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

DAIDS ES #11954

This file contains the current IMPAACT P1115 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #4, dated 14 December 2016
- Clarification Memorandum #4, dated 21 November 2016
- Clarification Memorandum #3, dated 27 September 2016
- Clarification Memorandum #2, dated 11 July 2016
- Letter of Amendment #3, dated 25 March 2016
- Letter of Amendment #2, dated 11 May 2015
- Letter of Amendment #1, dated 21 August 2014
- Clarification Memorandum #1, dated 27 May 2014
- Protocol Version 1.0, dated 12 March 2014
Letter of Amendment #4 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES # 11954

Letter of Amendment Date: 14 December 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1115 study and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. All sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1115.

If the IMPAACT P1115 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
Summary of Modifications and Rationale

The purpose of this LoA is to modify the study accrual plan with respect to infant feeding method.

Previously, LoA #3 and Clarification Memorandum (CM) #3 were issued to allow flexibility in enrolling breastfeeding mother-infant pairs in Cohort 1 and Cohort 2 and to clarify the number of breastfeeding mother-infant pairs permitted to be enrolled in Cohort 1.

To provide further flexibility, this LoA removes all participant accrual targets with respect to infant feeding method. The total number of mother-infant pairs targeted to be enrolled in each cohort remains unchanged; however, previously-specified targets for accrual of breastfeeding versus formula feeding pairs within each cohort are eliminated.

As noted in CM #3, the epidemiology of perinatal HIV infection has highlighted the importance of representing breastfeeding mother-infant pairs in this study. The modifications specified in this LoA will further expand representation of breastfeeding pairs in the study and thereby contribute to data collection and result reporting that is generalizable to this population.

Implementation

Throughout the protocol, all references to participant accrual targets are replaced to reflect the following:

- Up to 472 mother-infant pairs — comprised of 440 in Cohort 1 and up to 32 in Cohort 2 — are targeted to be enrolled in order to identify 54 infants with in utero HIV infection who enter Step 2.

- 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.

All of the above-listed accrual targets are specified regardless of infant feeding method. Consistent with these targets, the primary analysis population will include all Cohort 1 infants identified with in utero HIV infection who enter Step 2, regardless of infant feeding method.
Clarification Memorandum #4 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES# 11954

Clarification Memo Date: 21 November 2016

Summary of Clarifications

This Clarification Memorandum (CM) clarifies expectations for antiretroviral (ARV) regimen management in the event that genotypic resistance to one or more ARVs is identified.

Implementation

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

Clarification of ARV Regimen Management

Protocol Sections 5 and 6 describe expectations for ART regimen management. HIV-infected infants in Step 2 are generally expected to receive a four-drug regimen, composed of two nucleoside transcriptase inhibitors, nevirapine, and lopinavir ritonavir (2 NRTIs + NVP + LPV/r) starting at approximately two weeks of age (and 42 weeks postmenstrual age). The four-drug regimen is continued until 12 weeks after confirmed suppression of HIV viral load to below the lower limit of detection of the assay, at which time NVP is discontinued.

Protocol Section 6.322 further specifies that “in cases of ARV intolerance or toxicity subjects may discontinue the offending ARV and take a combination of at least 3 drugs (minimum 2 NRTIs and another highly active agent (e.g., PI, NNRTI, INSTI) that sustains suppression of HIV replication.”

Although not specifically mentioned, evidence of resistance to one or more ARVs should also warrant discontinuation of offending ARV(s) as failure to do so may pose an unfavorable risk-benefit ratio to the participant. This CM serves to clarify that site investigators, in consultation with the study Clinical Management Committee, are permitted to modify ARV regimens in response to resistance testing results, as clinically indicated and in the best interest of the participant.
Clarification Memorandum #3 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
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Version 1.0, dated 12 March 2014

DAIDS ES# 11954

Clarification Memo Date: 27 September 2016

Summary of Clarifications

This Clarification Memorandum (CM) clarifies expectations for enrollment of mother-infant pairs in Cohort 1. The protocol currently specifies enrollment of 440 mother-infant pairs in this cohort, with stratification by infant feeding method (approximately 320 formula feeding, approximately 120 breastfeeding). As described in greater detail below, this CM serves to clarify that more than 120 breastfeeding mother-infant pairs may be enrolled in Cohort 1, while still retaining the overall enrollment target of 440 mother-infant pairs in this cohort.

Implementation

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

Clarification of Enrollment into Cohort 1

This CM serves to clarify that more than 120 breastfeeding mother-infant pairs may be enrolled in Cohort 1 in order to identify 22 in utero HIV-infected breastfeeding infants as specified in protocol Letter of Amendment #3. The overall goal of enrolling 440 mother-infant pairs in Cohort 1 will remain unchanged; therefore, if more than 120 breastfeeding mother-infant pairs are enrolled, the number of formula feeding mother-infant pairs enrolled will be decreased to offset the increased number of breastfeeding pairs.

Current protocol specifications for participant management in Cohort 1 remain unchanged, as does the overall risk-to-benefit ratio for enrolled participants.

Background and Rationale

In the protocol Schema, Section 3, and Section 8, reference is made to enrolling 440 mother-infant pairs in Cohort 1. Reference is also made to the total of 440 being comprised of 320 formula feeding pairs and 120 breastfeeding pairs. More specifically, the protocol specifies enrollment of approximately 320 formula fed infants in Cohort 1 to identify 16 with in utero HIV infection, and enrollment of approximately 120 breastfed infants in Cohort 1 to identify 22 with in utero HIV infection when combined with breastfed infected infants in Cohort 2.
Overall, approximately 5% of infants enrolled in Cohort 1 are expected to be identified with *in utero* HIV infection. Infants identified with *in utero* infection are eligible to enter longer term follow-up in the study; infants not identified with *in utero* infection complete their study participation after approximately four weeks of follow-up.

Experience in P1115 to date, as well as the epidemiology of perinatal HIV transmission worldwide, has highlighted the importance of representing breastfeeding mother-infant pairs in this study. Whereas the study originally prioritized enrollment of formula feeding infants based on experience of the Mississippi Child (who was formula fed), subsequent experience has demonstrated that substantial numbers of breastfeeding mother-infant pairs meet the study eligibility criteria for Cohort 1.
Clarification Memorandum #2 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES# 11954

Clarification Memo Date: 11 July 2016

Summary of Clarifications

This Clarification Memorandum (CM) clarifies expectations for nucleoside reverse transcriptase inhibitor (NRTI) dosing for neonates in Step 1 and Step 2 of the study, consistent with current World Health Organization (WHO) guidelines for use of antiretroviral drugs for treating HIV infection.

Implementation

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

Clarification of NRTI Dosing for Neonates in Step 1 and Step 2

Letter of Amendment (LoA) #2, dated 11 May 2015, clarified expectations for nucleoside reverse transcriptase inhibitor (NRTI) dosing, including the following statement: “… current WHO guidelines for weight-based dosing with child-friendly solid and oral liquid formulations 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.”

With the issuance of updated WHO guidelines in June 2016, the P1115 Protocol Team would like to highlight that NRTI dosing guidelines — using oral liquid formulations — are now available for newborns. In addition, weight-band dosing guidelines — including dosing with fixed dose combination dispersible tablets — are now available for infants as young as four weeks of age who weigh at least 3 kg (refer to Annex 11, Section C, Tables 1-4 in the guidelines cited below).

For study sites in locations that have adopted WHO guidelines, in the absence of other local guidelines applicable to neonates, the P1115 Protocol Team recommends that the current WHO guidelines be followed for neonates enrolled in P1115. Study site clinicians are also encouraged to contact the P1115 Clinical Management Committee (impaact.p1115cmc@fstrf.org) with any questions or concerns related to NRTI dosing or any other aspects of antiretroviral regimen management in this study.

Letter of Amendment #3 for:

IMPAACT P1115

Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES # 11954

Letter of Amendment Date: 25 March 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1115 study, including one of the study informed consent forms, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. After all required approvals have been obtained, the consenting mother (or other legal guardian) of any infant currently in Step 2 should be re-consented using the updated informed consent form corresponding to this LoA; the updated informed consent form should also be used when obtaining informed consent for any infants newly enrolled in Step 2.

All sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1115.

If the IMPAACT P1115 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
Summary of Modifications and Rationale

The purpose of this LoA is three-fold:

- To allow greater flexibility in enrolling breastfeeding mother-infant pairs in Cohorts 1 and 2
- To modify requirements for suppression of plasma HIV-1 RNA (viral load) in the first year of infant follow-up in Step 2.
- To modify requirements for review by the IMPAACT Study Monitoring Committee

Each of these topics is addressed in more detail below.

A. Enrolling Breastfeeding Mother-Infant Pairs in Step 2

Protocol Version 1.0 specifies that up to 22 HIV-infected breastfeeding infants (and their mothers) may enroll in Step 2 of the study. The protocol further specifies that six of the 22 pairs will be enrolled from Cohort 1 (high-risk) and 16 will be enrolled from Cohort 2 (ART-started). To allow greater flexibility in enrolling breastfeeding mother-infant pairs in Step 2, this LoA removes the limits on the number of breastfeeding pairs that may be enrolled from each cohort. The total number of breastfeeding pairs (n=22) is retained, but the number to be enrolled from each cohort is no longer pre-specified in the protocol.

B. Requirements for Viral Suppression in Step 2

Protocol Version 1.0 requires suppression to below the limit of detection (LOD) of the HIV RNA assay by Step 2 Week 24, as well as continued suppression below the LOD thereafter; per protocol, infants who do not achieve these virologic requirements are discontinued from the study.

Based on experience with study implementation to date, with low-level plasma HIV viral loads observed through Step 2 Week 24 and assay variation at low-level viremia, additional time may be required for study infants to achieve persistently undetectable viral loads. To allow this additional time, this LoA modifies the virologic requirements in Step 2 as follows:

- To continue in the study between Step 2 Week 24 and Step 2 Week 48, HIV RNA levels must be below 200 copies/mL. Infants with confirmed HIV RNA levels ≥ 200 copies at Week 24 and up to but excluding Week 48 will be discontinued from the study.

- To continue in the study after Step 2 Week 48, HIV RNA must not be detected at Step 2 Week 48 or thereafter (i.e., no RNA may be detected, even if below the limit of quantification of the assay). Infants with any confirmed detectable HIV RNA at or after Week 48 will be discontinued from the study.

C. Requirements for IMPAACT Study Monitoring Committee Review

In consultation with the IMPAACT Study Monitoring Committee (SMC), the Protocol Team has determined that the guidelines for triggering a safety review in protocol Version 1.0 may result in unwarranted suspensions of participant accrual. As recommended by the SMC, this LoA modifies the guidelines to incorporate further specifications for hematologic adverse events, which are expected to occur commonly in the study population of HIV-infected infants.
Implementation

Modifications of protocol text are shown below, generally in order of appearance in the protocol, using strikethrough for deletions and bold type for additions.

A. Enrolling Breastfeeding Mother-Infant Pairs in Step 2

1. In the Schema, Sample Size:

Up to 472 infants, including 440 at high risk of in utero HIV infection and up to 32 with documented HIV infection, to yield a total of 54 HIV-infected infant subjects, will be enrolled. Mothers of enrolled infants will also be enrolled.

2. In Section 3.0, Cohort 1: Infants at high risk for HIV infection (High-Risk):

   Group B – Breastfed infants:
   
   Enroll approximately 120 high-risk infants to identify 6 up to 22 HIV-infected infants when combined with Cohort 2 Group B.

3. In Section 3.0, Cohort 2: HIV-infected infants (ART-started):

   Group B – Breastfed HIV-infected infants (up to N = 1622 when combined with Cohort 1 Group B)

4. In Section 8.1, General Design Issues, second paragraph:

   Infants are either formula fed or breastfed. The formula fed high risk HIV-infected infant group is the primary focus group for assessing this strategy for HIV remission and the target sample size is to identify 16 HIV-infected infants from this group. It is anticipated that approximately 320 infants (high risk cohort) will need to be enrolled for this target sample size of 16. Up to sixteen additional formula fed HIV-infected infants who start ART before enrollment (ART-started cohort) may also be enrolled. Up to 22 HIV-infected breastfed infants also will be enrolled to obtain preliminary data about this strategy in this group. These infants may be identified among up to 120 high risk infants anticipated to be enrolled or may be early treated (the target of 22 will be achieved across the high risk and early treated cohorts). An additional 6 breastfed high risk HIV-infected infants will be enrolled to obtain preliminary data about this strategy in this group, and 120 infants are anticipated to be required to reach this target. Among the HIV-infected infants who start ART before enrollment (ART-started cohort), the targeted sample size is up to 16 each in the formula and the breastfed groups. Thus up to 472 (320+120+16x2) infants will be enrolled.

5. In Section 8.3, Randomization and Stratification, first paragraph:

   This is not a randomized study. Four cohorts of neonates will be enrolled based on whether ART was started prior to enrollment high-risk versus ART-started status and on infant feeding intent:

   - Cohort 1A: Formula fed high-risk infants (up to 320 to identify 16 HIV-infected infants)
   - Cohort 1B: Breastfed high-risk infants (up to 120 to identify 6 22 HIV-infected infants when combined with Cohort 2B)
• Cohort 2A: Formula fed HIV-infected ART-started infants (N = 16 or when Cohort 1A is fully enrolled, whichever is earlier)
• Cohort 2B: Breastfed HIV-infected ART-started infants (N = up to 46 when combined with Cohort 1B and not more than Cohort 2A)

Table 1: Sample size for HIV-infected infants

<table>
<thead>
<tr>
<th></th>
<th>HIV infected from high-risk exposed infants cohort</th>
<th>HIV-infected ART-started cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Fed (Group A)</td>
<td>16</td>
<td>Up to 16</td>
</tr>
<tr>
<td>Breastfed (Group B)</td>
<td>6</td>
<td>Up to 16</td>
</tr>
<tr>
<td>Breastfed (Group B)</td>
<td>Up to 22</td>
<td></td>
</tr>
</tbody>
</table>

6. In Section 8.42, Sample Sizes for the Other Very Early Treated HIV-Infected Infant Groups:

The other three groups — breastfed high-risk infants, formula fed ART-started and breastfed ART-started — are of high interest but the primary group of interest for this protocol are the high risk formula fed infants, and the sample size is based on this primary interest group.

P1115 will obtain preliminary data for evaluating the strategy of very early treatment for HIV remission in breastfed infants. A sample size of 6 HIV-infected infants is targeted from this group. Based on the same HPTN 040 data mentioned above between 86 (6/0.07) and 120 (6/0.05) infants will need to be enrolled to ensure at least 6 HIV-infected neonates are identified from this group. Up to 120 breastfed high-risk infants will be enrolled and the infected infants from this cohort will be combined with the breastfed ART-started infants to achieve a sample size of 22 HIV-infected breastfed infants.

As mentioned in Section 8.1, the sample size for the high-risk breastfed group will provide preliminary data. For example, based on a 95% confidence interval, observing no HIV remission events among 6 children is consistent with a true probability of remission of ranging from 0 to as high as 0.46. With a sample size of 6 there will be good (0.80) probability of observing at least one remission if the remission probability is 0.24 or higher. Smaller probabilities of remission may still be clinically relevant.

With a similar approach as above for the formula fed high-risk group, a sample size of 16 infants is targeted for the formula fed ART-started group and up to 16 infants (up to 50% of sample size) for the breastfed group ART-started group.
7. In Section 8.533, Guideline for Triggering a Review of ART Cessation due to Viral Rebound, fourth paragraph:

ART cessation will continue within each cohort for all children who meet eligibility unless pausing guidelines are met. Therefore the maximum number of children per cohort who may be in the first 12 weeks of ART cessation, prior to when additional samples are obtained to assess HIV persistence, are: 16 formula fed infants at high risk for HIV infection (Cohort 1A), 6 breastfed infants at high risk for HIV infection (Cohort 1B), 16 formula fed HIV-infected infants ART-started (Cohort 2A), 16 22 breastfed HIV-infected infants (high risk or ART-started (Cohort 1B + Cohort 2B)). However, depending on the rate of accrual and probability of meeting criteria for ART cessation, this number may be smaller.

B. Requirements for Viral Suppression in Step 2

1. In the Schema, Study Design, Step 3:

HIV-infected infants with sustained HIV RNA below the limit of detection of the assay (LOD) on ART and who meet defined eligibility criteria (see Section 4.4) will undergo ART cessation at or after Step 2 Week 96 will enter Step 3 and undergo ART cessation and remain off ART unless there is a confirmed HIV RNA rebound to ≥ LOD.

2. In Figure 1, box for Off Study in Step 2:

Off study if:
- RNA ≥ LOD at Week 24
- Two consecutive RNAs ≥ LOD after Week 24
- Confirmed HIV RNA ≥ 200 copies/mL at Week 24 and up to but excluding Week 48
- Confirmed HIV RNA detected (even if below the limit of quantification of the assay) at Week 48 or thereafter

3. In Section 3.0, Study Design, last paragraph (as modified in LoA #1):

Refer to Section 4.0 for the eligibility criteria associated with each of the study steps and Section 6.3 for the detailed subject management plans associated with each step. As indicated in Section 4.4, entry into Step 3, with cessation of ART, is not expected to occur within the first 96 weeks (two years) of study participation. Anticipating that important scientific advances in the fields of HIV remission and reservoirs may occur during this time, and thereafter, an expert panel comprised of selected protocol team members and other leaders in the field of HIV remission and cure will be convened periodically to review the criteria for entry into Step 3 and provide recommendations to the protocol team on whether to retain or modify these criteria. The panel will be convened when the first enrolled child has no HIV RNA detected at Step 2 Week 48 who achieves sustained viral suppression (<LOD) in Step 2 reaches approximately 12 months of age. The panel will then be re-convened when the first child meets the established Step 3 criteria. Thereafter, the panel will meet periodically as additional scientific advances occur. Any modifications of the Step 3 criteria necessitated by the recommendations of the expert panel will be specified in a protocol amendment and entry into Step 3 will be deferred pending Institutional Review Board/Ethics Committee (IRB/EC) review and approval on a site-by-site basis.
4. In Section 4.4, Infant Inclusion Criteria, STEP 3, ART Cessation:

4.43 Must have achieved a no confirmed detectable plasma HIV RNA (even if below the limit of quantification of the assay) at Step 2 Week 48 and thereafter level < LOD by Step 2 Week 24 AND have no evidence of viral rebound (2 consecutive HIV RNA tests ≥ LOD) after Step 2 Week 24. Any detectable HIV RNA value (even if below the limit of quantification of the assay) at Step 2 Week 48 or thereafter 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 subject will NOT be eligible for treatment cessation.

5. In Section 6.322, Cohort 2, fifth paragraph:

Subjects who do not achieve HIV RNA < LOD by Step 2 Week 24 or have 2 consecutive HIV RNA levels ≥ LOD between Week 24 and Week 192 with confirmed HIV RNA ≥ 200 copies/mL at Step 2 Week 24 and up to but excluding Step 2 Week 48 will NOT be eligible for treatment cessation and will exit the study (and be referred for standard of care treatment per local guidelines). Any single HIV RNA value ≥ 200 copies/mL at Week 24 or up to but excluding Week 48 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 subject will exit the study. If the confirmatory test result is < 200 copies/mL, the subject will remain in the study.

6. In Section 6.323, Evaluation to determine eligibility for treatment cessation, first paragraph:

Subjects in Step 2 who achieved the plasma HIV RNA requirements specified in Section 4.43 level < LOD by Week 24 AND have no subsequent confirmed RNA levels ≥ LOD (defined as 2 consecutive RNA levels ≥ LOD) will undergo further evaluation for treatment cessation. Any detectable HIV RNA value ≥ LOD after Week 24 must be repeated as soon as possible. Any detectable HIV RNA value (even if below the limit of quantification of the assay) at Step 2 Week 48 or thereafter 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 subject will NOT be eligible for treatment cessation and will exit the study (with referral to standard of care treatment per local guidelines). If no HIV RNA is detected by the confirmatory test, the subject will remain in the study. At the Week 84 visit, these subjects will undergo screening for possible treatment cessation, to commence at or after Step 2 Week 96.
7. In Section 6.4, Permanent Discontinuation from Study Follow-up:

6.41 The infant will be discontinued from the study for the following reasons:

- HIV infection is not confirmed in the mother.
- In utero HIV infection is not confirmed in the infant.
- The HIV RNA level does not decline to < LOD by Step 2 study Week 24.
- The HIV RNA level rebounds to ≥ LOD after Step 2 study Week 24, confirmed by a second RNA level ≥ LOD.
- The infant’s HIV RNA level is ≥ 200 copies/mL at Step 2 Week 24 or thereafter up to but excluding Step 2 Week 48, with confirmation as specified in Section 6.322.
- The infant has detectable HIV RNA (even if below the limit of quantification of the assay) at Step 2 Week 48 or thereafter in Step 2, with confirmation as specified in Section 6.323.
- The infant does not meet criteria for treatment cessation (see Section 4.4) by Week 192.
- The infant is lost to follow up.

8. In Section 8.1, General Design Issues, third paragraph:

Cohort 1 infants (440 infants) will participate in Step 1 until their HIV infection status is determined. Cohort 1 infants with confirmed in utero HIV infection and Cohort 2 infants will enter Step 2. Step 2 infants whose HIV RNA level is not sustained < LOD (as specified in Section 6.41) will discontinue study follow-up. HIV-infected children who meet criteria for treatment cessation (defined in Section 4.4) will enter Step 3 and stop ART; children who do not meet these criteria by Week 192 will exit the study as specified in Sections 6.32 and 6.41. [paragraph continues]

9. In the Sample Informed Consent Form for Cohorts 1 and 2, STEPS 2, 3, and 4:

Step 2 Visits in the First 6 Months (Weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24),
(last paragraph)

By the time of the Week 24 visit, if your baby is responding well to ARVs, the amount of HIV in your baby’s blood is expected to drop to a low level that cannot be detected by the study tests. Because early control of HIV may be important for being able to stop taking ARVs at a later date, babies with no low levels of HIV detected in the blood at Week 24 will continue in the study (as described below). Babies with no higher levels of HIV detected in the blood will leave the study at Week 24 and will be referred for continued care and treatment outside the study.

Step 2 Visits from 6 to 18 Months (Weeks 28 to 72)
(last paragraph)

During this time, if no HIV is detected in your baby’s blood, the amount of HIV in your baby’s blood is expected to remain low and, by about 12 months, to drop to a very low level. If the study tests show that the amount of HIV stays as low as expected, your baby will continue in the study (as described below). If HIV is detected in the blood, Otherwise, your baby will leave the study and will be referred for continued care and treatment outside the study.
C. Requirements for IMPAACT Study Monitoring Committee Review

For reference in this section of the LoA, CMC = P1115 Clinical Management Committee and SMC = IMPAACT Study Monitoring Committee

1. Section 8.532, Guidelines for Triggering a Safety Review:

Triggers for safety reviews will require assessing drug relatedness for an event. Relatedness will be based on reports from the site and adjudication by the CMC. Ad hoc review safety triggers will be based on data that are combined across all cohorts. Enrollment into P1115 will be suspended if a safety trigger is met.

All Infants

All infants (to the time when the HIV infection is confirmed, which includes HIV uninfected infants): the proportion of infants who permanently discontinue any ARV for toxicity due to a possibly, probably or definitely related toxicity to ARVs or have a safety outcome as defined in Section 8.221 will be monitored. An SMC review for safety will be triggered if, after 30 infants have been enrolled, this proportion is greater than 10% (3 or more infants):

- This proportion is ≥ 0.10 for non-hematologic events.
- This proportion is ≥ 0.20 for hematologic events.

No guidelines are specified for triggering a review for fewer than 30 enrolled infants.

Similarly, among all infants, mortality will be monitored. An SMC review will be triggered if any death occurs that is possibly, probably or definitely related to any ARV.

Enrollment into the study will be suspended if any of the above-listed triggers for all infants are met, pending the outcome of the SMC review.

HIV-Infected Infants

HIV-infected infants: An SMC review for safety will be triggered if any of the following type of events is reported as possibly, probably or definitely related to an ARV on occurs among at least 2 infants:

a) Grade 4 life-threatening event assessed as possibly, probably or definitely related to any ARV, or
b) An ARV is permanently discontinued permanent discontinuation of any ARV for toxicity assessed as possibly, probably, or definitely related

If the above-listed triggers for HIV-infected infants are met based on the occurrence of at least one non-hematologic event, enrollment into the study will be suspended pending the outcome of the SMC review. If the above-listed triggers are met based only on the occurrence of hematologic events, the CMC will determine whether to suspend or continue accrual pending the outcome of the SMC review.

After a safety trigger for HIV-infected infants has been met, and the required SMC review has taken place, the threshold for future triggers will be reset (i.e., the two events that triggered a safety review will not be re-counted as triggers toward future reviews).
Letter of Amendment #2 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study Version 1.0, dated 12 March 2014

DAIDS ES # 11954

Letter of Amendment Date: 11 May 2015

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1115 study and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

This LoA does not impact the study informed consent forms, although the modifications specified in this LoA are intended to optimize the risk-to-benefit ratio for infants in Step 1 of this study.

Upon obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. All sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

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If the IMPAACT P1115 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
Summary of Modifications and Rationale

The purpose of this LoA is (i) to clarify expectations for nucleoside reverse transcriptase inhibitor (NRTI) dosing in Steps 1 and 2 and (ii) to modify nevirapine (NVP) dosing for preterm infants in Step 1.

Clarification of NRTI dosing in Steps 1 and 2

As currently specified in protocol Sections 5.111 and 5.112, NRTIs will be prescribed in this study consistent with World Health Organization (WHO) or individual country guidelines.

No changes of this protocol specification are being made at this time. For study sites in locations that have adopted WHO guidelines, the P1115 Protocol Team would like to clarify that current WHO guidelines for weight-based dosing with child-friendly solid and oral liquid formulations 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 United States Department of Health and Human Services guidelines for treatment of pediatric HIV infection, 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.

Study site clinicians are encouraged to contact the P1115 Clinical Management Committee (impaaact.p1115cmc@fstrf.org) with any questions or concerns related to NRTI dosing or any other aspects of antiretroviral regimen management in this study.

Modification of NVP dosing in Step 1

Protocol Section 5.111 originally specified that NVP should be provided to all infants in Step 1 at a dose of 6mg/kg twice daily. The Protocol Team recently reviewed available data on the pharmacokinetics of NVP in preterm infants and determined that the dose of NVP should be reduced for preterm infants in Step 1. Specifically, for infants born before 37 weeks of gestational age, the dose of NVP provided between study entry and the Step 1 Week 1 visit should be reduced from 6 mg/kg twice daily to 4 mg/kg twice daily. Beginning at the Step 1 Week 1 visit, the dose of NVP should then be increased to 6 mg/kg twice daily.

Pharmacokinetic data recently published by de Waal et al. provides new information on the extent to which prematurity affects NVP clearance in HIV-exposed infants. de Waal et al. demonstrated increases in NVP concentrations of 6.5% per week of prematurity, which projects to nearly a 40% reduction in NVP clearance among infants born at 34 weeks of gestational age. Based on these findings, the P1115 Protocol Team reviewed protocol specifications for NVP dosing and performed simulations of NVP concentrations for preterm infants dosed with 6 mg/kg twice daily from birth. These simulations indicated that most preterm infants would have elevated NVP concentrations, with trough concentrations greater than 10,000 ng/mL during the first 1-2 weeks of life, before auto-induction of NVP metabolism has occurred.

The Protocol Team then considered alternative reduced NVP dosing strategies for preterm infants, including a strategy with 4 mg/kg provided twice daily during the first week of life followed by 6mg/kg provided twice daily thereafter. Simulations of this dosing strategy predicted that therapeutic concentrations (>3,000 ng/mL) would be achieved within two days with median trough concentrations remaining below 10,000 ng/mL.
Based on these findings, for preterm infants born before 37 weeks of gestational age, the Protocol Team has determined that NVP should be provided at a dose of 4 mg/kg twice daily between study entry and the Step 1 Week 1 visit; thereafter, beginning at the Step 1 Week 1 visit, the dose should be increased to 6 mg/kg twice daily (consistent with dosing for full term infants). In making this determination, the Protocol Team identified that the reduced dose in the first week of Step 1 will optimize the risk-to-benefit ratio for preterm infants in Step 1, 95% of whom are expected to be HIV-uninfected. A similar dosing change is not indicated based on the risk-to-benefit ratio for full term infants in Step 1 or for HIV-infected infants of any gestational age in Step 2.

Given the change of dosing for preterm infants, the Protocol Team has further clarified that the planned assessment of the adequacy of NVP dosing to achieve NVP concentrations in the target range (between 3,000 and 10,000 ng/mL) will be performed among the first 30 full term infants (≥ 37 weeks gestational age) enrolled in Step 1.


**Implementation**

- In protocol Section 5.111, NVP dosing for Step 1 is updated as shown below, using strikethrough for deletions and bold type for additions.

5.111 Step 1

NVP: 6 mg per kg per dose orally twice daily

For infants ≥ 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 < 37 weeks gestational age at birth: 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

- Throughout the protocol, references to assessing the adequacy of NVP dosing among the first 30 infants enrolled in Step 1 are updated to specify that this assessment will be performed among the first 30 full term infants (≥ 37 weeks gestational age) enrolled in Step 1. NVP concentrations will also be explored concurrently among all preterm infants enrolled over the same period of time as the first 30 full term infants.
Letter of Amendment #1 for:

IMPAACT P1115
Very Early Intensive Treatment of
HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES # 11954

Letter of Amendment Date: 21 August 2014

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Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1115 study, including the study informed consent forms, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed and all required approvals of both protocol Version 1.0 and this LoA must be obtained before initiating this study. Likewise, all participants must provide written informed consent for this study using site-specific informed consent forms that correspond to this LoA.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received prior to implementation of this LoA. Receipt of this notification, as well as an initial registration notification for protocol Version 1.0, will be confirmed as part of the site-specific study activation process for this study.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1115.

If the IMPAACT P1115 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
Summary of Modifications and Rationale

IMPAACT P1115 is designed to explore the extent to which infants infected with HIV in utero who receive early intensive antiretroviral therapy (ART) in a manner similar to the child referred to as the “Mississippi Child” can achieve HIV remission. When the P1115 protocol was finalized in March 2014, the Mississippi Child had been in HIV remission, off ART, for approximately 24 months. In July 2014, however, the Mississippi Child was reported to have experienced viral rebound, with HIV detected in the blood approximately 27 months after stopping ART.

The case of the Mississippi Child provides important information for IMPAACT P1115. While the duration of this child’s HIV remission is unprecedented in the setting of pediatric HIV treatment, the viral rebound indicates that early intensive ART did not completely prevent the establishment and persistence of a latent viral reservoir. Thus, many research questions remain with respect to achieving and sustaining HIV remission. As currently designed, the P1115 study will begin to address many of these questions. A number of protocol modifications are required, however, to reflect the recent findings in the Mississippi Child. The purpose of this LoA is to specify those modifications, summarized as follows:

- Updating of the protocol and sample informed consent forms to include current information regarding the Mississippi Child and other relevant scientific updates; this will provide current information to protocol team members, site investigators, IRBs/ECs, and parents/guardians.

- Updating of the study design to include periodic expert panel review of protocol criteria for cessation of ART; as additional scientific advances related to HIV remission and reservoirs occur, this panel will recommend modifications of current protocol criteria as needed to reflect those advances.

- Extending the duration of follow-up up to five years for children who achieve HIV remission; the prolonged duration of remission experienced by the Mississippi Child demonstrates that long-term follow-up is needed to appropriately monitor the effects of early intensive treatment on remission.

- Expanding of subject management plans between Step 2 (on ART) and Step 3 (off ART) to include a documented discussion with the child’s parent/guardian to provide any new information relevant to the study and the decision to enter Step 3 and stop ART.

In addition to the above, this LoA adds information previously provided in protocol Clarification Memorandum #1, updates the protocol team roster, and addresses other administrative issues.
**Implementation**

Modifications of protocol text are shown below, using strikethrough for deletions and bold type for additions. For ease of reference, modifications are presented in five sections, labeled A-E, as follows:

A. Modifications to include current information regarding the Mississippi Child and other relevant scientific updates

B. Modifications to update the study design to include periodic expert panel review of protocol criteria for cessation of ART

C. Modifications to extend the duration of follow-up for children who achieve HIV remission

D. Modifications to expand subject management plans between Step 2 and Step 3 to include a documented discussion with the child’s parent/guardian to provide any new information relevant to the study and the decision to enter Step 3 and stop ART.

E. Modifications to add information previously provided in protocol Clarification Memorandum #1, update the protocol team roster, and address other administrative issues

**A. Modifications to include current information regarding the Mississippi Child and other relevant scientific updates**

*Note: In this LoA, all new references are identified with alphabetic identifiers, with full citations provided on page 15. In the next full amendment of the P1115 protocol, these references will be incorporated into the numeric listing of all references in protocol Section 13.0.*

1. Section 1.1, Background and Rationale

The capacity of the human immunodeficiency virus (HIV) to establish latency in long-lived cells, particularly in resting memory CD4+ T cells, precludes virus eradication with current combination antiretroviral therapy (ART) [1]. HIV latency in resting memory CD4+ T cells promotes viral quiescence, which renders latently infected CD4+ memory cells non-susceptible to antiretroviral drugs or HIV-specific immunity. These memory CD4+ T cells harbor latent HIV genomes and arise during development of immunologic memory [1]; those memory cells that arise directed towards HIV form the resting memory CD4+ T cell latent HIV reservoir [1]. Formation of the latent reservoir in the context of a developing immune system has important implications for the size and distribution of this reservoir in HIV-infected infants [2, New Refs A, B]. This feature distinguishes the latent HIV reservoir formation and its maintenance in pediatric HIV infection from HIV-infected adults, and has implications for targeting viral reservoirs formation with very early therapy to achieve HIV remission for pediatric populations.

A case of HIV cure in an adult (the “Berlin patient”) provided proof-of-concept that HIV can be eradicated from the body, including the central nervous system, whereby ART can be discontinued without viremic rebound [3, 4]. HIV cure occurred in this individual following treatment for acute myelogenous leukemia with total ablative chemotherapy, irradiation and repeat stem cell transplantation with donor cells homozygous for CCR5 delta32, accompanied by graft versus host disease. This case demonstrates that replication-competent HIV reservoirs can be reduced or cleared sufficiently to permit ART discontinuation without subsequent viremic rebound for at least seven years of follow-up [4]. The added benefit of sustained virologic control from receipt of donor
cells naturally resistant to CCR5-utilizing HIV variants is supported by the recent report of eventual viremic rebound in two HIV-infected adults following reduced intensity allogeneic bone marrow transplantation with CCR5-wild type donor cells. Return of viremia in these two cases at 12 and 32 weeks post-ART cessation highlights the current lack of biomarkers predictive of persistent HIV with capacity to re-ignite infection. In these two patients, circulating blood samples failed to reveal persistent HIV infection when tested using ultrasensitive HIV DNA and replication-competent viral outgrowth assays in large blood volumes [New Ref C].

A case of prolonged HIV remission (no viremic rebound within one year) was reported in a U.S. born child (the “Mississippi Baby”) who was treated with three drug ART by 31 hours of life for high-risk HIV-exposure from untreated maternal infection [5]. Longitudinal follow-up revealed eventual return of viremia at 46 months of age after being off ART for nearly 2.3 years [New Ref D].

In this infant, plasma viral load reached undetectable levels by 28 days of age on ART and remained undetectable even when ART was discontinued at age 18 months [5]. This child was intensively followed off ART because of the unusual finding of no rebound viremia despite being off ART for five months. At the time of the first report, the child had remained aviremic off ART for 12 months. Of note, there were no detectable HIV-specific immune responses or HLA-alleles known to confer spontaneous control of HIV replication. Together, these findings were interpreted to reflect control of viremia from lack of development of replication-competent HIV reservoirs [5].

A follow-up study reported on persistent lack of detectable replication-competent HIV reservoirs and sustained virologic control with absent viremia to <0.4 copies/mL off ART for 22 months at age 40 months [New Ref E]. However, proviral DNA was intermittently detected at extremely low levels near limits of detection of the quantitative HIV DNA droplet digital PCR assay and virologic control was sustained with continued virologic remission. The child was monitored closely every 4-8 weeks. During routine follow-up care at age 3.8 years of age, coinciding with 2.3 years of virologic remission, the child had clinically asymptomatic viremia above the limit of detection of clinical viral load assays that was subsequently confirmed 72 hours later. ART was restarted and the child exhibited a prompt response to ART with a 0.6-log decline in plasma viral load within 72 hours of ART. In addition, the CD4 counts returned to baseline normal levels within 72 hours of ART. Phylogenetic analysis confirmed the source of rebounding virus was transmitted virus from the mother [5], providing evidence for marked diminution in reservoir size to permit HIV remission for over two years in this child. The re-emergence of viremia in this child provides further support that viral remission is achievable in perinatal infection through time-limited very early ART, although the exact timing of ART initiation and duration of ART required to achieve cure is unknown and will be studied in P1115. This study will specifically address the hypothesis that very early therapy in HIV-infected neonates prevents substantially limits the establishment of HIV reservoirs, including the long-lived resting memory CD4+ T cell latent reservoir, possibly permitting to permit long-term control of HIV replication off ART, leading to HIV remission.
Importantly, there are emerging data that early therapy during acute HIV infection in adults and children quantitatively modifies HIV persistence and HIV-specific immune responses [New Refs F, G, H], though the extent to which ART can be discontinued in these children, as in the Mississippi Child is uncertain. A small (5-15%) subset of HIV-infected adults treated during early infection has been able to discontinue ART and still maintain control of virus replication to clinically undetectable levels [6,7]. These post-treatment controllers (PTC) have very low levels of cell-associated HIV provirus, which continue to decay over time off therapy. They also have lower levels of activated CD8+ T cells and HIV-specific T cell responses than the subset of HIV-infected adults (1-5%) who spontaneously control HIV replication to less than 50 copies/ml in the absence of antiretroviral drugs ("Elite Controllers") [8]; specific HLA-alleles (HLA-B57 and HLA-B27) and vigorous HIV-specific T cell responses are commonly found in these "Elite Controllers.”

Several lines of evidence suggest that early ART may also modify HIV persistence in children. Follow-up studies of early-treated infants have demonstrated lower levels of replication-competent virus than in later-treated children [9]. Moreover, Luzuriaga [10] and colleagues have shown that the absence of HIV-specific immune responses may be a marker for strict control of HIV replication following early therapy. A recent study of HIV persistence in HIV-infected youth with continuous suppression of HIV replication for 10 or more years after initiating ART prior to 3 months of age demonstrated low levels of circulating HIV provirus, undetectable plasma RNA by ultrasensitive assays, lack of replication-competent virus, and lack of HIV-specific immune responses [11]. Circulating HIV proviral DNA levels were lower than those reported in adult PTCs; decay over time was also observed. Data from these children, along with those from the Mississippi Baby and the Berlin Patient presented above, suggest that T cell activation markers and HIV-specific immune responses may be sensitive indicators of HIV replication (and that conversely, lack of T cell activation and HIV-specific immune responses are sensitive indicators of controlled HIV replication).

In a recent report [New Ref H], four perinatally HIV-infected children (2.5-7.5 years of age) from the Canadian registry also received a similar triple drug regimen from birth as the Mississippi Child. While these four children had undetectable proviral reservoirs to <2.6 copies/million circulating PBMCs enriched for CD4+ T cells, replication-competent virus was recovered in one of two children tested. All four children were HIV-seronegative but have persistent cell-associated HIV RNA. This indicates persistence of transcriptionally active viral genomes capable of rekindling viremic rebound if ART is stopped. Indeed, one of the four children underwent treatment cessation due to concerns of adherence and developed rebound viremia within weeks of ART cessation, confirming that virologic remission was not achieved. These cases highlight the need for ongoing studies of HIV persistence in children receiving early treatment to inform the research agenda investigating biomarkers of HIV remission, with the overarching goal of transforming HIV into an infection for which children do not face a lifetime of treatment. Together, these studies emphasize the need for a clinical trials approach to address these questions systematically to advance the field while minimizing safety risks.

Similar findings of early treatment limiting HIV reservoirs to achieve viral remissions have emerged from case studies in adults [6,7]. A small (5-15%) subset of HIV-infected adults treated during early infection has been able to discontinue ART and still maintain control of virus replication to clinically undetectable levels. These post-treatment controllers (PTC) have very low levels of cell-associated HIV provirus, with continued decay off therapy. They also have lower levels of activated CD8+ T cells and HIV-specific T cell responses than the subset of HIV-infected adults (1-5%) who spontaneously control HIV replication to less than 50 copies/ml in the absence of antiretroviral drugs ("Elite Controllers") [8]; specific HLA-alleles (HLA-B57 and HLA-B27) and vigorous HIV-specific T cell responses are commonly found in these “Elite Controllers.”
Currently, one limitation to immediate or very early therapy in HIV-infected infants is the lack of a widely available point of care nucleic acid tests to identify HIV infection in exposed neonates. Since it is likely that HIV establishes persistent infection in long-lived cells that preclude HIV remission, within days of infection, it will be critical to start antiretroviral therapy within the first one to two days of life.

2. Section 1.2, Treatment Cessation to Assess HIV Remission, first sentence

To test the hypothesis that very early therapy blocks HIV from establishing limits the establishment of persistent HIV infection in viral reservoirs, thereby leading to HIV remission, it will be essential to discontinue ART [12].

3. Section 1.4, Timing of Treatment Cessation in P1115 Subjects

The optimal time to cease ART after very early therapy to assess HIV remission is unknown. In the Mississippi infant, reported to have experienced prolonged HIV remission [5], albeit a single case, adherence was suboptimal at around 15 months of age and discontinued by 18 months of age. It is unclear if increased duration of therapy greater than 18 months would have further reduced the chances of rebound or prolonged the time to rebound or, alternatively, that limiting the time of viremia in the first days following birth is the key factor or a combination of both. Multiple factors may contribute to estimates of time to clearance of pre-existing HIV-infected cells before ART was started. These include the half-lives of the infected cell populations and the total body burden of HIV virions, some of which can be trapped on follicular dendritic cells for years. For P1115, Perelson and Ho’s estimates initially estimated [25] of that continuous ART for up to three years may lead to full clearance of HIV infected cells and or free virions bound to follicular dendritic cells to achieve cure will be used, assuming that the if very long-lived reservoirs were not present. With the assumption that very early treatment substantially reduces for HIV reservoirs, including those in central memory CD4+ T cells, the duration of ART to promote is unclear; however, stopping of ART will first be considered in P1115 at 2 years was prevented by very early treatment. It is expected that the feasibility of stopping ARV treatment by 2 years of age will vary significantly by the timing and duration of in utero infection during gestation prior to birth and the viral burden and state of the virus (quantity of integrated virus) present in the infant prior to initiation of treatment. Hence, infants in P1115 will undergo biomarker assessment of the state of HIV persistence at two consecutive visits to assess eligibility for stopping ART.

4. Section 1.8, Rationale for Formula and Breastfeeding Cohorts and Initial Focus on in utero HIV-Infected Infants, second paragraph

While the risk of occurrence of HIV super infection by transmission through breastfeeding is likely low to an infant with in utero HIV infection on ART, this risk still exists while exposure to breast milk continues. It is therefore possible that an in utero HIV-infected infant who received very early therapy and underwent HIV clearance could subsequently become infected through ongoing exposure to breast milk, impacting greatly on the study findings. The possibility of this occurring will be limited by assuring that the infants have ceased breastfeeding for a minimum of 6 weeks prior to any ARV interruption. Breastfeeding and non-breastfeeding cohorts will be studied simultaneously since the major burden of neonatal infection is in resource-constrained settings where breast-feeding is standard and critical for child survival. As outlined, this protocol focuses on in utero and not intrapartum infection. The latter is still a possibility for this cohort. The infants enrolled in Cohort 1 are at high risk of intrapartum HIV transmission because their mothers did not receive prenatal ARV treatment, which is similar to infants enrolled in the HPTN 040 clinical trial, and should minimally receive two or three drug antiretroviral prophylaxis to reduce intrapartum...
transmission by 50% [26]. The P1115 team recognizes this aspect of the study to be a limitation of the planned “early exit” of HIV exposed infants from this protocol who were not identified as in-utero infected. Therefore, these infants should receive the appropriate ARV prophylaxis, based on country-specific guidelines with continued assessment for intrapartum and breast-milk transmission, until infection is excluded.

5. Appendices IV-A, IV-B, and IV-C, Sample Informed Consent Forms for Infants and Mothers, WHY IS THIS STUDY BEING DONE, first paragraph

The purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs for a prolonged period of time and still stay healthy. This has only been seen in one baby so far who started ARVs soon after birth, then stopped ARVs, and was able to stay healthy, with no HIV detected in the blood, for more than two years. About 27 months after stopping ARVs, HIV was detected in this child’s blood and the child restarted ARVs. The amount of HIV in the child’s blood quickly dropped and the child has remained healthy. This study is being done to find out if this can be seen in other babies who start ARVs anti-HIV medicines very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies this young.

B. Modifications to update the study design to include periodic expert panel review of protocol criteria for cessation of ART

1. Section 3.0, Study Design, last paragraph:

Refer to Section 4.0 for the eligibility criteria associated with each of the study steps and Section 6.3 for the detailed subject management plans associated with each step. As indicated in Section 4.4, entry into Step 3, with cessation of ART, is not expected to occur within the first 96 weeks (two years) of study participation. Anticipating that important scientific advances in the fields of HIV remission and reservoirs may occur during this time, and thereafter, an expert panel comprised of selected protocol team members and other leaders in the field of HIV remission and cure will be convened periodically to review the criteria for entry into Step 3 and provide recommendations to the protocol team on whether to retain or modify these criteria. The panel will be convened when the first enrolled child who achieves sustained viral suppression (<LOD) in Step 2 reaches approximately 12 months of age. The panel will then be re-convened when the first child meets the established Step 3 criteria. Thereafter, the panel will meet periodically as additional scientific advances occur. Any modifications of the Step 3 criteria necessitated by the recommendations of the expert panel will be specified in a protocol amendment and entry into Step 3 will be deferred pending Institutional Review Board/Ethics Committee (IRB/EC) review and approval on a site-by-site basis.
2. Section 4.4, Infant Inclusion Criteria, STEP 3, ART Cessation, text added immediately following section title:

Note: The criteria in this section may be modified in response to expert panel review.

3. Section 6.323, Evaluation to Determine Eligibility for Treatment Cessation, text added immediately following section title:

Note: The criteria in this section may be modified in response to expert panel review.

C. Modifications to extend the duration of follow-up for children who achieve the primary study objective of HIV remission for at least 48 weeks

1. Schema, Study Duration

HIV-infected infants will be followed up to 5.4 years of age for ongoing evaluation for HIV remission, potential treatment toxicity, and clinical or laboratory progression in Step 2. Children who enter Step 3 will be followed in Step 3 for as long as they remain in remission, up to 5 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 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.

2. Figure 1, figure box at bottom right of page, below Step 3 and Step 4

   Off study
   • @ 5 years from entry into Step 3 (if still in Step 3) OR
   • @ 5 years of age or 6 months after viral re-suppression (whichever is later) in Step 4

3. Section 3.0, Study Design, Listing of Study Steps, third and fourth bullet points

   • STEP 3 (ART Cessation) – Subjects in Step 2 who meet all criteria for treatment cessation (see Section 4.4) will enter Step 3. At entry into Step 3, ART will be stopped and subjects will undergo frequent HIV RNA testing to monitor HIV remission and check for viral rebound until 5 years of age for as long as they remain in remission, up to 5 years from the date of entry into Step 3.

   • STEP 4 (ART Re-initiation) – Subjects in Step 3 who have 2 consecutive HIV RNA levels ≥ LOD (see Section 4.5) will enter Step 4 and restart ART. Subjects in Step 4 will undergo frequent HIV testing to monitor response to ART re-initiation and continue follow-up until 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.

4. Section 5.122, Duration

HIV-infected subjects will be followed up to 5.4 years of age in Step 2. Children who enter Step 3 will be followed in Step 3 for as long as they remain in remission, up to 5 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 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.
5. Section 6.33, ART Cessation in HIV-Infected Subjects to Assess HIV Remission (STEP 3), first sentence

At entry to Step 3, ART will be stopped and the subject will undergo plasma RNA testing weekly through the Step 3 Week 4 visit, then every 2 to 12 weeks for the duration of **follow-up in Step 3 (up to 5 years from entry into Step 3)** the study through 5 years of age.

6. Section 8.1, General Design Issues, sixth sentence

HIV-infected infants will be followed for up to 5 years of age in Step 2. Children who enter Step 3 will be followed in Step 3 for as long as they remain in remission, up to 5 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 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.

7. Section 8.6, Analyses, third paragraph, first sentence

Summary tables or listings will be provided for major secondary outcome measures of eligibility for ART cessation, HIV virology related outcomes, **including duration of remission (time to rebound)**, and for the safety outcome.

8. Appendix I, Maternal Schedule of Evaluations, table and footnote 2

<table>
<thead>
<tr>
<th>Table 1: Maternal Schedule of Evaluations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mothers of all infants</strong>&lt;br&gt;(HIV-uninfected and HIV-infected)¹</td>
</tr>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>Informed Consent</td>
</tr>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
</tr>
<tr>
<td>History³⁴</td>
</tr>
<tr>
<td>Infant feeding method</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
</tr>
<tr>
<td>HIV RNA⁵</td>
</tr>
<tr>
<td>CD4</td>
</tr>
<tr>
<td>Stored serum⁶</td>
</tr>
<tr>
<td>Stored plasma and cells⁶</td>
</tr>
<tr>
<td>TOTAL BLOOD</td>
</tr>
</tbody>
</table>

2. Mothers of HIV-infected infants, if available, will be followed every 6 months for up to 5 years and as long as the infant remains on study.
9. Appendix II-D, Schedule of Evaluations for Step 3, page 2 of 4, fifth column heading

Week 60, then every 12 weeks through 5 years of age after Step 3 entry (± 6 wks)

10. Appendix II-D, Schedule of Evaluations for Step 3, footnotes 9 and 11

9. Replication-competent virus sample will be used for additional testing for viral persistence. Sample at Step 3 Entry is not required if a sample was collected in Step 2 within 30 days of the visit. Collect 5 mL through < 3 years of age and 10 mL thereafter from ≥ 3 through 5 years of age. For US sites, samples will be processed in real-time with overnight shipment. For non-US sites, samples will be cryopreserved for shipment in batch. Samples will be shipped to the designated central pathogenesis laboratory.
   a. Beginning at Week 72, collect every other visit (i.e., every 24 weeks) through 5 years of age.

11. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot; HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR activation) following treatment cessation as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory.
   a. Beginning at Week 60, collect every other visit (i.e., every 24 weeks) through 5 years of age.

11. Appendix II-E, Schedule of Evaluations for Step 4, page 1 of 3, eleventh column heading

Week 24, then every 12 weeks* through 5 years of age (± 6 wks)

*Children who experience confirmed viral rebound in Step 3 will enter Step 4 and be followed in Step 4 through 5 years of age or until 6 months after viral re-suppression on ART, whichever is later.

12. Appendix II-E, Schedule of Evaluations for Step 4, footnotes 10 and 12

10. Replication-competent virus sample will be used for additional testing for viral persistence. At Week 24, collect 5 mL if < 3 years of age and 10 mL if ≥ 3 through 5 years of age then every 24 weeks thereafter. Samples will be processed in real-time with overnight shipment for US sites. For non-US sites, samples will be cryopreserved for shipment in batch. Samples will be shipped to the designated central pathogenesis laboratory.
   a. Beginning at Week 48, collect every 24 weeks through 5 years of age.

12. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot; HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR activation) following treatment cessation as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory.
   a. Beginning at Week 48, collect every 48 weeks through 5 years of age.
13. Appendix IV-A, Sample Informed Consent Form for Infants, Cohort 1 / Step 1, BRIEF INFORMATION ABOUT STEPS 2, 3, AND 4, second and third bullet points

- Babies who continue in the study will keep taking ARVs at least through 2 years of age. Blood tests will check on your baby’s health and the amount of HIV in the blood. Between 2 and 4 years of age, your baby may qualify to enter Step 3 and stop taking ARVs. If your baby qualifies, he or she will enter Step 3. If your baby does not qualify enter Step 3, he or she will leave the study at 4 years and will be referred for continued care and treatment outside the study.

- Babies in Step 3 will stop taking ARVs. They will be monitored closely, including checking the amount of HIV in the blood. If the amount of HIV in the blood rises, babies will enter Step 4 and start taking ARVs again. Otherwise, they will stay in Step 3, not taking ARVs, for up to 5 more years (up to 9 years of age). Babies in Step 3 and Step 4 will stay in the study through 5 years of age or until 6 months after HIV is not detected in their blood, whichever is later.

14. Appendix IV-B, Sample Informed Consent Form for Infants, Cohorts 1 and 2 / Steps 2, 3, and 4, WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY, Step 3 Visits, last paragraph

If HIV is detected in your child’s blood on two tests in a row, your child will enter Step 4 (as described below) and start taking ARVs again. Otherwise, your child will remain in Step 3, not taking ARVs, for up to 5 years after entering Step 3 until he or she reaches 5 years of age.

15. Appendix IV-B, Sample Informed Consent Form for Infants, Cohorts 1 and 2 / Steps 2, 3, and 4, WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY, Step 4 Visits, first paragraph

At Weeks 1 and 3, you will be contacted by phone and asked about your child’s health and medicines. Between Weeks 2 and 12, your child will have 6 visits (every 2 weeks). The visits then change to every 12 weeks until your child reaches 5 years of age or until 6 months after HIV is not detected in your child’s blood, whichever is later.

16. Appendix IV-B, Sample Informed Consent Form for Infants, Cohorts 1 and 2 / Steps 2, 3, and 4, HOW LONG WILL BABIES BE IN THIS STUDY

Babies will be in Step 2 of this study for at least 6 months and up to 4 years. Babies who qualify for Steps 3 and 4 will be in the study at least through 5 years of age and up to 9 years of age.

17. Appendix IV-C, Sample Informed Consent Form for Mothers, HOW LONG WILL I BE IN THIS STUDY

The amount of time you will be in this study depends on whether your baby is infected with HIV. If your baby is not infected with HIV, you will have one study visit. If your baby is infected with HIV, you will be in the study for as long as your baby, up to 9 years.
D. Modifications to expand subject management plans between Step 2 and Step 3 to include a documented discussion with the child’s parent/guardian to provide any new information relevant to the study and the decision to enter Step 3 and stop ART

1. Section 6.323, Evaluation to Determine Eligibility for Treatment Cessation, last paragraph

Subjects meeting all current criteria for ART cessation will ideally transition to Step 3 (see Appendix II-D). Prior to entry into Step 3, the site investigator will meet with the child’s parent/guardian to discuss the child’s current clinical status and laboratory test results and inform them that the child meets protocol criteria to enter Step 3 and stop use of ART. 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 parent/guardian questions will be answered and the discussion will be documented in detail in the participant’s study chart. If the parent/guardian requests additional time for consideration of entry into Step 3, this will be accommodated and follow-up discussions will be scheduled accordingly. Assuming the parent/guardian remains supportive of the child entering Step 3 and stopping use of ART, the child will proceed to this step. If the parent/guardian is not supportive, the child will remain in Step 2 (on ART) through Week 192 and then exit the study. If the parent/guardian changes his or her mind while the child is still on study, and the child continues to meet criteria to enter Step 3, the child may proceed to this step.

Subjects who do not meet all criteria for ART cessation will continue in Step 2 on 3-drug ART (2 NRTIs and LPV/r) and undergo rescreening at 12-week intervals. Subjects not meeting the above criteria by Week 192 will exit the study.

2. Section 10.1, Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendices IV-A, IV-B, IV-C and V), and any subsequent modifications must be reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for oversight of the study. 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. For infants eligible for Cohort 1, informed consent will first be obtained for participation Cohort 1 (Step 1 visits and evaluations) only. Separately, for infants eligible to take part in Cohort 2, informed consent will be obtained for Cohort 2 (Step 2, 3, and 4 visits and evaluations). The informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the consent forms will be offered to the mother. See also Section 6.323 for a description of information to be discussed with parents/guardians of children found to meet criteria for entry into Step 3, prior to cessation of ART.
3. Appendix II-D, Schedule of Evaluations for Step 3, new row (added) and footnote #1

<table>
<thead>
<tr>
<th>Step 3 Entry</th>
<th>Week 1 (±2 days)</th>
<th>Week 2 (±2 days)</th>
<th>Week 3 (±2 days)</th>
<th>Week 4 (±2 days)</th>
<th>Week 6 (±1 wk)</th>
<th>Week 8 (±1 wk)</th>
<th>Week 12 (±2 wks)</th>
<th>Week 16 (±2 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion of Step 3 entry and ART cessation in the context of latest scientific updates¹</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. **Discussion of Step 3 entry and ART cessation in the context of latest scientific updates, and documentation thereof, must occur prior to entry into Step 3** (refer to Section 6.323 for more information about this discussion). Visit weeks will restart at Week 0 on entry into Step 3 (Date of Step 3 Entry = Day 0). ART will be discontinued after blood collection at Step 3 Entry.

4. Appendix IV-B, Sample Informed Consent Form for Infants, Cohorts 1 and 2 / Steps 2, 3, and 4, Step 2 Visits from 18 to 48 Months (4 Years), last paragraph

   During this time, if no HIV is detected in your baby’s blood, the study doctor will see if your baby meets study requirements to stop taking ARVs. If these requirements are met by 48 months (4 years), your child will enter Step 3 (as described below) and stop taking ARVs. If not, your child the study doctor will meet with you to discuss this. The doctor will tell you about your child’s health and latest study test results. The doctor will also give you an update on what has been learned outside of this study about HIV remission (not being able to detect HIV in the blood) and starting and stopping ARVs. Because we expect to be learning new information over time, we want you to have the latest available information when your child may meet the requirements to stop taking ARVs. After discussing this information, if you choose to proceed with your child stopping ARVs, your child will enter Step 3 (as described below). If your child does not meet the criteria, or you do not choose to proceed with your child stopping ARVs, your child will remain in the study until 4 years of age. He or she will then leave the study at 4 years and will be referred for continued care and treatment outside the study.

**E. Modifications to add information previously provided in protocol Clarification Memorandum #1, update the protocol team roster, and address other administrative issues**

1. Protocol Cover Page

   The US Food and Drug Administration has indicated that this study is exempt from IND regulations; therefore, reference to a study IND number is removed:

   **IND # [TBA]**

2. Protocol Team Roster

   Entries for the Data Managers, Laboratory Center Specialists, and Laboratory Technologist are updated as follows:
Protocol Data Managers
Bonnie Zimmer, BS
FSTRF
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7260
Email: zimmer@fstrf.org

Adriane Hernandez, MA
FSTRF
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 x7495
Email: hernande@fstrf.org

Laboratory Center Specialists
Carolyn Yanavich
IMPAACT Laboratory Center
Children's Hospital Los Angeles
Smith Research Tower
4650 Sunset Boulevard, Room 902, MS 51
Los Angeles, CA 90027
Phone: 443-249-3851
E-mail: cyanavich@chla.usc.edu

Sarah Santos
IMPAACT Laboratory Center
Children's Hospital Los Angeles
Smith Research Tower
4650 Sunset Boulevard, Room 902, MS 51
Los Angeles, CA 90027
Phone: 323-361-8502
Email: sarahssantos.impaact@gmail.com

Laboratory Technologist
Cheryl Jennings
Rush University Medical Center
VQA Laboratory Manager
1750 W. Harrison Street, 1121 Jelke
Chicago, IL 60612
Phone: 312-942-5954
Email: cheryl_jennings@rush.edu
3. Section 13.0, References

New references added in this LoA are as follows:


4. Appendix II-A, Schedule of Evaluations for Step 1, VIROLOGY

Protocol Clarification Memorandum #1 clarified that all HIV nucleic acid testing methods specified for Step 1 Entry (DNA PCR, RNA PCR, TNA tests) are also permitted at Step 1 Week 2, as indicated in the following table of Step 1 virology evaluations:

<table>
<thead>
<tr>
<th></th>
<th>Step 1 Entry (0 to 48 hours of age, preferably before initiation of ART)</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2† (± 2 days)</th>
<th>Week 4† (Last study visit) (± 1 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV DNA PCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV nucleic acid⁷</td>
<td>Sample 1: 1.5-3.0mL</td>
<td></td>
<td></td>
<td>1.5 mL</td>
</tr>
<tr>
<td></td>
<td>Sample 2: 1.5-3.0mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored Plasma and PBMC⁶</td>
<td></td>
<td>2.5 mL</td>
<td>2.5 mL</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

5. Appendices IV-A and IV-B, Sample Informed Consent Forms for Infants, WHAT ABOUT CONFIDENTIALITY, US Sites, fifth paragraph (added) and Sites Outside the US, third paragraph (added)

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

6. Appendix IV-C, Sample Informed Consent Form for Mothers, WHAT ABOUT CONFIDENTIALITY, US Sites, fifth paragraph (added) and Sites Outside the US, third paragraph (added)

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this web site at any time.

7. Appendix V, Fact Sheet and Template Consent Form for Specimen Storage at Repositories Funded by the NICHD

Protocol Clarification Memorandum #1 clarified that the sample informed consent form for specimen storage and future research in protocol Appendix V is intended to apply to both maternal and infant specimens. As such, wording in the sample form such as “your child” and “your child’s specimens” is replaced with “you/your child” and “your/your child’s specimens.” In addition, the signature blocks are expanded to accommodate the signature requirements for maternal and infant specimens. For ease of reference, the entire form is attached to this document.
APPENDIX V

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

FACT SHEET

When you join/your child joins this NICHD-sponsored study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your/your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you/your child during a study are kept. Your/your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your/your child’s name.)

Why have a repository?

Researchers can learn a lot from a study, but as time goes by, the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered, and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your/your child’s rights are being protected.

How will my/my child’s privacy be protected?

The only record that you/your child participated in this NICHD-sponsored study is at the clinic, where it is kept separate from your/your child’s health records and locked away.

Your/your child’s specimens in the repository will not have your/your child’s name on them. The specimens will have a special study code. It will be the same code that is on your/your child’s information in the NICHD-sponsored study from your interviews and examinations. Again, none of this information will have your/your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD-sponsored repository in the future, he or she will write up the idea, and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.
Why wouldn’t I find out the results of the research using my/my child’s specimens?

You will not receive the results of research done with your/your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your/your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your/your child’s care right now, but they may be helpful to people like you/your child in the future. Your/your child’s specimens can last in the freezer for many years, and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my/my child’s specimens?

All of the studies to be done in the future on your/your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you/your child and others from this NICHD-sponsored study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead, since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my/my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use your/your child’s specimens in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your/your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my/my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.
As part of this study (P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study), you are/your child is being asked to have some blood taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your/your child’s time in this NICHD-sponsored study.

You do not have to agree to store your/your child’s specimens for future tests in order to take part in this study. You/your child will not lose any benefits to which you are/your child is entitled if you decide against storing your/your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from you/your child, and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.
TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your/your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have, like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your/your child’s DNA).

Benefits: There are no direct benefits to you/your child. You/your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your/your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test.

[Signatures for General Use of Mother’s Specimens:]

I give permission for the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ____________________________  ______
Participant Signature          Witness Signature             Date

[Signatures for General Use of Child’s Specimens:]

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ____________________________  ______
Parent/Legal Guardian Signature Witness Signature             Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ____________________________  ______
Participant Signature          Witness Signature             Date
What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your/your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your/your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your/your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your/your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you/your child. You/your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your/your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your/your child’s genetic makeup.

[Signatures for Special Use of Mother’s Specimens:]

I give permission for the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Participant Signature ___________________________ Witness Signature ___________________________ Date ____________

[Signatures for Special Use of Child’s Specimens:]

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Parent/Legal Guardian Signature __________________ Witness Signature ___________________________ Date ____________

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

Participant Signature ___________________________ Witness Signature ___________________________ Date ____________
What if I have more questions?

If you have any questions about the repository, about storage, or the use of your/your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your/your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

[Signatures for Refusal of Use of Mother’s Specimens:]

I refuse to have any specimen collected from me stored in the repository.

___________________________ ___________________________ ____________
Participant Signature Witness Signature Date

[Signatures for Refusal of Use of Child’s Specimens:]

I refuse to have any specimen collected from my child stored in the repository.

___________________________ ___________________________ ____________
Parent/Legal Guardian Signature Witness Signature Date
Clarification Memorandum #1 for:

IMPAACT P1115
Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

DAIDS ES# 11954

Clarification Memo Date: 27 May 2014

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Summary of Clarifications

This Clarification Memorandum (CM) clarifies options for infant HIV testing at Step 1 Week 2 and expectations for use of specimen storage informed consent forms at NICHD sites.

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Implementation

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

Clarification of HIV Nucleic Acid Testing Methods Permitted in Step 1

- In protocol Appendix II-A, the Schedule of Evaluations (SoE) for infants in Step 1 specifies that HIV nucleic acid testing will be performed at Step 1 Entry, with DNA PCR, RNA PCR, and total nucleic acid (TNA) tests being acceptable testing methods at this time point. The SoE also specifies that HIV DNA PCR will be performed at Step 1 Week 2.

- For consistency across study visits in Step 1, this CM clarifies that all testing methods specified for Step 1 Entry are also permitted at Step 1 Week 2. That is, DNA PCR, RNA PCR, and TNA tests may be performed at Step 1 Entry and at Step 1 Week 2.

- This clarification does not impact infant blood draw volumes or the risk-to-benefit ratio for infant study participation.
Clarification Memorandum #1

Page 2 of 8

27 May 2014

IMPAACT P1115 Protocol Version 1.0

Clarification of Expectations for Use of Specimen Storage Informed Consent Forms at NICHD Sites

- As stated in the main study informed consent forms in protocol Appendices IV-A, IV-B, and IV-C, participants at NICHD sites will be asked to provide informed consent for specimen storage and future research as explained in a separate consent form. A sample informed consent form for this purpose is provided in protocol Appendix V. However, the wording in this sample form is specific to infant specimens; corresponding wording for maternal specimens was erroneously omitted from this sample form.

- This CM clarifies that, for NICHD sites, the sample informed consent form for specimen storage and future research in protocol Appendix V is intended to apply to both maternal and infant specimens. As such, wording in the sample form such as “your child” and “your child’s specimens” is being replaced with “you/your child” and “your/your child’s specimens.” In addition, the signature blocks of the sample form are being expanded to accommodate the signature requirements for maternal and infant specimens. The corrected sample form is attached to this CM.
APPENDIX V

FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at Repositories funded by the
National Institute of Child Health and Human Development (NICHD)

FACT SHEET

When you join/your child joins this NICHD-sponsored study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your/your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you/your child during a study are kept. Your/your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your/your child’s name.)

Why have a repository?

Researchers can learn a lot from a study, but as time goes by, the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered, and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your/your child’s rights are being protected.

How will my/my child’s privacy be protected?

The only record that you/your child participated in this NICHD-sponsored study is at the clinic, where it is kept separate from your/your child’s health records and locked away.

Your/your child’s specimens in the repository will not have your/your child’s name on them. The specimens will have a special study code. It will be the same code that is on your/your child’s information in the NICHD-sponsored study from your interviews and examinations. Again, none of this information will have your/your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD-sponsored repository in the future, he or she will write up the idea, and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.
Why wouldn’t I find out the results of the research using my/my child’s specimens?

You will **not** receive the results of research done with your/your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your/your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your/your child’s care right now, but they may be helpful to people like you/your child in the future. Your/your child’s specimens can last in the freezer for many years, and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my/my child’s specimens?

All of the studies to be done in the future on your/your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you/your child and others from this NICHD-sponsored study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead, since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my/my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use your/your child’s specimens in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your/your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my/my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.
As part of this study (P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study), you are/your child is being asked to have some blood taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your/your child’s time in this NICHD-sponsored study.

You do not have to agree to store your/your child’s specimens for future tests in order to take part in this study. You/your child will not lose any benefits to which you are/your child is entitled if you decide against storing your/your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from you/your child, and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.
TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your/your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have, like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your/your child’s DNA).

Benefits: There are no direct benefits to you/your child. You/your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your/your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test.

[Signatures for General Use of Mother’s Specimens:]

I give permission for the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

_________________________  ___________________________  __________
Participant Signature       Witness Signature           Date

[Signatures for General Use of Child’s Specimens:]

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

_________________________  ___________________________  __________
Parent/Legal Guardian Signature  Witness Signature       Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

_________________________  ___________________________  __________
Participant Signature       Witness Signature           Date
What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your/your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your/your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your/your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your/your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you/your child. You/your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your/your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your/your child’s genetic makeup.

\[Signatures for Special Use of Mother’s Specimens:]\]

I give permission for the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

\[Participant Signature \hspace{2cm} Witness Signature \hspace{2cm} Date\]

\[Signatures for Special Use of Child’s Specimens:]\]

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

\[Parent/Legal Guardian Signature \hspace{2cm} Witness Signature \hspace{2cm} Date\]

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

\[Participant Signature \hspace{2cm} Witness Signature \hspace{2cm} Date\]
What if I have more questions?

If you have any questions about the repository, about storage, or the use of your/your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your/your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

[Signatures for Refusal of Use of Mother’s Specimens:]

I refuse to have any specimen collected from me stored in the repository.

___________________________  ___________________________  __________
Participant Signature        Witness Signature            Date

[Signatures for Refusal of Use of Child’s Specimens:]

I refuse to have any specimen collected from my child stored in the repository.

___________________________  ___________________________  __________
Parent/Legal Guardian Signature  Witness Signature        Date
IMPAACT P1115

VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

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

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID)
and
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by:
AbbVie

DAIDS ES #11954
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FINAL Version 1.0
12 March 2014
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IV-C MOTHER

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GLOSSARY

3TC LAMIVUDINE
ALT ALANINE AMINOTRANSFERASE
ART ANTIRETROVIRAL THERAPY/COMBINATION ANTIRETROVIRAL THERAPY
ARV ANTIRETROVIRAL
AST ASPARTATE AMINOTRANSFERASE
AUC AREA UNDER THE CURVE
CHAPAS-1 CHILDREN WITH HIV IN AFRICA – PHARMACOKINETICS AND ADHERENCE OF SIMPLE ANTIRETROVIRAL REGIMENS
CHER CHILDREN WITH HIV EARLY ANTIRETROVIRAL THERAPY
CI CONFIDENCE INTERVAL
CLIA CLINICAL LABORATORY IMPROVEMENT ACT
CMC CLINICAL MANAGEMENT COMMITTEE
CRF CASE REPORT FORM
CRPMC CLINICAL RESEARCH PRODUCTS MANAGEMENT CENTER
DACS 095 NEVIRAPINE PHARMACOKINETICS IN NEWBORNS AND INFANTS: A POPULATION ANALYSIS
DAIDS DIVISION OF AIDS
DAIDS PRO DIVISION OF AIDS PROTOCOL REGISTRATION OFFICE
DBS DRIED BLOOD SPOTS
DMC DATA MANAGEMENT CENTER
DNA DEOXYRIBONUCLEIC ACID
EAE EXPEDITED ADVERSE EVENT
EC ETHICS COMMITTEE
EQA EXTERNAL QUALITY ASSURANCE
FDA FOOD AND DRUG ADMINISTRATION
HAART HIGHLY ACTIVE ANTIRETROVIRAL THERAPY
HIV HUMAN IMMUNODEFICIENCY VIRUS
HPTN 012 PHASE IIIB TRIAL TO DETERMINE THE EFFICACY OF ORAL AZT AND THE EFFICACY OF ORAL NEVIRAPINE FOR THE PREVENTION OF VERTICAL TRANSMISSION OF HIV-1 INFECTION IN PREGNANT UGANDAN WOMEN AND THEIR NEONATE
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IMPAACT INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP
P1110 A PHASE I TRIAL TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF RALTEGRAVIR IN HIV-EXPOSED INFANTS AT HIGH RISK OF ACQUIRING HIV-1 INFECTION
IQA DAIDS IMMUNOLOGY QUALITY ASSURANCE PROGRAM
IRB INSTITUTIONAL REVIEW BOARD
IRIS IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
LAR LEGALLY AUTHORIZED REPRESENTATIVE
LOD LIMIT OF DETECTION (FOR AN HIV RNA ASSAY)
LDMS LABORATORY DATA MANAGEMENT SYSTEM
LPC LABORATORY PROCESSING CHART
LPV/r LOPINAVIR/RITONAVIR
MOP MANUAL OF PROCEDURES
NIAID  National Institute of Allergy and Infectious Diseases
NNRTI  Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI  Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
NVP  Nevirapine
OHRP  Office for Human Research Protections
OPH03  Optimizing Pediatric HIV-1 Therapy 03
PACTG 345  Phase I/II Study of Ritonavir Therapy in HIV-1 Infected Infants
PACTG 356  Early Intensive Antiretroviral Combination Therapy in HIV-1 Infected Infants and Children
PACTG P1030  Phase I/II Study of Lopinavir/ritonavir in HIV-1 Infected Infants < 6 Months of Age
PENTA  Paediatric European Network for the Treatment of AIDS
PENTA 11  Treatment Interruption in Children with Chronic HIV-Infection: The TICCH Trial
PI  Protease Inhibitor
PID  Patient Identification Number
PK  Pharmacokinetic
PRIMO-SHM  No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial
PTC  Post Treatment Controllers
PTI  Planned Treatment Interruption
RE  Regulatory Entity
RNA  Ribonucleic Acid
RSC  Regulatory Support Center
SES  Subject Enrollment System
SETPOINT  Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1-Infected Individuals: The Setpoint study/ACTG A5217
SID  Study Identification Number
SMART  Strategies for Management of Antiretroviral Therapy
SMC  Study Monitoring Committee
SPARTAC  Short Pulse Anti-Retroviral Therapy At seroConversion
STI  Structured Treatment Interruption
SUSAR  Suspected Unexpected Serious Adverse Reaction
TNA  Total Nucleic Acid
VISCONTI  Virological and Immunological Studies in CONTrollers After Treatment Interruption
VQA  DAIDS Virology Quality Assurance program
WHO  World Health Organization
ZDV  Zidovudine
KEY DEFINITIONS

*In utero* HIV infection is defined as at least one positive nucleic acid test from a blood specimen collected within 48 hours of birth, confirmed with a second positive nucleic acid test from a separate blood specimen.

HIV remission is defined as having no confirmed plasma HIV RNA ≥ the limit of detection (LOD) of the assay for 48 weeks following ART cessation.

Postmenstrual age is calculated by adding postnatal age to gestational age at birth.
SCHEMA

VERY EARLY INTENSIVE TREATMENT OF HIV-INFECTED INFANTS TO ACHIEVE HIV REMISSION: A PHASE I/II PROOF OF CONCEPT STUDY

DESIGN:
Phase I/II proof of concept exploratory study

SAMPLE SIZE:
Up to 472 infants, including 440 at high risk of *in utero* HIV infection and 32 with documented HIV infection, to yield a total of 54 HIV-infected infant subjects, will be enrolled. Mothers of enrolled infants will also be enrolled.

POPULATION:
High-Risk, Cohort 1: Infants aged ≤ 48 hours of birth born to women with HIV infection who did not receive any antiretrovirals (ARVs) during pregnancy

AND

ART-Started, Cohort 2: Infants ≤ 10 days of age with documented *in utero* HIV infection who initiated antiretroviral therapy (ART) outside of the study within 48 hours of birth

AND

Mothers of infants in both cohorts

Refer to Sections 4.12, 4.13, 4.2 and 4.3 for more information on ARV-related eligibility requirements for mothers and infants.

STRATIFICATION:
Infants will be enrolled into Cohorts 1 and 2 based on HIV infection status at entry and stratified within each cohort by feeding method: formula fed (Group A) or breastfed (Group B)

INFANT ART REGIMEN:
2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

determined by the primary provider and dosed by

WHO or individual country guidelines

+ Nevirapine (NVP):

6 mg/kg bid: Step 1 through Step 2 Week 4

200 mg/m² bid (or WHO weight band dosing):

beginning at Step 2 Week 4
If HIV infection is confirmed:
Lopinavir (LPV) 300mg/m² + ritonavir (RTV) 75 mg/m² bid (LPV/r) are added when the infant reaches ≥ 14 days of age AND ≥ 42 weeks postmenstrual age.

STUDY DESIGN:

Step 1: Cohort 1 infants will begin the study ART regimen within 48 hours of birth. If in utero HIV infection is confirmed, these infants will enter Step 2 two weeks after Step 1 entry; otherwise, they will remain in Step 1 for four weeks and then exit the study.

Step 2: Cohort 1 infants who are confirmed to have in utero HIV infection and all Cohort 2 infants will take the study ART regimen, which includes the addition of LPV/r when the infant reaches ≥ 14 days of age AND ≥ 42 weeks postmenstrual age.

Step 3: HIV-infected infants with sustained HIV RNA below the limit of detection of the assay (LOD) on ART and who meet defined eligibility criteria (see Section 4.4) will undergo ART cessation at or after Step 2 Week 96 and remain off ART unless there is a confirmed HIV RNA rebound to ≥ LOD.

Step 4: Infants with 2 consecutive HIV RNA levels ≥ LOD while in Step 3 (after ART cessation) will restart ART.

See Figure 1.

PHARMACOKINETICS:
Dried blood spots (DBS) for NVP concentrations will be collected in all infants in Step 1. Infants in Step 2 will have DBS for NVP and/or LPV/r drug concentrations collected at times of other study blood draws.
STUDY DURATION:

Mothers will be enrolled at the time of the infant’s study entry for demographic data collection, targeted clinical history and HIV RNA testing. Mothers of infants identified as HIV-infected will have a single blood draw as soon as possible after the infant is identified as infected and will continue to be followed for interval clinical history as long as their infant remains in the study.

HIV-infected infants will be followed up to 5 years of age for ongoing evaluation for HIV remission, potential treatment toxicity, and clinical or laboratory progression.

Cohort 1 HIV-exposed infants who do not have in utero HIV infection and their mothers will exit the study at the Step 1 Week 4 visit.

OBJECTIVES:

Primary Objective:
To assess HIV remission among HIV-infected neonates who initiate ART within 48 hours of birth. For purposes of this protocol, remission is defined as having no confirmed plasma HIV RNA ≥ LOD for 48 weeks following ART cessation.

Secondary Objectives:
1) To assess the safety of very early ART in neonates.
2) To assess the PK of NVP in neonates and young infants in order to determine the NVP dose needed to maintain NVP concentrations between 3,000 and 10,000 ng/mL required for HIV treatment.
3) To describe LPV exposures when dosed with NVP in neonates and young infants.
4) To assess the relationship between time to reach confirmed plasma HIV RNA < LOD and achievement of the virologic and immunologic criteria for ART cessation among infants who have no evidence of viral rebound.
5) To assess the extent of HIV persistence in infants who achieve HIV remission.
6) To evaluate immune activation and host and viral determinants, including maternal factors and HIV-specific immune responses, associated with HIV remission.
Figure 1. Study design

Cohort 1
High-risk Infants
study ART
initiated within 48 hours of birth

STEP 1

No evidence of *in utero* infection

Study ART discontinued no later than Week 2

Off Study @ Week 4 visit

*In utero* infection

Enter Step 2
(Instead of completing Step 1 Weeks 2 & 4 visits)

STEP 2

- If < 2 weeks of age OR < 42 weeks postmenstrual age, 2 NRTIs + NVP.
- At ≥ 2 weeks of age AND 42 weeks postmenstrual age, add LPV/r to 2 NRTIs + NVP regimen.
- When RNA < LOD for ≥ 12 weeks, switch to LPV/r + 2 NRTIs.

Starting at the Week 84 visit, evaluate for ART Cessation (see Section 4.4)

Not Eligible for ART Cessation → Re-evaluate

Continue 3 drug ART
Continue in Step 2

Eligible on Re-evaluation

- No Viral Rebound
- Eligible for ART Cessation

STEP 3

Not Eligible for ART Cessation on multiple re-evaluations

Off Study @ Step 2 Week 192 visit

Confirmed Viral Rebound ≥ LOD

STEP 4

Off Study @ 5 years of age
1.0 INTRODUCTION

1.1 Background and Rationale

The capacity of the human immunodeficiency virus (HIV) to establish latency in long-lived cells, particularly in resting memory CD4+ T cells, precludes virus eradication with current combination antiretroviral therapy (ART) [1]. HIV latency in resting memory CD4+ T cells promotes viral quiescence, which renders latently infected CD4+ memory cells non-susceptible to antiretroviral drugs or HIV-specific immunity. These memory CD4+ T cells harbor latent HIV genomes and arise during development of immunologic memory [1]; those memory cells that arise directed towards HIV form the resting memory CD4+ T cell latent HIV reservoir [1]. Formation of the latent reservoir in the context of a developing immune system has important implications for the size and distribution of this reservoir in HIV-infected infants [2]. This feature distinguishes the latent HIV reservoir formation and its maintenance in pediatric HIV infection from HIV-infected adults, and has implications for targeting viral reservoirs formation with very early therapy to achieve HIV remission for pediatric populations.

A case of HIV cure in an adult (the “Berlin patient”) provided proof-of-concept that HIV can be eradicated from the body, including the central nervous system, whereby ART can be discontinued without viremic rebound [3]. HIV cure occurred in this individual following treatment for acute myelogenous leukemia with total ablative chemotherapy, irradiation and repeat stem cell transplantation with donor cells homozygous for CCR5 delta32, accompanied by graft versus host disease. This case demonstrates that replication-competent HIV reservoirs can be reduced or cleared sufficiently to permit ART discontinuation without subsequent viremic rebound [4].

A case of HIV remission (no viremic rebound within one year) was recently reported in a U.S. born child (the “Mississippi Baby”) who was treated with three drug ART by 31 hours of life for high-risk HIV-exposure from untreated maternal infection [5]. In this infant, plasma viral load reached undetectable levels by 28 days of age on ART and remained undetectable even when ART was discontinued at age 18 months. This infant is considered in HIV remission since rebound viremia has not ensued for over one year following ART discontinuation. Using ultrasensitive quantitative methods, traces of HIV nucleic acid (DNA and RNA) remain detectable in peripheral blood of the infant, but no replication-competent virus has been recovered off ART. The absence of detectable T cell activation and adaptive HIV-specific immune responses (antibody and T cell responses) in this baby further suggest lack ongoing HIV-1 replication. Altogether, this case suggests that very early therapy may attenuate HIV reservoir formation, or block HIV persistence and provides the rationale to develop a proof-of-concept study of very early ART (initiated within 48 hours of birth) to achieve HIV remission/functional cure in infants. This study will specifically address the
hypothesis that very early therapy in HIV-infected neonates prevents establishment of HIV reservoirs, including the long-lived resting memory CD4+ T cell latent reservoir, possibly permitting long-term control of HIV replication off ART, leading to HIV remission.

Importantly, there are emerging data that very early therapy during acute HIV infection in adult and children quantitatively modifies HIV persistence and HIV-specific immune responses. A small (5-15%) subset of HIV-infected adults treated during early infection has been able to discontinue ART and still maintain control of virus replication to clinically undetectable levels [6,7]. These post-treatment controllers (PTC) have very low levels of cell-associated HIV provirus, which continue to decay over time off therapy. They also have lower levels of activated CD8+ T cells and HIV-specific T cell responses than the subset of HIV-infected adults (1-5%) who spontaneously control HIV replication to less than 50 copies/ml in the absence of antiretroviral drugs (“Elite Controllers”) [8]; specific HLA-alleles (HLA-B57 and HLA-B27) and vigorous HIV-specific T cell responses are commonly found in these “Elite Controllers.”

Several lines of evidence suggest that early ART may also modify HIV persistence in children. Follow-up studies of early-treated infants have demonstrated lower levels of replication-competent virus than in later-treated children [9]. Moreover, Luzuriaga [10] and colleagues have shown that the absence of HIV-specific immune responses may be a marker for strict control of HIV replication following early therapy. A recent study of HIV persistence in HIV-infected youth with continuous suppression of HIV replication for 10 or more years after initiating ART prior to 3 months of age demonstrated low levels of circulating HIV provirus, undetectable plasma RNA by ultrasensitive assays, lack of replication-competent virus, and lack of HIV-specific immune responses [11]. Circulating HIV proviral DNA levels were lower than those reported in adult PTCs; decay over time was also observed. Data from these children, along with those from the Mississippi Baby and the Berlin Patient presented above, suggest that T cell activation markers and HIV-specific immune responses may be sensitive indicators of HIV replication (and that conversely, lack of T cell activation and HIV-specific immune responses are sensitive indicators of controlled HIV replication).

Currently, one limitation to immediate or very early therapy in HIV-infected infants is the lack of a widely available point of care nucleic acid tests to identify HIV infection in exposed neonates. Since it is likely that HIV establishes persistent infection in long-lived cells that preclude HIV remission, within days of infection, it will be critical to start antiretroviral therapy within the first one to two days of life.
1.2 Treatment Cessation to Assess HIV Remission

To test the hypothesis that very early therapy blocks HIV from establishing persistent infection in viral reservoirs, thereby leading to HIV remission, it will be essential to discontinue ART [12]. All current and previous ART guidelines for all age groups recommend continuous lifelong ART, due to the prompt rebound in viremia that ensues (within 12 weeks) when ART is stopped. The rebounding virus is thought to come from the persistence of HIV despite ART, in replication-competent forms, in viral reservoirs. The incorporation of treatment cessation as a strategy for adult and pediatric HIV infection is largely disfavored. However, there is experience with planned treatment interruption (PTI) also referred to as structured treatment interruption (STI) both in acute and chronic established HIV infection in adults, adolescents and children. The study that has impacted significantly on PTI in HIV infected patients is the Strategies for Management of Antiretroviral Therapy (SMART) Study [13]. This large multi-center trial comparing CD4 guided PTI with continuous ART and enrolling 5472 adults was stopped because of an unexpected increase in risk of opportunistic infection or death in subjects undergoing PTI, with non-infectious renal, cardiovascular and hepatic disease contributing most to the primary endpoint. In children, however, PTI has thus far been safe in two randomized pilot studies, PENTA 11 (Treatment Interruption in Children with Chronic HIV-Infection: The TICCH Trial) in Europe and the OPH03 (Optimizing Pediatric HIV-1 Therapy 03) study in Kenya, which evaluated CD4-driven planned treatment interruptions in older HIV-infected children. Neither trial showed significant morbidity [14,15].

In the PENTA 11 pilot trial, 109 children with perinatal infection were randomized to PTI or continuous ART at a median age of 9.3 years. All had viral load < 50 copies/mL and CD4 > 30%. Thirty-two of 51 on PTI successfully completed 48 weeks of follow-up without meeting criteria to restart ART during interruption. PTI was not associated with adverse events. Younger age and higher nadir CD4% predicted both remaining off ART for at least 48 weeks and better CD4% recovery following PTI [14]. PENTA 11 established the safety of PTI in children. Of note, no neurodevelopmental consequences were noted after PTI in the PENTA 11 study [16,17]. A follow-up study, conducted 2 years later, again showed no consequences of PTI [17]. In the OPH03 study in Kenya, infants commenced ART at a median age of 5 months. Treatment was interrupted after 24 months, with 14 of 21 children reaching CD4 restart criteria within 3 months of PTI. In a small study of adolescents (N = 14) who were well-controlled on ART and underwent increasing sequential cycles off ART compared to 21 adolescents on continuous ART, a subset who were exposed to ≥ 13 progressively lengthening PTI cycles were able to stay off ART for more than 27 days. In this study, enhanced HIV-specific immune responses correlated with declining viral load [18,19]. One outcome of the cycling strategy was the development of antiretroviral drug resistance mutations in 3 of the 14 study participants. In P1115, the treatment cessation will occur at a defined period and
subjects will be followed closely and restarted on their ART regimen if rebound viremia ensues.

1.3 Planned Treatment Interruption After Acute Infection

Treatment interruption in the setting of treatment initiation during acute infection appears to be different. Three adult studies addressing early ART followed by treatment interruption showed benefit with higher CD4 count and lower viral set point but did not show clinical benefit [20-22]. The largest and most well conducted study was the randomized Short Pulse Anti-Retroviral Therapy At seroConversion (SPARTAC) trial, identifying adults within 6 months of infection. Subjects received either ART for 12 or 48 weeks followed by PTI, or standard of care. Early ART for 48 weeks favorably altered the trajectory of CD4 depletion and HIV RNA elevation, the two main markers of HIV disease progression. In a secondary analysis, more sustained virological control was directly related to closeness of ART initiation to time of primary infection [20]. Two relatively small studies, the Setpoint/ACTG A5217 study (Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1-Infected Individuals: The Setpoint study/ACTG A5217) and Primo-SHM trial (No Treatment versus 24 or 60 Weeks of Antiretroviral Treatment during Primary HIV Infection: The Randomized Primo-SHM Trial) also showed a lower average viral load after early limited ART compared to deferred ART [21,22]. The study shedding new light on early therapy and the potential to stop ART is the Virological and Immunological Studies in CONtrollers after treatment interruption (VISCONTI) cohort study from France. After primary ART for a median of 5 years, 5 of 32 adults controlled HIV replication for more than 6 years post PTI [6]. In an update, they describe immunological and virological control in 14 patients off ART for a median of 76 months, possibly explained by preservation of central memory CD4 cells. The VISCONTI cohort is phenotypically different from long-term non-progressors where factors such as HLAB27/57 phenotype are relevant [7]. There is also experience with treatment cessation in the context of early ART (within 3 months of life). The Children with HIV Early Antiretroviral (CHER) trial was an open label 3-arm trial in HIV-infected asymptomatic infants aged < 12 weeks with CD4% ≥ 25%. The main hypothesis was that early limited ART started close to primary infection would prevent disease progression and safely allow a subsequent period off ART, thus preserving future treatment options when compared with deferred ART. In the trial, 377 infants were randomized to deferred (ART-Def) or immediate ART for 40 weeks (ART-40W) or 96 weeks (ART-96W), followed by PTI. Criteria for ART initiation in ART-Def and re-initiation after interruption were CD4% < 25% in infancy; otherwise < 20% or CDC severe stage B or stage C disease. First line ART was lopinavir/ritonavir (LPV/r), zidovudine (ZDV) and lamivudine (3TC). The trial commenced in mid-2005. HIV DNA PCR was undertaken from 4 weeks of age with HIV infection confirmed by a quantitative HIV RNA >1000 copies/ml. Median age at baseline was between 7.1 and 7.5 weeks of age. In
June 2007, an interim analysis revealed that early ART reduced mortality by 74% [23]. In the full results, after a median of 5 years on study, the benefit of early limited versus deferred continuous ART was confirmed [24]. Clinical endpoints, mainly death, occurred early and remained significantly higher in the deferred arm despite a longer period on continuous ART. Outcomes were marginally better with longer primary therapy (ART-96W). Children in ART-96W remained off ART during PTI for a median of 70 (95% CI: 35 to 109) weeks compared to 33 (95% CI: 26 to 45) weeks in ART 40W (p = 0.13), also with fewer primary endpoints and reduced hospitalization. It is plausible that a longer period of primary ART in CHER might have sustained better long-term outcomes following interruption. There were 9 cases of HIV encephalopathy in ART-Def, 5 in ART-40W and 2 in ART-96W, again suggesting the importance of early ART for a longer period.

1.4 Timing of Treatment Cessation in P1115 Subjects

The optimal time to cease ART after very early therapy to assess HIV remission is unknown. In the infant reported to have experienced HIV remission [5], albeit a single case, adherence was suboptimal at around 15 months of age and discontinued by 18 months of age. Multiple factors may contribute to estimates of time to clearance of pre-existing HIV-infected cells before ART was started. These include the half-lives of the infected cell populations and the total body burden of HIV virions, some of which can be trapped on follicular dendritic cells for years. For P1115, Perelson and Ho’s estimates [25] of up to three years to clear HIV infected cells or free virions bound to follicular dendritic cells will be used, assuming that the very long-lived reservoir for HIV in central memory CD4+ T cells was prevented by very early treatment. It is expected that the feasibility of stopping ARV treatment by 2 years of age will vary significantly by the timing and duration of in utero infection during gestation prior to birth and the viral burden present in the infant prior to initiation of treatment.

1.5 Rationale for Potent Antiviral Dosing (4 drugs) and HIV Dynamics in High-risk HIV-exposed Infants Receiving Combination Prophylaxis Regimens

This protocol is designed to focus on the effect of starting ART within the first 48 hours of life on likelihood of achieving HIV remission in in utero infection. Based on viral loads of a similar cohort of infants enrolled in HPTN 040, Phase III randomized trial of the safety and efficacy of 3 neonatal ARV regimens for prevention of intrapartum HIV-1 transmission, in utero, infected infants (N = 93) had initial HIV RNA viral loads < 48 hours of birth which varied from as low as several hundred HIV RNA copies/mL to several million, with a median viral load of 100,000 copies/mL. Plasma viral load was significantly reduced ≥ 1.5 log by two weeks of combination ARV prophylaxis consisting of ZDV and three doses of nevirapine (NVP) or ZDV, 3TC and nelfinavir given during the first two weeks of life. Plasma levels of NVP were 100 ng/ml (10 x greater than inhibitory
concentrations) for a minimum of 10 days. However, despite the significant reduction of HIV plasma viral load in all infants receiving two or more drugs to as low as 100 HIV RNA copies/mL in a few cases, most infants still had significant plasma HIV RNA viremia on combination prophylaxis, and none of the in utero infected infants achieved undetectable plasma viremia by the two week time point. Furthermore, rebound viremia reached high levels by 4 to 6 weeks following discontinuation of prophylaxis. Therefore, combination antiretroviral drugs in short term prophylaxis are insufficient to achieve HIV remission. A more potent and prolonged antiviral effect is needed. [26].

The challenge of providing adequate drug concentrations with potent antiviral coverage in infants during acute/primary HIV infection was highlighted in PACTG 345, A Phase I/II Study of Ritonavir Therapy in HIV-1 Infected Infants. Here, a negative correlation between baseline plasma HIV RNA levels and the slope of decay of plasma viremia was demonstrated, likely reflective of suboptimal antiviral drug concentrations coupled with very high pretreatment baseline plasma levels [27]. The potential effect of even a small decrease in phase 1 decay for infants with high plasma virus levels may be significant, as it could delay prompt control of virus replication with potential to select for drug resistant virus. Results from analysis of an early ART regimen using LPV/r in young infants less than 6 months of age showed that the time to achievement of undetectable plasma viral load was highly correlated with the size of the resting CD4+ T cell latent HIV reservoir [9]. With the goal of rapidly reducing HIV viral load to undetectable levels and maintaining durability in infants with acute primary HIV infection, it is essential to provide a regimen with known potent antiviral activity in neonates. Due to the limitation in neonatal PK data and available pediatric formulation of antiretroviral drugs along with potential early toxicity, the optimal approach in this proof-of-concept study is to initiate empiric ART using antiretroviral drugs with a known track record in neonatal prophylaxis (ZDV, 3TC, NVP) but at anticipated treatment doses based on PK modeling from external data (see Section 1.6 below). LPV/r will be added to the three-drug ARV regimen at 2 weeks of life or an equivalent of 42 weeks postmenstrual age in infants with confirmed HIV infection. Treatment with a four drug regimen including both NVP and LPV/r will be used to ensure optimal suppression of HIV viral replication, given the limitations in the use of these drugs in neonates and young infants discussed below in sections 1.6 and 1.7. Combining LPV/r with NVP should provide adequate coverage if either has suboptimal drug concentrations. A four-drug regimen will be continued until plasma HIV RNA is durably suppressed for 12 or more weeks, expected to be approximately 6 months of age, by which time adequate lopinavir (LPV) exposure can be reliably achieved, NVP will be discontinued, and a three-drug LPV/r regimen will be used.
1.6 Rationale for Nevirapine Dosing

Current NVP pharmacokinetic (PK) data during the first months of life come from studies evaluating NVP regimens for prevention of peripartum and breast milk HIV transmission [28-30]. The PK goal for these regimens was to keep NVP plasma concentrations above 100 ng/mL, 10 times the NVP IC 50 for wild type virus. Peak concentrations with these regimens average between 1000 and 1500 ng/mL. The success seen with these regimens in efficacy protocols, such as HPTN 012, Phase IIIB Trial to Determine the Efficacy of Oral AZT and the Efficacy of Oral Nevirapine for the Prevention of Vertical Transmission of HIV-1 Infection in Pregnant Ugandan Women and Their Neonates, and HPTN 046, Phase III Trial to Determine the Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV-Infected Women to Prevent Vertical HIV Transmission During Breastfeeding, suggests that keeping NVP concentrations in the 100 ng/mL to 1500 ng/mL range is adequate for prevention of HIV transmission [31,32].

In contrast, the NVP concentration target with dosing in HIV-infected individuals is a trough of 3000 ng/mL and a peak of 10,000 ng/mL [33]. NVP concentrations within this range achieve sustained viral suppression and avoid NVP resistance while minimizing NVP toxicity in HIV-infected individuals. A NVP dosing regimen to maintain NVP concentrations within this range has not been established in infants during the first 2 weeks of life. NVP is metabolized primarily by CYP3A4 and CYP2B6, whose activities are low in neonates and to increase rapidly during the first months of life [34]. NVP auto-induces its own clearance, with more auto-induction at higher NVP concentrations [35]. The interaction between the developmental trajectory of NVP’s elimination pathways and NVP auto-induction at treatment concentrations is unknown.

Treatment NVP dosing in infants in PACTG 356, Early Intensive Antiretroviral Combination Therapy in HIV-1 Infected Infants and Children utilized 200 mg/m² in infants > 4 weeks of age. This approximates the WHO weight band dosing recommendations for NVP. In this protocol, we will dose NVP at 6 mg/kg bid for subjects < 6 weeks of age and use the WHO weight band doses (200 mg/m²) thereafter. The NVP dose for infants < 6 weeks of age was derived from data simulations using the DACS 095, Nevirapine Pharmacokinetics in Newborns and Infants: A Population Analysis, NVP population PK model, whose database combined data from young infants receiving doses designed to exceed the 100 ng/mL prophylactic target with data from older infants and children receiving doses designed to exceed the 3000 ng/mL treatment target [35]. This PK model also suggests low troughs can occur during lead-in once daily dosing. Starting pediatric NVP therapy on full dose (bid) NVP was recently evaluated in the CHAPAS-1 study, Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens. Nearly one third of infants < 2 years of age using standard lead-in (qd) dosing had sub-therapeutic troughs.
compared to only 12% of infants initiated on full dose (bid) NVP. While subjects initiating NVP at full bid dosing had a higher frequency of rash, it was primarily Grade 1 to 2, was easily manageable, and did not occur in any infants < 2 years of age [36]. Given these PK findings and low rash frequency, NVP will be initiated with bid dosing in this study.

To confirm that actual NVP concentrations achieved with this dose remain within the usual target treatment ranges (3,000 to 10,000 ng/mL), NVP plasma concentrations must be measured in infants receiving this dose. Due to the long half-life of NVP, this can be done using an opportunistic sparse sampling strategy limited to collection of a few dried blood spot samples obtained at the time of regularly scheduled study blood draw. Dried blood spot samples obtained from the first 30 subjects enrolling in the protocol will be assayed for NVP concentration shortly after collection and analyzed using descriptive statistics, to allow a rapid assessment of the adequacy of the NVP dosing regimen in neonates. Using the criteria outlined in Section 9.2, modification of NVP dosing may be considered based on the results of this analysis. Dried blood spots from subsequent infants will be stored, assayed in batch mode at the conclusion of the study, and analyzed using both descriptive statistics and population PK techniques.

1.7 Rationale for Lopinavir/ritonavir Dosing and Use with Nevirapine

LPV undergoes complex pharmacokinetic changes during the first year of life. While PACTG P1030, A Phase I/II Study of Lopinavir/ritonavir in HIV-1 infected Infants < 6 Months of Age found relatively low LPV concentrations in infants initiating therapy during the first 6 weeks of life [37], viral suppression was equal or better than in older infants. In addition, therapeutic drug monitoring in newborn infants during the first few days of life indicates that LPV levels may be higher in very young infants than seen in P1030 [38]. This may be due to metabolic and drug absorption changes seen during the first few weeks of life. The major enzyme responsible for LPV metabolism is CYP3A4. It has low expression at birth, while a related CYP3A isoform, CYP3A7 is preferentially expressed [39]. After birth there is a developmental switch from CYP3A7 to CYP3A4 [40] as the major CYP3A isoform in the newborn liver during the first month of life [41]. While there is considerable overlap in substrates metabolized by these two CYP3A enzymes, CYP3A7 is less efficient than CYP3A4 at metabolizing several CYP3A substrates in vitro [41]. If CYP3A7 metabolizes LPV less well than CYP3A4, the early changes in LPV PK could be due to this developmental switch in CYP3A metabolism and the ontogeny of CYP3A4 drug metabolizing enzymes as well as changes in absorption. The current FDA labeled pediatric dose of LPV is 300 mg/m² bid in infants between 14 days and 6 months of age. There are virtually no LPV PK data during the first 4 weeks of life and none in combination with NVP.
NVP produces a modest induction in LPV metabolism in adults and children, resulting in an adult AUC ratio (with NVP/without NVP) of 0.73 (90% CI 0.53-0.98). A similar increase in LPV metabolism has been observed in children where those receiving concomitant NVP therapy had a LPV AUC ratio of 0.78 (90% CI 0.56-1.09) compared to those without NVP (package insert). Thus, the recommended dose of LPV in children over 6 months of age also receiving NVP is 300 mg/m$^2$ bid. This higher dose produces similar LPV concentrations to standard LPV dosage given to children not receiving NVP [42]. A population analysis of LPV pharmacokinetics in infants predicts 300 mg/m$^2$ will give low troughs (< 1 µg/mL) in approximately 8% of infants between 2 and 8 weeks of age decreasing to below 1% in by 6 months of age using a dose of 300 mg/m$^2$ bid. With the induction of LPV metabolism by NVP these frequencies may increase but even with a 20 to 30% increase in LPV metabolism, the rate of low troughs should be negligible by 6 months of age at this dosage. To determine the time course of LPV concentration changes when given with NVP, samples for LPV/r assay will be collected at the time of routine study blood draws from all subjects receiving LPV/r during the first 6 months of life. At the conclusion of the study, these samples will be batch assayed and subsequently analyzed using population PK techniques.

1.8 Rationale for Formula and Breastfeeding Cohorts and Initial Focus on in utero HIV-infected infants

This proof-of-concept protocol will focus on a very early treatment strategy in infants with presumed in utero infection who are identified by positive nucleic acid testing within 48 hours of birth. Although the first infant described to have possibly achieved remission in this fashion was formula fed, it is also important to study breastfed infants, since the major burden of neonatal infection occurs in resource-constrained settings where breastfeeding is standard of care and critical for child survival. Studying these two cohorts sequentially would delay by years findings with implications for the epicenter of perinatal transmission. Stratifying into the two feeding method groups will allow for evaluation of HIV remission and safety of the approach under the two conditions.

While the risk of occurrence of HIV super infection by transmission through breastfeeding is likely low to an infant with in utero HIV infection on ART, this risk still exists while exposure to breast milk continues. It is therefore possible that an in utero HIV-infected infant who received very early therapy and underwent HIV clearance could subsequently become infected through ongoing exposure to breast milk, impacting greatly on the study findings. The possibility of this occurring will be limited by assuring that the infants have ceased breastfeeding for a minimum of 6 weeks prior to any ARV interruption. Breastfeeding and non-breastfeeding cohorts will be studied simultaneously since the major burden of neonatal infection is in resource-constrained settings where breast-feeding is standard and critical for child survival. As outlined, this
Protocol focuses on in utero and not intrapartum infection. The latter is still a possibility for this cohort. The P1115 team recognizes this aspect of the study to be a limitation of the planned “early exit” of HIV exposed infants from this protocol who were not identified as in-utero infected. Therefore, these infants should receive the appropriate ARV prophylaxis, based on country-specific guidelines with continued assessment for intrapartum and breast-milk transmission, until infection is excluded.

1.9 Rationale for enrolling HIV-infected infants started on ART < 48 hours in a clinical setting

With widespread media coverage of the “Mississippi Baby”, current clinical practices of early treatment of high-risk infants are rapidly evolving among clinical care providers. In P1115, HIV-infected infants who have been started on ART within 48 hours of birth in a non-study setting and are subsequently confirmed to have in utero HIV infection will be eligible for enrollment within 10 days of age into Cohort 2, at which time study-related treatment will be initiated and prospective analyses of HIV persistence biomarkers and assessment of HIV remission will be performed. These infants will also be subdivided into Group A, formula fed and Group B, breastfed cohorts. All infants diagnosed as HIV-infected will also undergo at least one confirmatory HIV DNA or RNA testing performed at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites). Potential limitations for assessing this ART-started cohort include possibly missing key early measurements and specimens and the likelihood of differences in ARV (particularly NVP, or off-label use of LPV/r before the appropriate age is reached) doses and/or administration schedules prior to enrollment. Eligibility criteria for this cohort are designed to insure that a minimum set of key information will be available before enrollment. The study team will also work with referring sites/providers to gather all relevant data collected prior to study entry to try to address these issues.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.11 To assess HIV remission among HIV-infected neonates who initiate ART within 48 hours of birth. For purposes of this protocol, remission is defined as having no confirmed plasma HIV RNA ≥ the limit of detection of the assay (LOD) for 48 weeks following ART cessation.

2.2 Secondary Objectives

2.21 To assess the safety of very early ART in neonates.
2.22 To assess the PK of NVP in neonates and young infants in order to determine the NVP dose needed to maintain NVP concentrations between 3,000 and 10,000 ng/mL required for HIV treatment.

2.23 To describe LPV exposures when dosed with NVP in neonates and young infants.

2.24 To assess the relationship between time to reach confirmed plasma HIV RNA < LOD and achievement of the virologic and immunologic criteria for ART cessation among infants who have no evidence of viral rebound.

2.25 To assess the extent of HIV persistence in infants who achieve HIV remission.

2.26 To evaluate immune activation and host and viral determinants, including maternal factors and HIV-specific immune responses, associated with HIV remission.

3.0 STUDY DESIGN

This is a Phase I/II proof of concept exploratory study investigating the hypothesis that very early therapy in HIV-infected neonates may permit long-term control of HIV replication off ART and lead to HIV remission. The study will also assess the safety and pharmacokinetics of very early combination antiretroviral therapy in neonates.

Infants and their mothers will be enrolled in the following cohorts:

- **Cohort 1: Infants at high risk for HIV infection (High-Risk)**

  Infants ≤ 48 hours of age assessed to be at high risk of acquiring HIV infection, defined as:
  
  - Born to a mother with confirmed or presumed HIV infection and mother did not receive ARVs during the current pregnancy
  
  OR
  
  - Mother first identified as HIV-infected in labor or postpartum.

  Maternal receipt of ARVs prior to this pregnancy (including NVP) or during labor and/or the intrapartum period for this pregnancy is permissible.

  Group A – Formula fed infants:
  
  Enroll approximately 320 high-risk infants to identify 16 HIV-infected infants.
Group B – Breastfed infants:

Enroll approximately 120 high-risk infants to identify 6 HIV-infected infants.

- Cohort 2: HIV-infected infants (ART-started)

Infants ≤ 10 days of age with:

≥ one positive HIV DNA or RNA assay drawn within 48 hours of birth who were treated daily with ≥ 3 antiretroviral drugs (see Section 4.33) starting within the first 48 hours of life and continuing until study entry.

HIV infection must be confirmed with a second test (see Section 6.31) within 7 business days of study entry (if not previously obtained).

Group A – Formula fed HIV-infected infants (up to N = 16)

Group B – Breastfed HIV-infected infants (up to N = 16)

The study consists of four steps:

- STEP 1 (Evaluation and Initial Treatment of High-Risk Infants) – HIV exposed high-risk infants, Cohort 1, will be enrolled in Step 1 for evaluation of HIV infection and initiation of treatment. Subjects in Cohort 1 in whom in utero HIV infection is not identified from blood samples obtained within the first 48 hours of life will exit the study at the Week 4 visit and receive standard prophylaxis per country guidelines. Subjects with confirmed in utero HIV infection will transition to Step 2 instead of completing the Step 1 Week 2 and Week 4 visits.

- STEP 2 (Management of Subjects with Confirmed HIV Infection) – Subjects in Cohort 1 with confirmed HIV infection will continue their initial treatment and transition to STEP 2. Infants with evidence of in utero HIV infection who have initiated ART within 48 hours of birth in a non-study setting, Cohort 2, will be enrolled in Step 2 and initiate study-designated ART. Both cohorts will be evaluated for possible treatment cessation beginning at the Step 2 Week 84 visit.

- STEP 3 (ART Cessation) – Subjects in Step 2 who meet all criteria for treatment cessation (see Section 4.4) will enter Step 3. At entry into Step 3, ART will be stopped and subjects will undergo frequent HIV RNA testing to monitor HIV remission and check for viral rebound until 5 years of age.

- STEP 4 (ART Re-initiation) – Subjects in Step 3 who have 2 consecutive HIV RNA levels ≥ LOD (see Section 4.5) will enter Step 4 and restart ART. Subjects in Step 4 will undergo frequent HIV testing to monitor response to ART re-initiation and continue follow up until 5 years of age.

Mothers of enrolled infants will be followed as long as their infant remains on study.

Refer to Section 6.3 for the detailed subject management plan.
4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Maternal Inclusion Criteria

4.11 Cohort 1 and Cohort 2

4.111 Mothers will be eligible to enroll with EITHER:

1) Presumed HIV infection defined as ≥ one positive rapid HIV antibody test obtained in the peripartum period. Confirmation of maternal infection must be made; test result must be available within 7 business days of study enrollment. (See Note below):

   OR,

2) Confirmed HIV infection defined as: positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma.

Sample #1 may be tested using any of the following:
- Two rapid antibody tests from two different manufacturers or based on different principles and epitopes
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Note: Women with presumed HIV infection must have confirmatory testing on a second specimen per the algorithm below.

Sample #2 may be tested using any of the following:
- Rapid antibody test for a total of 3 different rapid tests. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved, and all three rapid tests must be from different manufacturers or based on different principles or epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One qualitative HIV DNA PCR
- One quantitative HIV DNA PCR
• One quantitative HIV RNA PCR (above the limit of detection)
• One qualitative HIV RNA PCR
• One total HIV nucleic acid test

Samples #1 and #2 may be tested by non-study public or PEPFAR programs or in other laboratories that do not participate in DAIDS external quality assurance programs (if so, a 3rd sample will need to be tested in an appropriately certified laboratory, see end of this section). Both the result and the sample collection date must be recorded in the subject’s chart. Source documentation (patient’s medical record/chart, Ministry of Health register, laboratory results, etc.) must be available if requested.

Mothers who enroll with only one positive rapid HIV antibody test obtained in the peripartum period must have confirmatory testing (see Samples #1 and #2 above) with results available within 7 business days of enrollment. If maternal HIV infection is not confirmed within 7 business days of study enrollment, mothers and their infants will be removed from the study. If the mother’s two positive tests were performed in non-certified laboratories, a third confirmatory HIV test must be performed in a laboratory that is DAIDS VQA-certified (non-US sites) or CLIA-certified (US sites). The infant will be allowed to remain on study until these results are available.

4.112 Willing and able to sign informed consent for participation of herself and her infant. Subject must be of an age to provide legal informed consent as defined by the country in which she resides. If not, informed consent must be signed by a legal guardian.

4.12 Cohort 1 Only

4.121 Infant eligible and enrolled in Cohort 1

4.122 No receipt of ARVs during the current pregnancy.

Note: Receipt of ARVs prior to the current pregnancy (including NVP) or during labor and/or the intrapartum period for the current pregnancy is permissible.
4.13 Cohort 2 Only

4.131 Infant eligible and enrolled in Cohort 2

*Note:* Receipt of ARVs during the current pregnancy and/or the intrapartum period for the current pregnancy is permissible.

4.2 Infant Inclusion Criteria, STEP 1, Cohort 1A and Cohort 1B

4.21 \( \leq 48 \) hours of age

4.22 \( \geq 34 \) weeks gestational age at birth (assessment of gestational age will be based on the best clinical estimate determined by date of last menstrual period, antenatal ultrasound, fundal height or Ballard Score)

4.23 Mother with presumed or confirmed HIV infection as described in Section 4.111

4.24 Mother did not receive ARVs during the current pregnancy

*Note:* Maternal receipt of ARVs prior to the current pregnancy (including NVP) or during labor and/or the intrapartum period for the current pregnancy is permissible.

4.25 Able to take ARVs by mouth, nasogastric tube, or gastrostomy tube.

4.3 Infant Inclusion Criteria, STEP 2, Confirmed HIV Infection

4.31 Able to take ARVs by mouth, nasogastric tube, or gastrostomy tube.

4.32 Cohorts 1A and Cohort 1B only

4.311 Must have been enrolled in STEP 1

4.312 Confirmed evidence of *in utero* HIV infection (see Section 6.31)

4.33 Cohorts 2A and Cohort 2B only

4.331 \( \leq 10 \) days of age

4.332 \( \geq 34 \) weeks gestational age at birth (assessment of gestational age will be based on the best clinical estimate determined by date of last menstrual period, antenatal ultrasound, fundal height or Ballard Score)
4.333 Mother with presumed or confirmed HIV infection as described in Section 4.111

4.334 ≥ one nucleic acid test positive for HIV infection on a sample drawn within 48 hours of birth

4.335 Started ART within 48 hours of birth on a regimen including 2 NRTIs plus NVP at a dose of at least 8 mg/day for infants weighing ≤ 2 kg or 12 mg/day for infants > 2 kg AND/OR LPV/r*)

[*The U.S. FDA recommends avoiding LPV/r oral solution in infants < 14 days of age or < 42 weeks postmenstrual age.]

4.336 ART regimen (described in 4.335) was taken daily from date of initiation until study entry

4.4 Infant Inclusion Criteria, STEP 3, ART Cessation

4.41 Must have been enrolled in Step 2.

4.42 Must have reached Step 2 Week 96.

4.43 Must have achieved a plasma HIV RNA level < LOD by Step 2 Week 24 AND have no evidence of viral rebound (2 consecutive HIV RNA tests ≥ LOD) after Step 2 Week 24.

4.44 Must have met ALL of the following additional criteria while in Step 2, obtained at ≥ study Week 84 and ≤ study Week 192:

4.441 Two consecutive negative HIV antibody tests by 3rd generation (or greater) ELISA (performed in central laboratory) at least 8 weeks apart; AND

4.442 Two consecutive negative HIV DNA tests using the Roche Amplicor HIV-1 Test, v1.5 (performed in the study’s designated VQA-certified central laboratory), or the most sensitive validated HIV DNA or HIV total nucleic acid (TNA) assay available (performed in the study’s designated VQA-certified central laboratory) at least 8 weeks apart; AND,

4.443 No detectable HIV RNA at the time of the second consecutive negative HIV DNA test — even if below the limit of detection of the assay — based on testing performed in the study’s designated VQA-certified central laboratory; AND
4.444 CD4 ≥ 25% and normal for age (2-3 years ≥ 1000 cells/mL, 3-4 years ≥ 750 cells/mL); AND

4.445 If breastfed, permanent cessation of breastfeeding for > 6 weeks.

4.5 Infant Inclusion Criteria, STEP 4, ART Re-initiation

4.51 Must have been enrolled in Step 3.

4.52 Experienced viral rebound to ≥ LOD on two consecutive blood draws after ART cessation (in Step 3).

Note: Any single HIV RNA ≥ LOD must be repeated as soon as possible.

4.6 Infant Exclusion Criteria, Step 1 Cohort 1 and Step 2 Cohort 2

Any clinically significant diseases (other than HIV infection) or clinically significant findings during review of medical history or physical examination prior to entry that, in the investigator’s opinion, would interfere with study participation or interpretation.

4.7 Concomitant Medications Requiring Pre-approval

The following medications may not be prescribed for the infant unless approved by the Clinical Management Committee (CMC) due to potential drug interactions with LPV/r:

- Anti-infectives: ketoconazole, corticosteroids, ergot derivatives, systemic itraconazole, rifapentine, rifampin, or rifabutin.
- Antihistamines: terfenadine, cisapride, loratadine, astemizole
- Sedative Hypnotics: alprazolam, clorazapam, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem
- Anticonvulsants, except lamotrigine, gabapentin, and levetiracetam
- Analgesic Narcotics: meperidine, propoxyphene, alfentanil, fentanyl, methadone, hydrocodone, oxycodone, and tramadol
- Analgesic/non-steroidal: piroxicam
- Antiarrhythmics: amiodarone, encaidine, flecanide, propafenone, quinidine, lidocaine, disopyramide, and mexiletine
- Antibiotics: systemic erythromycin, clarithromycin
- Anticoaguulants: warfarin
- Tricyclics: amitriptyline, clomipramine, desipramine, imipramine, maprotiline, nortriptyline, and trimipramine
• SSRIs and non-tricyclics: bupropion, nefazodone, sertraline, fluoxetine, paroxetine, trazodone, and venlafaxine
• Antiemetics: cisapride, dronabinol, and ondansetron
• Beta-blockers: metoprolol, pentolbutolol, pindolol, and timolol
• Calcium channel blockers: bepridil, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, disoldipine, ditradipine, and verapamil
• Hypolipemics
• Immunosuppressants: cyclosporine, tacrolimus
• Neuroleptics: clozapine, pimozide, chlorpromazine, alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam (except during labor), triazolam, and zolpidem
• Stimulants: dexfluramine, methamphetamine
• Cancer chemotherapy: tamoxifen, etoposide, paclitaxel, vinblastine, and vincristine
• St. John’s wort
• Synthetic corticosteroids: fluticasone, budesonide
• Alpha-blockers: alfuzosin

4.8 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). A Site Implementation Plan (SIP) will be required from each site participating in the study. The SIP must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.
Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) \textit{WILL NOT} be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Enrollment of subjects onto the study will be done through the Subject Enrollment System (SES) on the DMC website (at https://www.fstrf.org) under the Systems heading.

4.9 Co-enrollment Procedures

Co-enrollment in other research protocols will require the consent of the protocol co-chairs of P1115 and the other research protocol.

5.0 STUDY TREATMENT

5.1 Drug Regimen, Administration and Duration

5.11 Regimens and Administration

For the purposes of this protocol, only LPV/r will be supplied through the study (see Section 5.31). Other ARV agents used as part of a combination regimen, including NVP and NRTIs, or anti-TB drugs if needed, will \textit{NOT} be supplied through the study and must be provided by non-study prescription.

5.111 Step 1

NVP: 6 mg per kg per dose orally twice daily
(This dose may be changed based on PK analysis of the first 30 subjects, see Section 9.21.)

PLUS
Two NRTIs: chosen by the primary provider and dosed using WHO guidelines or individual country guidelines

(U.S. Department of Health and Human Services dosing is available at:

WHO dosing guidelines is available at:
http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html [refer to page 247])

The Step 1 regimen should be initiated as soon as possible after enrollment and need not be deferred pending collection of specimens for HIV testing or the availability of HIV test results.

5.112 Step 2

NVP:

Initial dose: 6 mg per kg per dose orally twice daily until study Week 4 visit
(This dose may be changed based on PK analysis of the first 30 subjects, see Section 9.21.)

Increase dose to: 200 mg per meter square (m$^2$) orally twice daily OR WHO weight band dosing (refer to the WHO dosing guidelines web link below) at study Week 4 visit

PLUS

Two NRTIs: chosen by the primary provider and dosed using WHO guidelines or individual country guidelines

(U.S. Department of Health and Human Services dosing is available at:

WHO dosing guidelines is available at:
http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html [refer to page 247])

PLUS
LPV 300 mg per meter square (m$^2$) + RTV 75 mg per m$^2$ orally twice daily as LPV/r
(When infants are ≥ 14 days of age AND ≥ 42 weeks postmenstrual age.)

*Note: Postmenstrual age is calculated by adding postnatal age to gestational age at birth as determined using methods described in Section 4.332.*

From 14 days of age AND 42 weeks postmenstrual age, subjects will receive 4 drug ARV therapy with NVP + LPV/r + 2 NRTIs. Once they have had confirmed HIV RNA < LOD for at least 12 weeks, subjects will then continue on therapy with only 3 drugs, LPV/r + 2 NRTIs. Details about this timeline, along with discussion of acceptable alternatives, are outlined in Section 6.32.

5.113 Step 4

Subjects who enter Step 4 and re-initiate ART will restart the same regimen that they received in Step 2 prior to ART cessation and entry into Step 3.

5.12 Administration and Duration

5.121 Administration

Doses of LPV/r should be administered orally approximately 12 hours apart and within two hours of the regularly scheduled time. Tablets may be taken with or without food, swallowed whole and not chewed, broken, or crushed. Oral solution must be taken with food, infant formula, or breast milk.

5.122 Duration

HIV-infected subjects will be followed up to 5 years of age.

5.13 Dose/Formulation Adjustments

Site pharmacists must receive new prescriptions from an authorized prescriber if weight-based adjustments are required in subjects who outgrow their dose and are switched to the next dosing increment.

The switching of LPV/r oral solution to LPV/r pediatric tablets is allowed. Site pharmacists must receive new prescriptions from an authorized prescriber if a formulation change is required.
5.2 Drug Formulation

5.21 LPV/r Oral Solution

The oral solution formulation of LPV/r supplied for this study contains 80 mg LPV and 20 mg RTV per milliliter of solution (see Section 5.32). The solution also contains 42.4% alcohol by volume.

Store the oral solution at 2°C to 8°C (36°F to 46°F) until dispensed to subject. Avoid exposure to excessive heat. Refrigerated solution remains stable until the stated expiration date. For subject use, if the solution is stored at room temperature, 15°C to 25°C (59°F to 77°F), it should be used within 2 months. In settings where average room temperature exceeds 25°C, storage in a refrigerator at 2 to 8°C is recommended.

5.22 LPV/r Pediatric Oral Tablets

The oral tablet formulation of LPV/r supplied for this study contains 100 mg LPV and 25 mg RTV. The tablets are heat stable and film-coated and may not be cut, chewed or crushed. The tablets will be used in study subjects weighing 10 kg or greater with a demonstrated ability and willingness to swallow intact whole tablets. Decisions to change to tablets are at the discretion of the provider in discussion with the child’s family about which formulation is more likely to ensure good adherence.

Store the tablets at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F) until dispensed to subject. Exposure of this product to high humidity outside the original container or USP equivalent tight container for longer than 2 weeks is not recommended.

5.3 Product Supply, Acquisition/Distribution, and Accountability

5.31 Study Product Supply/Acquisition/Distribution

To initiate the study, sites will be allowed to use locally available LPV/r while waiting for the study-supplied LPV/r. Sites will be notified when the study-supplied LPV/r is available at the Clinical Research Product Management Center (CRPMC).

LPV/r will be supplied by AbbVie. (Alternatively, FDA-approved LPV/r can be obtained from within country through distribution sources approved by national regulatory authorities.)
LPV/r oral solution and pediatric oral tablets will be available through the NIAID CRPMC. The site pharmacist can obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

The NRTIs and any other ARVs taken by study infants will NOT be provided through this study. These ARVs must be provided by prescription and supplied from local non-study sources. NVP must be prescribed at protocol-specified doses.

Any study product not provided through the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or -sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Default.aspx

5.32 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed.

At US clinical research sites, all unused LPV/r must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section: Study Product Management Responsibilities.

At non-US clinical research sites, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused LPV/r.
6.0 SUBJECT MANAGEMENT

Toxicities will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 with Clarification dated August 2009. Site investigators will manage toxicities based on severity grade and, in some cases, relationship to study drug.

The study-specific toxicity management guidelines described below and in Sections 6.1 and 6.2 were developed with two aims: 1) to maximize the safety of subjects and 2) to minimize unnecessary interruptions in ART that could undermine the primary aim of the protocol – to maximally treat HIV infection. In this protocol, currently approved ARVs are administered in two ways that are outside of current guidelines. First, NVP is prescribed to infants < 14 days of age using an investigational dose (Sections 1.6 and 5.1). Second, from the age of ~14 days until 12 weeks after HIV RNA is < LOD, subjects will receive combination therapy with 4 drugs (LPV/r + NVP + 2NRTIs), which has the potential to introduce additional toxicity related to any of the ARVs.

The study-specific toxicity management guidelines take the above-listed considerations into account in that they specifically address anticipated possible NVP-associated adverse events (AEs), they apply only to AEs that are assessed as possibly, probably, or definitely related to one or more ARVs, and they apply only while infants are receiving ARVs at protocol-specified investigational doses, i.e., through the Step 2 Week 36 visit. Any AEs that occur after the Step 2 Week 36 visit, or that are assessed as probably not or not related to one or more ARVs, should be managed by site investigators consistent with current standards of care for pediatric clinical care and ARV management. Similarly, toxicities assessed as related to non-ARV concomitant medications should be managed by site investigators consistent with local standards of care.

Consultation on all aspects of clinical management is available from the CMC at any time (impaact.p1115cmc@fstrf.org). Consultation with the CMC is required for selected toxicities, as specified in Sections 6.1 and 6.2. The CMC should also be consulted as soon as possible and within 2 business days on any decision to hold or permanently discontinue any ARV at any time during follow-up, as continuous receipt of suppressive ARV therapy is considered essential for the primary aim of the protocol. Noting that anti-tuberculosis medications such as rifampicin, isoniazid and pyrazinamide can cause hepatic, skin and hematologic toxicity, site investigators should also consult the CMC on management of toxicities that occur among infants being co-treated for HIV and tuberculosis. Further operational guidance for consulting in the CMC is provided in the study Manual of Procedures (MOP).
Assessment of relatedness of an AE to a medication for the purposes of clinical management and recording on CRFs is made by the site investigator, based on the following guidelines:

- Definitely Related: The adverse event and administration of the medication are related in time, and a direct association can be demonstrated.
- Probably Related: The adverse event and administration of the medication are reasonably related in time, and the adverse event is more likely explained by the medication than other causes.
- Possibly Related: The adverse event and administration of the medication are reasonably related in time, and the adverse event can be explained equally well by causes other than the medication.
- Probably Not Related: A potential relationship between the medication and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the medication.
- Not Related: The adverse event is clearly explained by another cause not related to the medication.

NOTE: The above classification applies for AE documentation (source documentation and CRF completion) and management but does not apply for expedited adverse event (EAE) reporting. EAEs will be reported, per the DAIDS EAE Manual, as related or not related. Please see Section 7 below for more information on EAE reporting.

In order to minimize ARV interruptions, single suspect ARVs can be held for up to 3 days while continuing the remainder of the ARV regimen; the CMC should be contacted as soon as possible and within 2 business days to assist with decisions about holding the entire regimen or permanent discontinuation or substitution for individual ARVs. When any ARV is held for toxicity management, relevant clinical and laboratory evaluations should be repeated per the grade- or toxicity-specific guidance provided below until the toxicity resolves or is stabilized.

It is also important to consider the many other possible causes of clinical abnormalities during evaluation. Immune reconstitution inflammatory syndrome (IRIS), although not yet described in neonates, could be confused with toxicity. Therefore, possible causes such as cytomegalovirus, syphilis, hepatitis B and tuberculosis should be sought, if clinically indicated. Neonatal rashes such as erythema toxicum can be confused with drug-related rashes.
6.1 General Toxicity Management Guidelines

The following general guidelines (by grade) apply to management of ARV regimens in response to toxicities — other than those listed in Section 6.2 — that occur through the Step 2 Week 36 visit and are assessed as possibly, probably, or definitely related to an ARV. Management of the toxicities listed in Section 6.2 (i.e., anemia and neutropenia, rash, elevated AST/ALT (asymptomatic) and symptomatic hepatitis), should be guided by that section. All other management should be pursued by site clinicians consistent with current standards of care for pediatric clinical care and ARV management.

Grade 1 Toxicity:
- Continue all ARVs.

Grade 2 Toxicity:
- Continue all ARVs.

Grade 3 Toxicity:
- Upon the initial recognition of a Grade 3 clinical or laboratory toxicity:
  - Site investigator should repeat the laboratory test to confirm the Grade 3 value as soon as possible and generally within 2 business days of site awareness.
  - Non-ARV explanations for the toxicity should be considered.
  - If the initial Grade 3 clinical or laboratory toxicity is assessed as possibly, probably not, or not related to an ARV, the entire ARV regimen should be continued.
- If the Grade 3 toxicity is considered probably or definitely related to an ARV, the suspect ARV should be held while awaiting confirmation, but the remainder of the regimen should be continued. The CMC should be contacted within 2 business days.
- If the result of the repeat test is Grade 1 or 2, the relevant management guidelines (Grade 1 or 2) should be followed.
- If the result of the repeat test confirms a Grade 3 laboratory toxicity:
  - Non-ARV explanations for the toxicity should be considered.
  - If the confirmed Grade 3 laboratory toxicity is assessed as possibly, probably not, or not related to an ARV, the entire ART regimen should be resumed/continued.
• If the confirmed Grade 3 toxicity is assessed as probably or definitely related to an ARV:
  − The CMC should be notified AND the implicated ARV should be held, unless the site investigator feels that continuation of the current regimen is in the subject’s best interest.
  − The decision about whether to hold the entire ARV regimen or just the implicated ARV should be made in discussion with the CMC within 2 business days. If the site investigator feels that continuation of the current regimen is in the subject’s best interest, the CMC should be informed.
  − Following any confirmed Grade 3 toxicity, the subject should be re-evaluated weekly until improvement to ≤ Grade 2.
  − If the entire ART regimen is held due to a confirmed Grade 3 toxicity, the site investigator may resume the regimen once the toxicity improves to ≤ Grade 2. Following resumption of ARVs, if the Grade 3 toxicity recurs (and is confirmed), the implicated ARV should be permanently discontinued. If one or more ARVs are not clearly implicated, the site investigator should consult the CMC prior to permanent ARV discontinuation. Subjects experiencing confirmed Grade 3 toxicities requiring permanent discontinuation of an implicated ARV should be re-evaluated at least weekly until improvement to ≤ Grade 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.

Grade 4 Toxicity:
• Upon the initial recognition of a Grade 4 clinical or laboratory toxicity:
  − The site investigator should repeat the test to confirm the Grade 4 value within 2 business days of site awareness. If the test cannot be repeated within 2 business days, it should be repeated as soon as possible.
  − Non-ARV explanations for the toxicity should be considered.
  − If the initial Grade 4 clinical or laboratory toxicity is assessed as probably not or not related to an ARV, the entire ARV regimen should be continued.
  − If the initial Grade 4 toxicity is assessed as possibly, probably or definitely related to an ARV, the suspect ARV should be held pending the result of the repeat testing, and the CMC should be notified. The result of the repeat test should be used to guide management of the toxicity (based on severity grade).

• If the result of the repeat test is Grade 1, 2, or 3 the relevant management guidelines should be followed.
If the result of the repeat test confirms a Grade 4 clinical or laboratory toxicity:
- Non-ARV explanations for the toxicity should be considered
- If the confirmed Grade 4 laboratory toxicity is assessed as probably not or not related to an ARV, the previously suspect ARV regimen can be resumed/continued.

If the confirmed Grade 4 toxicity is assessed as possibly, probably, or definitely related to an ARV:
- The implicated ARV should continue to be held. The CMC should be contacted within 2 business days to advise on management of the remainder of the regimen. Alternatively, the site investigator may reinstate the previously held ARV if he or she has new and compelling evidence that the toxicity is probably not related or not related to the ARV. In this case, consultation with the CMC is required within 2 business days.
- The subject should be re-evaluated weekly until the toxicity improves to ≤ Grade 2.
- Once a Grade 4 toxicity that was felt to be possibly, probably, or definitely related to an ARV improves to ≤ Grade 2, ARV treatment may be resumed; but in these cases, alternative study-provided or non-study-provided drugs should replace the implicated ARV, if possible.
- Alternatively, if the Grade 4 toxicity is subsequently assessed as probably not or not related to the study drug, the original regimen may be resumed at the discretion of the site investigator, with approval in advance from the CMC.
- Subjects experiencing Grade 4 toxicities requiring permanent discontinuation of an implicated ARV should be followed weekly until improvement to ≤ Grade 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.

6.2 Special Toxicity Management Guidelines

The tables in this section were developed to specifically address selected toxicities that are most common and with which NVP specifically is associated: anemia and neutropenia, rash, elevated AST/ALT (asymptomatic) and symptomatic hepatitis. These guidelines apply to management of the selected toxicities through the Step 2 Week 36 visit. As noted in each section, the recommendations generally apply to toxicities thought to be possibly, probably, or definitely related to an ARV. All other management should be pursued by site clinicians consistent with current standards of care for pediatric clinical care and ARV management.
6.21 Anemia and Neutropenia

Hematologic toxicity is common among infants with HIV and receiving ARVs, particularly during the first months of life. Interpretation of abnormal values and management of ARVs is particularly challenging in the context of international clinical trials because there are distinct ethnic and geographic differences in the normal ranges of hematologic parameters [43-45]. The consequence of these differences is that what might be a normal value in some settings could be classified as toxic per current DAIDS toxicity tables, and potentially lead to inappropriate medication changes. In this context, we reiterate that while classification laboratory results will utilize current DAIDS toxicity tables to ensure uniformity across sites, the decision to modify ARV regimens will be deferred to the site clinician’s assessment that hematologic changes are abnormal and felt to be possibly related, probably related, or related to ARV use. We also provide the following guidelines for clinicians with regards to hematologic toxicities:

<table>
<thead>
<tr>
<th>ANEMIA and NEUTROPENIA possibly, probably or definitely related to an ARV</th>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Continue all ARVs</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Grade 3 possibly related</td>
<td>Continue all ARVs</td>
<td>Repeat test to confirm within 3 business days. Continue suspect ARV while awaiting result. If repeat assessment is ≤ Grade 2, manage as per Grade 2. If repeat assessment is Grade 3, repeat test again within 7 days. Consider substitution of other drugs (TS, ZDV, as below) that may contribute to toxicity. If Grade 3 persists, consult the CMC for ARV management and frequency of repeat assessments.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 probably or definitely related OR Grade 4 possibly, probably, or definitely related</td>
<td>Hold suspected ARV</td>
<td>Repeat test within 3 business days to confirm. If repeat assessment is ≤ Grade 2, manage as per Grade 2. If repeat assessment is Grade 3 or 4, hold suspected ARV and consult with the CMC within 2 business days about ARV changes.</td>
</tr>
</tbody>
</table>
ZDV, trimethoprim/sulfamethoxazole (TS), and NVP are associated with anemia and/or neutropenia. It can be difficult to ascertain which is the most likely cause of toxicity. Generally, ZDV is considered more likely than NVP to cause anemia, and TS more likely than NVP to cause neutropenia. The final decision on stopping or substituting a medication is up to the clinician, but the CMC should be consulted about any ARV changes. Acute changes in ARV management that the clinician deems critical to patient care need not wait for CMC approval. If TS is given for PCP prophylaxis, and the site investigator considers TS as a possible or probable cause of ≥ Grade 3 hematologic toxicity, an alternate PCP prophylaxis regimen may be substituted while ART continues (at the discretion of the clinician/investigator) and abnormal laboratory value(s) are followed weekly. If ≥ Grade 3 toxicity persists for ≥ 21 days, despite discontinuing TS, ZDV should be discontinued and substituted with another ARV. If toxicity resolves to ≤ Grade 2 within 21 days, resume/continue ARVs and continue routine monitoring.

6.22 Rash

Of the ARVs included in this protocol, NVP is the most likely to be associated with rash, both in isolation and as part of a systemic hypersensitivity reaction.

The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events (Appendix III) must be used for grading rash toxicities.
<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2A</td>
<td>Continue all ARVs</td>
<td>Monitor rash closely</td>
</tr>
</tbody>
</table>
| Grade 2B               | If on NVP: hold NVP if considered possibly, probably, or definitely related and continue other ARVs. | Test ALT within 3 business days, and evaluate for symptoms of clinical hepatitis and hypersensitivity reaction. Hold NVP while awaiting result; continue other ARVs.  
If any clinical symptoms of hepatitis or ALT elevation or hypersensitivity reaction, permanently discontinue NVP and consult with CMC on study drug regimen.  
If the rash is not generalized or if there is a definitive explanation for the rash (e.g., varicella), NVP may be continued with no additional evaluation required.  
If not on NVP: continue all ARVs.  
Rash may be treated symptomatically, but should be monitored closely by the site investigator. |
| Grade 3                | Continue suspect ARV if possibly related.  
Hold suspect ARV if probably or definitely related.  
If on NVP, discontinue immediately and consult with CMC for recommendations. | If there is no definitive explanation for the rash (e.g., varicella), test ALT and, if elevated, manage per the Hepatic Toxicity table.  
If not on NVP, hold suspect ARV if possibly, probably, or definitely related.  
Test ALT and consult the CMC on ARV management. |
### 6.23 Hepatic Toxicity

### Table: ELEVATIONS in AST or ALT possibly, probably, or definitely related to an ARV

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2 Asymptomatic</td>
<td>Continue all ARVs during evaluation (including NVP).</td>
<td>Repeat test as soon as possible and within 14 days. If repeat assessment is Grade 2, continue study drug and continue to monitor every 14 days until resolves. If subject becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
<tr>
<td>Grade 3 Asymptomatic</td>
<td>Continue all ARVs during evaluation, including NVP.</td>
<td>Repeat test within 3 business days. Assess for alternate cause of elevated transaminases. If repeat assessment is ≤ Grade 2, manage as per Grade 2. If repeat assessment is Grade 3 and is attributed to alternative cause (e.g. concomitant illness or medication [probably not or not related to suspected ARV]), suspected ARV may be continued at the discretion of the site investigator. Treat the underlying illness or remove the likely causative agent. If the repeat assessment is Grade 3 and is assessed as possibly, probably, or definitely related to suspected ARV, hold suspected ARV. Repeat testing weekly; once the toxicity grade is ≤ Grade 2, should the site investigator wish to resume NVP, consultation with the CMC is required in advance. If suspected ARV is resumed following a hold for Grade 3 AST/ALT, repeat testing should be performed one week after resumption. If the result of this testing is Grade 3 or 4, consult the CMC. If subject becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
<tr>
<td>Grade 4 Asymptomatic</td>
<td>If on NVP: Hold NVP, do not wait for laboratory confirmation. If not on NVP: consider holding LPV/r or other potentially associated ARV until confirmed and discuss with CMC.</td>
<td>Repeat test within 3 business days, in addition to total bilirubin and INR, if available at the site, and assess for alternative cause. If repeat assessment is ≤ Grade 4, manage per the grade of the repeat assessment. If repeat assessment is Grade 4, hold suspected ARV. Consult the CMC on study drug regimen and frequency of repeat assessments while following ALT/AST at least weekly. If the toxicity is assessed as probably or definitely related to suspected ARV, discontinue suspected ARV permanently. If subject becomes symptomatic, follow guidance for symptomatic hepatitis.</td>
</tr>
</tbody>
</table>
**SYMPTOMATIC HEPATITIS**

<table>
<thead>
<tr>
<th>CONDITION AND SEVERITY</th>
<th>ARV MANAGEMENT</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs and symptoms of hepatitis include but are not limited to fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, and/or hepatomegaly</td>
<td>If on NVP: can continue or hold NVP based on degree of clinical suspicion for hepatitis. If not on NVP: continue all other ARVs until evaluated.</td>
<td>Immediately perform AST and ALT tests, as well as total bilirubin and INR (if available). If AST or ALT is Grade 3 or 4, immediately hold NVP (if receiving) but can continue other ARVs during evaluation. Consult the CMC on ARV regimen and frequency of repeat assessments (in general, at least weekly re-assessment is recommended). If it is determined that the subject has clinical hepatitis and suspected ARV cannot be excluded as the cause, suspected ARV should be permanently discontinued.</td>
</tr>
</tbody>
</table>

6.3 Subject Management Plan

6.31 Evaluation and Initial Treatment of High-Risk Infants (STEP 1)

Cohorts 1A and 1B (high-risk) will empirically start ART with NVP + 2 NRTIs (see Section 5.111) within 48 hours of birth and undergo evaluation for HIV infection as outlined below. Investigators should aim to initiate ART as soon as possible after identification of the high risk status.

All subjects in Cohort 1 will have two separate blood draws at least 1 hour apart within 48 hours of birth for HIV nucleic acid testing (refer to Appendix II-A for the details on the acceptable tests and results). Results of nucleic acid tests must be available by Step 1 Week 2.

- HIV-uninfected subjects

Subjects with negative HIV DNA and RNA PCR tests from samples obtained through 48 hours of age will discontinue study ART no later than Week 2 and switch to perinatal ARV prophylaxis according to country guidelines. These subjects will exit the study at the Step 1 Week 4 visit with follow up diagnostic studies done by the primary care provider. Subjects with an ongoing toxicity ≥ Grade 2 at the Week 4 visit will continue to be followed until the toxicity has resolved or stabilized. The CMC will evaluate management of subjects with discordant HIV test results on a case by case basis, using stored specimens as necessary to confirm results.
HIV-infected subjects

Cohorts 1A and 1B subjects with two positive HIV nucleic acid tests performed on separate specimens, with at least one positive nucleic acid test performed in either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites), will meet diagnostic criteria for HIV infection and transition to Step 2.

6.32 Management of Subjects with Confirmed HIV Infection (STEP 2)

6.321 Cohort 1

Subjects from Cohorts 1A and 1B will continue taking NVP + 2 NRTIs; LPV/r will be added at ≥ 14 days of age AND ≥ 42 weeks postmenstrual age (see Note in Section 5.112 regarding calculation of postmenstrual age).

6.322 Cohort 2

Infants may enroll in Cohorts 2A and 2B (ART-started) with a single positive nucleic acid test drawn within 48 hours of birth, but must have HIV infection confirmed by a second positive nucleic acid test within 7 business days of study entry if not already obtained. The specimen used to confirm HIV infection must be positive by at least one of the following assays:

- HIV DNA PCR,
- Plasma HIV RNA (quantitative or qualitative)
- HIV total nucleic acid (TNA) test

At least one of the above tests must be done in either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites) that is approved to perform the assay for protocol testing. If the mother or infant is receiving antiretroviral drugs, then an HIV DNA or TNA assay may be more sensitive. If the second test does not confirm the initial positive result, the CMC should be notified, and a third specimen should be collected for HIV DNA PCR, with the result available within 7 additional business days. The infant may remain on study until this result is available and HIV status is confirmed. If the second and third tests are negative, the first test will be presumed to have been false-positive and the infant will exit the study (and be referred for standard of care prophylaxis per local guidelines).
Infants in Cohort 2 will have had ART initiated by their primary physician within 48 hours of birth outside of the study setting using at least 3 ARVs (2 NRTIs and NVP at a dose of at least 8 mg/day for infants weighing ≤ 2 kg or 12 mg/day for infants > 2 kg AND/OR LPV/r*), given daily until the time of study entry at ≤ 10 days of age. Treatment will commence with study-designated doses of NVP + 2 NRTIs at study enrollment. LPV/r will be added at ≥ 14 days of age AND 42 weeks postmenstrual age (See Note in Section 5.112 regarding calculation of postmenstrual age).

[*The U.S. FDA recommends avoiding LPV/r oral solution in infants < 14 days of age or < 42 weeks postmenstrual age. Infants given LPV/r and entering the study < 14 days of age or < 42 weeks postmenstrual age will discontinue LPV/r until meeting the FDA recommended age for LPV/r to be safely administered.]

HIV-infected subjects from Cohorts 1 and 2 will be treated with a four-drug ART regimen (2 NRTIs + NVP + LPV/r) until 12 weeks after they have 2 consecutive HIV RNA level < LOD, at which time NVP will be discontinued and 2 NRTIs and LPV/r will be continued. In cases of ARV intolerance or toxicity subjects may discontinue the offending ARV and take a combination of at least 3 drugs (minimum 2 NRTIs and another highly active agent (e.g., PI, NNRTI, INSTI) that sustains suppression of HIV replication. Serial plasma RNA testing initially will be performed every 2 to 6 weeks and then every 12 weeks once evaluation for possible treatment cessation begins at the Step 2 Week 84 visit. Serial CD4 count testing will be performed approximately every 12 weeks. (See Appendix II-B)

Subjects who do not achieve HIV RNA < LOD by Step 2 Week 24 or have 2 consecutive HIV RNA levels ≥ LOD between Week 24 and Week 192 will NOT be eligible for treatment cessation and will exit the study (and be referred for standard of care treatment per local guidelines).
6.323 Evaluation to determine eligibility for treatment cessation

Subjects in Step 2 who achieved plasma HIV RNA level < LOD by Week 24 AND have no subsequent confirmed RNA levels ≥ LOD (defined as 2 consecutive RNA levels ≥ LOD) will undergo further evaluation for treatment cessation. Any single HIV RNA value ≥ LOD after Week 24 must be repeated as soon as possible. At the Week 84 visit, these subjects will undergo screening for possible treatment cessation, to commence at or after Step 2 Week 96. Subjects will enter Step 3 and undergo ART cessation when they have met ALL of the following additional criteria:

- Two consecutive negative HIV antibody tests by 3rd generation (or greater) ELISA (performed in central laboratory) at least 8 weeks apart; AND
- Two consecutive negative HIV DNA tests using the Roche Amplicor HIV-1 Test, v1.5 (performed in the study’s designated VQA-certified central laboratory), or the most sensitive validated HIV DNA or HIV total nucleic acid (TNA) assay available (performed in the study’s designated VQA-certified central laboratory) at least 8 weeks apart; AND,
- No detectable HIV RNA at the time of the second consecutive negative HIV DNA test — even if below the limit of detection of the assay — based on testing performed in the study’s designated VQA-certified central laboratory; AND
- CD4 ≥ 25% and normal for age (2-3 years ≥ 1000 cells/mL, 3-4 years ≥ 750 cells/mL); AND
- Permanent cessation of breastfeeding for > 6 weeks.

Please see Appendix II-C and the Laboratory Processing Chart (LPC) for specific instructions on handling of laboratory assays to screen for Step 3 eligibility.

Subjects meeting all criteria for ART cessation will transition to Step 3 (see Appendix II-D). Subjects who do not meet all criteria for ART cessation will continue in Step 2 on 3-drug ART (2 NRTIs and LPV/r) and undergo rescreening at 12-week intervals. Subjects not meeting the above criteria by Week 192 will exit the study.
6.33 ART Cessation in HIV-infected Subjects to assess HIV Remission (STEP 3)

At entry to Step 3, ART will be stopped and the subject will undergo plasma RNA testing weekly through the Step 3 Week 4 visit, then every 2 to 12 weeks for the duration of the study through 5 years of age. Subjects who maintain HIV RNA < LOD for ≥ 12 weeks post ART cessation will have additional testing for evidence of HIV viral persistence (see Appendix II-D).

Subjects who experience viral rebound with two consecutive plasma HIV RNA values ≥ LOD following treatment cessation will transition to Step 4 to restart ART. Any single HIV RNA value ≥ LOD must be repeated as soon as possible.

6.34 ART Re-initiation in HIV-infected Subjects with confirmed viral rebound (STEP 4)

Subjects will re-initiate ART at entry to Step 4 and be monitored with HIV RNA testing every 2 weeks for 12 weeks then every 12 weeks (see Appendix II-E). Subjects who fail to decrease their HIV RNA to < LOD by the Week 12 visit on ART will have drug resistance genotyping performed if the RNA level is > 1000 copies/mL at the previous visit; if drug resistance is demonstrated, in consultation with the CMC, the ART regimen may be changed and the subject will continue to be followed on the study.

6.35 Management of Subjects Co-infected with Tuberculosis (TB)

If a subject on study develops tuberculosis, the clinician may change the ART regimen, with approval and input from the CMC, to allow co-administration of rifampin. The subject would remain on study and be eligible for treatment cessation as long as criteria outlined in Section 4.4 were met and TB treatment was completed.

6.36 Management of Mothers of Enrolled Infants

Mothers whose infants have confirmed HIV infection will be consented to provide demographic information and health history, and a blood sample for HIV RNA and stored samples for HIV sequencing and immune studies (HLA typing, host genetic factors) will be drawn. Sequencing of maternal and infant HIV will be conducted to further confirm mother-child HIV transmission and assess full-length HIV genomes for intact HIV. Interval maternal histories will be collected every 6 months including health status and current ARVs; clinical reports on maternal HIV RNA levels and CD4 counts will be collected if available.
If HIV-infected infants’ mothers become unavailable after enrollment (e.g., have expired or moved away, etc.), infants may remain on the protocol as long as the legal guardian is in agreement (see also Section 10.1 below).

Mothers of infants who are HIV exposed but uninfected (Cohort 1) will be enrolled and followed until their infants complete the Step 1 Week 4 visit.

6.37 Laboratory Evaluations

6.371 Pharmacokinetics

Dried blood spots (DBS) and plasma for NVP and LPV/r exposures will be collected during routine study blood draws. Analysis of DBS and plasma samples from the first 30 subjects during the first 2 weeks of life will be performed to assess NVP exposures achieved with the protocol designated dose of 6 mg/kg/dose BID (see Section 9.2). Based on these results, the NVP dose may be adjusted for subsequently enrolled subjects. If the NVP dose needs adjustment based on the results from the first 30 subjects that received the 6mg/kg dose, then the first 30 subjects on the new dose will be evaluated in a similar manner during the first 2 weeks of life to confirm that the NVP exposures are within the target range (see Section 9.2).

After the final NVP dose has been accepted by the protocol team, subsequently enrolled subjects will have NVP ± LPV/r DBS samples stored, and at the conclusion of the study, population analyses of NVP and LPV/r PK will be conducted. There will be no individual dose adjustments for either NVP or LPV/r.

6.372 Safety Laboratory Evaluations

Complete blood count with differential, and ALT and AST will be used to monitor NVP toxicity with the addition of lipase when LPV/r is added to the treatment regimen.
6.373 Studies of Viral Suppression and Persistence

Ultrasensitive methods to quantify HIV reservoirs will be carried out at regular intervals as detailed in Appendix II-C.

Immunologic correlates of HIV-1 suppression and persistence will also be studied. HIV-1 specific antibodies will be evaluated using ELISA and Western blot. HIV-specific CD4+ and CD8+ T cell responses will be measured by intracellular cytokine (IL-2, IFN-g) assays. The percentage of peripheral blood CD8+ T cells that co-express CD38 and DR will be measured using flow cytometry. These studies will be carried out at defined time points as outlined in Appendices II-B, II-C, II-D, and II-E.

Refer to Appendix I, Maternal Schedule of Evaluations and Appendices II-A to II-E, Infant Schedule of Evaluations, for a complete description of the clinical and laboratory evaluations, and the LPC for the complete laboratory procedures, to be performed.

6.4 Permanent Discontinuation from Study Follow-up

A subject who permanently discontinues from study follow-up will have the Premature Discontinuation visit per the schedule of evaluations (Appendices II-B to II-E as appropriate).

6.41 The infant will be discontinued from the study for the following reasons:

- HIV infection is not confirmed in the mother.
- *In utero* HIV infection is not confirmed in the infant.
- The HIV RNA level does not decline to < LOD by Step 2 study Week 24.
- The HIV RNA level rebounds to ≥ LOD after Step 2 study Week 24, confirmed by a second RNA level ≥ LOD.
- The infant does not meet criteria for treatment cessation (see Section 4.4) by Week 192.
- The infant is lost to follow up.
- The parent/guardian withdraws consent.
- The investigator determines that further participation would be detrimental to the infant’s health or well-being.
6.42 The mother will be discontinued from the study for the following reasons:

- HIV infection is not confirmed in the mother.
- *In utero* HIV infection is not confirmed in the infant.
- The mother is lost to follow up.
- The mother is not able to attend study visits as required by the study.
- The mother withdraws consent.
- The investigator determines that further participation would be detrimental to the mother’s health or well-being.

If the mother discontinues study follow-up, the infant will still continue follow-up if the infant is still able to attend study visits as required by the study and consent has not been withdrawn.

The study may be discontinued at any time by the IMPAACT network, the Office for Human Research Protections (OHRP), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), local IRB or EC, or other governmental agencies.

7.0 **EXPEDITED ADVERSE EVENT REPORTING**

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of adverse events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at [http://rsc.tech-res.com/safetyandpharmacovigilance/](http://rsc.tech-res.com/safetyandpharmacovigilance/).

The DAIDS Adverse Experience Reporting System (DAERS) internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: [http://rsc.tech-res.com/safetyandpharmacovigilance/](http://rsc.tech-res.com/safetyandpharmacovigilance/). For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).
7.2 Reporting Requirements for this Study

- The SAE (Serious Adverse Event) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study for the period of time defined in Section 7.4. Subsequently, the SUSAR (Suspected Unexpected Serious Adverse Reaction) Reporting Category will be used.

- Other medically-significant events for which expedited reporting is required include all Grade 3 or 4 rash/cutaneous toxicity and Grade 4 asymptomatic hepatic toxicity or Grade 3 or 4 symptomatic hepatic toxicity.

- The drugs for which expedited reporting is required are: nevirapine and lopinavir/ritonavir

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

The Supplemental Toxicity Table for Grading Severity of Cutaneous/Skin Rash/Dermatitis Adverse Events (Appendix II) will also be used. The parameters specified in this table supersede the DAIDS Toxicity Table when grading these events.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period at the SAE Reporting Category for this study includes the time when an infant is receiving the investigational dose of NVP and the period of time when an infant is receiving combination therapy with 4 ARVs.

  - In Step 1, this is operationalized as the period from Step 1 Entry through the Week 4 visit.

  - In Step 2, this is operationalized as the period from Step 2 Entry through the Week 36 visit.

This reporting period also applies to the other medically significant events for which expedited reporting is required (as listed in Section 7.2 above).

- The expedited AE reporting period at the SUSAR Reporting Category for this study includes the time from the end of SAE reporting period (after the Week 36 visit) until the end of study participation for each infant.
• After the protocol-defined AE reporting period, unless otherwise noted, only Suspected Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events (for infants off study after the protocol-defined AE reporting period, this would be on a passive basis (from publicly available sources)).

Every effort will be made by study staff to provide appropriate care and counseling to the subject or referral to appropriate resources for the safety of the subject as needed. Any unanticipated problems will be reported to the DAIDS Medical Officer at the same time as the problems are reported to the responsible site IRB/EC overseeing the research according to pre-established procedures as required by 45 CFR 46.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a multi-center, Phase I/II proof of concept exploratory study to assess HIV remission after ART cessation in HIV infected children initiated on ART within (≤) 48 hours of birth. Infants are enrolled as either 1) within (≤) 48 hours of birth at high risk of HIV infection (High-risk, Cohort 1) and not on ART, or 2) HIV-infected neonates within (≤) 10 days of birth who were treated daily with ART, started within 48 hours of birth (ART-started, Cohort 2). Infants in the high-risk group will receive ART empirically starting within 48 hours of birth. Infants with negative HIV test results (expected to be resulted within 7 to 14 days) from the specimens drawn within 48 hours of birth will discontinue study drug and receive standard of care when their test results become available. Uninfected infants will be followed through the Week 4 visit. HIV-infected infants will be followed for up to 5 years. HIV-infected infants’ mothers will have a single blood draw to store plasma, serum and cells for future studies and will be followed at 6 month intervals to update their health status, infant feeding method and ARV information.

Infants are either formula fed or breastfed. The formula fed high risk HIV-infected infant group is the primary focus group for assessing this strategy for HIV remission and the target sample size is to identify 16 HIV-infected infants from this group. It is anticipated that approximately 320 infants will need to be enrolled for this target sample size of 16. An additional 6 breastfed high risk HIV-infected infants will be enrolled to obtain preliminary data about this strategy in this group, and 120 infants are anticipated to be required to reach this target. Among the HIV-infected infants who start ART before enrollment (ART-started cohort), the targeted sample size is up to 16 each in the formula and the breastfed groups. Thus up to 472 (320+120+16x2) infants will be enrolled.
Cohort 1 infants (440 infants) will participate in Step 1 until their HIV infection status is determined. Cohort 1 infants with confirmed in utero HIV infection and Cohort 2 infants will enter Step 2. Step 2 infants whose HIV RNA level is not sustained < LOD (as specified in Section 6.41) will discontinue study follow-up. HIV-infected children who meet criteria for treatment cessation (defined in Section 4.4) will enter Step 3 and stop ART. HIV-infected children who stop ART and who do not have viral rebound (defined in Section 8.2) for ≥ 12 weeks after ART cessation will have additional testing done to assess HIV viral persistence. Children with rebound viremia (defined in section 8.2) after ART cessation will enter Step 4 and re-initiate ART and will be monitored for virologic response.

High-risk infants (Cohort 1) will start ART with 2NRTIs + NVP, with an investigational NVP dose (see Section 9.0 on Clinical Pharmacology plan for assessing this dose). ART-started infants (Cohort 2) will have initiated ART with ≥ 3 drugs with 2NRTIs + NVP or LPV/r and at study entry be switched to the study ART. HIV-infected infants will have LPV/r added at 14 days of age AND 42 weeks post menstrual age. Infants with viral load < LOD for at least 12 weeks will discontinue NVP.

Data will be analyzed separately within the 4 groups of formula fed high risk, breastfed high risk, formula fed ART-started and breastfed ART-started HIV-infected children.

Limitations:

The infant-feeding method groups may be confounded with the site of enrollment because sites are expected to have pre-dominant infant feeding methods.

Limitations for assessing ART-started children include potential selection bias (e.g., since these infants may enroll up to 10 days after birth and after starting ARVs) and possibly lack of key early measurements and specimens.

The sample size for the high risk breastfed group will provide only preliminary data. If no HIV remission events are observed among the sample size of 6 children, results will need to be carefully interpreted, as not seeing an event with this small sample size will not necessarily mean that remission cannot be achieved. Based on a 95% confidence interval, observing no HIV remission events among 6 children is consistent with a true probability of remission of ranging from 0 to as high as 0.46. With a sample size of 6 there will be good (0.80) probability of observing at least one remission if the remission probability is 0.24 or higher. Smaller probabilities of remission may still be clinically relevant.
8.2 Outcome Measures

8.21 Primary

8.211 HIV remission: No confirmed plasma HIV RNA ≥ LOD for 48 weeks following ART cessation, which includes all of the following:

1) No confirmed HIV RNA ≥ LOD by 48 weeks of ART cessation

AND

2) An HIV RNA < LOD at week 48 visit or the next available visit if Week 48 sample is missing after ART cessation.

8.22 Secondary

8.221 Grade 3, 4 signs/symptoms, laboratory values or diagnoses per DAIDS grading system, or death at least possibly, probably or definitely related to ARV. These will be based on data collected through the Case Report Form (CRF)/Laboratory Data Management System (LDMS). Relatedness to ARV will be based on reports from the site and adjudication by the CMC.

8.222 NVP concentration among treated neonates and young infants (see Section 9 for more detail).

8.223 LPV concentration among treated neonates and young infants (see Section 9 for more detail).

8.224 Meeting all eligibility criteria for ART cessation as defined in Section 4.4.

8.225 Meeting the selected eligibility criteria for ART cessation defined in Sections 4.441-4.445 among infants who also met the viral suppression criterion for ART cessation in Section 4.43.
8.2.26 The following endpoints among subjects who discontinue ART and do not rebound within 12 weeks of discontinuation and will be based on stored samples.

- HIV persistence as measured by plasma viremia (single copy), digital droplet DNA, replication competent HIV reservoirs.
- Immune activation markers (%CD8+/DR+ T cells) and HIV-specific immune responses: HIV-specific antibodies and HIV-specific T cell responses.

8.3 Randomization and Stratification

This is not a randomized study. Four cohorts of neonates will be enrolled based on whether ART was started prior to enrollment and on infant feeding intent:

- Cohort 1A: Formula fed high-risk infants (up to 320 to identify 16 HIV-infected infants)
- Cohort 1B: Breastfed high-risk infants (up to 120 to identify 6 HIV-infected infants)
- Cohort 2A: Formula fed HIV-infected ART-started infants (N = 16 or when Cohort 1A is fully enrolled, whichever is earlier)
- Cohort 2B: Breastfed HIV-infected ART-started infants (N = up to 16 and not more than Cohort 2A)

8.4 Sample Size and Accrual

Table 1: Sample size for HIV-infected infants

<table>
<thead>
<tr>
<th>Formula Fed (Group A)</th>
<th>HIV infected from high-risk exposed infants cohort</th>
<th>HIV-infected ART-started cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Fed (Group A)</td>
<td>16</td>
<td>Up to 16</td>
</tr>
<tr>
<td>Breastfed (Group B)</td>
<td>Up to 16</td>
<td>Up to 16</td>
</tr>
</tbody>
</table>

This Phase I/II proof of concept exploratory study will follow formula fed and breastfed HIV infected neonates who initiate ART. Infants will be enrolled either as high-risk neonates within 48 hours of birth or as HIV-infected neonates who had started daily ART within 48 hours of birth and are enrolled within 10 days of birth (ART-started). Analyses will be separate within each of the four enrollment groups: formula fed high-risk, breastfed high-risk, formula fed ART-started, and breastfed ART-started. The primary focus for this study is the formula fed high-risk neonates and the sample size is determined based on this group.
8.41 Sample Size for High Risk Formula Fed Group

The team is targeting 15 neonates in the formula fed high-risk infants group. Secondary analyses will be restricted to children who were exclusively formula fed (did not switch from formula feeding to breastfeeding). To account for these analyses, one additional HIV-infected neonate will be targeted for the sample size in this group. Therefore 16 HIV-infected neonates are targeted for the formula fed high-risk group.

In HPTN 040, among HIV-infected mothers who did not receive antenatal ART [26], a total of 93 in utero HIV-infected infants were observed among 1684 non-breastfeeding infants; Kaplan-Meier estimate 5.7% (95% confidence interval 4.7-6.9). Assuming that 5-7% of enrolled neonates enrolled are HIV infected, 229 (16/0.07) to 320 (16/0.05) infants from the high-risk formula fed group will need to be enrolled to ensure at least 16 HIV-infected neonates are identified from this group.

The following table summarizes the probabilities of observing 16 infected neonates with various sample sizes assuming a true probability of observing an infected infant of 0.07 or 0.05 using negative binomial distribution.

Table 2: Probability of observing 16 infected neonates with various sample sizes assuming a negative binomial distribution.

<table>
<thead>
<tr>
<th>True Probability of an event</th>
<th>N = Sample size</th>
<th>Probability of observing 16 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>300</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>320</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>420</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>440</td>
<td>0.93</td>
</tr>
<tr>
<td>0.07</td>
<td>300</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>320</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>340</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>380</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>420</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td></td>
<td>440</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>
To have an 80% chance of finding 16 infected subjects in Cohort 1A, the sample size is 380 infants if the true transmission probability is 0.05. The current sample size is 320, which is the expected sample size based on the negative binomial distribution (16/0.05). If the transmission probability is higher, for example 0.07, with 320 sample size, the chance of finding 16 infected subjects with our current sample size of 320 will be 94%. Since the true transmission probability rate is unknown (an estimate is used in the sample size calculation), the team feels with a sample size of 320 would have good chance of finding 16 infected subjects in Cohort 1A.

The following tables describe information that can be obtained over a range of sample sizes of between 5 and 20 HIV infected neonates who are followed for events of interest. Two types of events are of particular interest among very early treated HIV-infected infants: HIV remission after ART cessation, and meeting criteria for ART cessation.

Table 3 provides the probability of observing different event numbers with various samples sizes, assuming a range of hypothetical true event probabilities. For example, if the probability of HIV remission is 0.10 and 15 (10) very early treated HIV infected formula fed high risk children are enrolled then the probability of observing at least one HIV remission among those enrolled will be 0.79 (0.65). The probability of observing a remission decreases with decreasing sample size or probability of remission. The team feels that that a remission probability less than 0.10 among very early treated HIV infected subjects would not warrant continued study of this concept. A sample size of 15 HIV infected neonates would provide high (0.79) probability of observing at least one HIV remission among very early treated HIV infected children.
Table 3: Probability of observing no event (e.g., HIV remission), and of observing at least 1-5 events with sample sizes of 5, 10, 15, and 20 (e.g., of very early treated HIV-infected children).

<table>
<thead>
<tr>
<th>N = Sample size</th>
<th>True Probability of an event</th>
<th>Probability of</th>
</tr>
</thead>
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</tr>
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<tr>
<td>20</td>
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</table>

Table 4 provides 95% confidence intervals on the event probability for various observed events numbers across sample sizes of 5-20 subjects. For example, if HIV remission is observed in 5 out of 15 very early treated formula fed high-risk HIV infected children, based on the 95% confidence interval, these data are consistent with a probability of remission between 0.12 and 0.62. This confidence interval is also relevant if no remissions are observed. Notably, observing no remissions among 15 HIV infected very early treated formula fed high risk HIV-infected children is consistent with a remission probability of 0 to 0.22.
Table 4: 95% confidence interval (CI) for the probability of an event of interest, e.g., HIV remission with sample sizes (and event numbers) of 5, 10, 15, 20 (e.g., of very early treated HIV infected children).

<table>
<thead>
<tr>
<th>N = Sample size</th>
<th>N of events</th>
<th>Proportion with an event</th>
<th>95% CI Lower bound</th>
<th>95% CI Upper bound</th>
<th>Width</th>
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<td>0.44</td>
</tr>
</tbody>
</table>

Another parameter of interest is the probability of HIV remission among only the HIV-infected children who are eligible and discontinue ART. By selection, among this group of children the probability of remission is expected to be higher than among all very early treated HIV-infected infants. If, for example, 5 out of 10 HIV-infected children who discontinue ARVs meet the definition for HIV remission, then the 95% confidence interval is 0.19 to 0.81.
Table 5 provides the probability of observing at least 5, 10, 15, 20 children who meet an event of interest with various sample sizes, such as for the event of being eligible for ART cessation. For example, assuming a hypothetical probability of 0.80 for becoming eligible for ART cessation, with a sample size of 15 HIV infected children who are treated with ART, the probability of observing at least 10 subjects who are eligible for ART cessation is 0.94.

Table 5: Probability of observing at least 5, 10, 15 or 20 events across a range of sample sizes and hypothetical true event probabilities.

<table>
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<th>Probability of</th>
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</table>
8.42 Sample Sizes for the Other Very Early Treated HIV-Infected Infant Groups

The other three groups — breastfed high-risk infants, formula fed ART-started and breastfed ART-started — are of high interest but the primary group of interest for this protocol are the high risk formula fed infants, and the sample size is based on this primary interest group.

P1115 will obtain preliminary data for evaluating the strategy of very early treatment for HIV remission in breastfed high-risk infants, and a sample size of 6 HIV-infected infants are targeted from this group. Based on the same HPTN 040 data mentioned above between 86 (6/0.07) and 120 (6/0.05) infants will need to be enrolled to ensure at least 6 HIV-infected neonates are identified from this group.

As mentioned in Section 8.1, the sample size for the high-risk breastfed group will provide preliminary data. Based on a 95% confidence interval, observing no HIV remission events among 6 children is consistent with a true probability of remission of ranging from 0 to as high as 0.46. With a sample size of 6 there will be good (0.80) probability of observing at least one remission if the remission probability is 0.24 or higher. Smaller probabilities of remission may still be clinically relevant.

With a similar approach as above for the formula fed high-risk group, a sample size of 16 infants is targeted for the formula fed ART-started group and up to 16 infants (up to 50% of sample size) for the breastfed group ART-started group.

8.43 Accrual

Accrual to the high-risk groups will depend on identifying high-risk infants. Study HPTN 040 enrolled 1745 infants over a 6 year period at 17 sites, with 70% enrolled from sites in Brazil. Since ART availability is greater at this time compared to the period when HPTN 040 was conducted several years ago, and assuming a similar number of sites will be enrolling into P1115, but with a smaller accrual rate, the team anticipates enrolling 150 to 200 infants per year once sites are activated. The target sample sizes for the groups are estimated to be reached within 3 years after the majority of sites are activated.
8.5 Monitoring

A full study monitoring plan with more specific details will be prepared before the study opens to accrual.

8.51 Anticipated Accrual

Accrual to this study will be monitored by the IMPAACT leadership in accordance with standard operating procedures. In addition, the protocol team will monitor accrual feasibility, first based on site protocol activation and then on accrual. Initially, the team will monitor activation of sites to initiate the protocol quarterly to ensure that the number of sites participating is sufficient to complete the study. If less than one-half of eligible IMPAACT sites have been activated within 12 months after the protocol is opened to accrual, the team will re-assess the feasibility of the protocol, examine the reasons why sites have not been activated, and will possibly amend the protocol accordingly. Once one-half of eligible IMPAACT sites have been activated, the team will assess for barriers to accrual, if any, on a quarterly basis. If fewer than 100 infants have been enrolled within 12 months after one-half of all eligible IMPAACT sites have opened to enrollment, the team will identify and address the reasons for lack of accrual.

8.52 Routine Monitoring

The CMC will have regular conference calls to ensure that its members are aware of ongoing issues concerning the conduct of the study. The CMC will monitor safety closely. Safety will be monitored by means of adverse event reports (AERs) submitted to regulatory agencies and with toxicity reports summarizing laboratory and clinical data which will be reviewed regularly by the CMC.

In addition to regular toxicity reviews by the CMC, the study will be monitored every 6 months or on a schedule as specified by an independent Study Monitoring Committee (SMC) according to IMPAACT Standard Operation Procedure (SOP) on Study Data and Safety Monitoring. Potential safety issues that arise from CMC reviews will be brought to the attention of the SMC.
8.53 Interim Monitoring by SMC

At scheduled planned reviews, the SMC will review study conduct, including accrual, retention and safety. This review will take place every 6 months or on a schedule specified by the SMC. The primary safety outcome data will be reviewed, as well as permanent discontinuations of ARVs for safety reasons.

Additionally, the SMC will review the proportion of high-risk neonates who are identified as HIV-infected and the proportions of very early treated HIV infected children who meet specific ART cessation criteria as part of reviewing the initial sample size calculation assumptions and to provide input on any proposed adjustments to sample sizes.

Scenarios in which a sample size adjustment might be considered include:

1) Increase the number of infants to be enrolled: this might occur if the proportion of high-risk neonates who are infected or of infants meeting ART cessation criteria is lower than assumed.

2) Decrease the number of infants to be enrolled: this might occur if the proportion of high-risk neonates who are infected or of infants meeting ART cessation criteria is higher than assumed.

In addition to the regularly scheduled SMC reviews, an ad hoc SMC review may be triggered for safety, ART cessation or ART re-initiation related reasons.

8.531 Guideline for Accrual Monitoring

If by three years after the study opens to accrual, fewer than five HIV-infected infants have been enrolled into Cohort 1A (e.g., due to challenges with identifying and enrolling high risk mother-infant pairs or due to a lower than anticipated HIV transmission rate), the SMC will assess the futility of reaching the targeted sample size for this cohort or the team might seek guidance from IMPAACT and DAIDS leadership on whether accrual in that cohort or in the entire study should continue.

8.532 Guidelines for Triggering a Safety Review

Triggers for safety reviews will require assessing drug relatedness for an event. Relatedness will be based on reports from the site and adjudication by the CMC. Ad hoc review safety triggers will be based on data that are combined across all cohorts. Enrollment into P1115 will be suspended if a safety trigger is met.
All infants (to the time when the HIV infection is confirmed, which includes HIV uninfected infants): the proportion of infants who permanently discontinue ARV for toxicity possibly, probably or definitely related to ARVs or have a safety outcome as defined in Section 8.221 will be monitored. An SMC review for safety will be triggered if, after 30 infants have been enrolled, this proportion is greater than 10% (3 or more infants). No guidelines are specified for triggering a review for fewer than 30 enrolled infants.

Similarly, among all infants, mortality will be monitored. An SMC review will be triggered if any death occurs that is possibly, probably or definitely related to ARV.

HIV-infected infants: An SMC review for safety will be triggered if any of the following type of events is reported as possibly, probably or definitely related to an ARV on at least 2 infants:
  a) Grade 4 life-threatening event, or
  b) An ARV is permanently discontinued for toxicity

Guideline for Triggering a Review of ART Cessation due to Viral Rebound

Guidelines for a review will be applied separately to each cohort. If 10 out of the first 10 children in a cohort who cease taking ART have viral rebound (per definition in Section 8.2), ART cessation will be suspended in that cohort for an ad hoc SMC review to evaluate the future direction for this protocol. Enrollment into P1115 will not be suspended. ART cessation suspension guidelines are not specified if fewer than 10 children have ceased taking ART.

Given the small sample sizes the information available for decisions based on this guideline will be imperfect. The team does not feel that viral rebound is a safety issue, and the concern here is whether the probability of remission is low. An error for applying this pausing guideline would occur if the guideline is met when the true HIV-remission probability is still acceptable (not too low). Table 6 shows the probability that the guideline for pausing ART cessation will be met under a range of hypothetical true rebound probabilities.
Table 6: Probability of meeting the guidelines to pause ART cessation for an ad hoc SMC review under a range of hypothetical true rebound probabilities. Guideline: first 10 out of 10 children have viral rebound (or 0/10 with HIV remission).

<table>
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<th>True probability of rebound (P)</th>
<th>True probability of remission (1-P)</th>
<th>Probability of Meeting Study Pausing Guideline for SMC review</th>
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</thead>
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<td>0.30</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>0.70</td>
<td>0.30</td>
<td>0.03</td>
</tr>
<tr>
<td>0.80</td>
<td>0.20</td>
<td>0.11</td>
</tr>
<tr>
<td>0.90</td>
<td>0.10</td>
<td>0.35</td>
</tr>
<tr>
<td>0.95</td>
<td>0.05</td>
<td>0.60</td>
</tr>
<tr>
<td>0.99</td>
<td>0.01</td>
<td>0.90</td>
</tr>
</tbody>
</table>

For example, the probability of meeting the guideline for pausing ART cessation is 0.11 if the true probability of viral load rebound is 0.80 (probability of remission as high as 0.20). If the true probability of viral load rebound is high, for example 0.99, the probability of meeting the guideline for pausing ART cessation is 0.90. Table 4 provides that, based on the 95% confidence interval, observing 0 out of 10 remissions is consistent with a probability of remission ranging from 0 to 0.31.

ART cessation will continue within each cohort for all children who meet eligibility unless pausing guidelines are met. Therefore the maximum number of children per cohort who may be in the first 12 weeks of ART cessation, prior to when additional samples are obtained to assess HIV persistence, are: 16 formula fed infants at high risk for HIV infection (Cohort 1A), 6 breastfed infants at high risk for HIV infection (Cohort 1B), 16 formula fed HIV-infected infants ART-started (Cohort 2A), 16 breastfed HIV-infected infants ART-started (Cohort 2B). However, depending on the rate of accrual and probability of meeting criteria for ART cessation, this number may be smaller.

8.534 Guideline for Triggering a Review of ART Cessation due to lack of Re-suppression among Children who Experience Viral Rebound after ART Cessation

Guidelines for triggering a review will be applied separately to each cohort. If 5 children do not re-suppress (confirmed < LOD) by 6 weeks after ART re-initiation, ART cessation will be suspended in that cohort for an ad hoc SMC review to evaluate the future direction for this protocol. Enrollment into P1115 will not be suspended.
8.535 Considerations if HIV Remission is Observed

If remission is observed, enrollment to the projected sample size and follow up will continue in order to quantify the probability of remission, to study the generalizability of the result and to identify key parameters that need to be monitored to achieve remission. The team will have ongoing discussion and seek input from the SMC regarding public dissemination of information on remission(s) in this protocol. Other ancillary data such as PK results may be published as needed prior to completion of follow up.

8.54 Interim Monitoring for PK

PK samples collected during the first 2 weeks of life from the first 30 subjects enrolled in Step 1 will be assayed in real-time for NVP shortly after collection. These initial results will be analyzed using descriptive statistics by study week to provide an immediate assessment of NVP exposure with the 6 mg/kg bid dose during the first 6 weeks of life. Once NVP exposure data on 30 subjects are in the database, the protocol team will review the data to assess for adequate NVP exposure (see Section 9.2).

8.6 Analyses

Analyses will be carried out separately within each cohort: formula fed high risk, breastfed high risk, formula fed ARV-started, and breastfed ART-started infants. Primary analysis will be based on the formula fed high-risk cohort. Secondary analyses will exclude infants enrolled in each formula fed cohort who were breastfed subsequently.

This is a Phase I/II proof-of-concept exploratory study. The primary analysis will consist of descriptive statistics. Data summaries will provide point estimates with corresponding 95% confidence intervals for parameters of interest. For example, the proportion of formula fed HIV infected high risk neonates who meet the definition for HIV remission will be provided, along with a 95% confidence interval on this probability. For this endpoint, subjects who discontinue study follow-up prior to study completion will be treated as not achieving remission. Supplemental analyses will evaluate the sensitivity of results to different approaches to handling missing data.

Summary tables or listings will be provided for major secondary outcome measures of eligibility for ART cessation, HIV virology related outcomes and for the safety outcome. Point estimates for parameters of interest will be presented, along with 95% confidence intervals.
Safety data will be summarized for 3 groups a) all infants through the time when HIV infection is confirmed; b) HIV-uninfected infants; c) HIV-infected infants followed within each cohort.

A detailed statistical analysis plan describing analyses of both maternal and infant study data will be developed separately.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

9.11 To describe the PK of NVP in neonates and young infants in order to determine the NVP dose needed to maintain NVP concentrations between 3,000 and 10,000 ng/mL.

9.12 To determine LPV concentrations when dosed with NVP in neonates and young infants.

9.2 Primary and Secondary Data

The PK analyses will be performed on drug concentration data collected and summarized for LPV, RTV and NVP. The initial analyses will be descriptive statistics of drug concentration by study collection week. Subsequent population PK analyses will be performed for NVP and LPV. PK analyses will not be used for individual dose adjustments of NVP or LPV or group adjustments for LPV.

A preliminary analysis will be performed on the first 30 subjects enrolled into Step 1 to ensure study dosing of NVP is achieving the desired target concentrations. Based on the results, the NVP dose may be adjusted for subsequently enrolled subjects using the following guidelines:

- If the infant’s median NVP plasma concentration is <3,000 ng/ml for <20% of infants and is >10,000ng/ml for <20% of infants, the initial study dose will be deemed adequate.
- If the infant’s median NVP plasma concentration is <3,000 ng/mL in >=20% of infants, then the NVP dose will be deemed too low and the study team will review the data to consider increasing the dose to 8mg/kg.
- If the infant’s median NVP plasma concentration is >10,000ng/ml in >= 20% of infants, then the NVP dose will be deemed too high and the study team will review the data to consider decreasing the dose to 4 mg/kg.
If the NVP concentrations in the first 30 subjects do not meet the target and a dose adjustment is required, the first 30 subjects that receive the new dose will also have their NVP concentrations evaluated to confirm that the new NVP dose is achieving the target range.

Dried blood spot (DBS) samples for NVP, LPV and RTV concentration assays will be collected in HIV-infected subjects at study visits through Week 24 when blood samples are being collected for other study purposes. After Week 24, DBS samples for LPV and RTV concentrations will be obtained every 12 weeks in conjunction with other study related blood sample collections for the duration of Step 2. Additional dried blood spots will be collected at the time of the first PK sample for determination of genetic polymorphisms known to influence NVP (such as CYP2B6) or LPV pharmacology. This pharmacogenomic assessment will be determined in the first 30 (or 60) consenting Step 1 subjects included in the planned preliminary pharmacokinetic analyses and performed at the time of that task. The remaining pharmacogenomic assays from HIV-infected subjects will be performed at the end of the study.

9.3 Laboratory Analysis and Reporting

Samples will be collected as dried blood spots on filter paper and measured for NVP, LPV and RTV by a CPQA certified assay. The first 30 subjects included in the preliminary NPV PK analysis, and the first 30 in the modified dose (if needed) will also have plasma samples collected concurrently with the DBS samples for plasma NVP concentration determination. All pharmacokinetic samples will be registered in the Lab Data Management System (LDMS) database. Pharmacokinetic samples will be sent to the Pharmacology laboratory of the University of California San Diego for analysis. Data collected on PK CRFs will be provided to the pharmacologists for analysis by the DMC. These data will include the gestational age at birth, post-natal age, CYP 2B6 pharmacogenomics, gender, current weight, current height, dose, date and time of the current and most recent doses, date and times of sample collections and all relevant comments on the pharmacokinetic CRF.

9.4 Study Design, Modeling and Data Analysis

Samples for drug assays will be collected at the time of routine study blood draws during the first 12 months of life, along with information describing the dose amount (in mg), date and time of administration of the most recent drug doses.
Preliminary Analysis

While the majority of these samples will be assayed for NVP, LPV and RTV concentrations in batch mode at the conclusion of the study, samples collected during the first 2 weeks of life from the first 30 subjects from Step 1 will be assayed for NVP shortly after collection. These initial results will be analyzed using descriptive statistics by study week to provide an immediate assessment of NVP exposure with the 6 mg/kg BID dose during the first 2 weeks of life. This analysis will include study week, subject demographics, pharmacogenomic data, NVP dosing information, NVP concentrations and time from prior dose information.

Final Descriptive Analysis

After all pharmacokinetic samples have been collected, samples collected during the first 24 weeks of study in HIV-infected subjects will be analyzed for NVP, LPV and RTV concentrations. All pharmacokinetic samples collected between 24 and 48 weeks of the study will be analyzed for LPV and RTV concentration. The overall PK data during the first 48 weeks of the study will help describe the potential impact of NVP on LPV PK in this population. Pharmacogenetic assays will also be completed at this time. PK samples collected beyond 48 weeks of the study will be stored for potential future analysis to supplement adherence assessments, if needed. These results will be analyzed using descriptive statistics by study week to provide an assessment of NVP exposure with the 6 mg/kg BID dose and LPV/r using WHO dosing in neonates and young infants. This description will include study week, subject demographics, pharmacogenomic data, ARV dosing information, NVP, LPV and RTV concentrations and time from prior dose information.

Population pharmacokinetic analysis

Population pharmacokinetic analyses will be performed on the NVP and LPV PK data to determine compartmental PK parameters with the program NONMEM. The population pharmacokinetic analysis will assess clinical factors (e.g., age, weight, ethnicity, dosing, RTV concentration, CYP 2B6 genotype etc.) that may be associated with NVP or LPV pharmacokinetic parameters. The potential impact of NVP on LPV pharmacokinetics will assessed in the model by comparing changes in LPV PK prior to and after NVP discontinuation. It will also be used to quantify the unexplained inter-subject variability. Given the sparse nature of the data in this study, additional models may be developed nesting the analyses with existing IMPAACT NVP and LPV data in infants. Post-hoc empiric Bayesian estimates of individual subjects’ pharmacokinetic parameters will be generated. These parameters will be used as the input model to determine the frequency of therapeutic NVP (> 3,000 ng/mL) and LPV (> 1,000) troughs with the study dosing. Overall assessment of study dosing strategies will be performed using the final population pharmacokinetic model and Monte Carlo simulations.
Anticipated Outcomes

NVP concentrations using 6mg/kg BID will achieve target levels in greater than 80% of subjects at each of the sample collection weeks. NVP DBS concentrations are also expected to be nearly identical to those in plasma as seen in other populations [46]. In addition, LPV concentrations in combination with NVP will be maintained over 1 mcg/mL in > 95% of subjects. The population pharmacokinetics of NVP and LPV will determine NVP and LPV clearance and identify factors that influence their clearances. We expect there to be relationships between NVP and LPV clearance and exposure with:

- Age and growth parameters.
- CYP2B6 genotype
- NVP induction of LPV clearance

Auto-induction of NVP metabolism will be characterized both to its extent and rate of development. It is expected that the majority of increases in NVP clearance occurs during the first week of therapy. Monte Carlo simulations will determine the time to reach therapeutic concentrations.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendices IV-A, IV-B, IV-C and V), and any subsequent modifications must be reviewed and approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for oversight of the study. 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. For infants eligible for Cohort 1, informed consent will first be obtained for participation Cohort 1 (Step 1 visits and evaluations) only. Separately, for infants eligible to take part in Cohort 2, informed consent will be obtained for Cohort 2 (Step 2, 3, and 4 visits and evaluations). The informed consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the consent forms will be offered to the mother.

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR re-signs the consent.
The plan should follow all IRB/EC, local, state, national and/or host country guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the study staff, study monitors, drug companies supporting the study, and their designees, the OHRP, NIH, FDA, or the local IRB/EC.

10.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT network, the OHRP, NIH, FDA, or local IRB/EC, or other governmental agencies as part of their duties to ensure that research subjects are protected.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

Analyses of data collected for PK and safety in the first 6 months of life is separate and may be released publicly prior to completion of follow-up.

12.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
13.0 REFERENCES


Ref Type: Abstract


Ref Type: Abstract


Ref Type: Abstract


APPENDIX I
MATERNAL SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>Mothers of all infants (HIV-uninfected and HIV-infected)(^1)</th>
<th>Mothers of HIV-infected infants only(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry</td>
<td>When infant is confirmed infected (within 2 weeks of delivery)</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td>Every 6 months while infant is on study until infant is 5 years old(^4)</td>
</tr>
<tr>
<td>History(^3,4)</td>
<td>X</td>
<td>X (chart abstraction if available)</td>
</tr>
<tr>
<td>Infant feeding method</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LABORATORY</td>
<td></td>
<td>Every 6 months while infant is on study until infant is 5 years old(^4)</td>
</tr>
<tr>
<td>HIV RNA(^5)</td>
<td>3-5 mL</td>
<td>X (chart abstraction if available)</td>
</tr>
<tr>
<td>CD4</td>
<td></td>
<td>X (chart abstraction if available)</td>
</tr>
<tr>
<td>Stored serum(^6)</td>
<td>5 mL</td>
<td>X (chart abstraction if available)</td>
</tr>
<tr>
<td>Stored plasma and cells(^6)</td>
<td>20 mL</td>
<td>X (chart abstraction if available)</td>
</tr>
<tr>
<td>TOTAL BLOOD</td>
<td>3-5 mL</td>
<td>25 mL</td>
</tr>
</tbody>
</table>

1. The mothers of HIV-uninfected infants will be taken off study after the mother’s Entry visit and the infant’s Step 1 Week 4 visits have been completed and in utero HIV infection has been excluded.
2. Mothers of HIV-infected infants, if available, will be followed every 6 months for up to 5 years and as long as the infant remains on study.
3. Targeted history including documentation of HIV infection, WHO clinical staging, maternal ARV use (all ARVS taken prior to study entry), CD4 T cell and HIV RNA results within the last year (based on available medical record documentation), obstetrical history including prior pregnancies and mode of delivery for the current pregnancy; syphilis in the current pregnancy (based on available medical record documentation), and active hepatitis at the time of study entry (based on available medical record documentation). If documentation of HIV infection meeting requirements in protocol Section 4.111 is not available, blood should be collected for additional testing meeting protocol requirements. At least one positive HIV rapid test result must be available prior to entry and confirmatory results meeting protocol requirements must be available within 7 business days after study entry; otherwise, the mother and infant must be discontinued from the study.
4. Targeted interval history including WHO clinical staging, maternal ARV use, and chart abstraction for CD4 T cells and HIV RNA if available.
5. HIV RNA must be performed at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites) at the time of study entry.
6. Blood will be stored (serum, plasma, cells) for: HIV RNA, HIV drug resistance, HIV subtype, sequencing and immune studies which may include HLA typing, CCR5 delta 32 genotyping and SNP analyses for related host genetic factors.
APPENDIX II-A
SCHEDULE OF EVALUATIONS
STEP 1: HIGH-RISK INFANTS IN COHORT 1

<table>
<thead>
<tr>
<th></th>
<th>Step 1 Entry</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2* (± 2 days)</th>
<th>Week 4** (Last study visit) (± 1 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adherence3</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology4</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL6</td>
<td></td>
</tr>
<tr>
<td>Chemistries5</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL6</td>
<td></td>
</tr>
<tr>
<td><strong>Virology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV DNA PCR</td>
<td></td>
<td></td>
<td>1.5 mL</td>
<td></td>
</tr>
<tr>
<td>HIV nucleic acid7</td>
<td>Sample 1: 1.5-3.0mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample 2: 1.5-3.0mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored Plasma and PBMC6</td>
<td>2.5 mL</td>
<td>2.5 mL</td>
<td>1.0 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacology</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Sampling8</td>
<td></td>
<td>0.12 mL</td>
<td>0.12 mL</td>
<td></td>
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<tr>
<td><strong>Pharmacogenetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetics sampling10</td>
<td></td>
<td>0.12 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Blood</strong></td>
<td>7-10 mL</td>
<td>2.74 mL</td>
<td>4.12 mL</td>
<td>1.5 mL</td>
</tr>
</tbody>
</table>

Day of study entry = Day 0 for this schedule.

* Infants with confirmed HIV infection based on nucleic acid testing performed on two separate blood draws at least 1 hour apart within 48 hours of birth, per the requirements of footnote 7 below, will enter Step 2 (Appendix II-B) instead of completing the Step 1 Week 2 and Week 4 visits shown above.

† Infants for whom HIV infection is not confirmed per the requirements of footnote 7 below will complete the Step 1 Week 2 and Week 4 visits shown above and exit the study at the Week 4 visit. These infants will discontinue study ART as soon as possible after infection is excluded (no later than the Week 2 visit) and switch to perinatal ARV prophylaxis according to country guidelines.
APPENDIX II-A

FOOTNOTES

STEP 1: HIGH-RISK INFANTS IN COHORT 1

1. **At entry**, history should include sex and race/ethnicity; Apgar scores, weight, length, head circumference, and gestational age at birth (based on available medical record documentation); and clinical history (diagnoses, signs, and symptoms), ARVs and other concomitant medications, and method of feeding since birth. **After entry**, interval history should include clinical history (diagnoses, signs, and symptoms), ARVs and other concomitant medications, and method of feeding. All history should be recorded in source documents. The following should be recorded on case report forms: all Grade ≥ 2 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of ARV regimen (any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.

2. Physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.

3. Adherence will be measured using the standardized IMPAACT adherence questionnaire (refer to MOP for questionnaire details).

4. Hematology: CBC (complete blood count) with differential and platelet count.

5. Chemistries: AST and ALT.

6. HIV DNA PCR, quantitative and qualitative HIV RNA PCR, and total nucleic acid (TNA) tests are acceptable. At entry, two separate blood draws at least one hour apart within 48 hours of birth are required. One test must be a quantitative RNA PCR; the second test can also be a quantitative RNA PCR, but a DNA or TNA test is desirable. At least one of these tests must be performed at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites). Left-over blood should be stored for confirmatory testing if needed. Results must be available by Step 1 Week 2.

7. At Weeks 1 and 2, samples collected for stored plasma must be drawn at the same time as samples collected for pharmacology (PK Sampling). The Week 1 sample will be collected from all infants. The Week 2 sample will be collected from all infants until notification that the NVP dose evaluation described in protocol Section 9.2 has been completed. Samples will be used in conjunction with DBS for NVP dose evaluation and/or for future testing to identify host and viral factors associated with HIV-1 remission in the context of very early therapy, including drug resistance genotype, and viral sequencing. Samples for NVP dose evaluation will be shipped to the designated central pharmacology laboratory. Samples for host and viral factors will be batch shipped to the designated central pathogenesis laboratory (samples from uninfected infants will be used as controls for these evaluations).

8. NVP exposure will be measured using DBS on filter paper. At Week 2, collect only if subject is still taking NVP in study treatment doses. Samples will be shipped to the designated central pharmacology laboratory.

9. CYP2B6 polymorphisms will be analyzed in the first 30 subjects enrolled using DBS on filter paper. Samples from the rest of the subjects will be stored for future host genetics testing to help understand remission. Samples will be shipped to the designated central pathogenesis laboratory.
Notes:

a. For all stored samples, see the LPC for processing, storage and shipping instructions.

b. For all DBS samples, refer to the ACTG/IMPAACT Processing of Dried Blood Spots SOP (LTC-SOP-55 v2.0) for collection, packing, storage and shipping procedures.

The P1115 team has adopted the NIH recommendation for infant blood collection limits of 5 mL/kg in a single day and a limit of 9.5 mL/kg in any 8-week period. Refer to the blood draw priority list below. All sites should comply with local IRB limitations.

Blood draw priority list

1. Hematology
2. Chemistries
3. Virology
4. Pharmacokinetics
5. Pharmacogenetics
**APPENDIX II-B**

**SCHEDULE OF EVALUATIONS**

**STEP 2: HIV-INFECTED INFANTS IN COHORT 1 AND COHORT 2**

**ENTRY THROUGH WEEK 72**

<table>
<thead>
<tr>
<th></th>
<th>Step 2 Entry&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Week 1 (± 2 days)</th>
<th>Week 2 (± 2 days)</th>
<th>Week 4 (± 1 wk)</th>
<th>Week 6 (± 1 wk) by phone contact&lt;sup&gt;•&lt;/sup&gt;</th>
<th>Week 8 (± 1 wk)</th>
<th>Weeks 12, 16 &amp; 20 (± 2 wks)</th>
<th>Week 24 (± 2 wks)</th>
<th>Weeks 28, 32, 40,44, 52, 56, 64, 68 (± 2 wks) by phone contact&lt;sup&gt;•&lt;/sup&gt;</th>
<th>Weeks 36, 48, 60 &amp; 72 (± 2 wks)</th>
<th>Premature Discontinuation&lt;sup&gt;16&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
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<td></td>
<td></td>
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<td>History&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>X</td>
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<td></td>
<td>X</td>
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<tr>
<td>Physical exam&lt;sup&gt;3&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Adherence&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td><strong>LABORATORY</strong></td>
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<tr>
<td>Hematology&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.5 mL&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td>Chemistries&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
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<td>1 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
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</table>

*May be done in person if preferred by the site (e.g., if participant does not have a phone or in support of visit compliance and/or study drug adherence).
APPENDIX II-B
FOOTNOTES
STEP 2: HIV-INFECTED INFANTS IN COHORT 1 AND COHORT 2
ENTRY THROUGH WEEK 72

1. Visit weeks will restart at Week 0 for subjects in Step 1 who enter Step 2 (Day of Step 2 Entry = Day 0 for this schedule, both for subjects who enter Step 2 from Step 1 and for subjects who enter Step 2 directly).

2. For subjects who enter Step 2 directly, at entry, history should include sex and race/ethnicity; Apgar scores, weight, length, head circumference, and gestational age at birth (based on available medical record documentation); and clinical history (diagnoses, signs, and symptoms), ARVs and other concomitant medications, and method of feeding since birth. For subjects who enter Step 2 from Step 1, at entry, and for all subjects after entry, interval history should include clinical history (diagnoses, signs, and symptoms), ARVs and other concomitant medications, and method of feeding. All history should be recorded in source documents. The following should be recorded on case report forms: all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of ARV regimen (any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.

History at entry also includes documentation of HIV infection:
- For subjects entering Step 2 from Step 1, required HIV testing will be performed as part of Step 1, with results documented prior to entry into Step 2.
- For subjects entering Step 2 directly, if documentation of HIV testing meeting requirements in protocol Section 4.33 and 6.322 is not available, blood should be collected for additional testing. At least one positive nucleic acid test result must be available prior to entry, and results from a second test meeting protocol requirements must be available within 7 business days after entry; otherwise, the infant must be discontinued from the study. However, if the second test does not confirm the initial positive result, a third specimen should be collected for HIV DNA PCR, with the result available within an additional 7 business days. At least one of the first two tests must be performed at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites). If performed, the third test (HIV DNA PCR) must also be performed at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites).

3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.

4. Adherence will be measured using the standardized IMPAACT adherence questionnaire (refer to MOP for questionnaire details). At Entry, adherence during the 3-day period prior to entry should be collected.

5. Hematology: CBC (complete blood count) with differential and platelet count.


7. Hematology and Chemistry at Week 16 only.

8. Collect at Week 12 only (do not collect at Weeks 16 and 20).

9. Must be performed in real time at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites).
APPENDIX II-B
FOOTNOTES
STEP 2: HIV-INFECTED INFANTS IN COHORT 1 AND COHORT 2
ENTRY THROUGH WEEK 72

10. Sample will be stored for future testing to identify host and viral factors associated with HIV-1 remission in the context of very early therapy, including drug resistance genotype, viral sequencing, and if remission is achieved, DNA quantification to identify the time point when the virus was cleared. Samples collected at Entry, Week 4, Week 16, and Week 24 will also have HIV DNA PCR testing performed. All stored samples will be shipped to the designated central pathogenesis laboratory.
   a. Collect at Week 16 only.
11. Droplet digital DNA PCR will be used as additional testing for HIV viral persistence and for future evaluation of subjects in remission. Sample will be stored and batch shipped to the designated central pathogenesis laboratory.
   a. Collect at Week 12 only.
12. Virology DBS will be used for future viral sequencing and to evaluate host and viral factors associated with HIV-1 remission in the context of very early therapy. At early discontinuation, virology DBS will be used for HIV RNA level. Samples will be batch shipped to the designated central pathogenesis laboratory.
   a. Collect at Week 48 and Week 72 only.
13. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot; HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR by flow cytometry) as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory.
   a. Collect at Week 72 only
14. LPV/r ± NVP exposures will be measured using DBS on filter paper. Samples will be shipped to the designated central pharmacology laboratory.
15. CYP2B6 polymorphisms will be analyzed using DBS on filter paper. Samples will be shipped to the designated central pathogenesis laboratory. Do not repeat in subjects who had this test drawn in Step 1.
16. Refer to protocol Section 6.4 for the criteria for premature discontinuation from the study.

Notes:
   a. For all stored samples, see the LPC for processing, storage and shipping instructions.
   b. For all DBS samples, refer to the ACTG/IMPAACT Processing of Dried Blood Spots SOP (LTC-SOP-55 v2.0) for collection, packing, storage and shipping procedures.
The P1115 team has adopted the NIH recommendation for infant blood collection limits of 5 mL/kg in a single day and a limit of 9.5 mL/kg in any 8-week period. Refer to the blood draw priority lists below. All sites should comply with local IRB limitations.

Blood draw priority lists

- **Entry through Week 24**
  1. Hematology
  2. Chemistries
  3. Virology (except stored samples [see #7 below])
  4. CD4
  5. Pharmacokinetics
  6. Pharmacogenetics
  7. Stored samples (for infants < 3 kg, minimize to meet the NIH blood limits)

- **Week 30 through Week 72**
  1. Virology (except stored samples [see #6 below])
  2. CD4
  3. Pharmacokinetics
  4. Hematology
  5. Chemistries
  6. Stored samples (for infants < 3 kg, minimize to meet NIH blood limits)
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Day of Step 2 Entry = Day 0 for this schedule.
APPENDIX II-C
FOOTNOTES

STEP 2 (cont’d): INFECTED INFANTS IN COHORT 1 AND COHORT 2
ART CESSATION EVALUATION VISITS* – WEEK 84 THROUGH WEEK 192

* Beginning at Week 84, subjects will be evaluated for eligibility to move to Step 3 (ART cessation). Refer to protocol Section 4.4 for the Step 3 inclusion criteria and Section 6.323 for the evaluation procedure. Subjects meeting the ART cessation criteria will enter Step 3 (Appendix II-D) as soon as possible after the criteria have been met.

1. Interval history should include clinical history (diagnoses, signs, and symptoms), ARVs and other concomitant medications, and method of feeding. All history should be recorded in source documents. The following should be recorded on case report forms: all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of ARV regimen (any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.
2. Physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.
3. Adherence will be measured using the standardized IMPAACT adherence questionnaire (refer to MOP for questionnaire details).
4. Hematology: CBC (complete blood count) with differential and platelet count.

IMPORTANT INSTRUCTION for virology evaluations and footnotes 6-12: Following a participant’s first negative HIV-1 antibody test result, all virology specimens collected at the next scheduled visit will shipped for protocol-specified virology testing at designated central laboratories; at this specific time point, no virology evaluations will be performed at local laboratories.

6. Must be performed in real time at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites). Save extra plasma for shipment to the designated central laboratory for performance of a 3rd generation ELISA and Western blot. See also footnote 8 and the important instruction above.
7. HIV DNA samples will be stored and shipped to the designated central laboratory (see also footnote 8 and the important instruction above).
8. HIV-1 antibody by ELISA or rapid test will be performed locally in real time to test for a negative antibody; following a participant’s first negative antibody test result obtained at the local laboratory, all virology specimens collected at the next scheduled visit will shipped to the designated central laboratory.
9. Droplet digital DNA PCR will be used as additional testing for HIV viral persistence and for future evaluation of subjects in remission. Sample will be stored and batch shipped to the designated central pathogenesis laboratory. See also footnote 8 and the important instruction above.
10. Collect 8 mL through < 3 years of age and 10 mL from ≥ 3 through 4 years of age. Replication-competent virus sample will be used for additional testing for viral persistence and single copy HIV RNA will be run in subjects who are evaluated for remission. Samples will be processed in real-time with overnight shipment for US sites. For non-US sites, samples will be cryopreserved for shipment in batch. Samples will be shipped to the designated central pathogenesis laboratory. See also footnote 8 and the important instruction above.
APPENDIX II-C
FOOTNOTES

STEP 2 (cont’d): INFECTED INFANTS IN COHORT 1 AND COHORT 2
ART CESSATION EVALUATION VISITS* – WEEK 84 THROUGH WEEK 192

11. Sample will be stored for future testing to identify host and viral factors associated with HIV-1 remission in the context of very early therapy, including drug resistance genotype, viral sequencing, and, if remission is achieved, DNA quantification to identify the time point when the virus was cleared. Sample will be batch shipped to the designated central pathogenesis laboratory. See also footnote 8 and the important instruction above.

12. Virology DBS at follow-up visits will be used for future viral sequencing and to evaluate host and viral factors associated with HIV-1 remission in the context of very early therapy. Sample will be batch shipped to the designated central pathogenesis laboratory. See also footnote 8 and the important instruction above.

13. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot; HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR activation) as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150 C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory for testing.

14. LPV/r ± NVP exposures will be measured using DBS on filter paper. Samples will be shipped to the designated central pharmacology laboratory.

15. Refer to protocol Section 6.4 for the criteria for premature discontinuation from the study.

Notes:

a. For all stored samples, see the LPC for processing, storage and shipping instructions.

b. For all DBS samples, refer to the ACTG/IMPAACT Processing of Dried Blood Spots SOP (LTC-SOP-55 v2.0) for collection, packing, storage and shipping procedures.

The P1115 team has adopted the NIH recommendation for infant blood collection limits of 5 mL/kg in a single day and a limit of 9.5 mL/kg in any 8-week period. Refer to the blood draw priority list below. All sites should comply with local IRB limitations.

Blood draw priority list
1. Virology (except stored plasma and PBMC, see #7 below) – if insufficient blood draw, do not collect replication-competent virus sample
2. CD4
3. Pharmacokinetics
4. Hematology
5. Chemistries
6. Immunology
7. Stored Plasma and PBMC
## APPENDIX II-D
### SCHEDULE OF EVALUATIONS
#### STEP 3: ART CESSATION

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<th>Week 3 (± 2 days)</th>
<th>Week 4 (± 2 days)</th>
<th>Week 6 (± 1 wk)</th>
<th>Week 8 (± 1 wk)</th>
<th>Week 12 (± 2 wks)</th>
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<td>Stored Single copy HIV RNA⁸</td>
<td>5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 mL</td>
<td>5 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replication-competent virus⁹</td>
<td>5 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMC¹⁰</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>HIV-specific immune responses¹¹</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD</td>
<td>21 mL</td>
<td>3 mL</td>
<td>6 mL</td>
<td>3 mL</td>
<td>12 mL</td>
<td>3 mL</td>
<td>6 mL</td>
<td>4 mL</td>
<td>15 mL</td>
</tr>
</tbody>
</table>
## APPENDIX II-D
### SCHEDULE OF EVALUATIONS
#### STEP 3 (cont’d.): ART CESSATION

<table>
<thead>
<tr>
<th></th>
<th>Week 24 (± 4 wks)</th>
<th>Week 32 (± 4 wks)</th>
<th>Week 40 (± 4 wks)</th>
<th>Week 48 (± 4 wks)</th>
<th>Week 60, then every 12 weeks through 5 years of age (± 6 wks)</th>
<th>Premature Discontinuation(^{12})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History(^2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam(^3)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL(^4)</td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA PCR(^5)</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>Stored HIV DNA PCR(^6)</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Stored Droplet digital DNA PCR(^7)</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td></td>
</tr>
<tr>
<td>Stored Single copy HIV RNA(^8)</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL(^9a)</td>
</tr>
<tr>
<td>Replication-competent virus(^9)</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td></td>
</tr>
<tr>
<td>Stored plasma and PBMC(^{10})</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored HIV-specific immune responses(^{11})</td>
<td>3 mL</td>
<td></td>
<td></td>
<td></td>
<td>3 mL</td>
<td>3 mL(^{11a})</td>
</tr>
<tr>
<td><strong>TOTAL BLOOD</strong></td>
<td>24 mL</td>
<td>16 mL</td>
<td>9 mL</td>
<td>24 mL</td>
<td>24 mL</td>
<td>8-9 mL</td>
</tr>
</tbody>
</table>
APPENDIX II-D
FOOTNOTES
STEP 3: ART CESSATION

1. Visit weeks will restart at Week 0 on entry into Step 3 (Date of Step 3 Entry = Day 0). ART will be discontinued after blood collection at Step 3 Entry.
2. Interval history (at Step 3 Entry, history from the last visit in Step 2) should include date of breastfeeding cessation, clinical history (diagnoses, signs, and symptoms), and ARVs and other concomitant medications. All history should be recorded in source documents. The following should be recorded on case report forms: all Grade ≥ 3 signs and symptoms, all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs (infant and maternal if breastfeeding), and all concomitant medications.
3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.
4. CD4 is not required at Early Discontinuation if prior test done was within 12 weeks of the visit.
5. Must be performed in real time at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites). If HIV RNA is ≥ LOD, a confirmatory RNA must be repeated as soon as possible. If the repeat RNA is ≥ LOD, subject will enter Step 4 – ART Re-initiation (Appendix II-E) as soon as possible but no later than 2 weeks after result is available.
6. Sample will be stored and batch shipped to the designated central pathogenesis laboratory for future testing.
7. Droplet digital DNA PCR sample will be used for additional testing for HIV viral persistence and for future evaluation of subjects in remission. Sample will be stored and batch shipped to the designated central pathogenesis laboratory.
8. Sample will be stored for future evaluation of subjects in remission. Samples will be shipped to the designated central pathogenesis laboratory.
9. Replication-competent virus sample will be used for additional testing for viral persistence. Sample at Step 3 Entry is not required if a sample was collected in Step 2 within 30 days of the visit. Collect 5 mL through < 3 years of age and 10 mL from ≥ 3 through 5 years of age. For US sites, samples will be processed in real-time with overnight shipment. For non-US sites, samples will be cryopreserved for shipment in batch. Samples will be shipped to the designated central pathogenesis laboratory.
   a. Beginning at Week 72, collect every other visit (i.e., every 24 weeks) through 5 years of age.
10. Stored samples for future testing to identify host and viral factors associated with HIV-1 remission in the context of very early therapy, including drug resistance genotype, viral sequencing, and if remission is achieved, DNA quantification to identify the time point when the virus was cleared. Samples will be shipped to the designated central pathogenesis laboratory.
APPENDIX II-D
FOOTNOTES
STEP 3: ART CESSATION

11. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot); HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR activation) following treatment cessation as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150°C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory.
   a. Beginning at Week 60, collect every other visit (i.e., every 24 weeks) through 5 years of age.
12. Refer to protocol Section 6.4 for the criteria for premature discontinuation from the study.

Note: For all stored samples, see the LPC for processing, storage and shipping instructions.

The P1115 team has adopted the NIH recommendation for pediatric blood collection limits of 5 mL/kg in a single day and a limit of 9.5 mL/kg in any 8-week period. Refer to the blood draw priority list below. All sites should comply with local IRB limitations.

Blood draw priority list
1. Virology
2. CD4
3. Immunology
## APPENDIX II-E
### SCHEDULE OF EVALUATIONS
#### STEP 4 – ART RE-INITIATION

<table>
<thead>
<tr>
<th>Step 4 Entry¹</th>
<th>Week 1 (±2 days) by phone contact</th>
<th>Week 2 (±2 days) by phone contact</th>
<th>Week 3 (±2 days) by phone contact</th>
<th>Week 4 (±1 wk)</th>
<th>Week 6 (±1 wk)</th>
<th>Week 8 (±1 wk)</th>
<th>Week 10 (±1 wk)</th>
<th>Week 12 then every 4 weeks until viral suppression (±1 wk)¹³</th>
<th>Week 16 then every 4 weeks through 5 years of age (± 6 wks)</th>
<th>Premature Discontinuation¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Adherence⁴</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

| LABORATORY   |                                  |                                  |                                  |                |                |                |                |                                  |                                  |                  |
| Hematology⁵  | 0.5 mL                           | 0.5 mL                           | 0.5 mL                           | 0.5 mL         | 0.5 mL         | 0.5 mL         | 0.5 mL         | 0.5 mL⁶ᵃ                           |                                  |                  |
| Chemistries⁶  | 1 mL                             | 1 mL                             | 1 mL                             | 1 mL           | 1 mL           | 1 mL           | 1 mL           | 1 mL⁶ᵃ                           |                                  |                  |
| CD4          | 1 mL                             |                                  |                                  |                |                |                |                |                                  |                                  |                  |

| VIROLOGY     |                                  |                                  |                                  |                |                |                |                |                                  |                                  |                  |
| HIV RNA PCR⁷ | 3 mL                             | 3 mL                             | 3 mL                             | 3 mL           | 3 mL           | 3 mL           | 3 mL           | 3 mL                             | 3 mL                             |                  |
| Stored Drug resistance genotyping⁸ | 2 mL⁸ᵃ                           |                                  |                                  | 2 mL³ᵇ       | 2 mL³ᵇ       | 2 mL³ᵇ       | 2 mL³ᵇ       | 2 mL⁸ᵇ                           |                                  |                  |
| Stored Droplet digital DNA PCR⁹   |                                  |                                  | 2 mL                             | 2 mL           | 2 mL           |                                  |                                  |                                  |                                  |                  |
| Replication-competent virus¹⁰     |                                  |                                  |                                  |                |                |                                  |                                  |                                  |                                  |                  |
| Stored Virology DBS¹¹            | 0.25 mL                          |                                  |                                  | 0.25 mL        | 0.25 mL        |                                  |                                  |                                  |                                  |                  |

| IMMUNOLOGY   |                                  |                                  |                                  |                |                |                |                |                                  |                                  |                  |
| Stored HIV-specific immune responses¹² | 3 mL                             |                                  |                                  |                |                |                                  |                                  |                                  |                                  |                  |

| TOTAL BLOOD  | 10.75 mL                         | 3 mL                             | 4.5 mL                          | 5 mL           | 3-5 mL         | 3-5 mL         | 7.75-9.75 mL | 3 mL                             | 6.25-20.75 mL       | 4-6 mL           |
APPENDIX II-E

FOOTNOTES

STEP 4 – ART RE-INITIATION

1. Visit weeks will restart at Week 0 on entry into Step 4 (Date of Step 4 Entry = Day 0).

2. Interval history (at Step 4 Entry, history since the last visit in Step 3) should include clinical history (diagnoses, signs, and symptoms), and ARVs and other concomitant medications. All history should be recorded in source documents. The following should be recorded on case report forms: all Grade ≥ 3 signs and symptoms, all signs and symptoms (regardless of grade) that lead to a change of ARV regimen (any change of any ARV), all diagnoses except those noted on the “do not record” list (available at www.fstrf.org), all ARVs, and all concomitant medications.

3. Physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.

4. Adherence will be measured using the standardized IMPAACT adherence questionnaire (refer to MOP for questionnaire details).

5. Hematology: CBC (complete blood count) with differential and platelet count.
   a. Perform every 24 weeks beginning at Week 24.

   a. Perform every 24 weeks beginning at Week 24.

7. Must be performed in real time at either a CLIA-certified laboratory (US sites) or a DAIDS VQA-certified laboratory (non-US sites).

8. Sample will be stored for future testing.
   a. Sample collected at Entry will be stored and run at the end of the study if viral re-suppression does not occur after ART re-initiation to assess drug resistance mutations to the regimen.
   b. Collect sample if HIV RNA is > 1,000 copies/mL at the previous visit. Test should be run at a local laboratory if there is capability. If the local laboratory is unable to perform the test, sample will be shipped in real time to the designated central pathogenesis laboratory.

9. Droplet digital DNA PCR sample will be used for additional testing for HIV viral persistence. Sample will be stored and batch shipped to the designated central pathogenesis laboratory.

10. Replication-competent virus sample will be used for additional testing for viral persistence. At Week 24, collect 5 mL if < 3 years of age and 10 mL if ≥ 3 through 5 years of age then every 24 weeks thereafter. Samples will be processed in real-time with overnight shipment for US sites. For non-US sites, samples will be cryopreserved for shipment in batch. Samples will be shipped to the designated central pathogenesis laboratory.
   a. Beginning at Week 48, collect every 24 weeks through 5 years of age.

11. Virology DBS will be used for future studies of viral sequencing. Sample will be batch shipped to the designated central pathogenesis laboratory.
APPENDIX II-E
FOOTNOTES
STEP 4 – ART RE-INITIATION APPENDIX II-E

12. Sample will be used to evaluate HIV-1 specific immune responses (antibodies by ELISA and Western blot); HIV-1 specific CD4 and CD8 T cell responses by intracellular cytokine assays) and T cell activation (%CD8/CD38/DR activation) following treatment cessation as markers for control of HIV-1 replication and remission. At labs that participate in the IQA cryopreservation proficiency testing program and are able to store samples in LN2 or at -150°C prior to shipment, plasma and viably cryopreserved PBMC will be stored and batch shipped to the designated central immunology laboratory.
   a. Beginning at Week 48, collect every 48 weeks through 5 years of age.
13. If HIV RNA PCR is not < LOD at Week 12, conduct study visits every 4 weeks for continued monitoring of viral load. At these visits, history and adherence should also be evaluated. Once HIV RNA PCR is < LOD, continue with study visits every 12 weeks.
14. Refer to protocol Section 6.4 for the criteria for premature discontinuation from the study.

Notes:
   a. For all stored samples, see the LPC for processing, storage and shipping instructions.
   b. For all DBS samples, refer to the ACTG/IMPAACT Processing of Dried Blood Spots SOP (LTC-SOP-55 v2.0) for collection, packing, storage and shipping procedures.

The P1115 team has adopted the NIH recommendation for pediatric blood collection limits of 5 mL/kg in a single day and a limit of 9.5 mL/kg in any 8-week period. Refer to the blood draw priority list below. All sites should comply with local IRB limitations.

Blood draw priority list
1. Virology
2. CD4
3. Immunology
4. Hematology
5. Chemistry
APPENDIX III

SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EVENTS

<table>
<thead>
<tr>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema, with or without pruritis</td>
<td>A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritis (without the presence of any additional constitutional findings as described in Grade 3 of DAIDS Toxicity tables)</td>
<td>B. Urticaria OR typical target lesions without blistering, vesicles, or ulcerations in the lesions.</td>
<td>Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (&gt;10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)</td>
</tr>
<tr>
<td></td>
<td>A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to study drug:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. fever, &gt; 39°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 5 x ULN AST, ALT or 2 x baseline if baseline &gt; ULN.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. blistering and/or vesiculation of cutaneous eruptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. any site of mucosal lesions; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. angioedema; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (&lt; 10% body surface area), (Nikolski's sign)(Stevens Johnson Syndrome, SJS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For all Grade 3 and 4 cutaneous/skin rash/dermatitis adverse experiences, photo documentation of the rash is strongly recommended.
APPENDIX IV-A

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
INFANT: COHORT 1 / STEP 1

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

INTRODUCTION
You are being asked to allow your baby to take part in this research study because you have
tested positive for the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and
your baby may be infected with HIV. This study is sponsored by the National Institutes of
Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator).
Before you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you
about this information. You are free to ask questions at any time. If you allow your baby to take
part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of
birth can make it possible for babies who are infected with HIV to control HIV so well that HIV
cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they
usually need to keep taking them for life. For newborn babies who start ARVs very soon after
birth, it might be possible to later stop taking ARVs and still stay healthy. This has only been
seen in one baby so far. This study is being done to find out if this can be seen in other babies
who start anti-HIV medicines very soon after birth. This study is also looking at the levels of
ARVs that are safe and work well for babies.

WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. At this time, you are being asked to allow your baby to take part only
in Step 1. This step is for babies whose mothers have HIV and it is not yet known if the babies
have HIV. The study will do testing to confirm if your baby has HIV.

- If your baby DOES NOT have HIV, he or she will be in Step 1 of the study for only 4 weeks.

- If your baby DOES have HIV, you will be asked to allow your baby to take part in Steps 2, 3,
  and 4. These steps will be explained to you separately and you will be asked to sign another
  consent form for your baby to take part in them. An information sheet about Steps 2, 3, and
  4 is attached to this form.
The rest of this form explains Step 1, which involves four visits. If you allow your baby to take part, the first visit (Entry) will continue today. The next three visits will be in 1, 2, and 4 weeks. Each visit will take 1-2 hours.

At the Entry Visit
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Tests for HIV infection and the amount of HIV in the blood. For these tests, blood will be drawn two times, at least one hour apart, within the first 48 hours of birth.
  - Routine safety tests. These tests check for problems with your baby’s red and white blood cells and liver, which can sometimes be side effects of ARVs.
  - Other HIV-related tests.
- You will be provided ARVs for your baby and instructions on how to give them to your baby. The ARVs will include nevirapine and two other ARVs. The study staff will explain where to obtain the ARVs and whether your insurance will need to pay for them. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however, that the ARVs provided in this step are not considered study drugs and should be obtained from non-study sources.]

At the Week 1 and Week 2 Visits
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have less than one teaspoon (3-4 mL) of blood drawn for routine safety tests and HIV-related tests. A test of the amount of nevirapine in the blood will also be done.

The results of your baby’s first tests for HIV infection will be known by the time of the Week 2 visit.

If your baby does not have HIV, the ARVs started at the Entry Visit will be stopped and ARVs usually given to prevent babies from getting HIV will be given instead. The study staff will explain this change to you. Your baby will have one more study visit, at Week 4, and then will leave the study.

If your baby does have HIV, Steps 2, 3, and 4 of the study will be explained to you and you will be asked to sign another consent form to allow your baby to take part in those steps. If you agree, your baby will enter Step 2 around the time of the Week 2 visit (the Week 4 visit for Step 1 will not be done).

At the Week 4 Visit
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have less than one-half teaspoon of blood drawn only if the routine safety tests done at Week 2 showed abnormal results. Otherwise no blood will be collected.
● The study staff will refer you to other sources of care for your baby outside the study, including sources of ARVs and HIV testing. Even though your baby was not found to have HIV in this study, he or she could still test positive later, and it is important that he or she be tested again at 6 weeks of age.

GENETIC TESTING
Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important information for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s blood used for genetic testing. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s blood to be used for genetic testing, including future genetic testing, as part of this study.

____________ Yes   ____________ No   ____________ Date

STORAGE OF BLOOD FOR FUTURE USE

For NICHD Sites:
Some of your baby’s blood drawn for this study will be stored for testing at a later date as part of this study. This blood may be stored and tested at special laboratory facilities in the US and other countries outside of [insert site country]. There is a separate consent form to explain this and get your consent.

For NIAID Sites:
Some of your baby’s blood drawn for this study will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. In Step 1 of this study, up to 1 teaspoon (5 mL) of blood will be drawn for this purpose.

Your baby’s samples will be stored and tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facility will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies your baby. Your baby’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your baby’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your baby’s samples will be stored.
The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important information for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date

**HOW MANY BABIES WILL BE IN THIS STUDY?**
About 440 babies are expected to take part in Step 1 of this study.

**HOW LONG WILL BABIES BE IN THIS STUDY?**
Babies will be in Step 1 of the study for up to 4 weeks.

**WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?**
The study doctor may need to take your baby off Step 1 of this study early without your permission for the reasons listed below. If this happens, no further information will be collected and no further study visits or laboratory tests will be done.

- You do not have HIV infection.
- Your baby stops coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
- The study is cancelled by the IMPAACT network, the National Institutes of Health, the Office for Human Research Protections, the US Food and Drug Administration, the site’s Institutional Review Board (IRB) or Ethics Committee (EC), or other governmental agencies. An IRB/EC is a committee that watches over the safety and rights of research participants.
WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. The blood tests can also be done by heel stick. Heel stick test may cause some discomfort, bleeding, or bruising at the site of the heel stick. There is a small risk of an infection at the site of the heel stick.

Babies in Step 1 of this study will be given a combination of three ARVs, including nevirapine and two other ARVs chosen by your baby’s doctor. The three ARVs will be started earlier than usual (before your baby is confirmed to have HIV) and nevirapine will be given at a higher dose than usual. This dosing may have more side effects. Some of the possible side effects of nevirapine are listed below. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects.

Nevirapine (NVP, Viramune®)
Boehringer Ingelheim Pharmaceuticals, Inc.
This is a list of the serious or common side effects that have a known or possible relationship with nevirapine. This is not a complete list of all side effects.

The following serious side effects have been associated with the use of nevirapine:

Severe liver damage that can result in death may occur and is often associated with a rash. People who have abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are also at higher risk for liver damage.

If your baby is developing liver damage, he or she may have one or more of the following:
- Tiredness
- General feeling of illness or flu-like feeling
- Loss of appetite
- Nausea
- Pale stools
- Dark urine
- Yellowing of the skin or whites of your eyes
- Liver tenderness or abnormal liver function tests

Hypersensitivity reactions (“allergic reaction”) may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.

Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.
Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.

The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and the study doctor decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.

In addition to the serious side effects listed above, additional side effects include:
- Fever
- Headache
- Upset stomach (nausea, vomiting)

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about other choices available to your baby. Whether or not you choose to allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF YOUR BABY IS INJURED?
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

WHAT ABOUT CONFIDENTIALITY?
US sites:
Efforts will be made to keep your baby’s personal information confidential but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.
To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your baby’s study records may be reviewed by the Office for Human Research Protections, Food and Drug Administration, National Institutes of Health, site IRB/EC (insert name of site IRB/EC), study staff, study monitors, drug companies supporting the study, and their designees.

Sites outside the US:
Efforts will be made to keep your baby’s personal information confidential. We cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by the US Office for Human Research Protections, US Food and Drug Administration, US National Institutes of Health, (insert local regulatory and/or government authorities if applicable), site IRB/EC (insert name of site IRB/EC), study staff, study monitors, and drug companies supporting this study and their designees.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your baby’s study visits, examinations, or blood tests. [Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]
WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:

• name of the investigator or other study staff
• telephone number of above

For questions about your baby’s rights as a research participant, contact:

• name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
• telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

Participant’s Name (print)________________________________________

Parent or Legal Guardian Name (print) ____________________________

Parent or Legal Guardian Signature ________________________________

Date ________________

Study Staff Conducting Consent Process Name (print) ____________________________

Study Staff Signature ________________________________

Date ________________

Witness Name ____________________________

Witness Signature ________________________________

Date ________________
BRIEF INFORMATION ABOUT STEPS 2, 3, AND 4

This sheet is for your information only and does not obtain informed consent for Steps 2, 3 and 4.

If you allow your baby to take part in Step 1 of this study, your baby will have study visits over the next two weeks. If your baby is found to be infected with HIV, you will be asked to allow your baby to take part in Steps 2, 3, and 4 of the study. Steps 2, 3, and 4 will be explained to you in detail and you will be asked to sign a separate consent form at that time. Some information for you to know about these steps is as follows:

- In Step 2, babies will be given 4 anti-HIV medicines (ARVs). Blood tests will be done to check on your baby’s health and the amount of HIV in the blood. If the ARVs are given to your baby as instructed, the amount of HIV in the blood should drop to a level that cannot be detected by the study tests. At 6 months of age, babies with no HIV detected in the blood will continue in the study. Babies with HIV still detected in the blood will leave the study and will be referred for continued care and treatment outside the study.

- Babies who continue in the study will keep taking ARVs at least through 2 years of age. Blood tests will check on your baby’s health and the amount of HIV in the blood. Between 2 and 4 years of age, your baby may qualify to stop taking ARVs. If your baby qualifies, he or she will enter Step 3. If your baby does not qualify, he or she will leave the study at 4 years and will be referred for continued care and treatment outside the study.

- Babies in Step 3 will stop taking ARVs. They will be monitored closely, including checking the amount of HIV in the blood. If the amount of HIV in the blood rises, babies will enter Step 4 and start taking ARVs again. Otherwise, they will stay in Step 3, not taking ARVs. Babies in Step 3 and Step 4 will stay in the study through 5 years of age.

In Steps 2, 3, and 4, your baby will have study visits in which you will be asked about your baby’s health, medicines, and feeding. Your baby will have physical examinations and blood drawn for study tests. In the first six months of each step, study visits will be scheduled every 1-4 weeks. After that, visits will be scheduled every 8-12 weeks.

Please ask the study staff any questions you may have about this study. It is important that you have all of the information you need to decide whether to allow your baby to take part.
APPENDIX IV-B

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
INFANT: COHORTS 1 and 2 / STEPS 2, 3, and 4

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

INTRODUCTION
You are being asked to allow your baby to take part in this research study because your baby has
tested positive for HIV, the virus that causes AIDS, and started taking anti-HIV medicines
(ARVs) within 48 hours after birth. This study is sponsored by the National Institutes of Health.
The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before
you decide if you want your baby to participate, we want you to know about the study.

This is a consent form. It gives information about the study. The study staff will talk with you
about this information. You are free to ask questions at any time. If you allow your baby to take
part in the study, you will be asked to sign this form. You will be offered a copy to keep.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out if starting ARVs within 48 hours of birth can make it
possible for babies who are infected with HIV to control HIV so well that HIV cannot be
detected in their blood. As of now, when children with HIV start taking ARVs, they usually
need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it
might be possible to later stop taking ARVs and still stay healthy. This has only been seen in
one baby so far. This study is being done to find out if this can be seen in other babies who start
anti-HIV medicines very soon after birth. This study is also looking at the levels of ARVs that
are safe and work well for babies.

WHAT DOES YOUR BABY HAVE TO DO AS PART OF THIS STUDY?
This study has four steps. This form is for Steps 2, 3, and 4. If you allow your baby to take part,
he or she will enter Step 2 and may later qualify for Steps 3 and 4. The first visit (Step 2 Entry)
will continue today. This visit and all other visits will take about 1-2 hours.
STEP 2 (Baby is Treated for HIV)
To take part in Step 2, testing must be done to confirm that your baby is infected with HIV. If the required test results are available from Step 1 of this study or your baby’s medical record, those results can be used for Step 2. If not, additional testing will be done for the study. About 1-2 teaspoons of blood (5-10 mL) will be drawn for this testing. If infection is not confirmed, your baby will no longer be able to take part in the study. The study staff will explain this to you and refer you to other sources of care for your baby outside the study. It is important that your baby be tested for HIV again at 6 weeks of age.

Step 2 Entry
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 2 teaspoons (10 mL) of blood drawn for:
  - Routine safety tests. These tests check for problems with your baby’s red and white blood cells and liver, which can sometimes be side effects of ARVs.
  - Tests of how well the immune system is working and the amount of HIV in the blood.
  - Tests of the amount of ARVs in the blood.
  - Other HIV-related tests.
- Your baby will continue taking ARVs. The ARVs will include lopinavir/ritonavir, nevirapine, and two other ARVs. The study staff will provide you with instructions on how to give the ARVs to your baby. Lopinavir/ritonavir will be given as part of the study. The study staff will explain where to obtain the other ARVs and whether your insurance will need to pay for them. [Note to sites: This paragraph may be modified to reflect usual ARV prescribing and dispensing practices at your site; please note, however that the ARVs provided in this step, other than lopinavir/ritonavir, are not considered study drugs and should be obtained from non-study sources.]

Step 2 Visits in the First 6 Months
(Weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24)
There will be 9 visits in the first 6 months. The visits are close together at first (every 1-2 weeks) then further apart (every 4 weeks) as your baby gets older.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have up to 2 teaspoons (10 mL) of blood drawn for the same types of tests done at entry. Different safety and HIV-related tests will be done across visits; tests of the amount of HIV and ARVs in the blood will be done at each visit.
- At Week 6, no physical examination or blood draw will be done and it may be possible to complete the visit by phone.
- During this time, your baby’s ARVs may be changed. For example, as your baby grows, doses may be increased. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]
By the time of the Week 24 visit, if your baby is responding well to ARVs, the amount of HIV in your baby’s blood is expected to drop to a level that cannot be detected by the study tests. Because early control of HIV may be important for being able to stop taking ARVs at a later date, babies with no HIV detected in the blood at Week 24 will continue in the study (as described below). Babies with HIV detected in the blood will leave the study at Week 24 and will be referred for continued care and treatment outside the study.

Step 2 Visits from 6 to 18 Months
(Weeks 28 to 72)
Visits will occur every 4 weeks.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination and blood draw (about 2 teaspoons) at every third visit (every 12 weeks). Different safety and HIV-related tests will be done across visits; tests of the amount of HIV and ARVs in the blood will be done at each visit.
- At visits when physical examinations and blood draws are not done, it may be possible to complete the visits by phone.
- During this time, your baby’s ARVs may be changed. Depending on the amount of HIV detected in the blood, one of the ARVs (nevirapine) may be stopped. Other changes may also be made. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]

During this time, if no HIV is detected in your baby’s blood, your baby will continue in the study (as described below). If HIV is detected in the blood, your baby will leave the study and will be referred for continued care and treatment outside the study.

Step 2 Visits from 18 to 48 Months (4 Years)
(Weeks 84 to 192)
Visits will occur every 12 weeks.
- You will be asked about your baby’s health, medicines, and feeding.
- Your baby will have a physical examination.
- Your baby will have about 3-4 teaspoons (15-20 mL) of blood drawn. Different safety and HIV-related tests will be done across visits; tests of the amount of HIV and ARVs in the blood will be done at each visit.
- During this time, your baby’s ARVs may be changed. As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]

During this time, if no HIV is detected in your baby’s blood, the study doctor will see if your baby meets study requirements to stop taking ARVs. If these requirements are met by 48 months (4 years), your child will enter Step 3 (as described below) and stop taking ARVs. If not, your child will leave the study at 4 years and will be referred for continued care and treatment outside the study.
STEP 3 (Child Stops ARVs)

Step 3 Entry
• You will be asked about your child’s health, medicines, and feeding.
• Your child will have a physical examination.
• Your child will have about 4-5 teaspoons (20-25 mL) of blood drawn for HIV-related tests.
• You will be instructed to stop giving ARVs to your child.

Step 3 Visits
In the first 12 weeks, your child will have 7 visits. The visits are closer together at first (every 1-2 weeks) then further apart (every 4 weeks). The visits then change to every 8 weeks, then every 12 weeks.
• You will be asked about your child’s health and medicines.
• Your child will have a physical examination.
• Your child will have about 1-2 teaspoons (3-12 mL) of blood drawn at visits during the first 12 weeks and about 2-5 teaspoons (9-24 mL) drawn at later visits. Different HIV-related tests will be done across visits; tests of the amount of HIV in the blood will be done at each visit.
• If the amount of HIV in the blood rises to detectable levels, you will be contacted to return to the clinic with your child as soon as possible for the test to be repeated.

If HIV is detected in your child’s blood on two tests in a row, your child will enter Step 4 (as described below) and start taking ARVs again. Otherwise, your child will remain in Step 3, not taking ARVs, until he or she reaches 5 years of age.

STEP 4 (Child Re-Starts ARVs)

Step 4 Entry
• You will be asked about your child’s health and medicines.
• Your child will have a physical examination.
• Your child will have about 2 teaspoons (10 mL) of blood drawn for safety tests and other HIV-related tests, including the amount of HIV in the blood.
• You will be instructed to start giving ARVs to your child again. As needed, you will be provided ARVs for your child and instructions on how to give them to your baby. [Note to sites: same as above.]

Step 4 Visits
At Weeks 1 and 3, you will be contacted by phone and asked about your child’s health and medicines. Between Weeks 2 and 12, your child will have 6 visits (every 2 weeks). The visits then change to every 12 weeks until your child reaches 5 years of age.
• You will be asked about your child’s health and medicines.
• Your child will have a physical examination.
• Your child will have about 1-2 teaspoons (5-10 mL) of blood drawn at visits during the first 12 weeks and about 1-4 teaspoons (5-20 mL) drawn at later visits. Different safety and HIV-related tests will be done across visits; tests of the amount of HIV in the blood will be done at each visit.

• As needed, you will be provided ARVs for your baby and instructions on how to give them to your baby. [Note to sites: same as above.]

GENETIC TESTING
Some of the blood tests done for this study will look at how your baby’s genes (DNA) affect his or her response to HIV and ARVs. The researchers will not contact you or your baby’s regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important information for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s blood used for genetic testing. Your baby can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s blood to be used for genetic testing, including future genetic testing, as part of this study.

____________ Yes  ____________ No  ______________ Date

STORAGE OF BLOOD FOR FUTURE USE

For NICHD Sites:
Some of your baby’s blood drawn for this study will be stored for testing at a later date as part of this study. This blood may be stored and tested at special laboratory facilities in the US and other countries outside of [insert site country]. There is a separate consent form to explain this and get your consent.

For NIAID Sites:
Some of your baby’s blood drawn for this study will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. Up to about 5 teaspoons (25 mL) of blood will be drawn for this purpose.
Your baby’s samples will be stored and tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facility will also have access to your baby’s samples to keep track of them. These people won’t have information that directly identifies your baby. Your baby’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your baby’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your baby’s samples will be stored.

The researchers will not contact you or your baby’s regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your baby’s health care. However, if the researchers decide that a result is important information for your baby’s health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your baby’s samples stored for future research. Your baby can still be in this study even if you make this decision. You may also withdraw consent for storage and future use of your baby’s samples at any time. If you withdraw your consent, the stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my baby’s blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

_________ Yes  __________ No  ________ Date

HOW MANY BABIES WILL BE IN THIS STUDY?
About 54 babies are expected to take part in Steps 2, 3, and 4 of this study.

HOW LONG WILL BABIES BE IN THIS STUDY?
Babies will be in Step 2 of this study for at least 6 months and up to 4 years. Babies who qualify for Steps 3 and 4 will be in the study through 5 years of age.

WHY WOULD THE DOCTOR TAKE YOUR BABY OFF THIS STUDY EARLY?
The study doctor may need to take your baby off the study early without your permission for the reasons listed below. If this happens, no further information will be collected and no further study visits or laboratory tests will be done.
- Your baby does not have HIV infection.
- Your baby stops coming to the clinic for the study visits.
- The study doctor determines that further participation would be harmful to your baby’s health or well-being.
Your baby is not eligible to stay in Step 2 after 6 months because the amount of HIV in the blood does not drop to undetectable levels or does not stay undetectable.

Your baby is not eligible to enter Step 3 after 4 years in Step 2.

The study is cancelled by the IMPAACT network, the National Institutes of Health, the Office for Human Research Protections, the US Food and Drug Administration, the site’s Institutional Review Board (IRB) or Ethics Committee (EC), or other governmental agencies. An IRB/EC is a committee that watches over the safety and rights of research participants.

WHAT ARE THE RISKS OF THE STUDY?

Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur. The blood tests can also be done by heel stick. Heel stick test may cause some discomfort, bleeding, or bruising at the site of the heel stick. There is a small risk of an infection at the site of the heel stick.

Babies in Step 2 and Step 4 of this study will be given ARVs. In Step 2, babies will be given a combination of four ARVs, including lopinavir/ritonavir, nevirapine, and two other ARVs chosen by your baby’s doctor. Usually three ARVs are given to HIV-infected babies, but four ARVs will be given in Step 2. Also, in the first two weeks of Step 2, nevirapine will be given at a higher dose than usual. This dosing may have more side effects. Some of the possible side effects of lopinavir/ritonavir and nevirapine are listed below. These are the serious or common side effects that have a known or possible relationship with lopinavir/ritonavir and nevirapine. These are not complete lists of all side effects. The study staff will discuss these with you. They will also tell you about the side effects of other ARVs your baby will be given. Please ask the study staff any questions you may have about ARVs and their possible side effects.

**Lopinavir/Ritonavir (LPV/r, KALETRA™)**

AbbVie

The following serious side effects are associated with the use of lopinavir/ritonavir:

- Abnormal heart rhythm and electrocardiogram (EKG) changes. These changes can lead to serious heart problems. The risk for these problems may be higher if your baby:
  - Already has a history of abnormal heart rhythm or other types of heart disease
  - Take other medicines that can affect the heart rhythm while taking lopinavir/ritonavir
  If your baby develops abnormal heart rhythm he or she may experience lightheadedness, fainting spells or an abnormal heart beat.
- Pancreatitis (inflammation of the pancreas), which may cause death. If your baby develops pancreatitis, he or she may have one or more of the following: stomach pain, nausea, vomiting or abnormal pancreatic function blood tests
- Increases in triglycerides and cholesterol in the blood
Liver problems and worsening liver disease, which may result in death. People with these conditions may have abnormal liver function blood tests. If your baby is developing liver problems, he or she may have yellowing of the skin or whites of your eyes, dark urine, pain on the right side of your stomach, loss of appetite, upset stomach or vomiting, pale colored stools, and/or itchy skin.

- Rash, which could blister, and may be severe or life-threatening. Contact the study staff if your baby develops a rash.

Additional side effects may include:
- Abnormal bowel movements (stools), including loose or watery stools, upset stomach and stomach pain
- Feeling weak and tired
- Headache

Lopinavir/ritonavir is a type of ARV called a protease inhibitor. In addition to the side effects listed above, protease inhibitors may be associated with development of diabetes or worsening of high blood sugar. There have been reports of increased bleeding in HIV-infected persons with hemophilia who were treated with protease inhibitors. It is not known if the protease inhibitors were the cause of the increased bleeding.

Nevirapine (NVP, Viramune®)
Boehringer Ingelheim Pharmaceuticals, Inc.

The following serious side effects have been associated with the use of nevirapine:

Severe liver damage that can result in death may occur and is often associated with a rash. People who have abnormal liver function tests before starting nevirapine and people with active Hepatitis B or C infection are also at higher risk for liver damage.

If your baby is developing liver damage, he or she may have one or more of the following:
- Tiredness
- General feeling of illness or flu-like feeling
- Loss of appetite
- Nausea
- Pale stools
- Dark urine
- Yellowing of the skin or whites of your eyes
- Liver tenderness or abnormal liver function tests

Hypersensitivity reactions (“allergic reaction”) may occur. These reactions are rarely fatal. The symptoms that your baby may have are rash, fever, tiredness, muscle or joint aches, flu-like feeling, blisters, mouth sores, facial swelling, red eyes and irritation of the eyes, general feeling of discomfort, and/or liver damage described above, kidney problems, and/or changes in white blood cell levels.
Muscle break down causing muscle aches or pain has been observed in some people experiencing skin and/or liver reactions associated with nevirapine.

Rash is the most common side effect associated with nevirapine. Most rashes occur early during treatment. The rash may be severe and rarely may cause death.

The risk of developing any of the serious side effects listed above is greatest during the first few months of treatment, but these side effects also can occur later. If your baby develops any of the side effects listed above, no matter how long he or she has been receiving nevirapine, you must contact the study staff right away and before you give your baby the next dose. The study doctor will instruct you on what to do next. If you and your doctor then decide to stop your baby’s treatment because of liver damage, hypersensitivity or severe skin reactions, your baby should never take nevirapine again.

In addition to the serious side effects listed above, additional side effects include:
- Fever
- Headache
- Upset stomach (nausea, vomiting)

Stopping ARVs (Treatment Interruption)
Babies in Step 3 of this study will stop taking ARVs. The risk associated with this is that the amount of HIV in the blood may rise again to detectable levels. This could also lead to the HIV in your baby’s body becoming resistant to ARVs. To avoid this, tests will be done to check for HIV in your baby’s blood and ARVs will be started again if HIV becomes detectable.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to your baby. Information learned from this study may help others who have HIV. This study may also help control the amount of HIV in your baby’s body.

WHAT OTHER CHOICES DOES YOUR BABY HAVE BESIDES THIS STUDY?
You may choose to not allow your baby to take part in this study. You may take your baby out of this study at any time. Please talk to the study staff about other choices available to your baby. Whether or not you choose to allow your baby to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF YOUR BABY IS INJURED?
If your baby is injured as a result of being in this study, your baby will be given immediate treatment for the injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.
WHAT ABOUT CONFIDENTIALITY?

US sites:
Efforts will be made to keep your baby’s personal information confidential but we cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

To help us protect your baby’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about your baby or your baby’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your baby’s study records may be reviewed by the Office for Human Research Protections, Food and Drug Administration, National Institutes of Health, site IRB/EC (insert name of site IRB/EC), study staff, study monitors, and drug companies supporting this study, and their designees.

Sites outside the US:
Efforts will be made to keep your baby’s personal information confidential. We cannot guarantee absolute confidentiality. Your baby’s personal information may be disclosed if required by law. Any publication of this study will not use your baby’s name or identify your baby personally.

Your baby’s study records may be reviewed by the US Office for Human Research Protections, US Food and Drug Administration, US National Institutes of Health, (insert other local regulatory and/or government authorities if applicable), site IRB/EC (insert name of site IRB/EC), study staff, study monitors, and drug companies supporting this study, and their designees.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your baby’s study visits, examinations, or blood tests. [Note to sites: This statement can be modified as needed for your site.]
Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your baby is taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE YOUR BABY’S RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose not to allow your baby to take part in this study or take your baby out of the study at any time. Your decision will not have any impact on your baby’s participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which your baby is otherwise entitled.

If you choose to take your baby out of the study, the study staff will ask you to bring him or her back for a final visit. This visit will take about 1 hour and include answering questions about your baby’s health and medicines and a physical exam. About 1-2 teaspoons (5-10 mL) of blood will be drawn for HIV-related tests.

We will tell you about new information from this or other studies that may affect your baby’s health and welfare, or your willingness for your baby to stay in this study. If you want to learn the results of the study when they are available, please let the study staff know.

WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your baby’s rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to allow your baby to take part in this study, please sign your name below.

Participant’s Name (print)

Parent or Legal Guardian Name (print)          Parent or Legal Guardian Signature          Date

Study Staff Conducting Consent Process Name (print)          Study Staff Signature          Date

Witness Name          Witness Signature          Date
APPENDIX IV-C

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS
CLINICAL TRIALS GROUP (IMPAACT)

SAMPLE INFORMED CONSENT
MOTHER

P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission:
A Phase I/II Proof of Concept Study
Version 1.0, dated 12 March 2014

INTRODUCTION
You are being asked to take part in this research study because you have tested positive for the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and your baby may also be infected with HIV. This study is sponsored by the National Institutes of Health. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to participate, we want you to know about the study. This is a consent form. It gives information about the study. The study staff will talk with you about this information. You are free to ask questions at any time.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out if starting anti-HIV medicines (ARVs) within 48 hours of birth can make it possible for babies who are infected with HIV to control HIV so well that HIV cannot be detected in their blood. As of now, when children with HIV start taking ARVs, they usually need to keep taking them for life. For newborn babies who start ARVs very soon after birth, it might be possible to later stop taking ARVs and still stay healthy. This has only been seen in one baby so far. This study is being done to find out if this can be seen in other babies who start anti-HIV medicines very soon after birth. This study is also looking at the levels of ARVs that are safe and work well for babies.

Although this study is focusing on babies, mothers’ participation is also important. This form gives information about study participation for mothers. You will also be given information about study participation for babies. If you choose to take part in the study with your baby, you will be asked to sign this form and a separate form for your baby. You will be offered copies of the forms to keep.

WHAT DO I HAVE TO DO AS PART OF THIS STUDY?
You must agree to take part in this study in order for your baby to take part. The amount of time you will be in this study and the number of visits you will have depends on whether your baby is found to be infected with HIV.
• If your baby DOES NOT have HIV, you will have one study visit (the Entry Visit described below).

• If your baby DOES have HIV, you have two visits within 1-2 weeks. You will then have visits every 6 months for as long as your baby is in the study (up to 5 years).

If you agree to take part in the study, your first visit (Entry) will continue today. This visit and all other visits are described below. Each visit will take 1-2 hours.

At the Entry Visit
• You will be asked questions about your health and medicines, including anti-HIV medicines (ARVs).
• Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
• Depending on the information available in your medical record, it may be necessary to do additional HIV tests for the study. A test of the amount of HIV in your blood will also be done. About 1 teaspoon of blood (3-5 mL) will be drawn for this testing. The results of these tests will be given to you.

Within 2 Weeks After Entry
The results of your and your baby’s tests for HIV infection will be known within 2 weeks after you enter the study. If you and/or your baby are not infected with HIV, you will have no further study visits for yourself, but you are asked to return with your baby for his or her Week 2 and Week 4 visits.

If you and your baby are infected with HIV:
• You will be asked questions about your health and medicines, including ARVs.
• Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
• You will have about 5 teaspoons of blood (25 mL) drawn and stored for HIV-related testing to be done in the future. The results of these tests will not be given to you because the tests will be done in the future.

At Visits Every 6 Months
• You will be asked questions about your health and medicines, including ARVs.
• Your medical record will be reviewed and information about your HIV infection and how well your immune system is working will be collected.
GENETIC TESTING
Some of the blood tests done for this study will look at how your genes (DNA) may affect your baby’s response to HIV and ARVs. The researchers will not contact you or your regular health care provider with the results of these tests. This is because these tests are often done with experimental procedures and these results should not be used to make decisions about your health care. However, if the researchers decide that a result is important information for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.

You may decide that you do not want your blood used for genetic testing. You can still be in this study even if you make this decision. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my blood to be used for genetic testing, including future genetic testing, as part of this study.

____________ Yes  ____________ No  ____________ Date

STORAGE OF BLOOD FOR FUTURE USE

For NICHD Sites:
If you and your baby are infected with HIV, some of your blood drawn for this study will be stored for testing at a later date as part of this study. This blood may be stored and tested at special laboratory facilities in the US and other countries outside of [insert site country]. There is a separate consent form to explain this and get your consent.

For NIAID Sites:
If you and your baby are infected with HIV, some of your blood drawn for this study will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. About 5 teaspoons (25 mL) of blood will be drawn for this purpose.

Your samples will be stored and tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facility will also have access to your samples to keep track of them. These people won’t have information that directly identifies you. Your samples will not be sold or directly used to produce commercial products. All proposed research studies using your samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your samples will be stored.

The researchers will not contact you or your regular health care provider with the results of future research tests. This is because research tests are often done with experimental procedures and the results should not be used to make decisions about your health care. However, if the researchers decide that a result is important information for your health care, the study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes of your address and phone number.
You may decide that you do not want your samples stored for future research. You can still be in this study even if you make this decision. You may also withdraw your consent for storage and future use of your samples at any time. If you withdraw your consent, the stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I allow my blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 472 mothers are expected to take part in this study (with their babies).

HOW LONG WILL I BE IN THIS STUDY?
The amount of time you will be in this study depends on whether your baby is infected with HIV. If your baby is not infected with HIV, you will have one study visit. If your baby is infected with HIV, you will be in the study for as long as your baby, up to 5 years.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?
The study doctor may need to take you off the study early without your permission for the reasons listed below. If this happens, no further information will be collected and no further study visits or laboratory tests will be done.

- You and/or your baby do not have HIV infection.
- Your baby meets conditions to leave the study.
- You stop coming to the clinic for study visits.
- The study doctor determines that further participation would be harmful to your health or well-being.
- The study is cancelled by the IMPAACT network, the National Institutes of Health, the Office for Human Research Protections, the US Food and Drug Administration, the site’s Institutional Review Board (IRB) or Ethics Committee (EC), or other governmental agencies.

An IRB/EC is a committee that watches over the safety and rights of research participants.

WHAT ARE THE RISKS OF THE STUDY?
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body. A small blood clot may form at the site where the blood was drawn or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. Lightheadedness and fainting can also occur.
ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
This study may be of no direct benefit to you or your baby. Information learned from this study may help others who have HIV. If your baby is infected with HIV, this study may help control the amount of HIV in your baby’s body.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?
You may choose to not take part in this study. You may leave the study at any time. Please talk to the study staff about other choices available to you. This study does not provide HIV-related care and treatment for mothers. Whether or not you choose to take part in the study, the study staff will tell you about other sources of HIV-related care available to you and your baby.

WHAT HAPPENS IF I AM INJURED?
If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form. [Note to sites: This paragraph may be modified to reflect your institutional policies and procedures, but the statement regarding compensation through the NIH should not be changed.]

WHAT ABOUT CONFIDENTIALITY?
US sites
Efforts will be made to keep your personal information confidential but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Your study records may be reviewed by the Office for Human Research Protections, Food and Drug Administration, National Institutes of Health, site IRB/EC (insert name of site IRB/EC), study staff, study monitors, and drug companies supporting this study, and their designees.
Sites outside the US:
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by the US Office for Human Research Protections, US Food and Drug Administration, US National Institutes of Health, (insert local regulatory and/or government authorities if applicable), site IRB/EC (insert name of site IRB/EC), study staff, study monitors, and drug companies supporting this study, and their designees.

WHAT ARE THE COSTS TO ME?
There is no cost to you for your study visits or blood tests. [Note to sites: This statement can be modified as needed for your site.]

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study. [Note to sites: Language related to insurance can be deleted if it is not relevant to your site.]

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?
Taking part in this study is completely voluntary. You may choose to not take part in this study. However, if you choose to not take part, your baby cannot take part. If you choose to take part, you may leave this study at any time. If you leave the study, your baby can stay in the study, if you agree to that. Your decisions will not have any impact on your participation in other studies conducted by the National Institutes of Health and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want to learn the results of this study when they are available, please let the study staff know.
WHAT SHOULD I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

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<th>Participant’s Name (print)</th>
<th>Participant Signature</th>
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<th>Study Staff Conducting Consent Process Name (print)</th>
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APPENDIX V

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET

When your child joins this NICHD sponsored Study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child’s name.)

Why have a repository?

Researchers can learn a lot from a study, but as time goes by, the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your child’s rights are being protected.

How will my child’s privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The specimens will have a special study code. It will be the same code that is on your child’s information in the NICHD sponsored Study from your child’s interviews and examinations. Again, none of this information will have your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.
Why wouldn’t I find out the results of the research using my child’s specimens?

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my child’s specimens?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.
As part of this study (*P1115: Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV Remission: A Phase I/II Proof of Concept Study*), your child is being asked to have some blood taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.

You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.
TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________
Parent or Legal Guardian Signature

___________________________
Witness Signature

_________
Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________
Participant Signature

___________________________
Witness Signature

_________
Date

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.
Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  __________
Parent or Legal Guardian Signature  Witness Signature  Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  __________
Participant Signature  Witness Signature  Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

___________________________  ___________________________  __________
Parent or Legal Guardian Signature  Witness Signature  Date