A PROSPECTIVE SURVEILLANCE STUDY OF LONG-TERM OUTCOMES IN HIV-INFECTED INFANTS, CHILDREN AND ADOLESCENTS

A Domestic, Multicenter Long-Term Follow-up (LTFU) Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

and

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

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IMPAACT P1074 PROTOCOL TEAM ROSTER

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## APPENDICES

I. P1074 SCHEDULE OF INFORMATION COLLECTION
II. SAMPLE INFORMED CONSENT
SCHEMA

A Prospective Surveillance Study of Long-Term Outcomes in HIV-infected Infants, Children and Adolescents

**DESIGN:** A prospective surveillance study of long-term outcomes in infants, children, and youth with HIV infection. It will be designated as the IMPAACT Long-Term Follow-up (LTFU) study.

**SAMPLE SIZE:** Estimated Enrollment: up to 1800 subjects during the first year, and up to 200-300 subjects per year during subsequent years, depending on the activity of open protocols that are eligible for follow-up.

**POPULATION:** HIV-infected infants, children and adolescents who participated in PACTG 219C during 5/1/06-5/31/07 who are not currently participating in ongoing LTFU studies (such as the Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (PHACS AMP), or LEGACY).

Additional HIV-infected infants, children and adolescents who are participating in or have participated at domestic sites in IMPAACT treatment studies approved for P1074 coenrollment, and who are not currently participating in ongoing LTFU studies*, are eligible.

All potential subjects at IMPAACT sites in the United States are eligible regardless of age and mode of HIV acquisition.

**STUDY DURATION:** The interval from when a subject enrolls in P1074 until the subject discontinues participation at the site or until site or study closure.

*NOTE: A list of LTFU studies, for reference, will be available on the IMPAACT website ([http://www.impaactgroup.org](http://www.impaactgroup.org)). A list of IMPAACT eligible protocols for co-enrollment will also be made available.
SCHEMA (Cont.)

PRIMARY OBJECTIVE:

1. To identify possible long-term adverse outcomes of HIV infection and complications of antiretroviral therapy (ART) or experimental interventions other than ARTs in HIV-infected infants, children and adolescents at IMPAACT sites in the United States.

SECONDARY OBJECTIVES:

1. To utilize this prospective surveillance study together with compatible cohorts to detect signals of complications of HIV infection and/or of current and future ARTs or other experimental interventions in HIV-infected infants, children and adolescents.

2. To utilize this prospective surveillance study (separately or together with compatible cohorts) as a basis and/or population source for additional focused substudies to further investigate the incidence and prevalence of adverse outcomes related to HIV infection and complications of ART or other experimental interventions in HIV-infected infants, children and adolescents.
1.0 INTRODUCTION

1.1 Background

The Pediatric AIDS Clinical Trials Group (PACTG) supported 219/219C, “Pediatric Late Outcomes Protocol” for 15 years for HIV-infected and HIV-exposed children to assess the long-term effects of in utero and neonatal exposure to ART in perinatal HIV clinical trials; the late effects of ART and other experimental interventions, including immune-based interventions, prophylaxis and therapeutic vaccines; and the late effects of HIV infection. All children and youth enrolled in PACTG perinatal or treatment trials were eligible for enrollment into PACTG 219/219C. The last version (4.0) allowed enrollment of perinatally HIV-1-exposed infants whose mothers received ART outside of PACTG trials and HIV-infected children, regardless of participation in PACTG clinical trials. The protocol was facilitated by a diagnosis coding algorithm (Appendix 40). PACTG 219C (v 4.0) was closed to enrollment of new subjects on April 25, 2006, with final study visits completed by May 31, 2007. The four versions of P219/219C enrolled 5,854 infants, children and adolescents, which included 3,553 HIV-1 infected patients and 2,238 perinatally exposed, but uninfected infants, from 80 participating US sites.

The PACTG 219C study (referred to as 219C) measured late outcomes by documenting the course of pediatric HIV infection, while monitoring the impact of specific ART and other interventions applied to the treatment of HIV and its opportunistic disease complications. Descriptions of these late outcomes have appeared in over 40 peer-reviewed manuscripts which address critical issues in the care and treatment of pediatric HIV infection, such as survival (1-3), growth (4), neurological and neuropsychological function(5;6), quality of life (7;8), adherence to complex treatment regimens (9), organ system toxicity and metabolic disorders(10;11), development of opportunistic infections/malignancies (12-14), and CD4 levels (15). A complete listing of publications from 219/219C can be found on the IMPAACT Protocol Specific Webpage for 219C, under Publications (see Section 8.0).

1.2 Rationale

The IMPAACT group will continue outcomes research through collaboration and by supporting a limited LTFU protocol with many (but not all) of the goals of 219/219C in order to detect long-term complications of current and future prophylactic and treatment interventions (including experimental interventions) and to detect complications associated with long-term survival of children with HIV infection. This follow-up study is being conducted because of the possibility that ART (including prolonged use of current therapies), and
experimental therapies other than ART, could result in unexpected long-term toxicities when administered to HIV-infected children and adolescents (including enrolled youth who become pregnant and their fetuses/neonates), and that prolonged survival may reveal unexpected complications from HIV infection itself. It is noteworthy that the FDA suggests that experimental therapies have a 15 year follow-up period for adverse outcomes (16). P1074 will be limited in scope so as to maximize cost-effectiveness and will be designed so that the information can be readily extracted at domestic IMPAACT sites. The resulting database will be constructed to facilitate subsequent analyses in conjunction with long-term complications data from other such studies – such as PACTG 219/219C, Women and Infants Transmission Study (WITS), Centers for Disease Control and Prevention (CDC) LEGACY Project and the Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (PHACS AMP). A Memorandum of Understanding (MOU) has been signed to permit data sharing between IMPAACT, 219C, and LEGACY.

Specific areas of interest in which adverse events might be anticipated will include: 1) toxicities of current ART and experimental ART and other experimental therapies for HIV and its complications; 2) infectious and non-infectious complications of HIV infection; 3) end-organ disease (kidney, liver, pancreas, heart, lung); 4) metabolic and mitochondrial abnormalities; 5) growth abnormalities, lipodystrophy, and decreased bone mineral density including fractures; 6) hyperlipidemia and cardiac complications; and 7) neurologic, behavioral and psychological complications that are frequent in HIV-infected children. P1074, in concert with compatible databases, will serve to identify specific complications that justify more-detailed, focused study protocols.

Compatible studies are those which have collected similar data (e.g., antiretrovirals, diagnoses, etc.) and are conducted by groups willing to collaborate with the P1074 team. The IMPAACT studies that qualify for co-enrollment for P1074 will be domestic interventional studies that are recommended for co-enrollment by the P1074 team and subsequently approved by the IMPAACT leadership for inclusion. Some effort has already been made to harmonize data across some potential compatible cohorts, including PHACS AMP and LEGACY. For example, a similar method for coding diagnoses (Appendix 41, a modification of Appendix 40) is being used in the PHACS AMP study, and the same Data Management Center (DMC), Frontier Science & Technology Research Foundation, Inc. (FSTRF) will be used so that forms have a similar format and collect data in a compatible way. The Appendices are available to sites through https://www.fstrf.org.

The team will consider including future cohorts that do not currently exist if these studies fulfill the criteria described above. The type of reporting
of adverse events, expedited adverse events (EAE) vs. serious adverse events (SAE) for co-enrolling treatment studies is determined by these individual treatment studies and not by the P1074 team.

HIV- and ART-exposed uninfected children will not be enrolled in P1074, since follow-up of these children is a major focus of the PHACS Surveillance Monitoring for ART Toxicities Study (SMARTT).

To avoid duplicative effort, otherwise eligible subjects who are currently being followed in another ongoing long-term follow-up (LTFU) study (e.g. PHACS AMP, LEGACY) will not be enrolled into IMPAACT P1074. Rather, their long-term outcomes data will be accessed and included in combined analyses performed among the databases.

There are 44 IMPAACT sites within the US (13 NIAID-supported: 31 NICHD-supported): this number may change in the future. All sites will be required to participate in this protocol and will be required to offer participation in P1074 to all subjects who fulfill eligibility criteria. The protocol team expects that each site will enroll >90% of its P1074-eligible subjects.

Substudies addressing specific safety monitoring of specific drugs or devices or interventions may be developed when additional funding becomes available. The substudies, which may or may not include additional laboratory values or testing, additional visits and collection of adverse event reports, serious or expedited (SAE/EAE), will follow a team-approved development plan/process, and can be co-chaired/chaired by colleagues outside of the network, such as members of the pharmaceutical community or other networks such as the Pediatric European Network for Treatment of AIDS (PENTA), HIV Vaccine Trials Network (HVTN), etc. Final approvals for substudy design and funding will go through the IMPAACT leadership and NIH after approval by the P1074 team. The substudy specific development plan will be available on the P1074 website.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To identify possible long-term adverse outcomes of HIV infection and complications of antiretroviral therapy (ART) or experimental interventions other than ARTs in HIV-infected infants, children and adolescents at IMPAACT sites in the United States.
2.2 Secondary Objectives

2.21 To utilize this prospective surveillance study together with compatible cohorts to detect signals of complications of HIV infection and/or of current and future ARTs or other experimental interventions in HIV-infected infants, children, and adolescents.

2.22 To utilize this prospective surveillance study (separately or together with compatible cohorts) as a basis and/or population source for additional focused substudies to further investigate the incidence and prevalence of adverse outcomes related to HIV infection and complications of ART or other experimental interventions in HIV-infected infants, children, and adolescents.

3.0 STUDY DESIGN

This will be a prospective surveillance study of long-term outcomes in children and adolescents with HIV infection. Annual data collection from chart review will be conducted to include record of prior enrollment in long-term follow-up and other studies; and baseline and interval (or prior year for newly enrolled registrants) information on major diagnoses; pregnancy and neonatal outcome; death; medications; CD4 T-cell count/percentage and viral load data; and height/weight measurements (see Appendix I).

Several standardized chart abstraction forms based on the data collection template in Appendix I will be used to collect data once per year to achieve efficient and useful data collection with limited effort. Medical records at IMPAACT sites will be abstracted yearly. It is anticipated that all IMPAACT domestic sites will participate in P1074 and that such participation will be considered part of site registration for many new protocols. Subjects will be expected to have their entry forms completed at the time of P1074 enrollment, and subsequent chart abstraction is expected to be conducted once per year with a 3 month allowable window on either side of the scheduled chart abstraction date (anniversary of entry date).

The P1074 protocol team will undertake quarterly surveillance of the P1074 prospective surveillance study database to identify signals of adverse events that require additional evaluation. Results will be reported to the IMPAACT Complications Scientific Committee, which includes representatives from NIAID/DAIDS and NICHD.

A signal will be suspected on the basis of comparisons with the 219C study, using the final 219C surveillance reports summarizing incidence of a wide range of targeted diagnoses and conditions overall and by calendar year. Additionally, a signal may be suspected on the basis of comparisons within the P1074 study population based on exposure to specific antiretroviral or other
medications/vaccines (e.g. a comparison of those who received a particular agent vs. those who did not) or by detection of new, unexpected events. The evaluation of adverse effects of HIV infection is considered one of the key objectives of P1074.

Focused analyses utilizing this database can be proposed by any investigator within IMPAACT. These analyses can also be undertaken by pooling compatible data with other cooperating long-term follow-up studies (specifically 219/219C; LEGACY; and PHACS AMP; possibly WITS and others), thereby increasing the power to study uncommon events (see Statistics-Section 5.0). The LTFU Subcommittee will develop mechanisms for data sharing; provide oversight; and review proposals for analysis. This subcommittee will include representatives from LEGACY, PHACS, 219C, IMPAACT Community Advisory Board (ICAB), Statistical and Data Analysis Center (SDAC), DMC, NIAID, NICHD, and DAIDS.

The study populations will consist of the following:

- HIV-infected infants, children and adolescents who participated in PACTG 219C during 5/1/06-5/31/07 and who are not currently participating in ongoing LTFU studies (PHACS AMP, LEGACY).

- HIV-infected infants, children and adolescents who are participating or have participated at domestic sites in IMPAACT treatment studies approved for P1074 coenrollment, and who are not currently participating in ongoing LTFU studies.

- All potential subjects at IMPAACT sites in the United States who meet the criteria above are eligible regardless of mode of HIV acquisition.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Past or current documentation of a confirmed diagnosis of HIV-1 infection defined as two separate peripheral blood specimens from different days, and each specimen must be positive. The two positive results may have been obtained in any combination of the following:

- Positive HIV-1 ELISA or licensed HIV-1 rapid antibody test and confirmatory HIV-1 Western Blot (at age > 18 months)
- HIV-1 RNA viral load $\geq$ 1000 copies/mL plasma
- Positive HIV-1 DNA PCR or HIV-1 p24 antigen assay or HIV-1 culture
4.12 Subjects are eligible for P1074 if:

a. They are HIV-infected infants, children, or adolescents who participated in PACTG 219C during 5/1/06-5/31/07 and are not currently participating in ongoing LTFU studies (e.g., PHACS AMP, LEGACY). Please refer to the IMPAACT website for the current list of studies or contact the protocol team actg.teamp1074@fstrf.org.

OR

b. They are HIV-infected infants, children and adolescents at domestic sites who have participated in or are currently participating in IMPAACT treatment studies (including studies that have rolled over from the PACTG into IMPAACT) designated by the IMPAACT Network Executive Committee (NEC) for subsequent long-term follow-up in P1074, and are not currently participating in ongoing LTFU studies. Please refer to the IMPAACT website for the current list of studies or contact the protocol team (actg.teamp1074@fstrf.org).

4.13 Parent or legally accepted representative/guardian able and willing to provide signed informed consent for minor subjects (unless subject has emancipated minor status).

4.2 Exclusion Criteria

Current participation in another ongoing LTFU studies (e.g. PHACS AMP, LEGACY). Please refer to the IMPAACT website for the current list of studies or contact the protocol team (actg.teamp1074@fstrf.org).

4.3 Enrollment Procedures

Prior to implementation of this study, and any subsequent full version amendments, each site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB). Each site must complete the protocol registration process through the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office and receive DAIDS notification of approval to begin enrollment before subjects can be enrolled in this study. Subjects meeting the study eligibility criteria will be enrolled through the DMC procedures, using the Subject Enrollment System (SES). Written informed consent for study
participation must be obtained before any study related data collection is performed. Subjects are expected to have entry forms completed at the time of their enrollment.

4.4 Co-enrollment Procedures

The P1074 (LTFU) protocol team will suggest IMPAACT protocols that qualify for co-enrollment in P1074 (see 4.13b). These suggestions must be approved by the IMPAACT NEC and Scientific Oversight Committee (SOC). These IMPAACT eligible protocols will be listed on the IMPAACT website, http://www.impaactgroup.org, on the P1074 protocol specific webpage, and on the DMC website, under accrual reports, for P1074 and updated as necessary.

4.5 Subject Management

No clinical visits or laboratory assays will be performed specifically for this prospective surveillance study. Clinically obtained CD4 T-cell count/percentage and HIV RNA data that has been recorded will be collected.

No study medications will be provided as part of this prospective surveillance study.

4.6 Criteria for Study Discontinuation

- The subject or parent/legal representative/guardian refuses further study participation
- Death
- The subject is no longer followed at a domestic IMPAACT site and follow-up information can no longer be obtained
- The IMPAACT site closes, and subject transfer is not possible
- The investigator determines that further participation would be detrimental to the subject’s health or well-being.
- The study is discontinued (see Section 6.3)
5.0 STATISTICAL CONSIDERATIONS

5.1 General Design Issues

This is a prospective surveillance study which will obtain data on major diagnoses, complications, and adverse events in HIV-infected infants, children and adolescents, as well as antiretroviral therapy and limited immunological data. These data will be obtained from all eligible participants via a yearly chart review. The protocol team will review the P1074 data quarterly for signals of adverse events, and will engage in collaborative discussions with leading representatives of other long-term follow-up studies to develop scientific proposals and conduct related investigations. These data reviews may lead to development of additional hypotheses which require a more focused substudy; for example, identification of a number of cases of a rarely occurring diagnosis or adverse event may lead to development of a case-control study nested within the P1074 cohort study, or nested within the broader group of collaborating cohort studies including PHACS AMP and LEGACY.

5.2 Outcome Measures

Primary and Secondary Endpoints:

The protocol team will conduct quarterly surveillance of diagnoses, adverse pregnancy outcomes, deaths, etc. in order to identify and quantify any concerning signals and, when indicated, propose joint analyses with the other LTFU cohorts. A working group of the protocol team will also function to evaluate proposals from investigators within IMPAACT, and within other collaborating networks, to use the IMPAACT LTFU database. These analyses may be undertaken with the use of databases from collaborating networks. Endpoints used for analyses will be proposed by investigators and will be reviewed by the protocol team.

5.3 Randomization and Stratification

There will be no randomization to any study treatment, nor will subjects be stratified at registration. IMPAACT sites are required to approach all eligible subjects at their site in order to obtain their consent to participate in this prospective surveillance study. There are 44 IMPAACT sites within the US (13 NIAID-supported and 31 NICHD-supported); this number may change in the future.
5.4 **Sample Size and Accrual**

It is estimated that up to 1800 subjects may enroll in this long-term follow-up study the first year. This estimate is based on the approximately 1523 subjects who had participated in PACTG 219C (219C) and were still active as of 5/1/2006, and who were at sites included in the IMPAACT network (funded either by NIAID or NICHD). Of these 1523 subjects, approximately 300 were projected to be enrolled by the PHACS AMP study at a subset of 11 of the IMPAACT sites which are also participating in PHACS, lowering the number of 219C-eligible subjects to approximately 1200. To this estimate of 1200 subjects from 219C, the number of subjects currently enrolled in domestic treatment and perinatal studies plus the number of enrollees in newly developing trials were added. This was estimated to be 730 additional subjects (422 in current domestic studies, 310 in new studies in development). However many of these subjects had also been in 219C (for example, 150 of the subjects in P1065 were also in 219C). Thus, it is expected that a maximum of 600 additional subjects will be eligible for enrollment into P1074, yielding a total of 1800 eligible subjects. Some subjects may refuse to participate, which will further lower the total accrued.

**Sample Size and Power Considerations**

The data collected from the P1074 cohort will serve as a basis for evaluating scientific hypotheses regarding adverse events and complications of HIV infection and treatment, particularly for those events which occur more commonly in this population. However, one of the most important justifications for the continued follow-up and merging of data from HIV-infected children across various U.S.-based cohorts is the need for relatively large sample sizes to detect signals of adverse events. Based on various proposed sample sizes, merging data from the three groups thus far mentioned would provide for the detection of infrequent, but clinically important effects. The smallest effect that could be detected at 80% power for a range of event rates and group sizes, has been calculated (Table 1).
Table 1. Detectable Effects at 80% Power, Assuming Exposure is Associated with Increased Risk

<table>
<thead>
<tr>
<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N=1,000</td>
</tr>
<tr>
<td>1%</td>
<td>50%</td>
<td>3.61</td>
</tr>
<tr>
<td></td>
<td>30% or 70%</td>
<td>3.94</td>
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<td>10% or 90%</td>
<td>6.34</td>
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<td>5%</td>
<td>50%</td>
<td>2.02</td>
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<td></td>
<td>30% or 70%</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>10% or 90%</td>
<td>2.91</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
<td>1.70</td>
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<tr>
<td></td>
<td>30% or 70%</td>
<td>1.78</td>
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<tr>
<td></td>
<td>10% or 90%</td>
<td>2.32</td>
</tr>
<tr>
<td>20%</td>
<td>50%</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>30% or 70%</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>10% or 90%</td>
<td>1.97</td>
</tr>
</tbody>
</table>

For simplicity, it is initially assumed that a comparison of interest would be the percentage of exposed subjects with an event of interest versus the corresponding percentage in unexposed subjects with the effect size measured in terms of an odds ratio (OR). For example, it may be important to assess whether exposure to a particular antiretroviral regimen containing a particular protease inhibitor of interest is associated with high cholesterol levels (hypercholesterolemia, ≥ 220 mg/dL). If 20% of those unexposed (i.e., without protease inhibitor of interest) are assumed to have hypercholesterolemia, then there is 80% power to detect an OR ~ 1.60 (i.e., a 60% increase in the odds of hypercholesterolemia) for a total sample size of N=2,000 and 10% exposed to the PI of interest (i.e., 200 with exposure to the PI of interest, 1,800 without). Note that not all subjects within the merged cohort may be included in all analyses of interest. For example, the investigators may wish to restrict the analysis to subjects on antiretroviral therapy with a protease inhibitor, and within this subgroup compare subjects receiving ritonavir to those not receiving ritonavir. In this case, if the total cohort size was N=2,000, but 75% were on HAART with a PI, then the investigators would need to refer to the detectable differences presented under the column headed N=1,500 (i.e., 75% of 2,000).

Table 1 presents the minimum detectable differences at 80% power assuming that exposure increases the risk of an event. The differences range from 1.25 to 1.5 for more common events (occurring in ≥ 20% of unexposed subjects), from 1.4 to 2 for less common events (5-10% event rates, with at least 30% in each exposure group), and from 2.5 to 6 for rare
events. It is in this latter category that we will need to merge the IMPAACT, PHACS AMP and LEGACY data sets to more effectively evaluate associations with specific exposures of interest.

A similar summary is presented in Table 2, but under the assumption that exposure is protective. For example, if the investigators were interested in evaluating whether exposure to antiretroviral therapy from 1996 to 2000 (about 50% of infected subjects) was associated with a decreased odds of mortality, and a 10% mortality rate was assumed among a cohort of 1,500 subjects, then the study would have 80% power to detect an OR of 0.58 or less (i.e., a 42% decrease in the risk of death). Note that although we would ideally like to be able to detect ORs of 0.33 for a protective effect and some of the values in Table 2 fall below this level for less common events (occurring in 1% or 5% of unexposed), the absolute difference in event rates is actually very small. For example, with a sample size of N=1500 with 150 exposed and 1350 unexposed, we can detect a difference between an event rate of 5% in the unexposed and 1.1% in the exposed, for an absolute difference of 3.9%.

Table 2  Detectable Effects at 80% Power, Assuming Exposure is Associated with Decreased Risk

<table>
<thead>
<tr>
<th>Event Rate in Unexposed</th>
<th>Percent of Population in Unexposed Group</th>
<th>Maximum Detectable OR for Exposed vs Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N=1,000</td>
</tr>
<tr>
<td>1%</td>
<td>50%</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>30% or 70%</td>
<td>---</td>
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<tr>
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<td>10% or 90%</td>
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</tr>
<tr>
<td>5%</td>
<td>50%</td>
<td>0.36</td>
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<td></td>
<td>30% or 70%</td>
<td>0.32</td>
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<tr>
<td></td>
<td>10% or 90%</td>
<td>0.12</td>
</tr>
<tr>
<td>10%</td>
<td>50%</td>
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<td>30% or 70%</td>
<td>0.47</td>
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<td></td>
<td>10% or 90%</td>
<td>0.28</td>
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<tr>
<td>20%</td>
<td>50%</td>
<td>0.62</td>
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<tr>
<td></td>
<td>30% or 70%</td>
<td>0.59</td>
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<tr>
<td></td>
<td>10% or 90%</td>
<td>0.43</td>
</tr>
<tr>
<td>40%</td>
<td>50%</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>30% or 70%</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>10% or 90%</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Tables 1 and 2 consider endpoints which can be classified as binary and also provide approximate detectable differences for endpoints classified as “time-to-event”, especially for less common events. Another type of
outcome of interest might be a continuous outcome, such as body mass index (BMI, defined as weight in kg divided by squared height in meters).

Table 3 below, which shows the detectable mean differences comparing two groups of interest in terms of standard deviations, indicates that the proposed merged cohort sizes are well-powered to detect clinically meaningful differences of interest, since all detectable mean differences are less than 0.3 standard deviations and most are less than 0.2 standard deviations. For example, assuming 90% of infected subjects are currently receiving antiretroviral therapy, a cohort of N=2000 would provide 80% power to detect a mean difference between groups of 0.21 standard deviations between exposed and unexposed subjects. The P1074 cohort alone may provide sufficient numbers of subjects to evaluate many continuous endpoints, without the necessity of combining data from other cohort studies.

<table>
<thead>
<tr>
<th>Percent of Population in Unexposed Group</th>
<th>Maximum Detectable Difference in Standard Deviations Between Exposed vs Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,000</td>
</tr>
<tr>
<td>50%</td>
<td>0.18</td>
</tr>
<tr>
<td>40% or 60%</td>
<td>0.18</td>
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<tr>
<td>30% or 70%</td>
<td>0.19</td>
</tr>
<tr>
<td>20% or 80%</td>
<td>0.22</td>
</tr>
<tr>
<td>10% or 90%</td>
<td>0.30</td>
</tr>
</tbody>
</table>

To summarize, if the sample size enrolled onto the study or included in a specific analysis is at least 1000, then we have high power to detect differences in rates of any clinical event that occurs in at least 5% of the unexposed HIV-infected subjects. In addition, if at least 800 subjects are enrolled then we would still have 80% power to detect an OR of 2.2 as long at least 240 subjects were considered “exposed” to the treatment of interest; this corresponds to being able to detect a difference between 5% of unexposed with a particular event versus 10.7% of exposed. If the number of subjects enrolled (or included in an analysis) is lower than 800, then our analysis may be improved by relying on continuous outcomes such as CD4 percent or z-scores for height, weight, or body mass index. Comparison of continuous outcomes such as these will be well-powered even if the sample size is as low as 400 subjects; at 80% power we will be able to detect a change in z-scores of between 0.28-0.33 standard deviations or more between an unexposed and exposed group (depending on the percent in each group). In fact, a sample size as low as 140 subjects will provide 80% power to detect a less than 0.5 difference in BMI, height,
or weight z-scores, and this difference is typically considered of clinical interest.

5.5 Monitoring

The protocol team will monitor accrual, subject characteristics, and loss to follow-up based on routine monitoring reports prepared by SDAC. It is anticipated that these routine monitoring reports will be prepared monthly at the initial opening of the trial to closely track total enrollment, source of study subjects (by study site and prior study participation), age distribution of enrollees, etc.; subsequently these reports will be prepared and distributed to the protocol team on a quarterly basis.

Accrual Rate and Stopping Rules

There is no target enrollment for this study; the sample size stated in the protocol is the maximum possible estimate of eligible participants within IMPAACT, which will change, depending on the number of IMPAACT treatment studies that are available and selected for co-enrollment. If the total accrual is less than 400 subjects at the end of the first year after the study opens, and after at least 50% of eligible sites have protocol registered, then enrollment will be suspended, pending discussions with the Complications Scientific Committee regarding options for improving enrollment and/or study continuation, restructuring or expansion. The protocol team expects that each site will enroll more than 90% of its P1074-eligible subjects. In addition, a surveillance working group of the protocol team will develop and prepare summaries of major outcomes (death, pregnancies, certain major or targeted diagnoses), which will be distributed quarterly after their components have been agreed upon.

5.6 Analyses

Analyses will be based on events proposed by investigators and reviewed by the P1074 protocol team. An overview of general methodology to be applied and potential limitations of our analyses is provided below. It is anticipated that many of the analyses will be aimed at comparisons of outcomes for the HIV-infected subjects across groups defined by ART exposure groups (either by class of drugs or individual antiretroviral agents), by other experimental therapies, and by severity of HIV infection itself. The analysis approach will be tailored to provide an appropriate analysis based on the type of outcome of scientific interest. Specifically, outcomes which can be expressed as times-to-event (e.g., time-to-death, opportunistic infections, abnormal neurological status, hospitalization, and virologic failure) will be analyzed using standard survival methods for
failure time data, such as Kaplan-Meier estimates, log rank tests, and proportional hazards models. For some events, methods for counts of events, such as Poisson regression may be used. A surveillance approach will be used to evaluate the prevalence rates of major diagnoses (opportunistic infections, neoplasms, cardiovascular and metabolic outcomes, renal and hepatic diagnoses and conditions) and compare them between groups of children defined by type of ART exposure and other experimental therapies and, where possible, to rates in other pediatric populations in the U.S. Exact statistical methods based on the Poisson distribution will be used to give confidence intervals for rates and for comparisons between populations. For quantitative outcomes (e.g., weight or height z-scores, changes in viral load and CD4), regression methods including mixed effects models and generalized estimating equations methods will be used to evaluate associations of outcomes with ART, other experimental therapies, and HIV infection itself.

The major limitation of the study is the lack of a randomized control group of children who were not exposed to ART and in general, the lack of any randomization to study-provided medications. The observational nature of this prospective surveillance study means that analyses must consider the issue of confounding by indication; that is, the tendency for the sicker children to receive the most aggressive therapy. Thus, analyses of major outcomes must control to the extent possible for health status of the children at the time of ART initiation. There will also be likely confounding with calendar time because most of the children who initiated therapy in the mid-1990’s received mono- or dual-nucleoside reverse transcriptase inhibitors as their initial therapy, whereas those who initiated therapy in the late 1990’s to the present will have likely received more effective combination ART. Related to this chronological trend in available therapies, there is a potential for a survivor effect since the adolescents enrolled in this prospective surveillance study must have survived through periods when less effective therapies were available. Another limitation is that it is anticipated that information on prevalence rates of outcomes of interest in similar U.S. populations may be difficult to obtain, in that the socioeconomic background may be different for the P1074 study population. Thus, any perceived excess of these events will need careful investigation.

Some of these issues can be addressed by adjusting for, or matching on, characteristics such as disease status and age, and through use of more complex modeling strategies such as marginal structural models and propensity score models that attempt to control for time-dependent measures of disease status, which may in turn impact treatment management. Statistical methods such as those for truncated time-to-event
data may also help in reducing the survivor effects. In addition, the effects of calendar time might be investigated by evaluating changes in outcome within cohorts of children in successive years that have received the same type of therapy. A second limitation concerns the potential impact of losses-to-follow-up, particularly as very long-term follow-up may be required for evaluation of certain outcomes. Careful monitoring will be required to evaluate loss to follow-up and associated reasons for losses to follow-up, with the hope that such losses are not related to potential outcomes of interest.

6.0 HUMAN SUBJECTS

6.1 Institutional Review Board and Informed Consent

This protocol, the sample informed consent document (Appendix II), and any subsequent modifications must be reviewed and approved by the Institutional Review Board (IRB) responsible for oversight of the prospective surveillance study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the age of majority). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. Site IRBs will determine if re-consent is needed when subjects reach the age of majority.

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 subject (or parent or legal guardian).

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

All evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the Office for Human Research Protections (OHRP), other government agencies (e.g. CDC/LEGACY), the NIAID and/or NICHD, or the local IRB.

No laboratory specimens will be collected in P1074.

6.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT Network, NIAID and/or NICHD, the OHRP, the IRB, or other governmental agencies as part of their duties to ensure that research subjects are protected.

7.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies.
8.0 REFERENCES

An updated list of 219/219C Publications is available on the 219C webpage, IMPAACT website http://www.impaactgroup.org.

Reference List


Ref Type: Report
# APPENDIX I
## P1074 SCHEDULE OF INFORMATION COLLECTION

<table>
<thead>
<tr>
<th>Information Type</th>
<th>Screening (previous 219C participant or IMPAACT-eligible Treatment protocol)</th>
<th>Entry (may be done concurrently with Screening)</th>
<th>Q annual (+/- 3 months)</th>
<th>End of study (Voluntary discontinuation, subject no longer available for follow-up, death, or site/P1074 closure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL CHART INFORMATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History (LTFU and non-IMPAACT studies)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical measurements (Ht, wt)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Major Diagnoses</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy (if applicable)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Pregnancy Outcome (if applicable)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neonatal Outcome (if applicable)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medications (ARVs)</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Non-IMPAACT study medications or study vaccines</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Death (if applicable)</td>
<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>LABORATORY RESULTS</td>
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<td></td>
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<tr>
<td>HIV-1 RNA PCR</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CD4 count and percentage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Footnotes—with detailed information to match the above are on the following pages
APPENDIX I (Cont.)

1. Screening/Entry: Date of Form Completion (MMDDYY) to be completed at P1074 enrollment, annually thereafter (window of ± 3 months), and at P1074 discontinuation
   IMPAACT PID # _____________________ DOB __________________
   P1074 enrollment date __________________________

2. History: Long-term follow-up studies subject participated in prior to enrollment in P1074 and relevant study ID numbers (to be completed at P1074 enrollment)
   • IMPAACT/PACTG 219C, “Pediatric Late Outcomes Protocol”
   • IMPAACT/PACTG P1025, “Perinatal Core Protocol”
   • WITS-Women and Infants Transmission Study
   • PSD-Pediatric Spectrum of HIV Disease
   • CDC LEGACY Project
   • PHACS AMP-Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol
   • CDC PACTS HOPE-Perinatal AIDS Collaborative Transmission Study – HIV Follow-up of Perinatally Exposed Children
   • Other

Other long-term follow-up studies the subject is currently participating in and relevant study ID numbers (to be completed at P1074 enrollment and updated annually).

Clinical research studies not within IMPAACT participated in since last P1074 form completion and relevant study ID numbers (for initial P1074 enrollment, list non-IMPAACT studies participated in the preceding year or currently participating in)
   • Name of Sponsoring Network, Institution, or Pharmaceutical Sponsor
   • Study Number
   • Study Name
   • Start Date
   • Stop Date

3. Height/Weight: any units are acceptable; date (use most recently available measurement).
4. Major Diagnoses made since the last P1074 form completion
   [For initial P1074 enrollment, list major diagnoses during the prior year and ongoing diagnoses present at entry]

   P1074 Diagnoses of Interest
   - Diagnoses associated with hospitalization
   - Diagnoses associated with persisting disability
   - Diagnoses associated with death
   - Diagnoses (including, but not limited to, infectious, metabolic, psychological, end-organ, malignancy) considered significant in the eyes of the site investigator according to one (or more) of the following criteria:
     - Chronic (≥3 months) – excluding minor events such as non-severe viral infections, otitis media, superficial mucocutaneous infections, superficial mucocutaneous inflammatory conditions that are not thought to be potentially related to medication administration
     - Recurrent (≥3 episodes) – excluding minor events such as non-severe viral infections, otitis media, superficial mucocutaneous infections, superficial mucocutaneous inflammatory conditions that are not thought to be potentially related to medication administration
     - Major or unique impact on quality of life
     - Potentially related to medication or to medication administration/infusion – including mucocutaneous changes, injection site abnormalities
     - Abnormality of diagnostic testing that, in the opinion of the site investigator, arises to the level of a clinical diagnosis of underlying organ disease (record associated diagnosis, rather than laboratory abnormality; e.g., anemia, hepatitis, pancreatitis, cardiomyopathy, osteoporosis)
     - Congenital defect in infant born to HIV-infected woman
     - Diagnosis considered to be clinically significant by the site investigator

5. Pregnancy
   Indicate if the subject has been pregnant since the last P1074 form completion (for initial enrollment, indicate whether subject was pregnant during the prior year or at entry).
APPENDIX I (Cont.)

6. Pregnancy Outcome
   • Therapeutic abortion (indicate associated maternal or fetal diagnoses reason for therapeutic abortion and gestational age at the time of the event)
   • Elective abortion (indicate associated maternal or fetal diagnoses, and gestational age at the time of the event)
   • Spontaneous abortion (indicate associated maternal or fetal diagnoses, and gestational age at the time of the event)
   • Stillbirth (indicate associated maternal or fetal diagnoses and gestational age at the time of stillbirth)
   • Preterm delivery (< 37 weeks) (indicate associated maternal or fetal diagnoses)
   • Other pregnancy complications

7. Neonatal Outcome
   • Not applicable (termination or stillbirth)
   • Gestational age (weeks)
   • Birth weight
   • Congenital malformation (specify)
   • Neonatal diagnoses (hospitalization-associated, chronic, or associated with persisting disability) within 30 days of life
   • Neonatal death (≤ 30 days after birth); cause
   • HIV-infected
   • HIV-uninfected
   • HIV-indeterminate [If indeterminant, HIV status of the neonate should be updated at the time of the next maternal P1074 form completion.]

8. Medications
   Antiretrovirals
   • Continuing from the time of the last P1074 form completion (for initial enrollment, indicate antiretrovirals during the prior year with start dates, and, if appropriate, stop dates, and antiretrovirals at P1074 entry with start dates)-
   • Antiretrovirals stopped since last form completion and date stopped
   • Antiretrovirals started since last form completion and date started
   *At a minimum the month and year, is needed; prescription information may be used
9. Non-IMPAACT study medications or study vaccines
   - Continuing from time of last P1074 form completion (for initial enrollment, indicate study medications or study vaccines during the prior year with start dates and if appropriate, stop dates and study medications or study vaccines at entry with start dates)
   - Discontinued since last form completion and date stopped
   - Begun since last form completion and date started

10. Death
    - Date
    - Cause (as determined by the site)
    - Major autopsy diagnoses (if available)

11. HIV RNA viral load: assay (if specified); dates, viral load results (list those during the year prior to the initial P1074 enrollment or all interval measurements since last form completion).

12. CD4% and CD4 T-cell count: dates, CD4%, and total CD4 count (list those during the year prior to the initial P1074 enrollment or all interval measurements since last form completion).
APPENDIX II

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

SAMPLE INFORMED CONSENT

Note: This is a sample informed consent based on required elements. Standard template language can be found at the following: (http://rcc.tech-res.com/forms.htm).

P1074: A Prospective Surveillance Study of Long-Term Outcomes in HIV-infected Infants, Children and Adolescents, Version 1.0 dated February 2, 2009.

SHORT TITLE FOR THE STUDY: Long-Term Follow-up (LTFU) Study (US)

INTRODUCTION

You are/your child is being asked to take part in this research study because:

- you are/your child is infected with HIV, the virus that causes AIDS, and
- you have/your child has previously participated in the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 219C, “Pediatric Late Outcomes Protocol” or is participating/has participated in another IMPAACT/PACTG research study.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to:

- Use the information collected in your/your child’s medical or clinical record to form a long-term follow-up study, (called LTFU study for short), or official record, so that in the future, doctors can know how often treatment-related effects occur among infants, children and teenagers.
- Identify any long-term effects of having HIV infection, which may exist.
APPENDIX II (Cont.)

- Identify any long-term side effects of drugs used to treat HIV infection and drugs used to treat some complications of HIV, which may exist.
- Combine the information collected in this study with the information already collected about you or your child in the previous clinical research study/studies.

WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?

There are no study visits that are required for this study. All the information collected, will come from your routine care visits, or from the other studies you/your child is participating in, may have participated in, or will participate in, at this site.

This study is asking your permission to obtain the clinical information (such as medicines and vaccines that were administered, illnesses, outcomes of pregnancies and results of laboratory tests) from you/your child’s routine care visits and participation in other long-term follow-up studies and from other PACTG/IMPAACT studies that you are/your child is participating in now or has participated in the past, or in the future. Information will be collected once a year.

We are also asking for permission to obtain information from other studies in which you are/your child is currently participating in, or you have/your child has participated in, if you have given consent before, to share this data. You/your child will not be identified by name, but only by your/your child’s patient identification number (PID) which identifies participants in a particular study. No new samples will be taken for this LTFU study.

If you or your child participates in a new IMPAACT or other network treatment study, that study will ask for your permission to share data.

If we find information that should be investigated some more, in a new study, we will write a new consent form, for that study.

If you/your child are or become pregnant:

This study would like your permission to collect information on your baby/your child’s baby, for up to 30 days after delivery and until it is known whether your baby/your child’s baby is infected with HIV or not. Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my baby/my child’s baby’s medical information to be shared in this study.

__________ Yes ___________ No ___________ Date
HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A maximum of about 1800 infants, children and adolescents in the United States could take part in this study, in the first year. It is expected that more than 400 will enroll in the first year.

In the second year and others after that, about 200-300 more participants each year are expected to enroll in this study.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

Since this is a long-term follow-up study (LTFU), you/your child will be in this study until the study closes, or the site closes, or until you are no longer followed by an IMPAACT clinic in the United States and follow-up information can no longer be obtained, or you/your child no longer want to participate in the study.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off this study without your permission if:

- The study is cancelled by the IMPAACT Network, National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), or the site’s Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research subjects.
- You/your child no longer come(s) to the clinic for appointments.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is no direct benefit to you/your child for taking part in this study. Information learned from this study may help any person who has HIV.

WHAT ARE THE RISKS OF THE STUDY?

This is a clinical chart review study to collect information from medical records. There is no physical risk to you/your child. No test will be required for this study and no treatments or medications are provided in this chart review study. There may be a risk of breach of confidentiality in this study. This study will only look at your/your child’s medical records that are kept at the clinic. This study will also request links to your/your child’s data from previous clinical trials or those you/your child are co-enrolled in, and for which you have given this permission to share information that is HIV-related.
WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects. People who may review your records include the Office for Human Research Protections (OHRP) and other government agencies, the site IRB \textit{(insert name of site IRB)}, the National Institutes of Health (NIH), study staff, study monitors, and the investigators that have permission from IMPAACT and the other study networks that are sponsored by NIH or have agreements with IMPAACT to share information.

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

WHAT ARE THE COSTS TO ME?

There are no additional costs to participate in this study.

\textit{Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child/baby is/are taking part in a research study. [This section may be deleted at the discretion of the IRB].}

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take yourself/your child out of the study at any time. You/your child will be treated the same no matter what you decide.

We will tell you about new information learned from this study or other studies that you/your child may be co-enrolled in that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of future studies that may result from this study, let the staff at your clinic/IMPAACT site know.
WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study contact:
• name of the investigator or other study staff
• telephone number of above

For questions about your/your child’s rights as a research subject, contact:
• name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
• telephone number of above
OTHER INFORMATION

The information collected in this study may be used for other IMPAACT-approved HIV-related research. The information collected in this study may be shared with other clinical trials networks that have agreements with IMPAACT.

SIGNATURES TO USE STUDY INFORMATION COLLECTED ON YOU/YOUR CHILD IN WITS OR LEGACY OR PACTG/IMPAACT STUDIES

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the research staff to be able to use information already collected on you/your child in the Women and Infants Transmission Study (WITS) or the LEGACY Project or PACTG/IMPAACT studies to help this study, please sign your name below.

_____________________                              ____________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________                ____________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)
SIGNATURE PAGE

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

Participant’s Name (print)  Participant’s Signature and Date

Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

Witness’ Name (print)  Witness’s Signature and Date
(As appropriate)

Father’s Name  Father’s Signature and Date
(if father’s consent is required)  (If father’s consent is required)