Step 2

Following entry into Step 2, infants will complete nine visits in the first six months of follow-up in Step 2. These visits are described in Section 7.4.1 and 7.4.2. In the future, these sections will be updated to provide similar information for extended follow-up in Step 2.

Mothers of infants in Step 2 will complete follow-up visits approximately every six months. These visits are described in Section 7.4.3.

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 the Step 2 visit schedule, the figure also provides calendar dates for visits expected for a sample infant who enters Step 2 on 1 August 2014. Each visit should ideally be conducted on the target date but may be conducted on any day within the allowable window.

**Figure 7-3**

Follow-up Visit Schedule through Week 24

For a Sample Infant who Enters Step 2 on 1 August 2014

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td>Week 1</td>
<td>8 AUG 2014</td>
<td>±2 days</td>
</tr>
<tr>
<td>Week 2</td>
<td>15 AUG 2014</td>
<td>±2 days</td>
</tr>
<tr>
<td>Week 4</td>
<td>29 AUG 2014</td>
<td>±7 days</td>
</tr>
<tr>
<td>Week 6</td>
<td>12 SEP 2014</td>
<td>±7 days</td>
</tr>
<tr>
<td>Week 8</td>
<td>26 SEP 2014</td>
<td>±7 days</td>
</tr>
<tr>
<td>Week 12</td>
<td>24 OCT 2014</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 16</td>
<td>21 NOV 2014</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 20</td>
<td>19 DEC 2014</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 24</td>
<td>16 JAN 2015</td>
<td>±14 days</td>
</tr>
</tbody>
</table>

*Target visit dates are counted from the day of entry into Step 2. Day of entry = Day 0.
A listing of Step 2 infant follow-up procedures through Week 24 is provided on page 52. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.

As indicated in the procedural listing, ARV dosing changes are expected during follow-up in Step 2. All such changes should be implemented at an in-person visit, with the issuance of a new prescription and provision of detailed dosing instructions and adherence counseling to the infant’s mother. Refer to the operational notes at the bottom of page 52 as well as Section 7.4.2 for further guidance on this topic.
## STEP 2 INFANT FOLLOW-UP PROCEDURES
### WEEKS 1, 2, 4, 6, 8, 12, 16, 20, AND 24

- Collect interval (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Determine and document postmenstrual age (*until ≥ 42 weeks*)
- Administer adherence questionnaire to mother
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments (*all visits except Week 6*)
- Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting 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 (*Weeks 2, 4, 8, 16, 24; at sites with dual platform laboratories, also perform at Week 12, because a CD4 cell count is required at Week 12*)
  - AST, ALT, and lipase (*Weeks 2, 4, 8, 16, 24*)
  - CD4 cell count (*Weeks 2, 12, and 24*)
  - HIV RNA PCR (*Weeks 2, 4, 8, 12, 16, 20, 24*)
  - Plasma and PBMC storage (*Weeks 2, 4, 8, 16, 24*)
  - Digital droplet DNA PCR (*stored; Weeks 12 and 24*)
  - DBS for virology (*stored; Weeks 1, 4, and 24*)
  - Pharmacokinetics sampling (*DBS; Weeks 1, 2, 4, 8, 12, 16, 20 and Week 24*)
  - Pharmacogenetics sampling (*DBS; Week 1 only*)
- Prescribe and dispense ARVs as needed:
  - *Add LPV/r at ≥14 days of age and ≥42 weeks post menstrual age*
  - *Change NVP dose to 200 mg/m² or WHO weight band dosing* at Week 4
  - *Stop NVP at ≥12 weeks after two consecutive HIV RNA levels < LOD*
  - *Adjust doses when indicated based on ≥10% increase in weight or body surface area*
- 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 prophylaxis, care, and treatment for mother and/or infant 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
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

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**The Week 6 visit 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. An in-person visit should also be conducted if an ARV dosing change is indicated at the Week 6 time point.**

**Postmenstrual age is calculated by adding postnatal age (age since birth) to gestational age at birth. For example, at four weeks of age, an infant with a gestational age of 40 weeks at birth would have a postmenstrual age of 44 weeks. In contrast, at four weeks of age, an infant with a gestational age of 34 weeks at birth would have a postmenstrual age of 38 weeks.**

**Per protocol Section 5.13, a new prescription is required at the time of any ARV formulation change (e.g., change from solution to tablet) and for any ARV dosing change, including dose adjustments for infants who outgrow their previous dose and are switched to the next dosing increment.**
7.4.2 Virologic Monitoring and Infant Eligibility to Continue Follow-up in Step 2 after Week 24

**IMPORTANT NOTE:** This section of the MOP provides operational guidance consistent with LoA #3. Please refer to previous versions of this section for corresponding guidance applicable prior to LoA #3.

Infants in Step 2 will undergo HIV viral load (RNA PCR) testing at Weeks 2, 4, 8, 12, 16, 20, and 24. The results of these tests should be reviewed by study clinicians upon receipt and evaluated for the expected downward trend as infants continue on ART. If the expected downward trend is not observed, this information should be used to guide adherence counseling and inform clinical and ART management for the infant; please consult with the CMC regarding clinical and ART management as needed. Under LoA #3, every effort should be made to optimize ART regimens and adherence support such that viral load is suppressed to less than 200 copies/mL by Week 24.

**Dilution of specimens used for HIV RNA PCR should be avoided whenever possible and is not permitted at or after Step 2 Week 24. Prior to Step 2 Week 24, when dilution is necessary, a validated diluent must be used and the LOD of the assay must be adjusted accordingly. Refer to the LPC for more information on this topic.**

Per protocol Section 6.322, infants in Step 2 will receive a four-drug ART regimen (2 NRTIs + NVP + LPV/r) until 12 weeks after they have two consecutive HIV RNA levels below the LOD of the assay, at which time NVP will be discontinued. Two examples are as follows:

<table>
<thead>
<tr>
<th>Sample Case 1: Infant with HIV RNA levels &lt; LOD at Step 2 Weeks 8 and 12.</th>
</tr>
</thead>
<tbody>
<tr>
<td>This infant’s HIV RNA level would be considered confirmed &lt; LOD upon receipt of the Week 12 test result.</td>
</tr>
<tr>
<td>Twelve weeks after Step 2 Week 12 falls at Step 2 Week 24. If the HIV RNA level remains &lt; LOD at Weeks 16 and 20, NVP should be stopped for this infant at Step 2 Week 24.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Case 2: Infant with HIV RNA levels &lt; LOD at Step 2 Weeks 12 and 16.</th>
</tr>
</thead>
<tbody>
<tr>
<td>The infant’s HIV RNA level would be considered confirmed &lt; LOD upon receipt of the Week 16 test result.</td>
</tr>
<tr>
<td>Twelve weeks after Step 2 Week 16 falls at Step 2 Week 28. If the HIV RNA level remains &lt; LOD at Weeks 20 and 24, NVP should be stopped for this infant at Step 2 Week 28.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
Per protocol Section 6.322 (under LoA #3) and as shown in Figure 7-4, infants whose HIV viral load is not suppressed below 200 copies/mL at Week 24 will be discontinued from follow-up. If the Week 24 HIV RNA PCR result is 200 copies/mL or higher, the mother and infant should be recalled to the clinic for a confirmatory test. The confirmatory test must be repeated within three weeks (specimen collection for the confirmatory test must occur within three weeks of specimen collection for the initial test). 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 complete a Premature Discontinuation visit (see Section 7.4.5) and then exit the study. If the confirmatory test result is less than 200 copies/mL, the infant will remain on-study.

Figure 7-4
Virologic Monitoring and Infant Management at Step 2 Week 24 under LoA #3

Monitor HIV RNA at Step 2 Weeks 2, 4, 8, 12, 16, 20, and 24.

Is HIV RNA <200 copies/mL at Week 24?

yes

Continue follow-up in Step 2 (next visit at Week 28).

Is HIV RNA <200 copies/mL?

no or test not repeated within 3 weeks

Repeat test within 3 weeks

Complete Premature Discontinuation Visit then exit from study. Refer to non-study sources of HIV care and treatment.
7.4.3 Follow-up Visits and Procedures for Infants: Step 2 Week 28 to Week 72

Figure 7-5 lists the visits expected to be conducted between Weeks 28 and 72 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 August 2014. Each visit should ideally be conducted on the target date but may be conducted on any day within the allowable window of ±14 days.

### Figure 7-5
Week 28 to Week 72 Follow-up Visit Schedule
For a Sample Infant who Enters Step 2 on 1 August 2014

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day*</th>
<th>Visit Window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Duration</td>
</tr>
<tr>
<td>Week 28</td>
<td>13 FEB 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 32</td>
<td>13 MAR 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 36</td>
<td>10 APR 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 40</td>
<td>8 MAY 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 44</td>
<td>5 JUN 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 48</td>
<td>3 JUL 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 52</td>
<td>31 JUL 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 56</td>
<td>28 AUG 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 60</td>
<td>25 SEP 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 64</td>
<td>23 OCT 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 68</td>
<td>20 NOV 15</td>
<td>±14 days</td>
</tr>
<tr>
<td>Week 72</td>
<td>18 DEC 15</td>
<td>±14 days</td>
</tr>
</tbody>
</table>

*Target visit dates are counted from the day of entry into Step 2. Day of entry = Day 0.

The quarterly visits — at Weeks 36, 48, 60, and 72 — must be conducted in-person at the study clinic. The intervening monthly visits — 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.

Listings of infant follow-up procedures for monthly and quarterly visits through Week 72 are provided on pages 56 and 57. There is no specified ordering or required sequence for these procedures. Unless otherwise specified, all procedures should be performed at all visits.

As indicated in the procedural listings, ARV dosing changes are expected during follow-up in Step 2. All such changes should be implemented at an in-person visit, with the issuance of a new prescription and provision of detailed dosing instructions and adherence counseling to the infant’s mother.
### 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 (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Administer adherence questionnaire to mother
- Assess whether any other evaluations or procedures are clinically indicated; if so, recall the infant to the clinic if needed and proceed per protocol, consulting CMC if indicated
- Prescribe and dispense ARVs as needed (must be done at an in-person visit):
  - **Stop NVP at ≥12 weeks after two consecutive HIV RNA levels < LOD**
    (if not stopped previously)
  - **Adjust doses when indicated based on ≥10% increase in weight or body surface area**
- 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
- Provide reminders for next visit and site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit all required CRFs
- 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 (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Administer adherence questionnaire to mother
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments
- Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting 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
  - AST, ALT, and lipase
  - CD4 cell count
  - HIV RNA PCR
  - Plasma and PBMC storage
  - Digital droplet DNA PCR *(stored)*
  - DBS for virology *(stored; Weeks 48 and 72)*
  - HIV-specific immune responses *(stored; Week 72)*
  - Pharmacokinetics sampling *(DBS)*
- Prescribe and dispense ARVs as needed:
  - Stop NVP at ≥12 weeks after two consecutive HIV RNA levels < LOD *(if not stopped previously)*
  - Adjust doses when indicated based on ≥10% increase in weight or body surface area
- 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 prophylaxis, care, and treatment for mother and/or infant 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
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

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**Per protocol Section 5.13, a new prescription is required at the time of any ARV formulation change (e.g., change from solution to tablet) and for ARV dosing change, including dose adjustments for infants who outgrow their previous dose and are switched to the next dosing increment.**
7.4.4 Virologic Monitoring and Infant Eligibility to Continue Follow-up through Week 72

**IMPORTANT NOTE:** This section of the MOP provides operational guidance consistent with LoA #3. Please refer to previous versions of this section for corresponding guidance applicable prior to LoA #3.

Infants in Step 2 will undergo HIV viral load (RNA PCR) testing at Weeks 36, 48, 60, and 72 (and thereafter). The results of these tests should be reviewed by study clinicians upon receipt and evaluated for continued viral suppression. Under LoA #3:

- **After Week 24 and up to but excluding Week 48, HIV viral load must remain suppressed below 200 copies/mL.**

  During this period, 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). 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 complete a Premature Discontinuation visit (see Section 7.4.5) and then exit the study. If the confirmatory test result is less than 200 copies/mL, the infant will remain in follow-up.

  The requirements and approach taken during this period are consistent with the approach taken at Step 2 Week 24, which is illustrated in Figure 7-4.

- **At Week 48 and thereafter, HIV viral load must be suppressed such that no HIV RNA is detectable, even if below the limit of quantification of the assay.**

  During this period, any detectable HIV RNA value, even if below the limit of quantification of the assay, 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). 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 complete a Premature Discontinuation visit (see Section 7.4.5) and then exit the study. If no HIV RNA is detected on the confirmatory test, the infant will remain in follow-up.

  The requirements and approach taken in this period are illustrated in Figure 7-6.
Figure 7-6
Virologic Monitoring and Infant Management
Week 48 through Week 72 under LoA #3

Monitor HIV RNA at Step 2
Weeks 48, 60, and 72

Is HIV RNA detectable even if below the limit of quantification of the assay?

no
Continue follow-up in Step 2

yes \(\Rightarrow\) repeat test within 3 weeks

Is HIV RNA detectable even if below the limit of quantification of the assay?

no

yes or test not repeated within 3 weeks

Complete Premature Discontinuation Visit then exit from study. Refer to non-study sources of HIV care and treatment.
7.4.5 Premature Discontinuation Visits prior to Week 84

For any infant who discontinues follow-up prior to Step 2 Week 84, a listing of Step 2 Premature Discontinuation visit procedures is provided below. There is no specified ordering or required sequence for these procedures. **Critical among these procedures 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 Premature Discontinuation visit to provide her with 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 PREMATURE DISCONTINUATION PROCEDURES**

- Collect interval medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments
- 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
  - Plasma and PBMC storage
  - Digital droplet DNA PCR (stored)
  - DBS for virology (stored)
  - HIV-specific immune responses (stored)
  - Pharmacokinetics sampling (DBS)
- Provide HIV-related, infant feeding, and other applicable information and counseling to mother as needed
- Provide referrals for HIV-related care and treatment
- 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
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

Refer to Appendix III for guidance on assigning off-treatment, off-step, and off-study codes to be recorded on the ADM0030, PE4005, and F1601 CRFs.
7.4.6 Follow-up Visits and Procedures for Infants: Step 2 Week 84 to Week 192

As specified in protocol Version 1.0, evaluation for possible entry into Step 3 may begin at the Step 2 Week 84 visit. However, in consultation with the expert panel described in protocol Section 3.3, no children will be considered for entry into Step 3 under protocol Version 1.0. Rather, the recommendations of the expert panel will be incorporated into a protocol amendment, and children will be considered for entry into Step 3 after the amended protocol (Version 2.0) has been approved by site IRBs/ECs and other applicable regulatory entities.

Prior to review and approval of protocol Version 2.0, children who meet criteria to remain in Step 2 under protocol Version 1.0 will continue to complete Step 2 visits every 12 weeks (±4 weeks). At these visits, all evaluations specified in the Step 2 SoE (including collection of all specimens specified to be stored) will be performed, but no specimens will be shipped for evaluation for possible entry into Step 3 until after protocol Version 2.0 has been reviewed and approved.

Listings of procedures required during this phase of follow-up 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.

Throughout this phase of follow-up, the virologic requirements described in Section 7.4.4 of this manual, and illustrated in Figure 4-6, continue to apply. HIV viral load must remain suppressed such that no HIV RNA is detectable, even if below the limit of quantification of the assay. Any detectable HIV RNA value, even if below the limit of quantification of the assay, 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). 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 complete a Premature Discontinuation visit (see Section 7.4.7) and then exit the study. If no HIV RNA is detected on the confirmatory test, the infant will remain in follow-up.
### STEP 2 INFANT FOLLOW-UP PROCEDURES
#### WEEKS 84, 108, 132, 156, AND 180

- Collect interval (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Administer adherence questionnaire to mother
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments
- Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting 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
  - AST, ALT, and lipase
  - CD4 cell count
  - HIV RNA PCR
  - HIV-1 antibody (ELISA or rapid test)
  - Plasma and PBMC storage
  - HIV DNA PCR (*stored*)
  - Digital droplet DNA PCR (*stored*)
  - HIV-specific immune responses (*stored, Week 180*)
  - Pharmacokinetics sampling (*DBS*)
- Prescribe and dispense ARVs as needed:
  - Adjust doses when indicated based on ≥10% increase in weight or body surface area
- 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 prophylaxis, care, and treatment for mother and/or infant 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
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

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Per protocol Section 5.13, a new prescription is required at the time of any ARV formulation change (e.g., change from solution to tablet) and for ARV dosing change, including dose adjustments for infants who outgrow their previous dose and are switched to the next dosing increment.
STEP 2 INFANT FOLLOW-UP PROCEDURES
WEEKS 96, 120, 144, 168, AND 192

- Collect interval (since the last visit) medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method
- Administer adherence questionnaire to mother
- Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments
- Assess whether infant meets criteria for additional evaluations and/or modification of ART regimen; proceed per protocol, consulting 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
  - HIV RNA PCR
  - HIV-1 antibody (ELISA or rapid test)
  - HIV DNA PCR (stored)
  - Replication-competent virus and single copy HIV RNA (stored)
  - DBS for virology (stored)
  - Pharmacokinetics sampling (DBS)
- Prescribe and dispense ARVs as needed:
  - Adjust doses when indicated based on ≥10% increase in weight or body surface area
- 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 prophylaxis, care, and treatment for mother and/or infant 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
- Complete and submit all required CRFs
- Report expedited adverse events to the DAIDS Safety Office if applicable

Per protocol Section 5.13, a new prescription is required at the time of any ARV formulation change (e.g., change from solution to tablet) and for ARV dosing change, including dose adjustments for infants who outgrow their previous dose and are switched to the next dosing increment.
7.4.7 Premature Discontinuation Visits after Week 84

For any infant who discontinues follow-up after Step 2 Week 84, a listing of Step 2 Premature Discontinuation visit procedures is provided below. There is no specified ordering or required sequence for these procedures. **Critical among these procedures 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 Premature Discontinuation visit to provide her with 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.

<table>
<thead>
<tr>
<th>STEP 2 INFANT PREMATURE DISCONTINUATION PROCEDURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Collect interval medical and medications history including signs, symptoms, and diagnoses; ARVs; other concomitant medications; and feeding method</td>
</tr>
<tr>
<td>• Perform physical exam including temperature, heart rate, respiratory rate, weight, length, and head circumference assessments</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>– CD4 cell count</td>
</tr>
<tr>
<td>– Plasma and PBMC storage</td>
</tr>
<tr>
<td>– HIV-specific immune responses (<strong>stored</strong>)</td>
</tr>
<tr>
<td>– Pharmacokinetics sampling (<strong>DBS</strong>)</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 care and treatment</td>
</tr>
<tr>
<td>• Prescribe and dispense non-study ARVs as needed to avoid gaps in treatment during the transition to non-study care</td>
</tr>
<tr>
<td>• Document visit per site SOPs and DAIDS policies for source documentation</td>
</tr>
<tr>
<td>• Complete and submit all required CRFs</td>
</tr>
<tr>
<td>• Report expedited adverse events to the DAIDS Safety Office if applicable</td>
</tr>
</tbody>
</table>

Refer to Appendix III for guidance on assigning off-treatment, off-step, and off-study codes to be recorded on the ADM0030, PE4005, and F1601 CRFs.
7.4.8 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. Given that infants will remain in follow-up in Step 2 for a minimum of six months (24 weeks) and a maximum of four years (192 weeks), mothers of infants in Step 2 may complete as few as one and as many as six follow-up visits.

Figure 7-7 lists the visits expected to be conducted with mothers of infants in Step 2. To further illustrate the maternal visit schedule, the figure also provides calendar dates for visits expected for a sample mother enrolled in the study on 1 August 2014. 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 Cohort 1.
- For mothers enrolled in Cohort 2, the date of study entry is the day of enrollment in Cohort 2.

### Figure 7-7
Follow-up Visit Schedule
For a Sample Mother Enrolled on 1 August 2014

<table>
<thead>
<tr>
<th>Visit</th>
<th>Target Visit Day</th>
<th>Visit Window</th>
<th>Window Opens</th>
<th>Window Closes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>1 FEB 2015</td>
<td>21 DEC 2014</td>
<td>15 MAR 2015</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>1 AUG 2015</td>
<td>20 JUN 2015</td>
<td>12 SEP 2015</td>
<td></td>
</tr>
<tr>
<td>Month 18</td>
<td>1 FEB 2016</td>
<td>21 DEC 2015</td>
<td>14 MAR 2016</td>
<td></td>
</tr>
<tr>
<td>Month 24</td>
<td>1 AUG 2016</td>
<td>20 JUN 2016</td>
<td>12 SEP 2016</td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td>1 FEB 2017</td>
<td>21 DEC 2016</td>
<td>15 MAR 2017</td>
<td></td>
</tr>
<tr>
<td>Month 48</td>
<td>1 AUG 2017</td>
<td>20 JUN 2017</td>
<td>12 SEP 2017</td>
<td></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 PCR (viral load) test results
  - Any other relevant history
- Provide HIV-related, infant feeding, and other applicable information and counseling
- Provide or follow up on referrals for HIV-related care and treatment
- Schedule next visit, provide reminders for next visit, and provide site contact instructions
- Document visit per site SOPs and DAIDS policies for source documentation
- Complete and submit all required CRFs
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 standard operating procedures (SOPs), which should reflect all national, international, and local policies and guidelines that are applicable at each site. Site SOPs should be reviewed and updated at least once annually and upon issuance of any updated policies and guidelines.

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 on the referral to determine whether the participant sought the services to which he or she was referred, determine the outcome of the referral, and determine whether additional referrals are needed. Additional counseling may also be needed to help ensure that participants access services that may be beneficial to them.

All counseling must be documented in participant study records. Documentation should include the content of each counseling session, participant responses to the counseling provided, any concerns raised by the participant, action planned to be taken by the participant prior to the next counseling session, action to be taken by the counselor (or other study staff) prior to the next session, and issues to be reviewed or addressed at the next session. Specific to referrals, all follow-up actions, outcomes, counseling, and plans for next steps should also be documented. Study sites may choose to use checklists to document counseling sessions — particularly to document the content of each session — but it is expected that narrative notes will also be required to fully document each session. Careful attention should be paid to clearly identifying counseling issues to be addressed at the next session, given that different counselors may provide counseling at different visits.
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 HIV testing as a study procedure, for purposes of confirming 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:** Similar to their mothers, most infants enrolled in P1115 will undergo HIV testing as a study procedure, for purposes of confirming their eligibility for study participation. Infants in Step 1 will also undergo HIV testing at Step 1 Week 2. 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 their risk of re-infection and their risk of transmitting HIV to others. For mothers of infected infants, counseling should also address potential risks of transmission from the infant. 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.

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 likely to be 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 their country-specific guidelines and any other 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 antiretrovirals (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 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 ART 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 use of each ARV, paying particular attention to this issue at times of dose adjustment as the infant ages and grows.

• 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 dialog, 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.

• 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 in P1115. Maternal considerations are provided in Sections 9.1 and 9.2. Infant considerations are presented in Sections 9.3-9.8.

In this section, reference is made to CRFs that may be completed at various study visits. These references are not intended to be comprehensive or all-inclusive. Always refer to the data collection form schedules to determine CRF requirements for each visit.

9.1 Maternal Medical and Medications History

Complete medical histories are not required for mothers in P1115. 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 for study participation 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 CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of HIV infection</td>
<td>LBW0028</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 PCR 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 CRF</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 PCR results since the last visit*</td>
<td>F3109</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 recorded on CRFs 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 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 LBW0028 CRF 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/AIDS treatment guidelines. In Option B and Option B+ settings, for breastfeeding mothers of HIV-uninfected infants, referrals to PMTCT programs may also be required to help ensure maternal initiation of ARVs for infant prophylaxis.

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, determine the outcome of the referral, and determine 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 in P1115.

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 for study participation 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 and, 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. Refer to 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 CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex and race/ethnicity</td>
<td>DMW0021</td>
</tr>
<tr>
<td>Apgar scores at birth*</td>
<td>DMW0021</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 (signs, symptoms, diagnoses)</td>
<td>PE6832</td>
</tr>
<tr>
<td>ARVs taken since birth</td>
<td>PE6852</td>
</tr>
<tr>
<td>Concomitant medications taken since birth</td>
<td>TXW0284</td>
</tr>
<tr>
<td>Feeding method since birth</td>
<td>PE0412</td>
</tr>
<tr>
<td>Weight, length, and head circumference at birth</td>
<td>QLW0251</td>
</tr>
</tbody>
</table>

*Weight, length, and head circumference at birth are required as part of the baseline infant history, with data to be recorded on the PE0034 CRF. These same measurements are also required as part of the infant physical examination performed on the day of study entry (see Section 9.4 below). The at entry measurements will also be recorded on a PE0034 CRF, thereby resulting in two copies of this CRF 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 recorded on CRFs 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, the severity grade, assessed per the DAIDS Toxicity Table, must be documented, along with the onset date and resolution date (if applicable).

All clinical history should be recorded in source documents and the following signs, symptoms, and diagnoses should be recorded on CRFs:

- **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 except those noted on the “do not record” list

All ARVs and all concomitant medications should be recorded in source documents and on CRFs (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 nucleic acid tests, including tests performed outside of the study prior to study entry, should be recorded on CRFs. Quantitative HIV RNA PCR tests should be recorded on the F3109 CRF. Qualitative tests, including HIV DNA PCR tests, should be recorded on the LBW0082 CRF. One CRF should be completed for each test.

### 9.3.2 Follow-up Medical and Medications History

An _interval_ medical and medications history is required at all infant follow-up visits, with assessment of the following:

<table>
<thead>
<tr>
<th>Interval Infant History Element</th>
<th>Corresponding CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history since the last visit (signs, symptoms, diagnoses)</td>
<td>PE6832&lt;br&gt;PE6852</td>
</tr>
<tr>
<td>ARVs taken since the last visit</td>
<td>TXW0284</td>
</tr>
<tr>
<td>Concomitant medications taken since the last visit</td>
<td>PE0412</td>
</tr>
<tr>
<td>Feeding method since the last visit</td>
<td>QLW0251</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.**

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, resolution date (if applicable), and all other relevant clinical details. The assessed relationship to the ARVs that the infant is taking (or has taken previously while on study) must also be documented.

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 CRFs:

- **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 except those noted on the “do not record” list

Event Evaluation (PE6865) CRFs 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
- Chemistry and hematology results, signs, symptoms, and diagnoses that meet the ICH GCP definition of serious (see Section 10.1)
- Chemistry and hematology results, signs, symptoms, and diagnoses that meet protocol criteria for EAE reporting (see Section 10.3)

All ARVs and all concomitant medications — including vaccinations — should be recorded in source documents and on CRFs (with associated start and stop dates). As a reminder, 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 may not be prescribed for study infants unless approved by the CMC due to potential interactions with LPV/r; refer to this list as needed when reviewing and/or prescribing medications at each infant visit.
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 require pre-approval from the CMC. 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. Topical steroids do not require pre-approval.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2: Protocol Section 4.7 lists rifampin among the medications that require pre-approval from the CMC, and Section 6.35 states that clinicians may change infant ART regimens, with approval and input from the CMC, to allow for co-administration of rifampin. At our site, when a child is identified as co-infected with TB, we typically initiate TB treatment immediately, with ART regimen modifications as needed. For infants in P1115, are we required to obtain approval from the CMC before initiating TB treatment and/or changing ART 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 ART 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. Please see Section 9.8 and Appendix II for more information on TB treatment and modification of ART 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 with the CMC in advance for each case. However, please 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 P1115. These exams should minimally include the following assessments; additional assessments may be performed at the discretion of the examining clinician:

<table>
<thead>
<tr>
<th>Infant Physical Examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements and routine growth monitoring:</td>
</tr>
<tr>
<td>• Length</td>
</tr>
<tr>
<td>• Weight</td>
</tr>
<tr>
<td>• Head circumference</td>
</tr>
<tr>
<td>Assessment of vital signs:</td>
</tr>
<tr>
<td>• Temperature</td>
</tr>
<tr>
<td>• Heart rate</td>
</tr>
<tr>
<td>• Respiratory rate</td>
</tr>
<tr>
<td>Auscultation of chest:</td>
</tr>
<tr>
<td>• Breath sounds</td>
</tr>
<tr>
<td>• Heart sounds</td>
</tr>
</tbody>
</table>

**At entry,** examination of:
| • Skin |
| • Head |
| • Mouth |
| • Neck |
| • Abdomen |
| • Extremities |

**During follow-up,** examination of:
| • Body systems driven by prior and new signs, symptoms, and diagnoses |
All exam findings should be source documented; abnormal findings should be graded for severity per the DAIDS Toxicity Table and assessed for relationship to the ARVs that the infant is taking (or has taken previously while on study). Vital signs and measurements will be recorded on the Detailed Pediatric Vital Signs (PE0034) CRF. Exam findings may also be recorded on other CRFs, e.g., Signs and Symptoms (PE6832), if required per the forms instructions.

Length, weight, and head circumference measurements are required as part of all infant physical examinations, including at study entry, with data to be recorded on the PE0034 CRF. The same measurements, recorded at birth, are also required as part of the infant baseline history (see Section 9.3.1 above). The at birth measurements will also be recorded on a PE0034 CRF, thereby resulting in two copies of this CRF being completed at entry (one with at birth measurements and the other with at entry measurements).

9.5 Infant Virologic Monitoring: HIV RNA

**IMPORTANT NOTE:** This section of the MOP provides operational guidance consistent with LoA #3. Please refer to the prior version of this section for corresponding guidance applicable prior to LoA #3.

For infants in Steps 2, 3, and 4, quantitative HIV RNA PCR (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- or VQA-certified laboratory.

Dilution of specimens used for HIV RNA PCR should be avoided whenever possible and is not permitted at or after Step 2 Week 24. Prior to Step 2 Week 24, when dilution is necessary, a validated diluent must be used and the LOD of the assay must be adjusted accordingly. Refer to the LPC for more information on this topic.

The results of all 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 limit of detection (LOD) of the PCR assay. All study site laboratories should report HIV RNA PCR results as either below the LOD of the assay or as the number of RNA copies detected at or above the LOD of the assay. Any questions about this should be directed to the P1115 Questions Group, which includes representatives of the IMPAACT Laboratory Center.

At each testing time point, an HIV RNA Plasma Viral Load (F3109) CRF should be completed to document specimen collection for the test. For tests performed in LDMS laboratories, results will be transmitted to the IMPAACT Data Management Center via LDMS and will not be recorded in item 5 of the F3109 CRF. For tests performed in non-LDMS laboratories, results will be recorded in item 5 of the F3109 CRF 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 recorded in the RNA Plasma Viral Load boxes and “1” should be recorded for “equal to” in the box for Quantifier Code.

- When results are below the lower LOD of the assay, the lower LOD should be recorded in the RNA Plasma Viral Load boxes and “3” should be recorded for “less than” in the box for Quantifier Code.

- When results are above the upper LOD of the assay, the upper LOD should be recorded in the RNA Plasma Viral Load boxes and “2” should be recorded for “greater than” in the box for 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.** HIV RNA PCR is required at Weeks 2, 4, 8, 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). 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 complete a Premature Discontinuation visit and then exit the study. If the confirmatory test result is less than 200 copies/mL, the infant will remain in Step 2 follow-up.

- **After Week 24 in Step 2, while infants continue to receive ART.** HIV RNA PCR is required at all scheduled visits, i.e., every 12 weeks. Starting at Week 48, any detectable HIV RNA value, even if below the limit of quantification of the assay, 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). 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 complete a Premature Discontinuation visit and then exit the study. If no HIV RNA is detected on the confirmatory test, the infant will remain in Step 2 follow-up.

- **Following entry into Step 3, in which infants will stop ART.** HIV RNA PCR is required at all scheduled visits, i.e., Weeks 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 40, 48, and every 12 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.** If at any time a result at or above the LOD is obtained, the infant must be recalled to the clinic as soon as possible for confirmatory testing. If a result at or above the LOD is confirmed on two consecutive tests, the infant will enter Step 4 and re-initiate ART. In this scenario, entry into Step 4 should occur within two weeks after the confirmatory result is available.

- **Following entry into Step 4, in which infants will resume ART.** HIV RNA PCR is required at Weeks 2, 4, 6, 8, 12, 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 PCR is additionally required every four weeks until suppression below the LOD is achieved. At Weeks 8, 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. This testing should be performed at local laboratories when possible; otherwise, the blood sample should be shipped in real time for testing at the designated pathogenesis 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 at least 25% and the CD4 cell count must be normal for age (at least 1000 cells/mL for children 2-3 years old; at least 750 cells/mL for children 3-4 years old).

All CD4 count test results should be source documented in participant study records and recorded on the Lymphocyte Subsets (LBW0054) CRF.

9.7 Safety Monitoring and Toxicity Management

Site IoRs and their designees 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 ART 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 ART regimen; the CMC should be contacted as soon as possible and within two business days to assist with decisions about continuing to hold the suspect ARV, holding the entire ART regimen, replacing the suspect ARV, and/or permanently discontinuing any ARV.

Protocol Section 6.1 provides general guidance on toxicity management; Section 6.2 provides specific guidance on management of anemia and neutropenia, rash, asymptomatic elevated AST and ALT, and symptomatic hepatitis. 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

All other adverse events should be managed by site IoRs (or their designees) consistent with standards of care for pediatric clinical care and ARV management. All adverse events must be followed to resolution or stabilization. Please refer to 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 while on ART may change ART regimens to allow for use of rifampin, in consultation with the CMC. Site clinicians need not consult with the CMC prior to changing ART regimens if this would delay initiation of TB treatment; however, the CMC should be consulted immediately thereafter to discuss preferred ART 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 ART 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:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (DAIDS Toxicity Table), Version 1.0, dated December 2004, with Clarification dated August 2009
- Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events
- DAIDS Adverse Experience Reporting System (DAERS) Reference Guide for Site Reporters and Study Physicians
- Package inserts for NVP and LPV/r

With the exception of the Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events, which is provided in protocol Appendix III, all of the above are available on the DAIDS RSC web site:

http://rsc.tech-res.com/safetyandpharmacovigilance/

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 AE 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).*

The above 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 AE. If a pre-existing condition resolves after entry into the study, but then recurs at a later date, the recurrence is considered an AE.

All AEs occurring among infants enrolled in P1115 must be source documented in participant study charts, including the documented assessment of the Investigator of Record (IoR) or designee of the severity of the AE (see Section 10.2) and its relationship to each ARV the infant has taken (see Section 10.4).
**Serious AE (SAE)**

An AE 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 AEs 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).

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

- Grade 3 or 4 rash/cutaneous toxicity
- Grade 3 or 4 symptomatic hepatotoxicity
- Grade 4 asymptomatic hepatotoxicity

**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 AE may be related to an investigational agent
- **Unexpected** ⇒ the nature or severity of an AE is not consistent with an investigational agent’s current package insert

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.

---

**Figure 10-1**

Adverse Event, Serious Adverse Event, and SUSAR Subsets

![Diagram showing the subsets of adverse events, serious adverse events, and suspected unexpected serious adverse events](image-url)
**Expedited AE (EAE)**  
An AE that meets protocol criteria for reporting in an expedited manner to the DAIDS Regulatory Support Center Safety Office

### 10.2 AE Severity

The term severity refers to the intensity of an AE. All AEs occurring among infants enrolled in P1115 — other than rash — must be assessed for severity on the following scale according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, with Clarification dated August 2009:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Potentially Life-Threatening
- Grade 5 = Death

The severity of rash must be graded according to the guidance provided in protocol Appendix III.

### 10.3 AEs 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 ARVs the infant has received.

- **After the date of the Step 2 Week 36 visit,** SUSARs must be reported as EAEs.

  During this timeframe, only SAEs assessed as unexpected and related to the investigational dosing of NVP and/or LPV/r provided in this study (i.e., SUSARs) must be reported as EAEs. The investigational dosing of NVP is provided in the first 13 days of infant life. The investigational dosing of LPV/r is provided during the time when an infant is receiving four ARVs (2 NRTIs + NVP + LPV/r). Please refer to Section 10.4 for more information on relationship assessment.

  **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.**

Figure 10-2 illustrates the EAE reporting requirements for infants in each step. No EAE reporting is required for mothers.
Figure 10-2a
EAE Reporting Requirements in **Step 1**: Report SAEs

![Diagram showing EAE reporting requirements in Step 1: Report SAEs that occur between the date of Step 1 Entry and the date of the Step 1 Week 4 visit.]

Figure 10-2b
EAE Reporting Requirements in **Step 2**: Report SAEs through Week 36 then Report SUSARs

![Diagram showing EAE reporting requirements in Step 2: Report SAEs that occur between the date of Step 2 Entry and the date of the Step 2 Week 36 visit and Report SUSARs that occur between the date of Step 2 Week 36 visit and the end of follow-up in Step 2.]

Figure 10-2c
EAE Reporting Requirements in **Step 3**: Report SUSARs

![Diagram showing EAE reporting requirements in Step 3: Report SUSARs throughout follow-up in Step 3.]

Figure 10-2d
EAE Reporting Requirements in **Step 4**: Report SUSARs

![Diagram showing EAE reporting requirements in Step 4: Report SUSARs throughout follow-up in Step 4.]

10.4 AE Relationship Assessment

For purposes of *toxicity management* — as specified in protocol Sections 6.0, 6.1, and 6.2 — the IoR or designee must assess the relationship of all AEs to all ARVs an infant is taking according to the categories shown in Figure 10-3. The categories are also used when recording AEs on case report forms (CRFs).

**Figure 10-3**

Relationship Assessment Categories for Toxicity 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 ARV 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 ARV are reasonably related in time, and the event is more likely explained by the ARV than other causes.</td>
</tr>
<tr>
<td>Possibly related</td>
<td>The event and administration of the ARV are reasonably related in time, and the event can be explained equally well by causes other than the ARV.</td>
</tr>
<tr>
<td>Probably not related</td>
<td>A potential relationship between the event and the ARV could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than the ARV.</td>
</tr>
<tr>
<td>Not related</td>
<td>The event is clearly explained by another cause not related to the ARV.</td>
</tr>
</tbody>
</table>

For purposes of *EAE reporting*, the IoR or designee must report the relationship of EAEs to the investigational dose of NVP and/or LPV/r according to the categories shown in Figure 10-4.

**Figure 10-4**

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 the investigational dose of NVP and/or LPV/r. 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 the investigational dose of NVP and/or LPV/r. 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 drug  
  • A plausible biologic mechanism for the drug to cause the EAE  
  • Previous reports of similar events associated with the drug (or drugs of the same class)  
  • Resolution of the event after de-challenge (hold/discontinuation of drug)  
  • Recurrence of the event after re-challenge (resumption of drug 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 the investigational dose of NVP and/or LPV/r. |
| Not related           | There is not a reasonable possibility that the EAE may be related to the investigational dose of NVP and/or LPV/r. |

Figure 10-5 presents how the five relationship categories used for toxicity management should be mapped to the two relationship categories used for EAE reporting.
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 ARVs, and/or newly available information on cause of death.

When updated EAE reports are submitted, it is NOT necessary to complete and submit another Event Evaluation CRF (PE6865) to the DMC. Only one PE6865 CRF should be completed and submitted for each event.

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, email DAIDS-ESSupport@niaid.nih.gov. Questions also may be submitted 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. Completed paper EAE Forms may be faxed or digitally scanned and emailed to the DAIDS RSC Safety Office. The EAE Form and form completion instructions are available on the DAIDS RSC web site; contact details for submission of EAE Forms are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS, which is also available on the DAIDS RSC web site.
### 10.6 EAE Reporting Examples

Several EAE reporting examples are provided below. When reviewing these examples, please note that even when EAE reporting is not required, all infant AEs must be source documented and selected AEs must be recorded on relevant CRFs, per the P1115 SoE and CRF 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 4. Therefore, the event must be reported as an EAE regardless of relationship to investigational NVP or LPV/r.</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 investigational NVP or LPV/r.</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 4 and therefore must be reported as an EAE regardless of relationship to investigational NVP or LPV/r. Note: 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 9, 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 investigational NVP or LPV/r.</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 investigational NVP or LPV/r.</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 the investigational NVP or LPV/r the infant received prior to Step 2 Week 36. 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 investigational NVP or LPV/r.</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 the investigational NVP or LPV/r the infant received prior to Step 2 Week 36. 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 investigational NVP or LPV/r. Therefore, EAE reporting would be expected.</td>
</tr>
</tbody>
</table>
11.0 Specimen Collection and Laboratory Considerations

The P1115 SoEs and Laboratory Processing Chart (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.

P1115 has adopted NIH recommendations for maximum pediatric blood draw volumes in this study. As such, 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. At each study 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 as follows:

**Sample Case 1:** Infant who weighs 3.40 kg at Step 2 Week 8 and whose blood draw volume in the past eight weeks was generally consistent with the SoE:

<table>
<thead>
<tr>
<th>Step 2 Entry</th>
<th>9.6 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2 Week 1</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Step 2 Week 2</td>
<td>7.7 mL</td>
</tr>
<tr>
<td>Step 2 Week 4</td>
<td>6.9 mL</td>
</tr>
<tr>
<td>Total</td>
<td>24.7 mL</td>
</tr>
</tbody>
</table>

For this infant, on the day of the Week 8 visit:

- The “single day” maximum blood draw volume = (3.40 kg*5 mL/kg) = 17.00 mL.
- The “last 8 weeks” maximum blood draw volume = (3.40 kg*9.5 mL/kg) – 24.7 = 7.60 mL.

Therefore, up to 7.6 mL could be drawn at Week 8. This volume exceeds the volume specified in the SoE for Week 8 (6.62 mL), so the full volume specified in the SoE should be drawn.

**Sample Case 2:** Same as Case 1 except that the infant weighs 3.05 kg at Step 2 Week 8.

For this infant, on the day of the Week 8 visit:

- The “single day” maximum blood draw volume = (3.05 kg*5 mL/kg) = 15.25 mL.
- The “last 8 weeks” maximum blood draw volume = (3.05 kg*9.5 mL/kg) – 24.7 = 4.28 mL.

Therefore, up to 4.28 mL could be drawn at Week 8. This volume is less than the volume specified in the SoE for Week 8 (6.62 mL), so specimen collection must be prioritized per the SoE as follows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>0.50 mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>1.00 mL</td>
</tr>
<tr>
<td>HIV RNA PCR</td>
<td>2.78 mL</td>
</tr>
</tbody>
</table>

Other points to consider with this example are that (i) blood draw volumes should be combined whenever possible (in this case, it may be possible to combine the samples collected for hematology and HIV RNA PCR, as both samples are collected in EDTA tubes), and (ii) the sample collected for HIV RNA PCR at Week 8 may be diluted if needed to perform the assay (dilution is permitted prior to Week 24). With the volumes noted above, however, it would not likely be possible to store plasma and PBMC (which require an additional 2 mL of blood) at the Week 8 visit.
As highlighted in the above 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 infant 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 shown 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 with 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 with 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 ART 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 ART regimens consistent with their clinical judgment. In general, it is expected that the study ART 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.
• With respect to the Step 2 Week 24 visit in particular, critical infant management decisions will be made based on HIV RNA PCR results from this visit. As such, every effort should be made to ensure that blood can be collected for HIV RNA PCR at this visit. As noted above, site staff are encouraged to forecast forward to this visit and plan accordingly. Operational strategies that may be considered as needed, on a case-by-case basis, include minimizing blood draw volumes to the extent possible at the Week 16 and Week 20 visits (for example by using diluted samples for HIV RNA PCR at these visits) and utilizing the allowable visit window (±2 weeks) to shift the Week 24 visit to a date later in the window. In addition, if the required blood draw volume cannot be collected on a given date, the infant may be scheduled to return to the clinic to complete the blood draw on a later date within the window.
Appendix I  
Sample Flow Sheet for IMPAACT P1115 Infants

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

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.

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).

TB co-treatment requiring rifampicin (RMP)

Adjustment of ART for rifampicin (RMP) co-treatment (drug-susceptible 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 - 100m; 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]
**Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**

**Nevirapine**

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 (see protocol Section 6.322), expected at about 6 months of age. If RMP is required in this period, please refer to table below and discuss with the study team (P1115 Clinical Management Committee; CMC).

**Efavirenz (EFV)**

EFV is less affected by RMP than NVP. Until recently, EFV had no dosage for children below 3 years of age and weighing <10kg. More recently, dosing for children ≥ 3 months of age and weighing ≥3.5kg has been developed and approved by the FDA (package insert). For children requiring RMP co-treatment, EFV was used successfully in 45 children from Zambia under 3 years of age and with body weight below 10kg. Dosage was 300mg daily for children weighing between 4 and 20 kg and median body weight 7.2 (6.2 to 8.8) kg (41.7 [48.4 – 34.1] mg/kg/day). [12] Risk for failure was similar to that of matched children without TB receiving NVP-based ART. Previous exposure to NVP for prevention of vertical transmission of HIV supported efficacy of EFV in adjusted hazard ratio analysis. [12] Another factor to consider for young children on EFV is the relatively high frequency of the slow metabolizer genotype CYP2B6516TT in African children with consequent high EFV levels and possible toxicity. [13]

**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.

**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. [16]

A summary of guidance is provided in the table below.
<table>
<thead>
<tr>
<th>Scenario</th>
<th>TB post-exposure prophylaxis</th>
<th>ARV options</th>
<th>Other advice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug susceptible</td>
<td>*INH 10mg/kg/day</td>
<td>Follow P1115 guidance</td>
<td>Actively exclude TB disease. Be aware of potential hepatotoxicity but additional testing is unnecessary unless clinically indicated.</td>
</tr>
<tr>
<td>Mono-resistant: RMP-resistant) (Must have confirmed INH susceptibility)</td>
<td>Can use INH</td>
<td>Follow P1115 guidance</td>
<td>Please notify CMC. Prophylaxis depends on resistance pattern. For GeneXpert report of RMP-resistance, INH susceptibility must be confirmed by line-probe or phenotypic testing.</td>
</tr>
<tr>
<td>INH-resistant</td>
<td>Seek expert advice: RMP monotherapy often used in this setting. Levofloxacin + ethambutol is a good alternative</td>
<td>If RMP used, LPV/r requires super-boosting with additional RTV</td>
<td>Please notify CMC.</td>
</tr>
<tr>
<td>MDR</td>
<td>Seek expert advice</td>
<td>Follow P1115 guidance</td>
<td>Follow guidelines for TB treatment or consult an expert. Monitor for drug toxicity.</td>
</tr>
<tr>
<td><strong>TB disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>Rif 15mg/kg/day INH 10mg/kg/day PZA 35mg/kg/day</td>
<td>If &lt;42 weeks post-conception, 2NRTI’s + NVP (200mg/m²). Consider adding abacavir for 3NRTI + NVP regimen If &gt;42 weeks post conception &amp; on LPV/r (4:1); add RTV to boost LPV/r ratio to 1:1</td>
<td>Discuss with CMC. Monitor carefully for liver toxicity.</td>
</tr>
<tr>
<td>MDR</td>
<td>Seek expert advice</td>
<td>2 NRTI’s + NVP If Rif used If &lt;2 weeks 2NRTI’s + NVP (200mg/m²) If &gt;2 weeks 2NRTI’s + LPV/r with RTV boosting</td>
<td>Discuss with CMC. Monitor carefully for liver toxicity.</td>
</tr>
</tbody>
</table>

**NOTE:** Add pyridoxine 12.5mg daily when INH is used.
References


### Appendix III

**Off-Treatment, Off-Step, and Off-Study Codes for ADM0030, PE4005, and F1601 Case Report Forms under Letter of Amendment #3**

<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</td>
<td>WHEN DISCONTINUING STEP 1 Code 11, completed step as defined by the study; Description (question 3) = “infant not infected, completed follow-up Step 1”</td>
<td>WHEN DISCONTINUING STEP 1 REGIMEN Code 10, completed treatment as defined by the protocol; Description (question 2) = “infant not infected, completed Step 1 regimen”</td>
<td>Code 10, completion of protocol defined period of study evaluation; Description (question 2) = “infant not infected, completed follow-up in Step 1”</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 Code 11, completed step as defined by the study; Description (question 3) = “infant not infected, completed follow-up Step 1”</td>
<td>NA (form not required)</td>
<td>Code 10, completion of protocol defined period of study evaluation; Description (question 2) = “infant not infected, completed follow-up in Step 1”</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 Code 11, completed step as defined by the study; Description (question 3) = “infant confirmed infected and entered Step 2”</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 Code 11, completed step as defined by the study; Description (question 3) = “infant confirmed infected and entered Step 2”</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>
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</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 Code 99, other; Description (question 3) = “maternal HIV infection not confirmed”</td>
<td>Code 20, pending results at randomization did not confirm eligibility; Description (question 2) = “maternal HIV infection not confirmed”</td>
<td>Code 30, test results which were pending at the time of randomization subsequently did not meet the eligibility requirements for the study; Description (question 2) = “maternal HIV infection not confirmed”</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 Code 99, other; Description (question 3) = “maternal HIV infection not confirmed”</td>
<td>NA (form not required)</td>
<td>Code 30, test results which were pending at the time of randomization subsequently did not meet the eligibility requirements for the study; Description (question 2) = “maternal HIV infection not confirmed”</td>
</tr>
<tr>
<td>Case Description*</td>
<td>ADM0030</td>
<td>PE4005</td>
<td>F1601</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td><strong>4a. Infant</strong> in Step 2 with confirmed HIV RNA ≥ 200 copies/mL at Step 2 Week 24 and up to but excluding Step 2 Week 48</td>
<td>WHEN DISCONTINUING STEP 2 Code 16, other event defined by the study; Description (question 3) = “HIV RNA above protocol threshold at Step 2 Week [XX]”</td>
<td>Code 50, reached protocol-defined clinical event, disease progression or laboratory endpoint other than toxicity; Description (question 2) = “HIV RNA above protocol threshold at Step 2 Week [XX], not eligible to continue on study in Step 2”</td>
<td>Code 32, does not meet eligibility requirements for subsequent step; Description (question 2) = “HIV RNA above protocol threshold at Step 2 Week [XX]”</td>
</tr>
<tr>
<td><strong>4b. Mother</strong> of infant with confirmed HIV RNA ≥ 200 copies/mL at Step 2 Week 24 and up to but excluding Step 2 Week 48</td>
<td>WHEN DISCONTINUING STEP 2 Code 11, completed step as defined by the study; Description (question 3) = “infant not eligible to continue follow-up in Step 2”</td>
<td>NA (form not required)</td>
<td>Code 10, Completion of protocol-defined period of study evaluation; Description (question 2) = “infant not eligible to continue follow-up in Step 2”</td>
</tr>
<tr>
<td><strong>5a. Infant</strong> in Step 2 with confirmed detectable HIV RNA at or after Step 2 Week 48</td>
<td>WHEN DISCONTINUING STEP 2 Code 16, other event defined by the study; Description (question 3) = “HIV RNA detectable at Step 2 Week [XX]”</td>
<td>Code 50, reached protocol-defined clinical event, disease progression or laboratory endpoint other than toxicity; Description (question 2) = “HIV RNA detectable at Step 2 Week [XX], not eligible to continue on study in Step 2”</td>
<td>Code 32, does not meet eligibility requirements for subsequent step; Description (question 2) = “HIV RNA detectable at Step 2 Week [XX]”</td>
</tr>
<tr>
<td><strong>5b. Mother</strong> of infant with confirmed detectable HIV RNA at or after Step 2 Week 48</td>
<td>WHEN DISCONTINUING STEP 2 Code 11, completed step as defined by the study; Description (question 3) = “infant not eligible to continue follow-up in Step 2”</td>
<td>NA (form not required)</td>
<td>Code 10, Completion of protocol-defined period of study evaluation; Description (question 2) = “infant not eligible to continue follow-up in Step 2”</td>
</tr>
</tbody>
</table>

*None of the scenarios described in this table represent enrollment violations or any other type of protocol deviation.*