PERINATAL CORE PROTOCOL

An IMPAACT Multi-Center Trial

Sponsored by:
The National Institute of Allergy
and Infectious Diseases

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APPENDICES

I. MATERNAL SCHEDULE OF EVALUATIONS

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SUMMARY OF CHANGES FOR P1025
"PERINATAL CORE PROTOCOL" VERSION 4.0, DATED 12/31/07

All changes in this version appear in boldface type. Editorial changes, including corrections of typographical errors and other changes required to update information that does not affect regulatory issues or patient consent may also be included.

Major changes include the following:

1. The team roster was updated.
2. All references to PACTG 219C have been removed since that study is now closed to accrual.
3. References to enrollment of women in PACTG 367 have been removed, since that study is now closed to accrual.
4. Throughout the document “PACTG” was replaced with “IMPAACT” (where appropriate).
5. The projected sample size has been changed from 2400 mother infant pairs to 1600 mother infant pairs, plus an additional 180-240 mother-pairs per year thereafter if continued enrollment is approved by the IMPAACT Scientific Oversight Committee/Network Executive Committee (SOC/NEC), as indicated in the Schema and in Section 6.4 (Sample Size and Accrual).
6. Primary and secondary objectives have been revised in the Schema and in Section 2.
7. Mothers and infants will now be followed for 6 months rather than 12 months postpartum.
8. Enrollment of pregnant women may occur as early as eight weeks gestation (as opposed to 14 weeks gestation).
9. The possibility of co-enrollment in P1025 and the Surveillance Monitoring for Anti Retroviral Therapy Toxicities (SMARTT) study has been added to Section 3.
10. A sentence regarding the evaluation of subjects who are co-enrolled in P1025 and SMARTT was added to Section 4.4 (co-enrollment guidelines).
11. Section 6 (Statistical Considerations) has been revised to reflect modified objectives and sample size.
12. In Appendix I, Maternal Schedule of Evaluations, Abbreviation note B (applicable to hematology, chemistries, and urinalysis evaluations) was added to the top section of the document and reads as follows: “B = Abstract from the medical record the most recent results and all results ≥ Grade 2 since the last study visit. In the case of entry, abstract all results ≥ Grade 2 since the beginning of pregnancy. When greater than 10 results for a
single laboratory test are available that are all related to the same event (i.e., the same period of hospitalization, the same diagnosis, the same toxicity event) report only the first and last results at each reportable grade, and the first normal result afterward. In addition, report any results that lead to a change in ARV regimen.”

13. Maternal viral cultures have been discontinued, except as Standard of Care, as noted in Appendix I (Maternal Schedule of Evaluations): HIV-1 Qualitative PBMC Macroculture Evaluation and corresponding footnotes 13 and 14 were deleted.

14. Ultrasound, Amniotic Fluid Samples, and visits after 6 months postpartum were removed from Maternal Schedule of Evaluations.

15. In Appendix II, Infant Schedule of Evaluations, Abbreviation Notes A, C, and S now specify whether and when evaluations should be abstracted or conducted as part of the study visit.

16. Appendix II has been modified to reflect that infants are now followed for six months, and the neuropsychological evaluations were deleted from the protocol.

17. Appendix III, Amniotic Fluid Processing and Shipping Procedures, was deleted, and replaced by Appendix III, Definitions of HIV Infection Status in Infants.

18. Appendix IV, Part 2, the following sentence has been removed: Appendix IV, Part 2, the following sentence has been removed: “Entry evaluations must be completed within 2 weeks of study enrollment.”

19. Appendix IV, Part 2, language has been added to reflect the possibility of enrollment into future P1025 substudies (other than P1026).

20. Appendix IV, Part 2, language has been changed to reflect that “the randomization system will not be used to determine whether or not women with repeat pregnancies should be approached for co-enrollment”.

21. Appendix VII “Repository Consent Form for NICHD Sites” was added.
SCHEMA

PERINATAL CORE PROTOCOL

DESIGN: Prospective cohort study

SAMPLE SIZE: Primary objective 1 will require ongoing enrollment to provide safety data regarding new antiretrovirals (ARVs) and other interventions, as well as emerging safety issues, and a large sample size to assess rare adverse outcomes and more frequent adverse outcomes in small subgroups of women. The sample size will be 1600 mother-infant pairs, plus an additional 180-240 mother-pairs per year thereafter if continued enrollment is approved by the IMPAACT SOC/NEC.

POPULATION: HIV-infected women who
• are pregnant with a viable intrauterine pregnancy and ≥ 8 weeks gestation, OR
• have delivered a liveborn or stillborn infant and are within 14 days after delivery, OR
• are found to be HIV-infected at the time of labor and delivery or within 14 days after delivery, and their infants.

STUDY DURATION: Women: 6 months postpartum
Infants: 6 months of age

PRIMARY OBJECTIVES:

1. To assess maternal and infant safety of new and existing interventions prescribed for prevention of mother-to-child transmission (MTCT) of HIV and/or women’s health
   a. To address hypotheses pertaining to current and emerging safety issues
   b. To identify areas for focused clinical trials/Data Analysis Concept Sheets (DACS)
   c. To provide safety data to National Institutes of Health (NIH) and Food and Drug Administration (FDA) as requested

2. To assess the effectiveness of interventions prescribed for prevention of mother-to-child transmission (MTCT) and/or for women’s health with regard to immune and viral parameters.
3. To provide a framework and specimen repository for intensive substudies (such as P1026s, pharmacokinetics in pregnancy), New Works Concept Sheets (NWCS), and DACS that aim to further elucidate mechanisms of MTCT of HIV, as well as factors that affect maternal and infant outcomes.

SECONDARY OBJECTIVES:

1. To identify genotypic/phenotypic resistance mutations in HIV-infected mothers according to antiretroviral (ARV) history and to compare resistance genotypes in any mother-infant pairs where transmission occurred.

2. To describe HIV-infected pregnant women and their infants receiving care at IMPAACT sites in terms of clinical, immunological, and virological characteristics; receipt of ARVs; mode of delivery; and MTCT rates.

3. To facilitate the conduct of other relevant trials:
   a. Provide estimates of women with particular characteristics for development of clinical trials to further the MTCT/maternal health research agenda
   b. Referral of infants to available long term follow-up and/or early therapy protocols
   c. Referral of women into appropriate ACTG, IMPAACT, and other trials

4. To further assess adherence to ARVs among HIV-infected pregnant women during pregnancy and postpartum as follows:
   a. Assess the association between rates of adherence and reported clinical toxicities.
   b. Describe rates of new resistance mutations to ARVs received among subjects with high versus low adherence, and determine rates of MTCT of such mutations.
   c. Assess the association of ARV adherence with women's health, mode of delivery and pregnancy outcomes
1.0 INTRODUCTION

1.1 Background and Rationale

Approximately 500-600 cases of MTCT of human immunodeficiency virus type 1 (HIV) now occur annually in the United States. The dramatic reduction in MTCT rates in the United States is related to several factors, including: increased provision and acceptance of voluntary counseling and HIV testing of pregnant women, improvements in the medical management of HIV-infected pregnant women, and the development and increased acceptance of interventions to decrease the risk of MTCT of HIV. Review of transmission data collected by PACTG protocols from different eras show rates of transmission of 22.6% and 7.6% among women receiving no antiretroviral therapy (ARVs) and perinatal zidovudine (ZDV) respectively who were enrolled in ACTG 076 between 1991 and 1994; 4.5% among women who were enrolled into ACTG 185 from 1993 to 1997, all of whom were receiving perinatal ZDV; and 1.7% among women who were enrolled into PACTG 316 from 1997 to 2000, the majority of whom were receiving multiple agent ARV regimens. The proportion of women who delivered by cesarean section before labor and before ruptured membranes increased dramatically over this time period (1991-2000). A reduction in the rate of MTCT of HIV to less than two percent throughout the U.S. is feasible and is close to being achieved. The current low rate of MTCT in the U.S. limits the number and types of questions concerning transmission risk and pathogenesis. However, important questions remain unanswered regarding risk factors for MTCT and why interventions fail, and the safety of interventions for women and their infants.

Specific U. S. Public Health Service (USPHS) guidelines recommend receipt of ARVs during pregnancy appropriate to maximize the health of the woman. However, data regarding the effectiveness and safety of and adherence to ARVs during pregnancy are limited. For example, preliminary analyses of data collected through PACTG 367, Medical Chart Abstraction of HIV-infected Pregnant Women and Their Infants Receiving Care or Consultation at Study Sites, showed that although 94% of women are receiving ARVs by the time of delivery, only 57% of women had undetectable virus at the time of their last antepartum assessment. Although a large number of HIV-infected pregnant women are receiving care at IMPAACT sites, there are no large-scale perinatal clinical trials scheduled to open in the foreseeable future that can address these issues. Also, because of prior experience with ARVs in women known to be HIV-infected prior to pregnancy and relatively late-in-gestation knowledge of infection of those identified to be...
HIV-infected during pregnancy, many women are not candidates for ongoing, smaller Phase I or Phase II trials. Other large multicenter studies that followed HIV-infected pregnant women and their infants prospectively, such as the Women and Infants Transmission Study (WITS) and the Perinatal AIDS Collaborative Transmission Studies (PACTS), have been discontinued. Thus, the P1025 cohort can continue to provide important information about safety, trends in the implementation of interventions for prevention of MTCT of HIV as well as in the prescription of ARVs for maternal health, the safety, virologic and immunologic effects of these interventions, the impact of viral resistance and complications associated with ARVs during pregnancy. In addition, P1025 will be an important source of uninfected infants with detailed maternal ARV exposure data to assess safety and complications of ARVs in infants and for co-enrollment in the SMARTT study.

Although the major mission of IMPAACT has traditionally been to conduct clinical trials, at this time in the epidemic of HIV-infection in childbearing women, it is both appropriate and necessary for IMPAACT to recruit pregnant women into a non-interventional study in order to methodically collect clinical and laboratory data from the women and their infants. In this way, IMPAACT can achieve the important aims of evaluating management of HIV-infected women during pregnancy and determining the safety and effectiveness of ARVs and other interventions intended to prevent MTCT and/or improve maternal health. Furthermore, these data can be analyzed on an ongoing basis to provide important information used not only for the design of clinical trials but also for modification of clinical care.

An abstract on factors affecting maternal adherence to ARVs was presented at the 13th Conference on Retroviruses and Opportunistic Infections in 2006. Three hundred thirty-four (334) out of 445, or 75% of women, reported perfect adherence with ARVs during pregnancy with a decrease in adherence to 64% postpartum. Adherence was higher in women who initiated ARVs during pregnancy, did not have AIDS, did not miss their prenatal vitamins, and did not use marijuana and were not depressed. The P1025 protocol also serves as the data collection tool for P1026s. Combining results from these two protocols is cost saving and provides a mechanism to collect pharmacokinetic data for new drugs or drug combinations used in pregnant HIV-infected women. This has resulted in two important papers which showed that abacavir pharmacokinetics was not affected by pregnancy and that lopinavir exposure during late pregnancy was lower compared to postpartum and non-pregnant control subjects and that only small amounts of lopinavir cross the placenta.
The primary goal of a perinatal core protocol is to enroll pregnant, HIV-infected women receiving prenatal care or who deliver at IMPAACT sites and their children into a study in which clinical and laboratory (virologic, immunologic, and biochemical) data and specimens for repository storage are obtained according to a standardized protocol. It is anticipated that complementary, well-designed substudies will be developed as adjuncts to the standardized core protocol. Longitudinally collected core protocol data and repository specimens will enable completion of core protocol objectives as well as future substudies. Utilizing laboratory results obtained for routine clinical care whenever possible, and using efficient epidemiologic study designs (e.g., case-control studies) for substudies to address research questions of interest, will minimize the cost impact of this protocol.
2.0 OBJECTIVES

2.1 Primary

2.11 To assess maternal and infant safety of new and existing interventions prescribed for prevention of MTCT of HIV and/or women’s health

a. To address hypotheses pertaining to current and emerging safety issues
b. To identify areas for focused clinical trials/DACS
c. To provide safety data to NIH and FDA as requested

Hypotheses

1. The incidence and severity of maternal toxicities (e.g., abnormal glucose metabolism; gastrointestinal symptoms) will differ according to ARV regimens.
2. The incidence of adverse infant outcomes (e.g., low birth weight, preterm birth, anemia, hypoglycemia and liver enzyme abnormalities) will differ according to the in utero, perinatal, and postnatal exposure to ARVs.
3. The incidence of maternal morbidities will differ according to both actual and intended mode of delivery.
4. The incidence of infant morbidities will differ according to both actual and intended mode of delivery.

2.12 To assess the effectiveness of interventions prescribed for prevention of MTCT and/or for women’s health with regard to immune and viral parameters.

Hypotheses

1. The maternal virologic and immunologic responses to ARVs are associated with:
   a. What ARVs were prescribed (specific drugs, doses, routes, duration of therapy)
   b. What ARVs were received (tolerance and adherence)
   c. Specific history of receipt of ART prior to index pregnancy
   d. When ARVs were initiated (before or during pregnancy; if during pregnancy, at what gestational age)
   e. Maternal disease stage (as assessed clinically, immunologically and virologically)
f. Other maternal characteristics

Definition of virologic response will be:

For women with detectable peripheral blood viral loads prior to initiation or change in ARV regimen:

1. After initiation of ARVs, or change in ARV regimen, the proportion who achieve peripheral blood viral loads below the lower level of detection (according to the assay performed) within 2-8 weeks, 12-16 weeks and every 3-4 months subsequently.
2. After initiation of ARVs or change in ARV regimen, the log decrease in peripheral blood viral load after 2-8 weeks and 12-16 weeks.
3. The proportion of women with undetectable viral load at delivery.

For women with undetectable peripheral blood viral loads at the beginning of pregnancy:

1. The proportion with peripheral blood viral loads remaining below the lower level of detection during the second and third trimester, at delivery, and throughout the postpartum follow-up period.
2. Time to development of detectable peripheral blood viral load.

For women with undetectable peripheral blood viral loads at delivery:

1. The proportion with peripheral blood viral loads remaining below the lower level of detection throughout the postpartum follow-up period.

Definition of immunologic response will be:

1. Increases in CD4+ cell count and percent, to be assessed each trimester, at delivery and throughout the postpartum period.

To provide a framework and specimen repository for intensive substudies (such as P1026s, pharmacokinetics in pregnancy), New Works Concept Sheets (NWCS), and Data Analysis Concept Sheets (DACS) that aim to further elucidate mechanisms of MTCT of HIV, as well as factors that affect maternal and infant outcomes.

Hypotheses

See Appendix V
2.2 Secondary

2.21 To identify genotypic/phenotypic resistance mutations in HIV-infected mothers according to ARV history and to compare resistance genotypes in any mother-infant pairs where transmission occurred.

2.22 To describe HIV-infected pregnant women and their infants receiving care at IMPAACT sites in terms of clinical, immunological, and virological characteristics; receipt of ARVs; mode of delivery; and MTCT rates.

2.23 To facilitate the conduct of other relevant trials:
   a. Provide estimates of women with particular characteristics for development of clinical trials to further the MTCT/maternal health research agenda
   b. Referral of infants to available long term follow-up and/or early therapy protocols
   c. Referral of women into appropriate ACTG, IMPAACT, and other trials

2.24 To further assess adherence to ARVs among HIV-infected pregnant women during pregnancy and postpartum as follows:
   a. Assess the association between rates of adherence and reported clinical toxicities.
   b. Describe rates of new resistance mutations to ARVs received among subjects with high versus low adherence, and determine rates of MTCT of such mutations.
   c. Assess the association of ARV adherence with women’s health, mode of delivery and pregnancy outcomes

3.0 STUDY DESIGN

P1025 is a prospective cohort study that provides a framework for collection and evaluation of data and collection of repository specimens from HIV-infected pregnant and postpartum women and their infants. All HIV-infected women who are ≥ 8 weeks gestation with a viable intrauterine pregnancy and intend to continue the pregnancy, or have delivered a liveborn or stillborn infant and are within 14 days after delivery, or are found to be HIV-infected at the time of labor and delivery or within 14 days after delivery, will be eligible for enrollment. Women will be followed until six months postpartum, regardless of the outcome of the pregnancy (e.g. miscarriage, spontaneous abortion). Infants will be followed for six months in P1025. Pre-entry assessment
may be conducted as early as 8 weeks of gestation. At the time of study enrollment, evidence of HIV infection will be required. Women who are substance abusers are eligible for enrollment, as are women enrolled into IMPAACT or ACTG studies that do not otherwise disallow coenrollment. At the time of study enrollment, women will be informed of all data collection to be performed on themselves and their infants, will confirm willingness to be followed for study visits at an IMPAACT or collaborative site for the duration of the study, and will sign informed consent for her participation and the participation of her infant.

P1025 is designed to enroll a large representative sample of pregnant HIV-infected women who receive care at IMPAACT and collaborating sites. The annual accrual at the sites will be restricted (capped) according to site resources, the number of HIV-infected pregnant women at the site, and NICHD/NIAID recommendations. It is anticipated that most sites will be able to meet the targeted accrual level for P1025. In order to achieve the accrual goals of the protocol, accrual will be closely monitored by the P1025 protocol team (see Section 6.6). The accrual cap for each site will be reviewed every six months by the P1025 team, and will be subject to adjustment based on the site’s ability to accrue more or less than the cap, actual accrual, and the number of sites participating in P1025. All sites will use the IMPAACT randomization system to randomly select which women should be approached for participation in P1025. Details and exceptions are discussed in Section 4.3 and Appendix IV. Whenever possible, PACTG 367 data will be used to augment the data available from P1025 for data analysis.

All participating sites will be asked to keep an enrollment log of all HIV-infected pregnant women receiving prenatal care at the site. The enrollment log will collect limited grouped data on women at the time when they first present for prenatal care (see Section 4.3 Enrollment Procedures). In most cases, this information is routinely collected by the sites. The enrollment log also will collect reasons for non-enrollment in P1025. Grouped data from the enrollment log will be submitted to the Statistical Data Management Center (SDMC) each calendar quarter. The enrollment log data constitute an important component of the prospective cohort study design, and will be used to: (i) enumerate and broadly characterize the population of HIV-infected pregnant women seen at each site; (ii) compare the group-level characteristics of women who participate in P1025 to the characteristics of women who receive care at the sites but do not participate in P1025, to assess potential selection bias.

To address the study objectives, the core protocol will rely heavily upon abstraction of medical records from routine clinical care supplemented by focused patient interviews and laboratory assessments (See Appendix I). Medical records will be abstracted to obtain data concerning medical history, physical examination, and laboratory studies conducted as part of clinical care. Specifically, supplemental data concerning ARV use, adherence to medications, and review of
symptoms relevant to side effects and toxicities will be collected through administration of questionnaires. At study visits, phlebotomy will be conducted in order to obtain specimens for a repository. Further details of maternal and infant study visits follow.

**Women (See Appendix I, Maternal Schedule of Evaluations)**

There will be a maximum of 10 study visits for women from the time of entry and enrollment through 12 months postpartum. **Women enrolled between ≥ 8 and <14 weeks gestation will complete the entry evaluation separate from the 14-20 week antenatal visit.** Ideally, study visits taking place from enrollment through the 6 week postpartum visit will take place at the same time as a regularly scheduled clinical visit, in order to maximize efficiency of study participation for the woman. The number of antepartum study visits will be determined by the gestational age at the time of enrollment. The maximum number of antepartum visits including the entry visit will be four. These visits will take place a minimum of 4 weeks apart, during windows to correspond to 14-20 weeks of gestation, >20-30 weeks of gestation, and >30 weeks of gestation to delivery. Entry requirements may be completed along with the antepartum visit requirements at the woman’s first antepartum visit, or with the labor and delivery visit requirements. Postpartum study visits will take place at 6 weeks ± 4 weeks, and then at 12 and 24 weeks ± 8 weeks with a minimum of 4 weeks between visits through 6 months postpartum.

All study visits will include questionnaire administration for adherence assessment, medical record abstraction, and the collection of biological specimens. The enrollment study visit will collect baseline data relevant to the woman’s sociodemographics, and complete medical and obstetrical history, including all laboratory test results available since the beginning of pregnancy. Subsequent study visits will collect interval data. All visits will include assessment of adherence through previously designed questionnaires. At a minimum, biological specimens will consist of blood samples designated for storage at a central repository. In general, laboratory evaluations will be abstracted from the medical chart and should not be performed as study procedures. At limited time points (entry, labor and delivery, and 6 months postpartum), HIV RNA and lymphocyte subsets will be obtained as a study procedure only if results are not available through medical chart review within the specified timeframe for the study visit.

At labor and delivery, we will encourage that placentas be sent to clinical pathology laboratories, and will request copies of all placental reports.

Adherence will be assessed by utilizing forms for adherence to medication that have been previously validated and are utilized in the ACTG ALLRT study. In addition, there will be supplemental forms to collect predictors of adherence during the antepartum and postpartum time period. The perinatal adherence form was devised by the Adherence Subcommittee and
approved by the Community Constituency Group. Although this form has not been validated, it is a modification of an adherence form used in PACTG 377 that has been validated for use in children and adolescents.

Infants (See Appendix II, Infant Schedule of Evaluations)

There will be a 7 day window for the infant delivery visit. Data for this protocol will be abstracted from the infant’s medical record at the time of birth and at each postnatal visit. Laboratory test results obtained for routine clinical care will be abstracted from the infant’s medical record whenever possible. A glucose level by heel stick or venipuncture (glucometer reading or Dextrostick) will be required prior to first feeding.

Infants will have data collected for P1025 for 6 months. Infants who are co-enrolled in P1025 and SMARTT will require P1025 visits through 6 months of age as specified in the P1025 infant visit schedule.
4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Age ≥ 13 years

4.12 HIV-infected women who
- are ≥ 8 weeks gestation with a viable intrauterine pregnancy and who intend to continue the pregnancy, or
- have delivered a liveborn or stillborn infant and are within 14 days after delivery, or
- are found to be HIV-infected at the time of labor and delivery or within 14 days after delivery, and receive care at IMPAACT and other collaborative sites, and their infants.

4.13 Evidence of HIV infection as documented by one of the following:
- Previous enrollment into an ACTG or IMPAACT treatment protocol.
- Two different, appropriate tests.
  Appropriate tests can include ELISA confirmed by an appropriate test (e.g., Western blot), bDNA, DNA PCR, RNA PCR, or a positive culture for HIV from blood or CSF.
  Appropriate evidence of HIV infection for women enrolled at the delivery visit may include a rapid test confirmed either by another rapid test or another test as described above within 14 days.
- Historical data. If source documentation is not available, repeat ELISA with confirmatory Western blot is acceptable.

4.14 Women who are enrolled into P1025 (or were previously enrolled in P1025) and have a subsequent pregnancy are eligible for re-enrollment into P1025 according to the enrollment procedures as outlined in Section 4.3.

4.15 Women who are substance abusers are eligible.

4.16 Women who are enrolled into other IMPAACT or ACTG studies that do not prohibit coenrollment are eligible for coenrollment.

4.17 Willingness to be followed at an IMPAACT or collaborative site for the duration of the study.
4.18 Women who are mentally capable of giving informed consent for their own and for their infant’s health care.

4.19 Signed informed consent from the subject or guardian for her participation and the participation of her infant. For emancipated minors, local IRB regulations will apply.

4.2 Exclusion Criteria

4.21 Intent to terminate pregnancy.

4.22 Inability to complete entry evaluations within 14 days after delivery (if woman known to be HIV-infected prior to delivery) or within 28 days after delivery (if woman found to be HIV-infected at the time of labor and delivery or within 14 days after delivery).

4.3 Enrollment Procedures

An approved site implementation plan (SIP) is required for participation in P1025. The SIP will collect the following information from each site (including sub-sites).

- Annual number of HIV-infected pregnant women, who receive prenatal care and/or deliver at the site, who are eligible for the study.
- Annual number of HIV-infected pregnant women the site deems they have sufficient resources to enroll in the protocol.
- Percentage of women expected to refuse participation in the protocol when approached for participation.

The site implementation plan will be reviewed and approved by members of the protocol team, and sites will be notified by e-mail that authorization to participate has been granted. This authorization is required to complete protocol registration for all sites.

The annual accrual at the sites will be restricted (capped) according to site resources, the number of HIV-infected pregnant women at the site, and NICHD/NIAID recommendations. It is anticipated that most sites will be able to meet the targeted accrual level for P1025. In order to achieve the accrual goals of the protocol, accrual will be closely monitored by the P1025 protocol team (see Section 6.6). The accrual cap for each site will be reviewed every six months by the P1025 team, and will be subject to adjustment based on the site’s ability to accrue more or less than the cap, actual accrual, and the number of sites participating in P1025. Sites may be queried concerning any changes in the number of eligible women receiving care at the site, the number of women the site has the resources
to enroll, the number of women who refuse study participation, and the preferred allocation of enrollment slots among the site’s subunits.

All sites will be required to use the IMPAACT randomization system to randomly select which women should be approached for participation in P1025 (see Appendix IV for Detailed Enrollment Procedures). Exceptions to the randomization process include:

- Women who are eligible and consent for the P1026s substudy, but are randomized not to be approached for P1025. These women may be enrolled in both P1026s and P1025, over and beyond the P1025 accrual cap. However, these women cannot be enrolled in P1025 until consent for P1026s participation is obtained.

- Women who are eligible and consent for future P1025 substudies (other than P1026), but are randomized not to be approached for P1025. These women may be enrolled in both the substudy and P1025. Whether the enrollment will be over and beyond the P1025 accrual cap or will count toward the P1025 accrual cap will be determined at the time of substudy approval and specified in the substudy protocol. These women cannot be enrolled in P1025 until consent for substudy participation is obtained.

- Women who are perinatally HIV-infected, but are randomized not to be approached for P1025. These women may be enrolled, but will still count toward the P1025 accrual cap.

- Women who are identified as HIV-infected at labor and delivery (or within 14 days after delivery), but are randomized not to be approached for P1025. These women may be enrolled, but will still count toward the P1025 accrual cap.

- Women with repeat pregnancies occurring during the six month postpartum follow-up period or after completion of P1025 follow-up. These women will not be re-randomized and may be re-enrolled into P1025, provided that the inclusion/exclusion criteria are met, but will still count toward the P1025 accrual cap.

Women should be enrolled in P1025 as early as possible during pregnancy (with the exception of women who will be enrolled in both P1025 AND P1026s, or a future substudy as noted above). Women may be screened and enrolled as early as 8 weeks of gestation. Women who are diagnosed as HIV-infected at the time of labor and delivery (or within 14 days after delivery) may be enrolled up to 28 days after delivery.

4.31 Enrollment Log

The process of enrollment to P1025 requires the site’s maintenance of a log of all HIV-infected pregnant women who receive care at the site (whether or not they
are eligible for or eventually participate in P1025). The enrollment log will collect limited grouped data on women at the time they first present for prenatal care: age (e.g. categories: 13-19, 20-24, 25-29, 30-35, >35 years), race/ethnicity, history of ARV use (e.g. categories: ARV naïve or experienced), and trimester of gestation at first visit to the site. The enrollment log will also collect reasons for non-participation in P1025, including:

- Patient refusal (e.g. reasons: time, distance, concerns about confidentiality, mistrust in research, participation in a conflicting protocol, concerns about specimen collection);
- Patient not available/could not be reached for consent and potential enrollment;
- Approach Screening Procedure did not select a patient to be approached for P1025 participation;
- Other.

The site will be required to submit grouped summary data for each calendar quarter (i.e., the total number of women in each category of each characteristic collected in the log) to the IMPAACT Data Management Center.

4.4 Co-enrollment Guidelines

Co-enrollment in other IMPAACT or ACTG protocols and in the SMARTT study is permitted, with the approval of both Protocol Chairs. Co-enrollment in perinatal trials in other networks should be documented on the appropriate case report form. However, subject identifiers for the other trials will not be collected.

Blood specimen drawing priority tables will be developed for P1025 and each protocol approved for coenrollment with P1025. These tables will assign highest priority to those samples that are gestational age, visit, or time dependent (e.g., PK samples or samples to be drawn only in fasting state).

5.0 ADVERSE EXPERIENCE REPORTING

The Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences (August, 1992), the DAIDS Toxicity Table for Grading Severity of Pediatric Adverse Experiences for Children > 3 months of age (April 1994) and the DAIDS Toxicity Table for Grading Severity of Pediatric Adverse Experiences for Children ≤ 3 months of age (November 1993) will be used to report adverse events (AE) in this protocol.
Because this is an observational study, Serious Adverse Experiences (SAEs) are not required to be submitted to the Regulatory Compliance Center Office. However, any treatment-related SAE or Grade 2, 3, or 4 AE must be documented on the appropriate CRF.

For abnormalities NOT found on the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1 Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
GRADE 2 Moderate: Mild to moderate limitation in activity – some assistance may be needed; minimal or no medical intervention/therapy required
GRADE 3 Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4, which may be life-threatening: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

All Grade 2, 3, and 4 adverse events and deaths will be recorded on study CRFs, with the exception of those events listed below. All Grade 3 and 4 AEs and deaths for both mothers and infants, and all Grade ≥ 1 neurological events in infants, must be further evaluated via study CRFs. Further evaluation will entail the answering of additional questions, on the CRFs, to more fully assess the nature of the events.

The following signs and symptoms for mothers must be reported on the study CRFs only after they reach the following grades:

Nausea, constipation, headache and fatigue: ≥ Grade 3.
Hypertension and proteinuria ≥ Grade 2 to be recorded for all occurrences prior to 20 weeks gestation. After 20 weeks gestation, record only if it is clear that the diagnosis of preeclampsia has been excluded.

6.0 STATISTICAL CONSIDERATIONS

6.1 General Design and Methodological Issues

The Perinatal Core Protocol is a prospective cohort study designed to enroll a large representative sample of pregnant HIV-infected women who receive perinatal care at the IMPAACT sites. No protocol specific treatment or other intervention is provided as part of this study. The study involves the follow up of HIV-infected women enrolled during
pregnancy or at the time of delivery to six months postpartum, and their infants during the first six months of life. The primary objectives of the protocol focus on assessing the safety and virologic/immunologic effects of interventions prescribed for prevention of MTCT and for women’s health. Another major objective of the Perinatal Core Protocol is to collect data and specimens to permit the conduct of focused substudies and DACS/NWCS investigating virologic and immunologic response to ARVs, pharmacokinetics, and pathogenesis of MTCT of HIV.

The prospective cohort study design was chosen because it is the design of choice for investigating multiple outcomes, describing their incidence, and monitoring trends over time in treatment and other interventions prescribed for prevention of MTCT. The prospective cohort study design also provides the opportunity to measure accurately and completely various risk factors and potential confounders before the outcomes are observed. In addition, this design will provide a framework for conducting efficient epidemiological (e.g. case-control) sub-studies to address specific questions related to, for example, pathogenesis of HIV transmission or safety of a particular ARV regimen. Finally, the observational study design was chosen because, for clinical and ethical reasons, it is unlikely that the important remaining questions can be addressed by randomized clinical trials, as discussed in the Background/Rationale section.

As described in the Study Design, Section 3.0, the annual accrual at the sites will be restricted (capped) proportional to the number of HIV-infected pregnant women who receive care annually at the site. Selection bias may arise if all eligible patients are not enrolled at a site, and each site selects which patients to enroll on the basis of characteristics that are related to the exposure and outcome of interest. To minimize possible selection bias, the IMPAACT randomization system will be used at the sites to randomly select which women will be approached for participation in P1025, according to a site-specific allocation ratio (described in Section 6.3). To obtain results representative of the entire IMPAACT population, some analyses will require weighting the results for sites by their respective allocation ratio and exclusion of women who were randomized not to be enrolled in P1025 but enrolled anyway because of one of the exceptions listed in Section 4.3.

To further prevent possible selection bias, every attempt should be made to offer enrollment to P1025 to women as soon as they reach 8-14 weeks of gestation, and retain them on study through the entire six-month postpartum follow-up. In addition, it is essential to minimize the rates of non-response and refusal to participate, so that the descriptive findings in our study population concerning the frequency of MTCT or certain morbidities are valid. High rates of non-participation among selected eligible women may
seriously distort the observed prevalence of the outcome, if the outcome itself is associated with non-participation. For example, if women who are less adherent to ARVs also are less likely to participate, the rates of MTCT may be underestimated. Furthermore, in the data collection stage, it will be important that identical methods (in terms of timing and intensity) are used for assessment of toxicities and morbidities for all mother-infant pairs, regardless of mode of delivery or maternal ARV regimen, to ensure that excess of these events in any subgroup of patients is not due to detection bias.

As with any non-randomized study, an association that is identified between an outcome measure and another variable, such as a subject characteristic or response to therapy, may arise due to confounding with other variables. Of particular concern is the non-random assignment of the interventions (such as ARVs and mode of delivery) during pregnancy. For example, an apparent association that is identified between MTCT and actual mode of delivery may really be due to differences in other variables, such as HIV viral load, CD4 count, and prior ARV use, among women who delivered by cesarean section before labor and before ruptured membranes compared with those who delivered vaginally and those who delivered by other cesarean section. Analyses will attempt to limit the effect of confounding by adjusting for important variables.

Women who become pregnant more than once while P1025 is open to accrual may be enrolled in P1025 for each pregnancy as noted in Section 4.3. This will result in clustered observations, since the data collected from different pregnancies of the same woman are likely to be correlated. The level of clustering is expected to be relatively low based on the WITS experience (approximately 15% of all WITS subjects later enroll again for a subsequent pregnancy). Nonetheless, the clustering may make it inappropriate to use standard statistical methods, which typically assume that the observations are statistically independent (and therefore uncorrelated). To ensure valid findings, analyses will be repeated with all pregnancies included and with only one pregnancy per women included (e.g., the first, or a randomly selected pregnancy), and statistical methods that correctly handle clustered observations will be used as appropriate.

6.2 Outcome Measures

6.2.1 For Primary Objective 2.11:

Hypothesis 1: Maternal toxicities possibly associated with receipt of ARVs during pregnancy.

a. Abnormal glucose loading test
b. Diagnosis of gestational diabetes
c. All toxicities of ≥ Grade 2 with the following exceptions:
   i. Nausea: ≥ Grade 3
   ii. Constipation: ≥ Grade 3
   iii. Headache: ≥ Grade 3
   iv. Fatigue: ≥ Grade 3
   v. Hypertension and proteinuria ≥ Grade 2 to be recorded for all occurrences prior to 20 weeks gestation. After 20 weeks gestation record, only if it is clear that diagnosis of preeclampsia has been excluded.

Hypothesis 2: Adverse neonatal outcomes possibly associated with in utero or perinatal exposure to ART.
   a. Stillbirth ≥ 20 weeks gestation
   b. Neonatal (in the first 28 days of life) death
   c. Low birth weight categorized as <2500 g and <1500 g
   d. Preterm birth categorized as <37 weeks and <32 weeks.
   e. Inappropriate size for gestational age, categorized as either SGA (<10 percentile) or LGA (>90 percentile)
   f. Hypoglycemia ≥ Grade 3 according to the parameters in the DAIDS toxicity table for infants ≤ and > 3 months of age
   g. Liver enzyme abnormalities ≥ Grade 3
   h. Anemia, leukopenia, neutropenia, or platelet count ≥ Grade 3 according to the DAIDS toxicity table for infants ≤ and > 3 months of age
   i. Congenital anomalies and structural abnormalities will be recorded and tabulated
   j. Potential mitochondrial toxicities will be evaluated with the screening tool, and review of data recorded on other CRFs
   k. Other adverse pregnancy/neonatal outcomes

Hypothesis 3: Postpartum morbidities possibly associated with mode of delivery.
   a. Standard febrile morbidity (puerperal fever, fever without a source)
   b. Infections, to include abdominal or perineal wound, endometritis, bacteremia, urinary tract infection, septic pelvic thrombophlebitis
   c. Hemorrhage requiring a surgical procedure or transfusion
   d. Other complications to include thromboembolic disease
   e. Gastrointestinal complications including ileus and antibiotic-associated colitis
   f. Length of stay
   g. Re-hospitalization within one month of delivery
Hypothesis 4: Infant morbidities possibly associated with mode of delivery.

a. Respiratory morbidity - defined by use of assisted ventilation or positive pressure, and categorized as transient tachypnea with respiratory rate > 60/min and requiring oxygen by mask for at least 12 hours, or respiratory distress syndrome, or aspiration/chemical pneumonitis by physician diagnosis and/or X-ray, or persistent pulmonary hypertension.

b. Length of stay adjusted for gestational age and comorbidities.

c. Infectious morbidity including pneumonia, bacteremia, meningitis, urinary tract infection

d. Preterm birth categorized as < 37 weeks and < 32 weeks

e. Admission to the NICU

f. Anemia ≥ Grade 2

g. Neonatal trauma (e.g., hematoma, lacerations, fractures).

6.22 For Primary Objective 2.12:

Hypothesis 1: Definition of Virologic Response

For women with detectable peripheral blood viral loads prior to initiation or change in therapy:

a. After initiation of ARVs or change in ARV regimen, the proportion who achieves peripheral blood viral loads below the lower level of detection (according to the assay performed) within 2-8 weeks, 12-16 weeks and every 3-4 months subsequently.

b. After initiation of ARVs or change in ARV regimen, the log decrease in peripheral blood viral load after 2-8 weeks and 12-16 weeks of therapy.

c. The proportion of women with undetectable viral load at delivery.

For women with undetectable peripheral blood viral loads at the beginning of pregnancy:

1. The proportion with peripheral blood viral loads remaining below the lower level of detection during the second and third trimester, at delivery, and throughout the postpartum follow-up period.

2. Time to development of detectable peripheral blood viral load.

For women with undetectable peripheral blood viral loads at delivery:
1. The proportion with peripheral blood viral loads remaining below the lower level of detection throughout the postpartum follow-up period.

Definition of immunologic response will be:

Increases in CD4+ cell count and percent, to be assessed each trimester, at delivery and throughout the postpartum period.

6.23 For Primary Objective 2.13:
See Appendix V for examples.

6.24 For Secondary Objective 2.21
a. First maternal viral genotype/phenotype obtained during pregnancy and last viral genotype/phenotype obtained during pregnancy, analyzed according to:
   • timing of diagnosis of HIV infection
   • receipt of ARVs prior to pregnancy (immediately prior to pregnancy and during previous pregnancies) and
   • receipt of ARVs during pregnancy
   • Site of enrollment
b. Maternal viral genotype/phenotype obtained during first six months postpartum, analyzed according to:
   • Type and duration of ARV use during pregnancy
   • ARV use postpartum
c. Viral genotype for drug resistance obtained from first positive HIV DNA/RNA sample on infants and any positive maternal HIV RNA plasma repository specimens during pregnancy, at delivery, or postpartum.
d. Any positive viral genotypes/phenotypes clinically obtained during pregnancy.

6.25 For Secondary Objective 2.22:
a. Clinical: CDC HIV disease classification, timing of HIV diagnosis, and gestational age at first prenatal visit
   Immunological: CD4 cell counts and percents
   Virological: viral load
b. ARV use before pregnancy, antepartum, and intrapartum

c. Mode of delivery: Vaginal, cesarean section with no membrane rupture and no labor, cesarean section with membrane rupture or labor

d. Infant HIV infection status (refer to Appendix III, Definitions of HIV Infection Status in Infants)

6.26 For Secondary Objective 2.23: Enrollment of women in IMPAACT, ACTG, and other studies

6.27 For Secondary Objective 2.24:
Adherence to ARVs
a. Percentage of doses taken over preceding three days
Other measures from the adherence module

6.3 Randomization and Stratification

All eligible subjects will be randomized to determine whether the woman should be approached for enrollment into P1025 (as described in Section 4.3 and Appendix IV). The allocation ratio for each site (i.e., ratio of women randomized to be approached vs. not approached) will be chosen based on the accrual cap assigned by the P1025 team, the number of eligible women seen by the site, and the patient refusal rate. There will be no further randomization at the time of enrollment into P1025 and no stratification of subjects.

6.4 Sample Size and Accrual

The sample size required to address each primary objective varies considerably and depends on several factors, including the prevalence or incidence of the outcomes of interest, the size of the effects to be detected, the subpopulation of interest (e.g., ARV-naïve), the number of groups to be compared, and the number of confounders to be controlled. Primary objective 1, to assess the safety of interventions, will require the largest sample size if it is desired to assess rare adverse outcomes or more frequent adverse outcomes in small subgroups of women, and will require ongoing enrollment to provide data on new interventions and emerging safety issues. To address this objective, we propose to enroll 1,600 mother-infant pairs, with the possibility of further extending the enrollment period by decision of the

Prevention of Mother-to-Child Transmission Scientific Committee (PMTCT SC), Scientific Oversight Committee (SOC), and Network Executive Committee (NEC). The protocol team will monitor accrual on a regular basis (see section 6.6), and accrual will also be monitored by the IMPAAACT leadership according to standard operating procedures. At least six months before accrual is projected to reach 1,600 mother-infant pairs, the protocol team will make a recommendation to the PMTCT SC and SOC/NEC about whether the enrollment period should be extended.

Estimates of feasible accrual rates to the Perinatal Core Protocol during IMPAACT can be based upon past accrual rates to this study. As of the end of May 2007, a total of 1,209 mother-infant pairs had been enrolled to the Perinatal Core Protocol. In 2005 and 2006, the mean monthly accrual was 28 mother-infant pairs per month (median 27, range 18-38). In January-May 2007, after several NIAID sites were defunded and stopped enrolling, the monthly accrual to the Perinatal Core Protocol was 28, 22, 22, 21, and 19 mother-infant pairs, respectively. It is difficult to project the accrual rate going forward, because continuing NIAID sites are in the process of reassessing staffing levels in light of reduced funding and NICHD site funding levels after November 1, 2007 are not yet known. However, an average monthly accrual rate of 15-20 mother-infant pairs per month (180-240 per year) seems achievable. At this rate, the total number of mother-infant pairs enrolled to the study would reach 1,600 mother-infant pairs between January and August, 2009, and an additional 180-240 mother-infant pairs per year could be enrolled thereafter if approved by the IMPAAACT SOC/NEC.

In discussing the differences that could be detected with the projected accrual rates, we first focus on the hypotheses regarding adverse outcomes, which will require the largest sample sizes to address. We have calculated the smallest effect (measured as the odds ratio for the increase in event rate among women or infants exposed to an intervention compared with the event rate in women or infants who are not exposed) that could be detected at 80% power for a range of event rates and group sizes, allowing for up to 7% of subjects being non-evaluable (see Table 1). These calculations were performed using PASS 2002 software (Number Cruncher Statistical Systems, Kaysville, UT) for calculating the sample size needed to compare a proportion between two groups, using the continuity correction. Note that in Table 1, one would want the minimum detectable odds ratio to be as small as possible, i.e., to be able to detect as small an increase in the risk of an adverse event as possible. The minimum detectable odds ratio gets smaller as the sample size increases. The column for N=1,613 (1,500 evaluable) indicates the smallest
odds ratios that would be detectable based on the target sample size of 1,600 mother-infant pairs.

Table 1. Detectable Effects at 80% Power, Assuming Exposure to an Intervention is Associated with Increased Risk

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<th>Event Rate in Unexposed</th>
<th>Percent of Population in Unexposed Group</th>
<th>Minimum Detectable Odds Ratio (OR) for Exposed vs. Unexposed</th>
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For example, we plan to assess whether protease inhibitor (PI) use during pregnancy is associated with an increased risk of preterm birth (<37 weeks gestation) compared with PI-sparing regimens. Approximately two-thirds of women enrolled in P1025 have been exposed to a PI during pregnancy and most of the remaining women have not received a PI during pregnancy. Overall in P1025, the rate of preterm birth is approximately 14%. If the rate of preterm birth among women who did not receive a PI were approximately 10%, then we would need to refer to the row in Table 1 for a 10% event rate and 30% of women unexposed. Table 1 indicates that an overall sample size of 1,500 evaluable women (with approximately 450 evaluable PI-unexposed and 1050 evaluable PI-exposed) would provide 80% power to detect an odds ratio of 1.65. This odds ratio would correspond to a 55% increase in the risk of preterm birth, from 10% among PI-unexposed women to 15.5% among PI-exposed women.
Note that not all P1025 subjects may be included in all analyses of interest. For example, we may wish to restrict our analysis to subjects receiving ARV regimens with a PI, and within this subgroup compare subjects receiving nelfinavir to those not receiving nelfinavir. In this case, if the total cohort size were N=1,500 evaluable women, but 67% were on HAART with a PI, then we would need to refer to the detectable differences presented under the column headed N=1,000 evaluable (i.e., 67% of 1,500). If the preterm birth rate among nelfinavir-unexposed women were 10%, the detectable odds ratio would be 1.83 (i.e., a 64% increase in the risk of preterm birth, from 10% to 16.9%).

Table 1 presents the minimum detectable odds ratios at 80% power assuming that exposure increases the risk of an event. The odds ratios range from 1.3 to 2 for more common events (occurring in ≥20% of unexposed subjects), from 1.4 to 2.2 for less common events (5-10% event rates, with at least 30% in each exposure group), and from 2.6 to 8.7 for rare events. It is in this latter category that we would need the largest sample size to evaluate associations with specific exposures of interest.

For example, we plan to assess whether there is an association between signs of possible mitochondrial dysfunction and in utero exposure to lamivudine (3TC) or ZDV/3TC during pregnancy. If approximately 90% of infants are exposed to 3TC or ZDV/3TC during pregnancy and approximately 1% of unexposed infants have signs of possible mitochondrial dysfunction, Table 1 indicates that with 1,500 evaluable mother-infant pairs, the detectable odds ratio would be 6.44, which corresponds to an increase in the rate of signs of possible mitochondrial dysfunction from 1% among unexposed infants to 6.1% among exposed infants.

One of the most important goals of P1025 is to provide data on the safety of individual ARVs during pregnancy. A recent review of ARV use in pregnancy among the 1,154 women who enrolled in P1025 as of March 31, 2007 revealed that a significant number of women had received tenofovir (135 women), newer fixed ARV combinations (Truvada®: 95 women; Trizivir®: 246 women; Epzicom®: 33 women), efavirenz (57 women), nevirapine (168 women), and lopinavir/ritonavir (309 women), as well as other newer PIs such as atazanavir (103 women). To illustrate the ability to estimate the incidence of adverse events among women who received a specific ARV during pregnancy, we have calculated the precision (width) of the confidence interval for the incidence of abacavir hypersensitivity according to the number of women exposed to abacavir (allowing for up to 10% being non-evaluable) if the true (unknown) incidence of abacavir hypersensitivity
were between 4% and 8%. With a sample size of 100-150 women, the width of the 95% confidence interval would be approximately +/-3.3-5.3% if the true incidence were 4-8%. Also, if no cases of abacavir hypersensitivity reaction were observed with sample sizes of 100, 150, and 200 women, the upper limit of the exact 95% confidence interval (actually a one-sided 97.5% confidence interval) would suggest that an incidence >4%, >2.7%, and >2.0%, respectively, is unlikely.

Table 2: Width of 95% confidence interval for the incidence of abacavir hypersensitivity reaction according to sample size and true incidence rate

<table>
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<tr>
<th>Sample Size*</th>
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<tr>
<td></td>
<td>4%</td>
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<tr>
<td>50</td>
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<tr>
<td>100</td>
<td>**</td>
</tr>
<tr>
<td>150</td>
<td>+/-3.3%</td>
</tr>
<tr>
<td>200</td>
<td>+/-2.9%</td>
</tr>
</tbody>
</table>

*Total number of women enrolled, with allowance for up to 10% of women being non-evaluable.

**Sample size too small for convergence. The precision for these cases can be illustrated using the exact 95% confidence interval corresponding to the observed incidence, which would be 0.5-13.7%, 1.3-16.5%, and 1.1-9.9% if the observed incidence were 2/50, 3/50, and 4/100, respectively.

Similarly, Table 3 shows the width of the 95% confidence interval for more frequent adverse events (true incidence between 10% and 90%). Table 3 indicates that the confidence interval gets wider (less precise) as the true incidence rate increases. With a sample size of 100-150 women exposed to a specific ARV, reasonably precise estimates are possible regardless of the true incidence rate (the width of the 95% confidence interval would be between +/-5% and +/-10%).
Table 3: Width of 95% confidence interval for the incidence of an adverse event among women who received a specific ARV

<table>
<thead>
<tr>
<th>Sample Size*</th>
<th>10% or 90%</th>
<th>20% or 80%</th>
<th>30% or 70%</th>
<th>50%</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>+/-8%</td>
<td>+/-11%</td>
<td>+/-12%</td>
<td>+/-14%</td>
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<td>100</td>
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<td>150</td>
<td>+/-5%</td>
<td>+/-7%</td>
<td>+/-8%</td>
<td>+/-9%</td>
</tr>
<tr>
<td>200</td>
<td>+/-4%</td>
<td>+/-6%</td>
<td>+/-7%</td>
<td>+/-7%</td>
</tr>
</tbody>
</table>

*Total number of women enrolled, with allowance for up to 10% of women being non-evaluable.

The numbers of pregnant women required to study the hypotheses regarding toxicities and morbidities that are not rare (hypotheses 2.11.1-2.11.4), and virologic and immunologic response to therapy (hypotheses 2.12.1), are generally much smaller than the sample size required to assess rare adverse outcomes. For these hypotheses, we provide illustrative calculations to indicate approximately how many subjects will be needed.

Hypothesis 2.11.1: To detect a difference of 20% vs. 30% in the incidence of an abnormal glucose loading test with PI-sparing vs. PI-containing ARV regimen, a total of 696 women (313 evaluable per group, after allowing for 10% non-evaluable) would be required for 80% power (with 2-sided alpha=.05).

Hypothesis 2.11.2: Anemia is of concern with nucleoside ARV use and hypoglycemia is of concern with PI use. In the PACTG 076 placebo group, 8% of the infants experienced grade 2 or worse anemia within the first 6 weeks of life. A sample size of 392 infants (356 evaluable, after allowing for 10% non-evaluable) would be required to detect an incidence of 12% anemia (a 50% increase above the baseline incidence) with 80% power (two-sided alpha=.05). The incidence of hypoglycemia is expected to be <1% among infants born at term (>37 weeks gestation) to mothers who did not have gestational diabetes. If the baseline risk is assumed to be 0.5%, a sample size of 157 such infants (142 evaluable, after allowing for 10% non-evaluable) would be required to detect an incidence of 3% hypoglycemia with 80% power (two-sided alpha=.05).

Hypothesis 2.11.3: Among PACTG 367 deliveries from July 1999 through February 2000, 50% of deliveries were vaginal, 35% were cesarean sections before labor and before ruptured membranes, and 15% other cesarean sections. Assuming this distribution of mode of delivery, and assuming the risk of any maternal morbidity is 6% with vaginal delivery, 15% with cesarean sections before labor and before ruptured membranes, and 20% after delivery, the total number of women needed to study rare outcomes (hypotheses 2.11.1-2.11.4) is calculated as follows:

- Vaginal delivery: 696 women (313 evaluable per group, after allowing for 10% non-evaluable)
- Cesarean sections before labor and before ruptured membranes: 102 women (92 evaluable, after allowing for 10% non-evaluable)
- Other cesarean sections: 55 women (49 evaluable, after allowing for 10% non-evaluable)

Total: 853 women (754 evaluable, after allowing for 10% non-evaluable)
membranes and 30% with other cesarean section, a sample size of 873 (786 evaluable, after allowing for 10% non-evaluable) would be required for 80% power (for three pair wise comparisons using two-sided alpha = .017, which is the Bonferroni correction to yield an overall two-sided alpha = .05).

Hypothesis 2.11.4: Current recommendations from ACOG are that elective cesarean section is performed between 39 and 40 weeks of gestation. Recommendations for HIV-infected parturients are to perform elective cesarean sections between 38 and 39 weeks of gestation to decrease the chances for spontaneous labor. According to Morrison et al\textsuperscript{15}, the relative risk of neonatal respiratory morbidity after delivery by cesarean section before the onset of labor during week 39 compared to week 38 is 2.4, supporting the hypothesis of an association of respiratory morbidity and cesarean section before the onset of labor in HIV-infected women. According to Levine et al\textsuperscript{16}, the relative risk of respiratory morbidity comparing cesarean section to vaginal delivery is 3.3, while according to Morrison, the relative risk for respiratory morbidity in elective cesarean section compared to non-elective cesarean section and vaginal delivery was 2.9 and 6.8, respectively. Baseline rates for respiratory morbidity in these studies are 0.53–1.4%. If it is assumed that the intended mode of delivery will be trial of labor for 60% of women and scheduled cesarean section for 40% of women and that 85% of pregnancies go to term (≥37 weeks gestation), a total of 864 mother-infant pairs (778 evaluable, after allowing for 10% non-evaluable) would be required to detect a difference of 1% vs. 5% in the risk of respiratory morbidity among term infants with 80% power (with 2-sided alpha = .05).

Hypothesis 2.12.1: Data from PACTG 367 (deliveries from January 1, 1998 through February 2000) can be used to illustrate the sample sizes needed to assess differences in virologic response to PI-sparing vs. PI-containing ARV regimens. Of the PACTG 367 participants whose first plasma viral load during pregnancy was >1,000 copies/ml and who had a second plasma viral load measurement recorded 4-8 weeks later, 25% had a plasma viral load <1,000 copies/ml at the second measurement. To detect a difference of 20% with PI-sparing vs. 30% with PI-containing ARV regimens, a total of 696 women (313 evaluable per group, after allowing for 10% non-evaluable) would be required for 80% power (with 2-sided alpha = .05) to detect a difference of 86.5% having a plasma viral load <1,000 copies/ml with PI-sparing vs. 93.5% having a plasma viral load <1,000 copies/ml with PI-containing ARV regimens. However, if the subpopulation of interest for this comparison were the approximately 40% of P1025 participants who were not on ARVs when they became pregnant (whether ARV-naive or experienced) and did not require ARVs for their own health (i.e., had first antenatal plasma viral load <100,000 copies/ml and CD4+ cell count >350
cells/mm$^3$), the overall sample size for P1025 would need to be 1,750 women in order to have approximately 700 women in this subpopulation of interest.

6.5 Evaluation of Hypotheses

This section briefly describes how each of the primary hypotheses will be evaluated, including the population for analysis, the planned analyses, and potential limitations. A detailed analysis plan will be prepared for each individual analysis before it is started (and after team approval of a manuscript proposal as described in section 6.6).

In the interest of brevity, this section does not describe how each analysis will handle the clustering due to multiple pregnancies per woman. Section 6.1 describes the general approach that will be used to handle this clustering and each individual analysis plan will discuss the specific approach to be used for that analysis.

6.51 Maternal and infant safety of interventions (e.g., ARVs and mode of delivery) (Hypotheses 2.11.1-2.11.4).

Population for analysis: All HIV-infected pregnant women and their infants.

Analysis and potential limitations: Exact statistical methods based on the binomial distribution will be used to give 95% confidence intervals for the incidence of maternal toxicities (any toxicity and toxicities of specific grades) and adverse neonatal outcomes according to type of ARVs (e.g., PI sparing vs. PI containing regimens). Exact 95% confidence intervals will also be calculated for the incidence of maternal and infant morbidities according to actual mode of delivery (e.g., vaginal delivery, cesarean section before labor and before ruptured membranes, and other cesarean section) and intended mode of delivery (intended trial of labor, intended scheduled cesarean section). Comparisons of toxicities among ARV groups and morbidities among mode of delivery groups will be performed using the chi-square test or Fisher’s exact tests for rare outcomes.

Most likely, there will be no suitable comparison group of women who do not receive ARVs. Consequently, while it will be possible to compare the prevalence of maternal toxicities and adverse neonatal outcomes according to major ARV groups, it may not be possible to distinguish whether some toxicities and outcomes are associated with ARVs or with HIV disease.
Overall analyses for all available mother-infant pairs, and stratified analyses according to infant HIV infection status will be conducted. Moreover, mothers who do and do not transmit HIV to their infants may differ in terms of potential confounders such as tobacco, alcohol, or intravenous drug, history of ARVs and prior toxicities. It will be important to consider these factors and other potential confounders, (e.g., gestational age and maternal diabetes when evaluating neonatal hypoglycemia) in evaluations of the frequency of maternal and infant toxicities and morbidities according to ARVs and mode of delivery. In the case of more frequent morbidities, it will be possible to adjust for major confounders using logistic regression models.

6.52 Virologic and immunologic responses of women to ARVs during pregnancy and postpartum (Hypothesis 2.1.1).

Populations for analysis: Separate analyses will be conducted for HIV-infected pregnant women with detectable peripheral blood viral loads prior to initiation or change of therapy in pregnancy, and for women with undetectable peripheral blood viral loads at the beginning of pregnancy or at delivery.

Analysis and potential limitations: For women with detectable HIV RNA viral load measures prior to initiation or change of therapy, the proportions who achieve undetectable viral load measures within 2-8 weeks and 12-16 weeks of initiation of therapy, at delivery, and postpartum will be assessed according to type of ARV regimen, adherence level, baseline viral load, and other factors of interest. Multivariate logistic regression analysis will be used to identify clinical and sociodemographic factors associated with achieving undetectable viral load after initiating therapy. The average log change in plasma viral load at 2-8 weeks and within 12-16 weeks of therapy will be also assessed in univariate analyses stratified by clinical and sociodemographic characteristics. Regression analyses, including mixed effects models and generalized estimating equations, will be used to analyze within individual changes in plasma viral loads over time during pregnancy and the postpartum period.

For women with non-detectable plasma viral loads at the beginning of pregnancy, the proportions with undetectable plasma viral loads at each trimester will be assessed, according to clinical and sociodemographic factors of interest. In addition, the time to development of detectable virus will be assessed.
using methods for failure time data, such as Kaplan-Meier estimates, logrank tests, and proportional hazards’ models.

Analyses of change in plasma viral load and CD4 count will be limited to women who have at least one plasma viral load measurement and CD4 count available before and after the receipt of therapy, or before and after delivery. Characteristics of women with and without the requisite plasma viral load and CD4 measurements will be compared to assess the potential for bias due to missing data. If appropriate, statistical methods that attempt to account for informative missingness will be used.

In studying the effects of initiation of ARVs on maternal health, it will be important to account for the fact that women with more advanced HIV disease and potentially worse clinical prognosis may also receive more aggressive ARV regimens. Consequently, the response to potent ARV regimens may be underestimated. Multivariate analyses will attempt to adjust for various clinical factors associated with indications for ARVs. In particular, adjustment for confounding using a disease severity index (comprised of various clinical indicators) will be explored.

6.6 Monitoring and Analyses

This study does not involve any protocol specific treatment interventions. Therefore, no formal monitoring by the Data and Safety Monitoring Board is required.

Accrual and retention will be monitored by the IMPAACT leadership in accordance with standard operating procedures. In addition, monthly accrual reports will be circulated to the protocol team by e-mail. If after January 2008 (allowing time for newly funded NICHD sites to begin enrollment, and NIAID sites to adjust to their Year 2 funding), the average monthly accrual rate over a consecutive three-month period drops below 15 mother-infant pairs per month, the protocol team will identify the reasons for lack of accrual and possibly amend the protocol.

As discussed in Sections 3.0 and 4.3, the accrual cap for each site will be reviewed by the P1025 team every six months and will be subject to adjustment based on the site’s ability to accrue more or less than the cap, actual accrual, and the number of sites participating in P1025. The sites will provide information collected in the enrollment log to SDMC on a quarterly basis. The summary log data will be used to compare group
characteristics of HIV-infected pregnant women at the sites who do not enroll in P1025 to the characteristics of women enrolled in P1025, and to assess potential selection bias.

Every three months a monitoring report including information on reasons for non-enrollment, baseline demographics, trends in ARV use, rates of MTCT of HIV, accrual and loss to follow-up will be produced and distributed to the study team for discussion on team calls. Data and specimen completeness also will be assessed regularly. Surveillance reports of maternal and infant adverse events will be prepared and circulated every six months for discussion on team calls. Details will be specified in a separate P1025 protocol monitoring plan, which will be updated as needed.

Once per year, the SDMC will assess the number of subjects available to address the various hypotheses. Analyses of the major research hypotheses will be timed to occur when the appropriate, projected sample size has been accrued and data has been entered and cleaned. Before a study is undertaken to address a P1025 objective or new objective, a detailed study design will be prepared and sent to the P1025 team for review as described in the guidelines for P1025 manuscript proposals (see the P1025 protocol-specific web page on the IMPAACT web site). P1025 data will be analyzed and reported in a manner that will ensure the integrity of ongoing randomized treatment trials.

7.0 HUMAN SUBJECTS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

7.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix VI), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The mother must give written informed consent for herself and her baby's participation in the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the mother.

7.2 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 NIAID.

7.3 **Study Discontinuation**

The study may be discontinued at any time by the NIAID or the IMPAACT.

8.0 **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.

9.0 **BIOHAZARD CONTAINMENT**

As the transmission of HIV and other bloodborne 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.
10. REFERENCES


**APPENDIX I**

**MATERNAL SCHEDULE OF EVALUATIONS***

A = Abstract from the medical record all results available since the last study visit. In the case of entry, abstract all results available since the beginning of pregnancy. Do NOT perform as a study procedure.

B = Abstract from the medical record the most recent results and all results ≥ Grade 2 since the last study visit. In the case of entry, abstract all results ≥ Grade 2 since the beginning of pregnancy. When greater than 10 results for a single laboratory test are available that are all related to the same event (i.e. the same period of hospitalization, the same diagnosis, the same toxicity event) report only the first and last results at each reportable grade, and the first normal result afterward. In addition, report any results that lead to a change in antiretroviral therapy.

C = Lymphocyte subsets and plasma HIV RNA concentration (HIV viral load) data are routinely obtained at sites as standard of clinical care and therefore abstractable from the medical record. However, if these data are not collected as standard of care or are otherwise unable to be abstracted, lymphocyte subsets and plasma HIV RNA concentration (HIV viral load) must be obtained at 1025 entry (regardless of gestational age), L&D visit, and the 6 month postpartum visit. In the case of entry, abstract all results available since the beginning of pregnancy.

X = Perform as a study procedure

R = Recommended, not required

<table>
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<th>LABOR/DELIVERY</th>
<th>POST PARTUM</th>
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* No evaluations are required if the subject discontinues study prematurely.
APPENDIX I (Cont.)

1. **Subjects may enter the study as early as 8 weeks gestation.** Entry evaluations must be completed within 14 days of study enrollment. Entry evaluations must be completed within 14 days after delivery for women known to be HIV infected prior to delivery. For women diagnosed within 14 days after delivery (either through maternal or infant testing), entry evaluations must be completed within 28 days after delivery. **If someone is enrolled between 8 and 14 weeks of gestation the entry visit must be separate from the 14 - 20 week scheduled antepartum visit.**
   
   Antepartum: These visits will take place a minimum of 4 weeks apart. Only 1 visit per gestational age window is required.
   
   L&D: Evaluations must be completed within 14 days after delivery.
   
   Postpartum: The maximum time interval for the 6 week postpartum evaluation is +/- 4 weeks. For postpartum evaluations ≥ 3 months (12 weeks), +/- 8 weeks.

2. **Height at baseline, then track weight.**
   
   Concomitant medications: ARVs, prophylaxis and/or treatment of HIV related complications, blood products and transfusions, antibiotics, medications to treat other medical problems
   
   Assessment of HIV disease: diagnoses and CDC category
   
   Obstetrical history: all events, diagnoses, medications. Record ‘ongoing’ only at the final visit.
   
   Prior history of antiretroviral therapy.

3. **Recommends reporting to the Antiretroviral Pregnancy Registry, at entry and at 6 weeks postpartum.**

4. **Hematology:** CBC with differential, platelets. For women coenrolled in P1026s: hematology is required if not done clinically (refer to P1026s protocol for laboratory requirements).

5. **Chemistries:** AST, ALT, and lactate. Also abstract lipase and amylase if on ddI, ddC, or d4T. If any chemistry values were abnormal during pregnancy, abstract all values done during pregnancy and all postpartum values. For women coenrolled in P1026s: chemistries are required if not done clinically (refer to P1026s protocol for laboratory requirements).

6. **Dipstick urine for protein only during pregnancy.** Obtain microscopic urinalysis antepartum and postpartum only if woman on indinavir or atazanavir. For women coenrolled in P1026s: urinalysis is required if not done clinically.

7. **1 hour, 50 gm glucose loading test (1 hour diabetes screen, glucola test); collect all values available in medical record.**

8. **Abstract all positive results for Hepatitis A (antibody, PCR); Hepatitis B (antibody, antigen, PCR, genotype) and/or Hepatitis C (antibody, RIBA, Hep C RNA PCR, genotype) obtained during pregnancy since the last reporting interval.**
APPENDIX II
INFANT SCHEDULE OF EVALUATIONS

Note: If results are available in the medical record, abstract all results available since the last study visit, or in the case of the first study visit at which the evaluation is required, abstract all results available since birth. No evaluations are required if the subject discontinues prematurely.

X = Not infected or indeterminate status
I = HIV-infected
A = Abstract from the medical record all results available since the last study visit. At the first study visit where this evaluation is required, abstract all results available since birth. Do NOT perform as a study procedure.
C = Obtain ONLY if not done as part of clinical care and cannot be abstracted from the medical record at some time within the visit window. At the first study visit where this evaluation is required, abstract all results available since birth.
S = Perform as a study procedure

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**CLINICAL EVALUATIONS**

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<tbody>
<tr>
<td>PE (including neurologic)</td>
<td>X/I</td>
<td>X/I</td>
<td>X/I</td>
<td>X/I</td>
<td>X/I</td>
</tr>
<tr>
<td>Quality of Life Assessment</td>
<td>X/I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence Module</td>
<td>X/I</td>
<td>X/I</td>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LABORATORY EVALUATIONS**

<table>
<thead>
<tr>
<th>Hematology</th>
<th>X/I C - 0.25 ml</th>
<th>X/I C 0.25 ml</th>
<th>X/I C 0.25 ml</th>
<th>X/I C 0.25 ml</th>
<th>X/I C 0.25 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistries</td>
<td>X/I C 1.0 ml / 1.5 ml</td>
<td>X/I C 1.0 ml / 1.5 ml</td>
<td>X/I C 1.0 ml / 1.5 ml</td>
<td>X/I C 1.0 ml / 1.5 ml</td>
<td>X/I C 1.0 ml / 1.5 ml</td>
</tr>
<tr>
<td>Serum glucose</td>
<td>X/I S - .25 ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>X/I A</td>
<td>X/I A</td>
<td>X/I A</td>
<td>X/I A</td>
<td>X/I A</td>
</tr>
</tbody>
</table>

**IMMUNOLOGY**

<table>
<thead>
<tr>
<th>Lymphocyte Subsets</th>
<th>X/I A</th>
<th>X/I A</th>
<th>X/I A</th>
</tr>
</thead>
</table>

**VIROLOGY**

<table>
<thead>
<tr>
<th>HIV DNA PCR</th>
<th>X/I A</th>
<th>X/A</th>
<th>X/A</th>
<th>X/A</th>
<th>X/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA PCR</td>
<td>I A</td>
<td>I A</td>
<td>I A</td>
<td>I A</td>
<td>I A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stored Cells and Plasma</th>
<th>X/I (2 ml)</th>
<th>X/I (2 ml)</th>
<th>X/I (2 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Blood Volumes: Uninfected or Indeterminate (X)</td>
<td>X/I 0.25 ml / .25 ml</td>
<td>X/I 1.25 ml / 1.75 ml</td>
<td>X/I 3.25 ml / 3.75 ml</td>
</tr>
<tr>
<td>Infected (I)</td>
<td>X/I 3.25 ml / 3.75 ml</td>
<td>X/I 1.25 ml / 1.75 ml</td>
<td>X/I 3.25 ml / 3.75 ml</td>
</tr>
</tbody>
</table>
* For infants born to women identified as HIV-infected within 14 days of delivery, begin infant evaluations according to the closest scheduled infant visit.
APPENDIX II (Cont.)

1. Window of time: Birth to 7 days of life (ideally within the first 3 days of life).
2. Include labor and delivery record.
3. Include weight, length, head circumference, vital signs. Record birth weight at earliest infant visit.
4. See Neurological Assessment/Quality of Life Assessment documents on the P1025 website
5. Hematology: CBC with differential and platelets.
6. Chemistries: Glucose, AST, and ALT for all infants through 6 months of age. For INFECTED infants, through six months of age, add electrolytes, glucose, BUN, creatinine, bilirubin (total and direct), lipase, albumin, total protein, triglycerides, cholesterol, CPK and amylase.
7. Serum glucose: Serum glucose should be obtained by heelstick glucometer or test strip prior to first feeding and exact value recorded. If initial check by test strip is abnormal or an exact value is not obtained, obtain a serum sample and the low glucose should be promptly treated with intravenous or oral feeding.
8. If mother is positive for Hepatitis C antibody and/or Hepatitis RNA PCR, abstract any positive or negative viral diagnostic Hepatitis C data for the infant.
9. Abstract DNA PCR at every time point throughout the period of study follow-up. If any DNA PCR test is positive, confirm with either positive repeat DNA PCR or RNA PCR >10,000 copies/ml done in a commercial laboratory. Obtain real time HIV culture, done in ACTG certified lab, as soon as possible. Note: The final HIV infection status (infected or uninfected) of each infant should be determined (and reported to P1025 database) by 6 months of age, based on Appendix III.
10. If DNA PCR is positive at birth, genotype should be done from stored specimen. Contact the protocol virologist for specific instructions.

NOTE: Study visit window is at least ± 1 week at the 2 week visit, and should be at least 7 days from the previous visit. Windows for subsequent visits are: ± 2 weeks at 6 weeks and 4 months, and ± 4 weeks at 6 months
APPENDIX III
DEFINITIONS OF HIV INFECTION STATUS IN INFANTS

In a child less than 18 months of age, a case of HIV infection must meet at least one of the following criteria:

a. **Laboratory Criteria**

   **Definitive**

   - Positive results on two separate specimens (excluding cord blood) using one or more of the following HIV virologic tests:
     - HIV nucleic acid (DNA or RNA) detection
     - HIV p24 antigen test, including neutralization assay, in a child ≥ 1 month of age
     - HIV isolation (viral culture)

   **Presumptive**

   A child who does not meet the criteria for definitive HIV infection but who has:

   - Positive results on only one specimen (excluding cord blood) using the above HIV virologic tests and no subsequent negative HIV virologic or antibody tests

   **OR**

b. **Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met)**

   - Diagnosis of HIV infection, based on the laboratory criteria above, that is documented in a medical record by a physician

   **Or**

   - Conditions that meet criteria included in the CDC 1987 pediatric surveillance case definition of AIDS
2. A child less than 18 months of age born to an HIV-infected mother will be categorized as “HIV-uninfected” if the child does not meet the criteria for HIV infection but meets the following criteria:

   a. Laboratory criteria

      Definitive

      - At least two negative HIV antibody tests from separate specimens obtained at greater than or equal to 6 months of age
      
      Or

      - At least two negative HIV virologic tests from separate specimens, both of which were performed ≥ 1 month of age and one of which was performed at ≥ 4 months of age

      AND

      No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition)

      Or

      Presumptive

      A child who does not meet the above criteria for definitive ‘HIV-uninfected’ status but who has:

      - One negative EIA HIV antibody test performed at ≥ 6 months of age and NO positive HIV virologic tests, if performed

      Or

      - One negative HIV virologic test performed at ≥ 8 weeks of age and NO positive HIV virologic tests, if performed

      Or

      - Two negative HIV virologic tests performed at ≥ 2 weeks of age and ≥ 4 weeks of age

      Or

      - One positive HIV virologic test with at least two subsequent negative virologic tests, at least one of which is at ≥ 8 weeks of age; or negative HIV antibody test results, at least one of which is at ≥ 6 months of age.
APPENDIX III
(continued)

AND

• No other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition).

OR

b. Clinical or Other Criteria (if the above definitive or presumptive laboratory criteria are not met)

• Determined by a physician to be ‘uninfected’, and a physician has noted the results of the preceding HIV diagnostic tests in the medical record.

AND

• NO other laboratory or clinical evidence of HIV infection (i.e., has not had any positive virologic tests, if performed, and has not had an AIDS-defining condition).

This information was adapted from:

APPENDIX IV

DETAILED ENROLLMENT PROCEDURES

1. Approach Screening Procedure:

   Note: The Approach Screening Procedure should only be used for women who are thought to be eligible for P1025. Women who are known not to meet the inclusion/exclusion criteria should not be included in the Approach Screening Procedure.

   Once the site has been approved, the site will then begin to use the Approach Screening Procedure for all eligible women seen at the site. This procedure will determine which subjects will be approached for participation in P1025. This procedure is designed to make the P1025 patient population as representative as possible of all eligible patients seen at the site and to avoid the bias that can occur if each site chooses which patients to enroll. The procedure is as follows:

   a. Randomize each eligible woman to DM1025 using the IMPAACT randomization program (PSM). Subjects may be randomized a few days before a scheduled visit or on the day that they arrive at the clinic.

   b. The IMPAACT randomization program will indicate whether or not to approach the subject for enrollment in P1025. A screening number will be given automatically through the DM1025 randomization process. Screening information will not be linked to a subject unless she enrolls into P1025.

2. Enrollment Procedure:

   If the IMPAACT randomization program indicates that the subject is to be approached for P1025 participation and she consents, she can be enrolled into P1025 by using the IMPAACT randomization screens. If the subject has been previously enrolled in an IMPAACT or ACTG study, the site is to use the same IMPAACT PID number. Otherwise, the site should assign each consented woman an IMPAACT PID number. This PID number will be used for all subsequent IMPAACT and ACTG participation.

   To clarify further - when a subject enrolls on P1025 for the first time she uses the PID# she was originally given if she had ever been on any other IMPAACT or ACTG study. If this is her first enrollment to an IMPAACT or ACTG study, the site will assign her a PID#. (This number will be used for all subsequent IMPAACT and ACTG studies.) If the subject becomes pregnant again, while still on P1025 or after follow up for P1025 has been completed, she will be
assigned a CASE ID number for the subsequent pregnancy. This is because a PID# can only be used once per study. The Randomization Desk will register the subject using the site's next available PID as the subject's CASE ID.

Women should be enrolled in P1025 as early as possible during pregnancy. Women may be screened as early as 8 weeks of gestation in order to be ready for enrollment at 14 weeks gestation.

Women who are eligible and consent for the P1026s substudy, but are randomized not to be approached for P1025, should be enrolled in both P1026s and P1025, over and beyond the P1025 accrual cap. However, these women cannot be enrolled in P1025 until consent for P1026s participation is obtained.

**Women who are eligible and consent for future P1025 substudies (other than p1026s), but are randomized not to be approached for P1025, should be enrolled in both the substudy and P1025. Whether the enrollment will be over and beyond the P1025 accrual cap or will count toward the P1025 accrual cap will be determined at the time of substudy approval and specified in the substudy protocol. These women cannot be enrolled in P1025 until consent for substudy participation is obtained.**

3. **Enrollment Procedures for Subsequent Pregnancies**

Women with repeat pregnancies occurring during the six month postpartum follow-up period will stop follow-up for the first P1025 pregnancy and be re-enrolled into P1025, provided that the inclusion/exclusion criteria are met. The randomization system will not be used to determine whether or not these women should be approached for re-enrollment. The site will be required to call the DMC randomization desk to re-register the woman to P1025 by using the site’s next available PID as the woman’s CASE ID.

Women with repeat pregnancies occurring after the six month postpartum follow-up period can also be re-enrolled into P1025, provided that the inclusion/exclusion criteria are met. The randomization system will not be used to determine whether or not these women should be approached for re-enrollment. The site will be required to call the DMC Randomization Desk during registration to register the woman to P1025 by using the site’s next available PID as the woman’s CASE ID.

For all subsequent pregnancies, the site will be required to call the DMC Randomization Desk during registration to P1025 to complete the screening procedure, as directed in the eligibility list.
The site will then use the CASE ID to identify the woman when filling out the forms for the second pregnancy. This procedure will be repeated for any subsequent pregnancies for the same patient during the life of P1025. Each fetus and newborn in a subsequent pregnancy will receive its own PID number.
APPENDIX V

EXAMPLES OF FUTURE STUDIES DESIGNED TO USE DATA AND REPOSITORY SAMPLES COLLECTED IN THE PERINATAL CORE PROTOCOL.

1. To describe viral resistance patterns in women when first seen during pregnancy and at delivery and correlate resistance to:
   a. ART regimen
   b. prior ART history
   c. gestational age at initiation of therapy in ART naive women
   d. adherence to ART during pregnancy
   e. measurable viral burden at the earliest assessment of the woman's BMI during pregnancy

2. To calculate the rate of a) vertical transmission and b) ART resistance in women who have both stable and significant rises in viral load during pregnancy.

3. To characterize the immune response in HIV-infected pregnant women compared to non-pregnant women (including uninfected controls):
   3 color flow cytometry: CD4, CD8, CD20 (B cells)
   Activation markers CD38, DR and CD95
   Lymphoproliferative assays: mitogen, recall antigens and HIV antigens

4. To assess levels of recent thymic emigrant cells (TREC) between ART regimens initiated in women who are ART naive and 1) pregnant and 2) not pregnant at the start of therapy and at 3 month intervals thereafter.

5. To assess the role of the presence of maternal neutralizing antibody to autologous and infant virus (first virus isolate) on rate of disease progression in the infant.

Pathogenesis of Perinatal Transmission

6. To assess the effect of maternal virus load (plasma, cell-associated, integrated, nonintegrated) on vertical transmission in a multivariate analysis that takes into consideration maternal ART as well as other clinical and epidemiological factors.

7. To compare the pattern of replication and durability of antiretroviral response through the third trimester and delivery with the timing of vertical transmission.
8. To assess of the differences in virus tropism (for cell lines, macrophages, other specific cells such as placental Hofbauer, dendritic cells, etc), and coreceptor usage in virus from transmitting and non-transmitting women and the first isolates from infected infants.

9. To compare the frequency of ART resistance by genotypic and phenotypic assays in women who transmit and do not transmit and determine the risk for transmission of resistant virus to the infant.

10. To determine the importance of HIV genetic diversity to risk for and timing of vertical transmission as follows:
   a. Compare the HIV genetic diversity in non-transmitters compared to those who transmit in utero or intrapartum, and to examine this as a factor of stage of maternal illness.
   b. Assess whether selective transmission of either multiple HIV quasi species or single major or minor variants to the infant will differ by the timing of transmission or the presence or absence of maternal or infant neutralizing antibody.

11. To assess the importance of autologous neutralizing antibody to vertical transmission and to disease progression in the infected infant as follows:
   a. compare both the level of autologous neutralizing antibody and the breadth of neutralizing antibody capabilities (against a panel of primary isolates) in transmitting and non-transmitting women.
   b. assess the differences in neutralizing antibody in women who transmit in utero vs. at the time of birth and the ability of the mother's serum to neutralize the infant's isolates.
   c. assess maternal neutralizing antibody to fusion domains among transmitters vs. non-transmitters.
APPENDIX VI

SAMPLE INFORMED CONSENT TEMPLATE
Pediatric AIDS Clinical Trials Group
Division of AIDS, NIAID, NIH

REMINDER TO CLINICAL SITES: DO NOT USE PREAMBLE IN LOCAL CONSENTS

NOTE FROM OPRR (OFFICE OF PROTECTION AGAINST RESEARCH RISKS) TO SITES
ENROLLING SUBJECTS IN THIS STUDY:
PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBs ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OF SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB, AND NOTED IN THE IRB MINUTES. JUSTIFICATION AND IRB APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE PROTOCOL REGISTRATION OFFICE FOR ANY DAIDS-SPONSORED TRIAL OR ANY OTHER NIH-SPONSORED TRIAL AS MAY BE OTHERWISE SPECIFIED. SPONSOR-APPROVED CHANGES IN A DAIDS PROTOCOL MUST BE APPROVED BY THE LOCAL IRB BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB MAY OTHERWISE ADDITIONALLY REQUIRE.


PRINCIPAL INVESTIGATOR:

INFORMED CONSENT*

You and your baby are being asked to take part in the research study named above, because you are infected with HIV. Before you can decide whether or not to take part and/or allow your baby to take part in this study, we would like to explain the purpose of the study, and what is expected of you and your baby.

YOUR/YOUR BABY'S PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study, which will be discussed with you. Once you understand the study, and if you agree to participate and allow your baby to take part, you will be asked to sign this consent form. You will be given a copy to keep.

Before you learn about the study, it is important that you know the following:
- Your/your baby's participation is voluntary;
- You may decide not to take part and/or not to allow your baby to take part, or to withdraw yourself and/or your baby from the study at any time without losing the benefits of your/your baby's routine medical care.

* Participating sites are free to develop an IC with only the pertinent information for subjects who deliver still-born births. The sites must have this separate IC reviewed and approved by their IRB/EC and submitted to DAIDS for review in the usual manner.
PURPOSE OF THE STUDY

The purpose of this study is to collect and study clinical and laboratory information about you and your medical care in order to increase our knowledge of the best care for HIV-infected pregnant women and their children. One of the main goals of the study is to evaluate maternal and infant safety of new and existing drugs prescribed for prevention of mother-to-child transmission of HIV. The study will also look at how different medicines work to lower the amount of virus in the blood or increase the blood cells that help the body fight infection. Side effects of medicines will be studied, as well as problems that make it hard for women or children to take the medicines that are prescribed for HIV infection or its complications. The study will also provide a place for blood samples to be stored for future testing. The information collected in this study may be combined with data from other IMPAACT-approved studies and/or used for other IMPAACT-approved research.

The study will enroll about 1600 mothers and their infants. Your participation in this study will be until six months after you deliver your baby. Your baby will be in the study until he/she reaches 6 months of age.

PROCEDURES

The number of study visits will depend upon when you are enrolled in relation to your pregnancy. Some women will enroll in the study during the early stages of pregnancy, while others will enroll in late pregnancy or just after delivery of their baby. The time that study tests are done, and how often some tests are done, will depend upon the time of enrollment.

Before Entering the Study

If you agree to participate and allow your baby to participate in this study, your medical record will be reviewed to check for blood reports of your previous HIV testing, and to check how many weeks pregnant you are or you were at the time you gave birth to your baby. Your doctor may speak to you about reporting the medication you take to a national registry, which collects information anonymously on the use of HIV medication during pregnancy, and any effects these medications may have on infants.

Study Visits During Pregnancy

You will have no more than 4 study visits during pregnancy, and one of these will occur after your 30th week of pregnancy.
At each visit, your medical record will be reviewed and you will be asked questions about your medications and health. You will also be asked about how well you take your anti-HIV medications and about things in your life that may make it hard for you to take your anti-HIV medications. The questions will take less than 25 minutes. You may skip questions you do not want to answer. Some questions about your use of cigarettes, alcohol and other drugs are in a separate survey. To keep your answers confidential, you will be able to put this survey form in a sealed envelope so that the study staff will not see your answers. Your name will not be on the questionnaire; it will only be identified by your study number. Your answers to these questions will not be put in your medical chart.

Many of the blood tests required for the study may have already been done by your doctor as part of your routine care, and if so, these results will be collected from your medical record. If not already done as part of your routine care, blood will be drawn to check the amount of HIV in your blood and to see how your body is fighting infection.

Blood will also be drawn strictly for study purposes. At each visit, blood will be drawn to store for study tests (explained under Storage of Blood Samples), and at your first study visit, up to an additional 1½ teaspoons of blood will be drawn for routine testing if these results are not available in your chart. The total amount of blood to be drawn at each visit strictly for study purposes is about 4 teaspoons.

Labor and Delivery Visit-Mother

At this visit, within 7 days of the time your baby is delivered, your medical record will be reviewed for information about the labor and delivery, medical history, medicines you are taking, problems you may be having, and about how you are taking the HIV medication. Four teaspoons of blood will be drawn strictly for study purposes. Up to an additional 1½ teaspoons of blood will be drawn for routine testing if these results are not available in your chart.

After Delivery-Mother

Six weeks, 3 months and six months after your baby is born, you will be seen for a study visit. Your medical record will be reviewed for information about your medical history and medicines you are taking. You will be asked questions about any problems you may be having, and about how you are taking the HIV medication. About 1 ½ teaspoons of blood will be drawn for routine tests at the 6 month visit, if routine laboratory test results are not available in your chart.
APPENDIX VI (Cont.)

Labor and Delivery Visit - Baby

After your baby is born, his/her medical record will be reviewed by study staff for medical history and information, measurements, and medications. Your baby will have a physical examination. About 1 teaspoon of blood will be drawn from your baby's vein for routine tests and a test used to look for HIV infection.

Follow-Up Visits - Baby

Your baby will be seen at 2 and 6 weeks of life. At these visits, you will be asked about how you are giving your baby prescribed medicine, and any problems you may have giving the medication. About ½ teaspoon of blood will be drawn from your baby's vein for routine tests if these results are not available on your chart. In addition, up to 1 teaspoon of blood will be drawn at each visit strictly for study purposes.

Your baby will be seen at 2 weeks, 6 weeks, 4 months and 6 months of life. At these visits, a medical history will be obtained (from you and from the baby's medical record), and a physical exam will be performed. At the 6 month visit, you will be asked a number of questions about how you feel the baby is doing (in terms of health, growth, development). These questions will take about 15-30 minutes of your time. At each visit, about ½ teaspoon of blood will be drawn from a vein for routine tests unless already performed by your baby's doctor. In addition, up to ½ teaspoon of blood will be drawn at the two week, six week and six month visit strictly for study purposes.

There will be a final study visit for your baby at around the age of 6 months. At this visit, your baby will have a physical examination and a review of medical history (information from you and from the baby's medical record).

If your baby has been diagnosed with HIV infection, then you will be asked some additional questions about giving your baby medicine.
Storage of Blood Samples

Some study blood obtained at each visit will be drawn and stored (with usual protectors of identity) and used for future IMPAACT approved HIV related research. Up to 4 teaspoons of your blood and 1 teaspoon of your baby’s blood will be used for this purpose. You and your baby may still participate in this study without allowing the collection of these storage specimens, and you may withdraw your consent for the use of these specimens at any time. Once you withdraw your consent, these samples will no longer be used and will be destroyed.

These stored samples will only be used to learn more about HIV infection and its complications, and will not benefit you directly. The research may include studies to understand how HIV causes diseases and complications. Testing may include studies of HIV, studies of other infections that affect people with HIV (for example hepatitis viruses), studies of your cells, proteins, and other chemicals in your body, and studies of your genes (DNA).

If any research involves the study of your and your baby’s genes, the results will ONLY be used to assess how susceptible you are to develop AIDS, and not to any other disease.

The researchers do not plan to contact you or your regular doctor with any results from these studies done on your stored samples. This is because research tests are often done with experimental procedures and, in general, results from one research study should not be used to make a decision on how to treat your disease. Should a rare situation come up where the researchers decide that a specific test would provide important information for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give your study doctor or nurse your most current contact information.

These samples will not be sold or used directly to produce commercial products. Research studies using your and your baby’s stored samples will be reviewed by the National Institutes of Health (NIH).

There is no time limit on how long your samples will be stored.

Please carefully read the statement below and think about your choice. No matter what you decide it will not affect your care.
I agree to have study blood (up to 4 teaspoons) **at each study visit** taken for the purpose of storage for future research related to HIV infection and its complications.

_____ Yes  __________ Date

_____ No  __________ Date

I agree to have study blood (up to 1 teaspoon) taken from my baby **at the two week, six week, and six month study visit** for the purpose of storage for future research related to HIV infection and its complications.

_____ Yes  __________ Date

_____ No  __________ Date

**RISKS OF DRAWING BLOOD**

Taking blood may cause some discomfort, bleeding, or bruising where the needle pricks your skin, and in rare cases, fainting or infection.

**BENEFITS**

This study will be of no more direct benefit to you or your baby than regular, routine care. However, you or your baby or others may benefit in the future from the information that will be learned from this study.

**NEW FINDINGS**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study, or allowing your baby to stay in the study. At the end of the study, you will be told when study results may be available, and how to hear about them.

**COSTS**
There is no cost for study-related clinic visits, examinations, or laboratory tests in this study. Any medical costs for your/your child's treatment outside this study, including your/your child's prescribed medications for HIV, will be charged to your/your child's health insurance company.

APPENDIX VI (Cont.)

REASONS WHY YOU/YOUR BABY MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You/your baby may be withdrawn from the study without your consent for the following reasons:

• the study is cancelled by the National Institute of Allergy and Infectious Diseases (NIAID) or IMPAACT;
• other administrative reasons.

CONFIDENTIALITY

Everything will be done to protect your/your child’s privacy. In addition to the efforts of study staff to keep your/your baby’s personal information private, your/your baby’s confidentiality is further protected by a Certificate of Confidentiality issued by the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your/your baby’s participation. Also, any publication of this study will not use your/your baby’s name or identify you/your baby personally.

People who may review your/your baby’s records include: (insert name of site) IRB, National Institutes of Health (NIH), study staff, and study monitors.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or to others, we will be required to tell the proper authorities.

RESEARCH-RELATED INJURY

If you/your child are/is injured as a result of being in this study, the ________ (name of the clinic) will give you/your child immediate necessary treatment for your/your child's injuries. The cost for this treatment will be charged to you or your insurance company. You will then be told where you/your child may receive additional treatment for injuries. There is no program for monetary compensation or other forms of compensation for such injuries.
PROBLEMS OR QUESTIONS

If you have questions about this study, or in case of research-related injuries, you should contact (name of investigator) at (telephone number). If you have questions about research subject's rights, you can call (name and title of IRB members) at (telephone number).
SIGNATURE PAGE

This is only a suggested Signature page. Sites may use their own signature page.

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you voluntarily agree to join this study and allow your child/your baby to join this study, please sign your name below.

Volunteer's Name (typed or printed)  Volunteer's Signature  Date

OR

Volunteer's legal guardian or representative  Legal Guardian's Signature  Date

Witness' Name (Typed or printed)  Witness's Signature  Date

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the volunteer. A copy should be placed in the volunteer's medical record, if applicable.

The Division of AIDS strongly encourages a witness for the subject's signature.
APPENDIX VII

SAMPLE CONSENT FORM FOR REPOSITORY STORAGE FOR NICHD SITES
INFORMATION SHEET

TITLE: P1025 PERINATAL CORE PROTOCOL

This information sheet is to tell you about a change that has been made in how the special laboratory called a specimen repository will be managed.

As part of PACTG 1025 you agreed to have some of your blood or your child’s blood stored in the repository of the National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH).

NICHD has a repository because although researchers can learn a lot from a study, as time goes by sometimes the tests that they use get improved or brand new tests are developed, and more can be learned with these better tests. When study volunteers consent, like you did, to put specimens in the repository, and also consent to have the researchers do new tests on the specimens – at some time in the future after their time in the study is ended - researchers might learn new information by being able to use the stored specimens.

We are very grateful for your trust and willingness to help researchers keep learning more from the time you gave to the study.

The change we are making is in the group of people who oversee your stored specimens to make sure that your rights and privacy are protected in any future studies.

Before, the Institutional Review Board (IRB) at Westat, a data and operations center, was responsible for reviewing each future study.

Now we have a new procedure, approved by the NICHD IRB, that will have NICHD program staff review each future study. These NICHD staff members are very knowledgeable of the rules and procedures for oversight of specimen repositories, and they will be responsible for ensuring that your rights and privacy are protected.

If you have any questions about this change, you may contact:

[Add site research staff contact information here.]
NICHD program staff and everyone working on this study thank you for all you have done to make it successful.
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 (Version 2.0- 29 November 2005)

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 brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your child’s rights and privacy will be protected in any of these new studies.

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 study proposal and it will have to be approved by a committee to make sure the research is worthwhile. If the study proposal 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 it is unlikely that these study results will 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 Study has to be reviewed to make sure that what is planned is the same kind of study that you 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 (insert title), your child is being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) 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
FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD)

YOUTH FACT SHEET (Version 2.0- 29 November 2005)

When you join this NICHD sponsored Study, you will be asked to consent to having some specimens that the doctor or nurse will take from your 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 the study are kept. Your name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your 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 brand new tests are developed, and more can be learned with these better or new tests. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens at some time in the future after their time in the study is ended, researchers can learn new information by being able to use the specimens. Your rights and your privacy will be protected in any of these new studies.

How will my privacy be protected?

The only record that you participated in this NICHD sponsored Study is at your clinic where it is kept separate from your health records and locked away.

Your specimens in the repository will not have your name on them, only a special study code. It will be the same code that is on your information in the NICHD sponsored Study from your interviews and examinations. Again, none of this information will have your 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 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 specimens?

You will not receive the results of research done with your 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 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 care right now, but they may be helpful to people like you in the future. Your 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 specimens?

All of the studies to be done in the future on your specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you 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 consent to testing my 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 you 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 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 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 or 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 (insert title), you are being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken from you. 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 time in this NICHD sponsored Study.

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

**TEMPLATE CONSENT/ASSENT FORM**

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

Researchers would like to store your 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 DNA).

Benefits: There are no direct benefits to you. You 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 study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).
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 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 DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your 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. You 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 study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your 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 genetic makeup.

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

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).
If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

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<thead>
<tr>
<th>I refuse to have any specimen collected for storage in the repository.</th>
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<td>Participant Signature</td>
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