Evaluation of Immunologic Memory Following Pneumococcal, Hepatitis B, and Measles Vaccination in HIV-Infected Children Treated with Highly Active Antiretroviral Therapy (HAART)

A Multicenter Trial of the Pediatric AIDS Clinical Trials Group (PACTG)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

Pharmaceutical Support Provided by:

Wyeth Lederle Vaccines
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IND # BB9599

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Version 1.0
FINAL
August 2, 2005
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    FOR CLINICAL SITES FUNDED BY NICHD
EVALUATION OF IMMUNOLOGIC MEMORY FOLLOWING PNEUMOCOCCAL, HEPATITIS B, AND MEASLES VACCINATION IN HIV-INFECTED CHILDREN TREATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

DESIGN: Follow-up substudy of P1024 “Evaluation of the Immunogenicity of Pneumococcal Conjugate Vaccine and Routine Pediatric Immunizations in HIV-Infected Children Treated with Highly Active Antiretroviral Therapy” to evaluate the persistence of immunologic memory to pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV), measles vaccine (MMR), and hepatitis B virus (HBV) vaccine in HIV-infected subjects on HAART who participated in, and completed, P1024.

SAMPLE SIZE: Approximately 149 subjects, up to a maximum of 224 subjects.

POPULATION: HIV-infected subjects ages 6 to 23 years (at screen/entry) who enrolled into P1024 between June 1, 2001 and March 31, 2002 while receiving HAART and completed the initial two-year P1024 study period.

STRATIFICATION: Subjects will be stratified into four stratification groups, described in Table 1 below, based on the lowest CD4% prior to entry into P1024 and the CD4% at screening for entry into P1024. Subjects will remain in the stratification groups to which they were assigned during their participation in P1024. Perinatal HIV acquisition is required for stratification groups 2-4; HIV acquisition by any route is allowed for stratification group 1. Subjects will be randomized in a 1:1 ratio, within stratification groups, to receive either PCV or PPV. All eligible subjects will receive MMR and HBV vaccines.

TABLE 1:

<table>
<thead>
<tr>
<th>Group</th>
<th>Lowest CD4% prior to HAART</th>
<th>CD4% At P1024 Screening</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>&lt;15%</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>2</td>
<td>&lt;15%</td>
<td>≥15%</td>
</tr>
<tr>
<td>3</td>
<td>15% – &lt;25%</td>
<td>≥15%</td>
</tr>
<tr>
<td>4</td>
<td>≥25%</td>
<td>≥25%</td>
</tr>
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SCHEMA (Cont.)

REGIMEN:

Subjects will receive antiretroviral medication as prescribed by their HIV care provider. No antiretroviral study drugs will be supplied as part of this study. Subjects will receive up to a total of three vaccinations at screen/entry (included in Table 2).

TABLE 2:

<table>
<thead>
<tr>
<th>Immunizations</th>
<th>Screen/Entry</th>
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<tbody>
<tr>
<td>Pneumococcal 7-valent Conjugate Vaccine (7V PCV), 0.5 mL IM or</td>
<td>X</td>
</tr>
<tr>
<td>Pneumococcal Polysaccharide Vaccine (23V PPV), 0.5 mL IM</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B Vaccine (HBV), 0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Measles, Mumps, and Rubella Virus Vaccine Live (MMR ® II), 0.5 mL SC</td>
<td>X</td>
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TREATMENT
DURATION: 28 days: One treatment visit and follow-up visits at 7 and 28 days.

OBJECTIVES:

Primary

1. To determine whether HIV-infected children have evidence of pneumococcal type-specific immunologic memory 3-4 years after receiving two doses of PCV and one dose of PPV while on HAART.

2. To determine whether HIV-infected children have evidence of hepatitis B-specific immunologic memory 3-4 years after receiving a booster dose of HBV vaccine while on HAART (subsequent to receiving a primary HBV vaccine series previously).

3. To determine whether HIV-infected children have evidence of measles-specific immunologic memory 3-4 years after receiving a booster dose of MMR vaccine while on HAART (subsequent to receiving one or more doses of MMR vaccine previously).
Secondary

1. To compare the immune response to a booster dose of PCV versus a booster dose of PPV subsequent to previous administration of two doses of PCV followed by one dose of PPV while on HAART.

2. To evaluate factors that may correlate with memory response to vaccines, including CD4% (nadir, at P1024 study entry, and at P1061s screen/entry), HIV-1 RNA (peak, at P1024 study entry, and at P1061s screen/entry), age, duration of HAART, and change in antiretroviral therapy due to virologic failure (between the end of the P1024 vaccination period and P1061s screen/entry).

3. To determine the immunogenicity of PCV, PPV, HBV, and MMR vaccine boosters in HIV-infected children who lack evidence of immunologic memory to these vaccines previously received while on HAART.

4. To determine the safety of PCV, PPV, HBV, and MMR booster vaccine doses in HIV-infected children.
1.0 INTRODUCTION

1.1 Background

*Streptococcus pneumoniae*
Rapid declines in antibody (Ab) titers to near-pre-immunization levels occur within months of primary vaccination of HIV-uninfected infants with pneumococcal conjugate vaccine (PCV). Evidence of immunologic memory, subsequent to primary vaccination with PCV, has been demonstrated by anamnestic responses with a boosting dose of PCV or pneumococcal polysaccharide vaccine (PPV) during the second year of life, leading to approximately 10-fold increases in Ab levels (1-7). This finding is consistent with PCV being a T cell-dependent antigen. In HIV-infected children < 2 years of age, Ab titers fell rapidly following administration of 5-valent PCV; < 50% of subjects maintained an ELISA titer > 1 mcg/mL eight months following vaccination (8). Likewise, among HIV-infected children administered a primary 7-valent PCV series during infancy in PACTG 292, “A Double Blind, Placebo Controlled Trial of the Safety and Immunogenicity of a Seven Valent Pneumococcal Conjugate Vaccine in Presumed HIV-Infected Infants,” significant declines in Ab levels occurred by 15 months of age. After a booster PCV dose at 15 months, four-fold increases in Ab ranged from 30% to 72%, depending on serotype. Significant waning of Ab then occurred by 24 months of age. The declines in Ab titers pre-booster and the rise post-booster were similar between asymptomatic and symptomatic HIV-infected children, and similar to that seen in HIV-uninfected children (9). Data regarding long-term persistence of Ab or memory following PCV administration in HIV-uninfected and HIV-infected children are not available.

Ab levels after vaccination with PPV (without previous PCV) generally decline substantially (often to pre-vaccination levels) within 3-10 years post-vaccination in HIV-uninfected populations. This has been described in the elderly, in asplenic patients, in patients with chronic renal disease, and in sickle cell disease patients (10-15). The fall in Ab concentration is more rapid in HIV-infected adults, occurring within 1-3 years (16-18). PPV is a T cell-independent antigen and, does not, by itself, elicit immunologic memory; in addition, anamnestic responses are not observed following revaccination.

Data describing the durability of Ab and memory responses in HIV-infected children and adults vaccinated with regimens consisting of both PCV and PPV are not available.
Hepatitis B
The durability of Ab levels following vaccination of HIV-uninfected populations with HBV is variable. In some reports, substantial percentages (15-65%) of children and adults do not maintain Ab concentrations considered to be protective, or lose all detectable Ab, within 3-15 years of vaccination (19-37). In other reports, the majority (>70-90%) of children and adults maintain protective levels 5-10 years following vaccination (38-42). Induction of immunologic memory is evidenced by an anamnestic response to boosting in 73 to >95% of patients who had lost detectable Ab 5-13 years after initial vaccination (31;32;35-37;43-56). Additionally, investigators have demonstrated persisting immunologic memory, in the absence of sustained protective Ab titers, by detecting persistent hepatitis B-specific T lymphocyte proliferative responses and hepatitis B-specific B cells by ELISPOT assay (57;58). Further evidence of long-term memory in immunologically normal individuals vaccinated with HBV is the demonstration of continued protection against clinical and chronic HBV infection, despite loss of significant Ab levels, in most populations. Nevertheless, loss of Ab has been associated with increased risk of infection in some populations (21;23;59-64). This is of particular concern in immune-compromised populations. For example, hemodialysis patients are protected only while they maintain HBsAb levels > 10 mIU/mL (44). In one series, only 51% of hemodialysis patients with low Ab titers, remote from prior vaccination, developed an anamnestic response to a booster dose of HBV, further suggesting incomplete memory induction or persistence (65). These observations may be relevant to HIV-infected children, in whom Ab responses are less durable than in HIV-uninfected controls, with seroreversion occurring in periods as short as one year (66;67).

Measles
Decline in measles Ab to less than protective levels, and occasionally to undetectable levels, can occur following measles vaccination in HIV-uninfected patients. However, most children and adults retain detectable neutralizing Ab for periods of 4-26 years (68-75). Of those lacking persisting Ab, many, though not all, will manifest an anamnestic response upon revaccination or exposure to wild virus (76). This is in concert with the experience that most, but not all, normal hosts have lifelong protection following vaccination if initial seroconversion occurs (77;78). In HIV-infected patients, Ab responses to measles vaccine decline in periods as short as 9-15 months post-vaccination (79-83).
1.2 Rationale: the P1024 Experience

P1024, “Evaluation of the Immunogenicity of Pneumococcal Conjugate Vaccine and Routine Pediatric Immunizations in HIV-Infected Children Treated with Highly Active Antiretroviral Therapy,” examines the serologic response to vaccination with PCV, PPV, hepatitis B vaccine (HBV) and measles vaccine (MMR) in HIV-infected children on HAART. Subjects received 2 doses of PCV and 1 dose of PPV (at 8-week intervals) and booster doses of HBV and MMR (previously vaccinated subjects) and were followed for 18 months post-vaccinations. Subjects were stratified based on their nadir CD4% prior to HAART and their CD4% at study screening.

Initial data analyses suggest favorable early responses to vaccination that are followed by declining titers within the subsequent 18 months. For example, eight weeks following the conclusion of the pneumococcal vaccination series, 76-96% of subjects achieved serotype-specific pneumococcal ELISA concentrations ≥ 0.5 mcg/mL and 62-88% achieved serotype-specific pneumococcal ELISA concentrations ≥ 1.0 mcg/mL. Geometric mean concentrations (GMCs) for the serotypes tested ranged from 1.44-4.25 mcg/mL. Over the subsequent 18 months, GMCs fell to 0.9-3.42 mcg/mL and the proportion of subjects with ELISA concentrations ≥ 1.0 mcg/mL fell to as low as 42% and 55% for 2 of the 5 serotypes evaluated. Declines occurred in each of the immune strata studied (stratum 1: nadir CD4% <15%/screening CD4% <15%; stratum 2: nadir CD4% <15%/screening CD4% ≥15%; stratum 3: nadir CD4% 15-25%/screening CD4% ≥15%; stratum 4: nadir CD4% ≥25%/screening CD4% ≥25%). Overall, GMCs were directly related to increasing stratum at all timepoints. GMCs fell after 18 months to <1.0–~2 mcg/mL for several serotypes, particularly in strata 1-3. These decreases in Ab titers are not surprising, as they mirror the experience in the general HIV-uninfected population. The key question is whether, despite waning Ab levels following vaccine administration, immunologic memory that may be protective upon re-exposure to the related pathogen persists.

The experience of P1024 is reassuring with regard to the safety of administration of the study vaccines, even to subjects who were seropositive for the relevant immunogen. No treatment-related or possible treatment-related grade 4 events occurred. Treatment-related or possibly treatment-related grade 3 events occurred in 7.6% of subjects, the majority of which were associated with pneumococcal vaccines. Although 75% of subjects had received PPV prior to P1024 entry and 25-87% of subjects had serotype-specific Ab concentrations ≥0.5 mcg/mL at entry, treatment-related or possibly treatment-related grade 3 events occurred in only 1.7% of subjects after the first dose of PCV. Similarly, although 65-93% of subjects had PCV-containing serotype-specific Ab concentrations ≥0.5 mcg/mL after the first dose of PCV, treatment-related or possibly treatment-related grade 3 events occurred in 1.3% of subjects receiving the second dose.
of PCV. Treatment-related or possibly-related grade 3 events occurred in 4.0% of subjects following PPV, despite 74-94% of subjects having had PPV- and PCV-containing serotype-specific Ab concentrations ≥0.5 mcg/mL at the time of PPV administration. The majority of PCV- and PPV-related grade 3 events were local reactions (erythema, localized induration, and localized pain); 1 event consisted of generalized erythema. Additional grade 3 events that were possibly related to PCV or PPV included high fever (4 events), pharyngitis (1 event), and neutropenia (1 event). Grade 3 events that were associated or possibly associated with MMR were fever (4 events), pharyngitis (1 event), fatigue (1 event), and neutropenia (1 event), and grade 3 events that were associated or possibly associated with HBV were localized induration (1 event), localized erythema (1 event), and generalized erythema (1 event). These data are reassuring that vaccine-related adverse events occur at low rates even in the presence of pre-existing seropositivity.

[Note: Response to pertussis vaccine (DTaP), also evaluated in P1024, is not included in this substudy.]

2.0 STUDY OBJECTIVES

2.1 Primary:

2.11 To determine whether HIV-infected children have evidence of pneumococcal type-specific immunologic memory 3-4 years after receiving two doses of PCV and one dose of PPV while on HAART.

2.12 To determine whether HIV-infected children have evidence of hepatitis B-specific immunologic memory 3-4 years after receiving a booster dose of HBV vaccine while on HAART (subsequent to receiving a primary HBV vaccine series previously).

2.13 To determine whether HIV-infected children have evidence of measles-specific immunologic memory 3-4 years after receiving a booster dose of MMR vaccine while on HAART (subsequent to receiving one or more doses of MMR vaccine previously).

2.2 Secondary:

2.21 To compare the immune response to a booster dose of PCV versus a booster dose of PPV subsequent to previous administration of two doses of PCV followed by one dose of PPV while on HAART.

2.22 To evaluate factors that may correlate with memory response to vaccines, including CD4% (nadir, at P1024 study entry, and at P1061s screen/entry), HIV-1
RNA (peak, at P1024 study entry, and at P1061s screen/entry), age, duration of HAART, and change in antiretroviral therapy due to virologic failure (between the end of the P1024 vaccination period and P1061s screen/entry).

2.23 To determine the immunogenicity of PCV, PPV, HBV, and MMR vaccine boosters in HIV-infected children who lack evidence of immunologic memory to these vaccines previously received while on HAART.

2.24 To determine the safety of PCV, PPV, HBV, and MMR booster vaccine doses in HIV-infected children.

3.0 STUDY DESIGN

P1061s is a follow-up substudy to evaluate the persistence of immunologic memory to pneumococcal, hepatitis B and measles vaccines 3-4 years after being administered in P1024, to HIV-infected children on HAART.

The study population is HIV-infected subjects who enrolled into P1024 between June 1, 2001 and March 31, 2002 and completed the initial two-year study period. This includes approximately 224 subjects, out of the original 263 subjects who participated in P1024. Approximately 149 subjects, out of the 224 subjects, are expected to enroll. Enrollment will be completed by January 18, 2006 to allow for the completion of study visits prior to the discontinuation of the PACTG.

Subjects will be stratified into four stratification groups, described in Table 1 below, based on the lowest CD4% prior to entry into P1024 and the CD4% at screening for entry into P1024. Subjects will remain in the stratification groups to which they were assigned during their participation in P1024.

### TABLE 1. Stratification Groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lowest CD4% prior to HAART</th>
<th>CD4% At P1024 Screening</th>
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<tbody>
<tr>
<td>1</td>
<td>&lt; 15%</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 15%</td>
<td>≥15%</td>
</tr>
<tr>
<td>3</td>
<td>15% – &lt;25%</td>
<td>≥15%</td>
</tr>
<tr>
<td>4</td>
<td>≥25%</td>
<td>≥25%</td>
</tr>
</tbody>
</table>

This study plans to accrue approximately 149 subjects from P1024 and will include three study visits – an immunization visit at screen/entry and two follow-up visits at days 7 and 28. Subjects
will receive three immunizations at screen/entry, unless there are contraindications to one or more of the vaccines, in which case they will not receive all study vaccines. Subjects will be randomized in a 1:1 ratio, within stratification groups, to receive either PCV or PPV. All eligible subjects will receive MMR and HBV vaccines. Table 2 below outlines the schedule of study vaccinations and specifies which subjects are/are not eligible to receive each of the study vaccines.

**TABLE 2. Immunizations**

<table>
<thead>
<tr>
<th>Immunizations</th>
<th>Screen/Entry¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>7V PCV²³ or 23V PPV³</td>
<td>X</td>
</tr>
<tr>
<td>HBV⁴</td>
<td>X</td>
</tr>
<tr>
<td>MMR ® II⁵</td>
<td>X</td>
</tr>
</tbody>
</table>

¹Screen and entry will both occur at Visit 1.
²PCV is not FDA-approved for use in children > 9 years of age, but has been used successfully in studies of older children, including in P1024. PCV will be administered in P1061s to subjects from 6-23 years of age.
³Subjects will be randomized in a 1:1 ratio through the Data Management Center (DMC), within stratification groups, to receive either PCV OR PPV at entry. Neither PCV nor PPV will be administered, nor will pneumococcal immune responses be evaluated, if the subject (a) did not receive two doses of PCV plus one dose of PPV in P1024 or (b) has received PCV or PPV since the conclusion of the P1024 vaccination period. Subjects who have had a proven infection with S. pneumoniae, since the end of the P1024 vaccination period, will not be excluded from any evaluations or any of the study vaccines. History of interval pneumococcal infections will be documented in study records.
⁴Subjects who participated in the HBV portion of P1024 (including receipt of HBV vaccine booster) will have their immune response to HBV vaccine evaluated and will receive an additional dose of HBV vaccine at screen/entry. HBV vaccine will not be administered, and HBV-related immune responses will not be evaluated, if the subject (a) did not receive one dose of HBV vaccine in P1024; (b) has received HBV vaccine since the conclusion of the P1024 vaccination period; or (c) has had a documented history of previous, or current, acute or chronic HBV infection.
⁵MMR vaccine will be administered at screen/entry to subjects, all of whom will be ≥ 6 years of age, who previously received the P1024 dose of MMR vaccine, and for whom the two preceding, consecutive, lymphocyte subset measurements indicate a CD4% ≥ 15%, and an absolute CD4 cell count of ≥ 200/mm³. MMR will not be administered, and measles-related immune responses will not be evaluated, if the subject (a) did not receive one dose of MMR vaccine in P1024; (b) has received MMR since the conclusion of the P1024 vaccination period; or (c) has had proven measles infection since the end of the P1024 vaccination period.
Note: Exclusions to a particular vaccine do not apply to the evaluation of immunogenicity of the other study vaccines, nor receipt of the other study vaccines.

Subjects with a grade 3 or higher adverse event (AE) or an allergic reaction, judged to be possibly, or definitely, related to one of the study vaccines, will not receive an additional dose of that vaccine in P1061s. (Subjects with a grade 3 or higher AE or an allergic reaction, judged to be possibly or definitely related to PCV or PPV, will not receive an additional dose of PCV or PPV.) They will be eligible to receive additional doses of the other study vaccines, however.

No antiretroviral study drugs will be supplied as part of this study. This study does not have specific requirements regarding subjects’ current antiretroviral regimen, other than that no changes in antiretroviral therapy be anticipated during the P1061s study period. Subjects will receive up to a total of three vaccinations at screen/entry. All subjects will be monitored for one hour immediately following vaccinations. Telephone contact will be made by study staff three days (+/- 1 day) after the first study visit and, for subjects receiving MMR vaccine, 21 days (+/- 1 day) after the first study visit to evaluate for any vaccine-related complications. Additionally, parents/guardians will be advised to call clinic staff if they are concerned about any signs or symptoms their children are having, or if any symptom appears severe. If there are any ≥ Grade 3 adverse reactions, subjects should be directed to return to the clinic for further evaluation within 48 hours.

Subjects will receive a history, physical exam, and assessment of HIV-related symptoms at each study visit. At screen/entry, PPV or PCV and HBV will each be administered intramuscularly (IM) as a single dose of 0.5 mL. MMR will be administered subcutaneously (SC) as a single dose of 0.5 mL. Blood will be drawn for a series of immunologic tests at the screen/entry visit (prior to vaccine administration) and at the 7 day and 28 day follow-up visits. These tests include pneumococcal type-specific IgG ELISA and Avidity ELISA, hepatitis B ELISA, and measles plaque reduction neutralization and lymphocyte proliferation assays. Peripheral blood mononuclear cells (PBMCs) will also be collected for assays of immunogen-specific memory B cells. Parents/guardians or, when age-appropriate, subjects will complete a diary of vaccine-related events for three days after the screen/entry visit. Additionally, they will be asked to record any symptoms that develop beyond day 3 in the diary. The schedule of laboratory and clinical evaluations for this study is outlined in Appendix I “Schedule of Evaluations.”

The primary endpoints of this study will be the rates of immunologic memory to pneumococcal, measles, and hepatitis B vaccines administered in P1024. Immunologic memory will be evaluated, for each vaccine/serotype tested, by each of the following definitions:

- A secondary (anamnestic) response, defined as a four-fold rise in Ab concentration between day 0 (booster dose) and day 7; OR
- Seropositivity (as defined for each assay) on day 0 or change from seronegative to seropositive between day 0 and day 7.
The first of these definitions represents the classic definition of immunologic memory, providing specific evidence of memory. However, as persisting seropositivity or seropositivity soon after boosting is also suggestive of immunologic memory, the second definition will also be analyzed separately. Responses fulfilling these criteria are not likely to occur in the absence of immunologic memory.

Additionally, for subjects without evidence of immunologic memory, the rates of primary responses (suggestive of a response to booster vaccine dose but not suggestive of immunologic memory) will be characterized according to each of the following definitions:

- A four-fold rise in Ab concentration between day 0 and day 28, but not between day 0 and day 7; OR
- A change from seronegative on Day 0 to seropositive on Day 28, but not between day 0 and day 7.

Subjects with primary responses will be interpreted as having de novo responses to study booster vaccine doses, under the assumption that the failure to detect seropositivity at day 0, or a response at day 7, is an indication of lack of development or loss of memory cells following P1024 vaccination.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Age 6 years to 23 years at screen/entry.

4.12 Completion of the initial 96 week study period in PACTG P1024, with enrollment into P1024 occurring between June 1, 2001 and March 31, 2002.

4.13 Fulfillment of the P1024 definition of HAART (≥ 3 antiretrovirals, from at least two of the available therapeutic classes, i.e., NRTI, NNRTI, PI) during the P1024 vaccination period (P1024 weeks 0-24). (Note: 3 NRTIs without an NNRTI or a PI did not fulfill the P1024 definition of HAART. Additionally, for Kaletra® and other ritonavir-boosted PI regimens, non-therapeutic boosting doses of ritonavir were not counted as a separate antiretroviral).

[For entry in P1061s, treatment with HAART beyond the P1024 vaccination period, subsequent to P1024 participation, or during P1061s participation is not a requirement.]

4.14 Anticipated ability to complete all study vaccinations and evaluations.
4.15 Stable antiretroviral therapy regimen in the four weeks preceding study entry and no anticipated changes to antiretroviral therapy during the P1061s study period.

4.16 Females of child-bearing potential must have a known negative pregnancy test within seven days of the screen/entry visit or at the screen/entry visit, prior to the administration of study vaccines. If sexually active, subjects must agree to consistently use contraception until 3 months after receipt of the last vaccine. Subjects may use any two of the following methods:
- Hormonal contraceptive
- Male or female condoms
- Diaphragm or cervical cap with spermicide
- Intrauterine device

4.17 Parent/legal guardian or subject able and willing to provide signed informed consent and/or assent.

4.2 Exclusion Criteria

4.21 Any of the following laboratory findings on the most recent set of hematology and chemistry studies:
- ALT (SGPT) ≥ 5.0 times the upper limit of normal
- Total bilirubin ≥ 3 times the upper limit of normal (with the exception of known indirect hyperbilirubinemia thought to be due to the use of Atazanavir)
- Serum creatinine ≥ 1.5 mg/dL if < 12 years of age; ≥ 2.0 mg/dL if ≥ 12 years of age
- Absolute neutrophil count ≤ 749 cells/mm³
- Platelet count ≤ 30,000 cells/mm³

4.22 Administration of PCV, HBV, PPV, and MMR vaccines during the P1024 vaccination period in a sequence not concordant with the regimen specified in P1024 (PCV, HBV at entry visit; PCV at 2-month visit; PPV, MMR at 4-month visit).

4.23 Receipt of one or more doses of each of PCV (or PPV), MMR, and HBV vaccines since the conclusion of the P1024 vaccination period.

4.24 Previous grade 3 or higher AEs or allergic reactions judged to be possibly, or definitely, related to each of the PCV (or PPV), MMR, and HBV vaccines.

4.25 Receipt of any killed vaccine within the previous four weeks or any live vaccine within the previous six weeks, or planned killed or live vaccine (other than study vaccines) between the first and third P1061s substudy visits. [Non-study vaccines
may be administered at the third visit but not at the first visit or during the interval between the first and third visits].

4.26 Presence of an underlying condition that contraindicates use of any of the study vaccines (except for HIV infection with CD4% < 15%, which contraindicates MMR administration, but does not otherwise exclude participation in P1061s).

4.27 Current immunomodulatory therapy, including IL-2, any interferon product, GM-CSF, and thalidomide. G-CSF and erythropoietin are not excluded. Subjects for whom immunomodulatory treatment is anticipated during the period of evaluation specified in P1061s are excluded.

4.28 Any intramuscular immune globulin product within the previous six months, intravenous immune globulin within the previous 11 months, and platelets or plasma products within the previous seven months. Subjects for whom immune globulin products, platelets, or plasma products are anticipated during the period of evaluation specified in P1061s are excluded.

4.29 Current systemic immunosuppressive therapy, including the equivalent of ≥ 1 mg/kg/day of prednisone in the preceding two weeks. Subjects for whom treatment with systemic corticosteroids or other systemic immunosuppressive therapy is anticipated during the period of evaluation specified in P1061s are excluded. Subjects receiving inhaled/aerosolized corticosteroid therapy and concurrent ritonavir (boosting or therapeutic dose) in the preceding two weeks and/or subjects for whom inhaled/aerosolized corticosteroid therapy and concurrent ritonavir (boosting or therapeutic dose) is anticipated during the P1061s evaluation period are also excluded. Inhaled corticosteroids in the absence of concurrent ritonavir, topical corticosteroids, and non-steroidal anti-inflammatory agents are not excluded.

4.210 Other known or suspected diseases of the immune system.

4.211 Presence of malignancy within the previous three months or treatment for malignancy currently, or within the previous three months.

4.212 Pregnancy.

4.213 Other acute or chronic medical or surgical conditions or contraindications that, in the opinion of the investigator, may interfere with the evaluation of the protocol objectives.

4.214 Presence of a known bleeding diathesis.
4.215 Presence of any ≥ Grade 2 clinical toxicity at the screening/entry visit, as per P1061s Appendix II, Supplemental Toxicity Table – Vaccine Related Toxicities and Timetable for Reactions. (Note: This exclusion is NOT referring to toxicities outlined in the Division of AIDS Standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences).

4.3 Ineligibility Criteria for Specific Vaccines

4.31 Subjects who did not receive two doses of PCV plus one dose of PPV in P1024 will not have the immune response to PCV/PPV evaluated, nor will they receive PCV or PPV.

4.32 Subjects who did not receive HBV vaccine in P1024 will not have the immune response to HBV vaccine evaluated, nor will they receive HBV vaccine.

4.33 Subjects who did not receive MMR vaccine in P1024 will not have the immune response to measles evaluated, nor will they receive MMR vaccine.

4.34 Subjects for whom the two preceding, consecutive lymphocyte subset measurements do not indicate a CD4% ≥ 15% and an absolute CD4 cell count of ≥ 200/mm³ will not receive MMR vaccine.

4.35 Subjects with a previous Grade 3 or higher AE or an allergic reaction, judged to be possibly, or definitely, related to one of the study vaccines, will not receive an additional dose of that vaccine in P1061s. (Subjects with a previous Grade 3 or higher AE or an allergic reaction, judged to be possibly, or definitely, related to PCV or PPV, will not receive an additional dose of PCV or PPV in P1061s.)

NOTE: These subjects will be eligible to receive additional doses of the other study vaccines, however.

4.36 Subjects who have received one or more doses of PCV or PPV, HBV, or MMR since receipt of the P1024 vaccines will not have the immune response to that specific vaccine evaluated, nor will they receive an additional dose of that vaccine. (Subjects who have received either PCV or PPV since receipt of P1024 vaccines will not have pneumococcal Ab responses evaluated, nor will they receive a dose of PCV or PPV in P1061s.)

NOTE: These subjects will have the immune response to the other study vaccines evaluated and will be eligible to receive additional doses of the other study vaccines, however.
4.37 Previous or current acute or chronic hepatitis B infection excludes subjects from the evaluation of HBV immunogenicity and of receipt of an HBV booster. It does not exclude the evaluation of immunogenicity of the other study vaccines, nor receipt of the other study vaccines.

4.38 Subjects who have had a proven infection with measles since the end of the P1024 vaccination period will be excluded from evaluation of measles vaccine immunogenicity and from receipt of MMR. It does not exclude the evaluation of immunogenicity of the other study vaccines, nor receipt of the other study vaccines.

4.39 Subjects who have had a proven infection with S. pneumoniae since the end of the P1024 vaccination period will not be excluded from any evaluations or any of the study vaccines. History of interval pneumococcal infections will be documented in study records.

4.4 Disallowed Medications/Therapies

The following medications are disallowed:

- Any immune globulin, platelet, and plasma products in the periods defined in 4.28 and during the P1061s substudy period.

- Systemic corticosteroids (equivalent of ≥ 1 mg/kg/day of prednisone) in the two weeks preceding the vaccine visit and during the duration of the P1061s substudy period. Inhaled/aerosolized corticosteroids and concurrent ritonavir (boosting or therapeutic dose) in the two weeks preceding the vaccine visit and during the duration of the P1061s substudy period are also disallowed. Inhaled corticosteroids in the absence of concurrent ritonavir, topical corticosteroids, and non-steroidal anti-inflammatory agents are allowed.

- Other immunosuppressive medications.

- Any interferon product.

- Experimental immune modalities (including IL-2, GM-CSF, or thalidomide). G-CSF and erythropoietin are allowed.

- Live vaccines six weeks before the screen/entry visit and between the first and third P1061s substudy visits. [Non-study vaccines may be administered at the third visit but not at the first visit or during the interval between the first and third visits].
• Killed vaccines four weeks before the screen/entry visit and between the first and third P1061s substudy visits. [Non-study vaccines may be administered at the third visit but not at the first visit or during the interval between the first and third visits].

4.5 Allowed Medications/Therapies

Any medication that is not immune suppressing or immune modulating is allowed in this protocol.

4.6 Enrollment Procedures

Protocol registration for the P1061s substudy, with the DAIDS Protocol Registration Office at the Regulatory Compliance Center (RCC), must occur before any subjects can be enrolled. Eligible children who elect to participate, and meet study entry criteria, will be enrolled according to standard Data Management Center (DMC) procedures. Consent forms will be approved by each participating site’s Institutional Review Board (IRB) and the Protocol Registration Office. Once it has been determined that the subject may qualify for the protocol, the study details will be discussed, questions answered, and written informed consent/assent will be obtained from the parent, legal guardian, or subject before any study-related procedures are performed.

4.7 Co-Enrollment Guidelines:

4.71 Co-enrollment with primary therapy protocols is permitted (as long as all P1061s inclusion and exclusion criteria are met). Enrollment into PACTG 219C, Pediatric Late Outcomes Protocol, is permitted.

4.72 Subjects who are enrolled in protocols evaluating investigational antiretroviral agents may be subsequently co-enrolled in P1061s, as long as all P1061s inclusion and exclusion criteria are met. No impending changes to the current antiretroviral regimen should be planned during the P1061s study period.

Subjects who are enrolled in P1061s may be subsequently co-enrolled in protocols evaluating investigational antiretroviral agents. Whenever possible, changes to the antiretroviral regimen should not be made during the P1061s study period. The primary indication for any change in therapy should be to improve efficacy or reduce toxicity associated with the prior antiretroviral treatment regimen. Exceptions may be made on a case-by-case basis if the new therapy is considered biologically equivalent to the previous treatment regimen. These determinations will be made by the P1061s study chairs, in consultation with the NIAID and NICHD Medical Officers. Changes in antiretroviral therapy should be documented using the appropriate Case Report Form (CRF).
The P1061s study team must be notified regarding any potential co-enrollments into protocols employing investigational antiretroviral agents. In the case of co-enrollments into non-PACTG investigational primary therapy protocols, the P1061s study team will request a copy of the relevant protocols and investigator brochures. All co-enrollments in P1061s and investigational primary therapy protocols, either PACTG or non-PACTG, must be approved by a chair of the P1061s study team. Co-enrollments into non-PACTG investigational primary therapy protocols must also be approved by the NIAID and NICHD Medical Officers. P1061s chairs will be permitted discretion in their consideration of co-enrollments. Sponsors of protocols employing investigational antiretroviral agents must also approve of co-enrollments and, for non-PACTG protocols, the P1061s study team must be supplied with written confirmation of approval by the relevant sponsors.

4.73 Subjects may co-enroll into opportunistic infection protocols, provided that no study drug offered is contraindicated in section 4.4.

4.74 Co-enrollment into studies using any of the vaccines administered in this study is contraindicated. Co-enrollment into studies using vaccines other than those evaluated in this study is also contraindicated if vaccines in the other studies are to be administered during the P1061s study period.

4.75 Co-enrollment into studies which include immunomodulatory therapy is prohibited.

4.76 All co-enrollments, with the exception of PACTG 219C or subsequent versions of PACTG 219, require the assent of the chairs of PACTG P1061s and the co-enrollment protocols, respectively.

5.0 STUDY TREATMENT

5.1 Study Treatment Regimens, Administration, and Duration

5.11 Regimen

AT SCREEN/ENTRY:

Pneumococcal 7-valent Conjugate Vaccine (PCV) 0.5 mL IM**
plus Hepatitis B Vaccine (5 mcg) 0.5 mL IM**
plus Measles, Mumps, and Rubella Virus Vaccine Live 0.5 mL SC**

OR

Pneumococcal Polysaccharide Vaccine (PPV) 0.5 mL IM**
plus Hepatitis B Vaccine (5 mcg) 0.5 mL IM**
plus Measles, Mumps, and Rubella Virus Vaccine Live 0.5 mL SC**

**NOTE: Not all vaccines will be administered to every subject, see special considerations below. Written prescription sent to site pharmacist should clearly state which vaccine(s) to be dispensed to each subject.

Pneumococcal 7-valent Conjugate Vaccine (PCV) 0.5 mL IM OR Pneumococcal Polysaccharide Vaccine (PPV) 0.5 mL IM, to be determined by random assignment in a 1:1 ratio. Neither PCV nor PPV should be administered if the subject:

- did not receive two doses of PCV plus one dose of PPV in P1024;
- has received PCV or PPV since the conclusion of the P1024 vaccination period; or
- had a Grade 3 or higher AE or an allergic reaction, judged to be possibly, or definitely, related to PCV or PPV.

Hepatitis B Vaccine (5 mcg) 0.5 mL IM, to be administered if subject previously received HBV in P1024. HBV vaccine will not be administered if the subject:

- did not receive one dose of HBV vaccine in P1024;
- has received HBV vaccine since the conclusion of the P1024 vaccination period;
- has had a documented history of previous or current acute or chronic HBV infection; or
- had a Grade 3 or higher AE or an allergic reaction, judged to be possibly, or definitely, related to HBV vaccine.

Measles, Mumps, and Rubella Virus Vaccine Live (M-M-R®II) 0.5 mL SC. This should only be given to:

- subjects, all of whom will be ≥ 6 years of age, who previously received the P1024 dose of MMR vaccine and for whom the two preceding, consecutive, lymphocyte subset measurements indicate a CD4% ≥ 15% and an absolute CD4 cell count of ≥ 200 cells/mm³.

MMR will not be administered if the subject:

- did not receive one dose of MMR vaccine in P1024;
- has received MMR since the conclusion of the P1024 vaccination period;
• has had proven measles infection since the end of the P1024 vaccination period; or
• had a Grade 3 or higher AE or an allergic reaction, judged to be possibly, or definitely, related to MMR vaccine.

5.12 Administration

**PNEUMOCOCCAL 7-VALENT CONJUGATE VACCINE (Prevnar®)** may* be administered as a single dose of 0.5 mL IM at screen/entry. Do not inject intravenously. Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. The vaccine should not be used if it cannot be resuspended.

*Note: Subjects will be randomized to receive either PCV or PPV, not both.

**PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PNEUMOVAX 23)** is a clear, colorless liquid preparation. A single dose of 0.5 mL may* be administered IM at screen/entry. Intradermal administration should be avoided. Do not inject intravenously.

*Note: Subjects will be randomized to receive either PCV or PPV, not both.

**MEASLES, MUMPS, AND RUBELLA VIRUS VACCINE LIVE (M-M-R ® II)** is a live virus vaccine administered SC as a single dose of 0.5 mL at screen/entry. Do not inject intravenously.

Reconstitution Instructions: To reconstitute M-M-R ® II, use only the diluent supplied. Single Dose Vial – withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix M-M-R ® II thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine SC. Following reconstitution with the diluent provided, the vaccine is a clear, yellow solution. Discard if not used within eight hours.

**HEPATITIS B VACCINE (Recombinant) (RECOMBIVAX HB®), PEDIATRIC/ADOLESCENT FORMULATION** (preservative free), should be used as supplied; no dilution or reconstitution is necessary. A single dose of 0.5 mL (5 mcg), administered IM, given at screen/entry (if subject was previously fully immunized against HBV). Do not inject intravenously or intradermally. Shake well before use. After thorough agitation, the vaccine is a slightly opaque, white suspension.
FOR ALL VACCINES:

Shake the vial/syringe well to resuspend the contents before withdrawal and before use. Administer by IM or SC injection, as indicated for the specific vaccine. DO NOT inject intravenously or intradermally. Vaccines administered must be recorded in the subject’s permanent medical record and CRF.

Due to the administration of multiple vaccines at the same study visit, vaccines should be administered at separate anatomic sites (i.e., separate extremities) if possible. If vaccines are given in the same extremity, at least one inch should separate injection sites. Vaccination sites should be recorded in the subject’s permanent medical record and CRF.

5.13 Duration

Subjects will be on study for 28 days. Subjects will receive treatment at screen/entry and receive follow-up at 7 and 28 days.

5.2 Study Treatment Formulation

Pneumococcal 7-Valent Conjugate Vaccine (Prevnar®) contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV is a homogeneous, white suspension after shaking. Each 0.5 mL dose contains 2 mcg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 mcg of serotype 6B per dose (16 mcg total saccharide); approximately 20 mcg of CRM 197 carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant. PCV is supplied as ready-to-use single-dose 0.5 mL vials. PCV is stored at refrigerated temperatures of 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Do not use if the vaccine has been frozen.

Pneumococcal Polysaccharide Vaccine (Pneumovax 23) consists of a mixture of purified capsular polysaccharides from 23 types of S pneumonieae. Each 0.5 mL dose of vaccine contains 25 mcg of each polysaccharide type dissolved in isotonic saline solution containing 0.25% phenol as preservative. The 23 pneumococcal capsular types are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F. PNEUMOVAX 23 is supplied as a single-dose vial of liquid vaccine. Store between 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Do not use if the vaccine has been frozen.

Measles, Mumps, and Rubella Virus Vaccine Live (M-M-R® II) is supplied as a single-dose vial of lyophilized vaccine and a vial of diluent. Each 0.5 mL dose contains not less than 1,000 TCID₅₀ (tissue culture infectious doses) of measles virus; 20,000 TCID₅₀ of mumps virus; and 1,000 TCID₅₀ of rubella virus. Each dose of the vaccine is calculated to contain 25 mcg of neomycin. Protect the vaccine from light at all times, since such exposure may inactivate the virus. Before reconstitution, store the vial of lyophilized
vaccine at 2°C to 8°C (36°F to 46°F) or colder. The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. Store reconstituted vaccine in the vaccine vial in a dark place at 2°C to 8°C (36°F to 46°F) and discard if not used within eight hours. DO NOT FREEZE. Do not use if the vaccine has been frozen.

**Hepatitis B Vaccine (Recombinant) (RECOMBIVAX HB®) Pediatric/Adolescent Formulation (preservative free),** 5 mcg/0.5 mL (the standard pediatric dose will be used for assessing booster responses for all subjects, regardless of age). Hepatitis B Vaccine for use in infants, children, and adolescents is supplied as 5 mcg/0.5 mL of HBsAg in a 0.5 mL single-dose vial. The vaccine should be stored at 2-8°C (36°F-46°F). DO NOT FREEZE. Do not use if the vaccine has been frozen.

For all vaccines, refrigerate immediately on arrival. Store at 2°C to 8°C (36°F -46°F). DO NOT FREEZE. For vaccine that has been frozen, the pharmacist should follow the return instructions in the manual, “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks.” Return to the NIAID Clinical Research Products Management Center (CRPMC).

### 5.3 Study Agents Supply, Distribution, and Pharmacy

- **Pneumococcal 7-Valent Conjugate Vaccine (Prevnar®)** will be provided by Wyeth-Lederle Vaccines.

- **Pneumococcal Polysaccharide Vaccine (Pneumovax 23)** will be provided by Merck and Co.

- **Measles, Mumps, and Rubella Virus Vaccine Live (M-M-R ® II)** will be provided by Merck and Co.

- **Hepatitis B Vaccine (Recombinant) (RECOMBIVAX HB®), Pediatric/Adolescent Formulation (preservative free),** will be provided by the PACTG.

Study agents will be available through the NIAID CRPMC. The ACTU pharmacist can obtain the study agents for the protocol by following the instructions in the manual “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks” in the section entitled Study Product Control.

The NIAID CRPMC will not provide antiretroviral therapy, syringes, or supplies for administration of vaccines as part of this study.

The ACTU pharmacist is required to maintain complete records of all study vaccine received from the NIAID CRPMC and subsequently dispensed. All unused study vaccine must be returned to the NIAID CRPMC after the study is completed or terminated. The
procedures to be followed are given in the manual, “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks” in the section entitled Study Product Control.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (>3 mos [April, 1994]) and the Supplemental Toxicity Table for Vaccine-Related Toxicities (Appendix II) will be used for grading toxicities for all subjects, regardless of age. Appendix II supersedes the Division of AIDS Toxicity Table when grading vaccine-related clinical toxicities.

Toxicities will generally be considered potentially vaccine-associated if their onset occurs within the following periods post-immunization:

- PCV, HBV, PPV - 7 days
- M-M-R®II- 28 days

In addition, any severe and unexplained toxicities will be evaluated for possible vaccine-association, regardless of the interval since immunization. Toxicities will not be considered vaccine-associated AEs if alternative, clearly recognized etiologies are identified.

At screen/entry, a determination should be made about the subject's eligibility to receive his/her scheduled study vaccines. Current clinical status, vaccine-associated toxicities identified following previous P1024 immunizations, and laboratory results obtained will dictate whether a subject is eligible to receive the vaccines scheduled at screen/entry.

A clinic visit is required within 48 hours for all toxicities that are ≥ Grade 3 that were not present at screen/entry, as defined in Appendix II or The Division of AIDS Standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (1994). For all toxicities of ≥ Grade 3 not present at screen/entry, sites should submit an SAE report and notify the protocol co-chairs within 48 hours. All PACTG investigators will perform appropriate clinical evaluation and management of AEs, according to the situation. Abnormal clinical and laboratory tests should be repeated, according to clinical indications, until toxicity falls to ≤ Grade 1 or to status at screen/entry. The protocol co-chairs may be contacted to discuss AEs if the investigator is unsure of the relationship of the toxicity to study vaccines.

6.2 Study Management Plan
6.21 Study immunizations may be administered in the presence of a mild acute illness with or without low-grade fever (< 100.4°F). Study immunizations should be withheld in the presence of moderate or severe illness.

6.22 The immunogenicity of an HBV booster dose will only be studied in children who had previously received an approved primary HBV series and a booster dose of HBV vaccine while participating in PACTG P1024. HBV vaccine should not be administered to subjects who, in the opinion of the investigator, have had a previous severe adverse reaction that should preclude receipt of subsequent HBV vaccine. The immunogenicity of an HBV booster will not be studied in subjects with documented previous, or current, acute or chronic HBV infection. Subjects will, however, be able to participate in the rest of the study.

6.23 MMR®II should not be administered to subjects who, in the opinion of the investigator, have had a previous severe adverse reaction that should preclude receipt of subsequent M-M-R®II vaccine. Greater than six months since receipt of any intramuscular immune globulin product, greater than 11 months since receipt of any intravenous immune globulin, and greater than seven months since receipt of any platelets or plasma products should have elapsed prior to administration of M-M-R®II. Females of child-bearing potential must have a documented negative pregnancy test performed at the screen/entry visit or within seven days prior to receiving M-M-R®II vaccine (a negative result must be known prior to the administration of study vaccines).

6.24 Parents/guardians or, when age-appropriate, subjects will complete a diary of vaccine-related events for three days after the screen/entry visit. Additionally, they will be asked to record any symptoms that develop beyond day 3 in the diary. All subjects will be monitored for one hour immediately following vaccinations. Telephone contact will be made by study staff three days (+/- 1 day) after the first study visit and, for subjects receiving MMR vaccine, 21 days (+/- 3 days) after the first study visit to evaluate for any vaccine-related complications. Additionally, parents/guardians will be advised to call clinic staff if they are concerned about any signs or symptoms their children are having, or if any symptom appears severe. If there are any ≥ Grade 3 adverse reactions not present at entry, as defined in Appendix II or The Division of AIDS Standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (1994), subjects should be directed to return to the clinic for further evaluation within 48 hours. Vaccine-related events diaries will be collected and reviewed at the day 28 visit.

6.3 Criteria for Treatment or Study Discontinuation

Indications for treatment discontinuation, but continuing scheduled study-dictated evaluations include the following:
• The investigator determines that receipt of additional study immunizations would be detrimental to the subject’s health or well-being.

• The subject or legal guardian refuses additional study immunizations.

Indications for discontinuing participation in the study include the following:

• The subject or legal guardian refuses follow-up evaluations.

• The subject/guardian fails to comply with the study requirements, so as to cause harm to the subject or seriously interfere with the validity of the study results.

• The investigator determines that further participation would be detrimental to the subject's health or well-being.

Subjects who are to discontinue study participation should complete the evaluations listed in Appendix I, in the column entitled Premature Study Discontinuation, at their off-study visit.

Subjects who require treatment with disallowed medications, or other disallowed therapies, subsequent to the screen/entry visit, but while still on study or follow-up, should complete the day 7 and day 28 study visits.

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

This protocol follows intensive reporting requirements, which are defined in the Division of AIDS Serious Adverse Experience (SAE) Reporting Manual (August, 1998). Serious Adverse Experience (SAE) forms should be submitted to the DAIDS RCC Safety Office, as described in the SAE Reporting Manual.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

P1061s is a substudy of P1024. P1024 enrolled 263 HIV-infected children, between the ages of 2 and < 19 years, who had been on the same HAART regimen \( \geq 6 \) months for CD4% Groups 2-4; or \( \geq 3 \) months for CD4% Group 1. For these children, HIV-1 RNA levels at screening were below 30,000 copies/mL, for CD4% Groups 2-4; or below 60,000 copies/mL for CD4% Group 1. To ensure adequate accrual of subjects representing a broad range of immunologic status, both before receipt of HAART, and at the time of study entry, P1024 was stratified into four groups based on the subjects’
CD4% at the time of study screening and lowest pre-HAART CD4%. The most impaired children were enrolled into the stratum with a pre-HAART nadir CD4% < 15% and a CD4% at study screening < 15%. Only 16 subjects were accrued to this stratum, well short of its target accrual of 75 subjects. The remaining strata met or exceeded the targeted accrual goal of 75 subjects per stratum. Since age may be a factor in immunogenicity, these four immunologic groups were further stratified by age at entry, with a maximum of 50 subjects ≥ 7 or < 7 years of age within each CD4% group.

Subjects participating in P1061s will remain in the stratification groups to which they were assigned during their participation in P1024. The purpose of stratifying subjects by immunologic history and age was to ensure adequate accrual across a range of immunologic histories and ages, but P1024 was not powered to detect anything other than very large differences in response rates among stratification levels. Likewise, P1061s is not powered for such comparisons. Thus, the primary results will consist of estimates of immunologic response rates and AEs, bounded by 95% confidence intervals (CIs), within immunologic strata.

8.2 Outcome Measures

8.21 Safety:

≥ Grade 3 laboratory values (hematologic and chemistry), signs or symptoms not present at the day 0 baseline evaluation of this substudy, as specified in Appendix II and The Division of AIDS Standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (>3mos [April, 1994]). The relationship to vaccination boosters administered in this substudy will be assessed by the site and subsequently reviewed by the study team.

8.22 Immunogenicity:

- Seropositivity:

PCV and PPV: Serotype-specific Ab (serotypes 1, 6B, 14, 19F, 23F) will be measured at days 0, 7, and 28 by ELISA (IgG). Positive assays will be defined as an Ab concentration ≥ 0.5 mcg/mL. An alternative criterion of ≥1.0 mcg/mL will also be examined, as this threshold has been suggested by some investigators.

Measles: Ab levels will be measured at days 0, 7, and 28, by plaque reduction neutralization (IgG). Positive assays will be defined as a titer ≥ 1:120.

HBV: Ab levels will be measured at days 0, 7, and 28, by EIA (total Ig). Positive assays will be defined as an Ab concentration ≥ 10 mIU/ml.

[Note: for all assays, day 0, 7, and 28 specimens from each subject will be tested concurrently.]

- Immunologic Memory:
Evidence of immunologic memory will be analyzed separately, according to each of the following definitions:

(a) Secondary (anamnestic) response defined as a four-fold rise in Ab concentration between day 0 (booster dose) and day 7;

OR

(b) Seropositivity (as defined for each assay) on day 0 or change from seronegative to seropositive between day 0 and day 7.

• Evidence of a primary response (suggestive of a response to the booster vaccine dose, but not suggestive of immunologic memory) will be analyzed separately according to each of the following definitions:

(a) A four-fold rise in Ab concentration between day 0 and day 28, but not between day 0 and day 7;

OR

(b) A change from seronegative on day 0 to seropositive on day 28, but not between day 0 and day 7.

• Additional measures of immunologic memory:

Pneumococcal type-specific avidity ELISA (serotypes 1, 6B, 14, 19F, 23F), measles lymphocyte proliferation assays, and immunogen-specific (measles, hepatitis B, pneumococcal) memory B cell assays will also be performed; results will be correlated with evidence of immunologic memory, as defined above.

8.3 Randomization and Stratification

Subjects will be randomized in a 1:1 ratio within strata to receive either PCV or PPV.

Subjects participating in P1061s will remain in the stratification groups to which they were assigned during their participation in P1024. The four immunologic strata are as follows:

TABLE 3:

<table>
<thead>
<tr>
<th>Pre-HAART nadir CD4%</th>
<th>&lt;15%</th>
<th>15.0 to &lt;25%</th>
<th>≥ 25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15%</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Numbers 1-4 in table 3 refer to the stratification groups outlined in the Schema. Each of the four groups was further stratified by age (≥ 7 years and < 7 years), with a maximum of 50 subjects ≥ 7 or < 7 years of age within each CD4% group.

No further stratification will occur as part of this substudy; however, subject distribution will be influenced by the stratification groups assigned in P1024.

8.4 Sample Size and Accrual

244 of the 263 subjects enrolled in P1024 were accrued between June 1, 2001 and March 31, 2002. Accrual significantly decreased following this period of rapid enrollment. Of the 244 subjects enrolled during the period of rapid enrollment, 20 subjects were subsequently removed from P1024 due to eligibility issues, withdrew consent prior to the conclusion of the P1024 study period, or came off study prior to the conclusion of the P1024 study period. To expedite the completion of evaluations of subjects at a similar interval following P1024 study vaccinations, enrollment into P1061s will be limited to the 224 subjects who enrolled into P1024 during the peak accrual period and completed the P1024 study period. Based on when the four-month P1024 study visits occurred for each subject (conclusion of the pneumococcal, hepatitis B, and measles vaccinations) and the planned period of P1061s enrollment (8/01/05-1/18/06), the potential range of intervals from P1024 vaccinations to P1061s screen/entry is 3.0 – 4.3 years. It is anticipated that 2 out of 3 of potentially eligible subjects will be enrolled into P1061s, yielding a sample size of approximately 149 subjects. However, it is possible that actual accrual may be more (up to a maximum of 224) or less than this number. Table 4 demonstrates the distribution of potential P1024 study subjects eligible for recruitment into P1061s, according to P1024 immunologic strata. This distribution suggests that enrollment into P1061s for strata 2-4 will likely exceed enrollment for stratum 1. Because enrollment into P1024 stratification Group 1 was low, especially prior to 3/31/02, the number of subjects in this group in P1061s will also be low. However, because this group represents the most immune-compromised subjects in P1024, it will be retained as an important observational cohort.

| 15.0 to ≤25% | 3 | 3 |
| ≥ 25% | 4 |

TABLE 4. Eligible subjects for P1061s.
Among the 224 subjects potentially eligible for participation in P1061s, large majorities received each of the P1024 study vaccinations, overall, and within each stratification group (with the exception of MMR in group 1, for which a low CD4% precluded most from receiving MMR):

- 216/224 (96%) received PCV1, PCV2, and PPV: 9 in group 1, 69 in group 2, 78 in group 3, and 60 in group 4
- 210/224 (94%) received MMR: 2 in group 1, 69 in group 2, 78 in group 3, and 61 in group 4
- 200/224 (89%) received HBV: 7 in group 1, 59 in group 2, 73 in group 3, and 61 in group 4

In order to demonstrate how the precision with which rates of immunologic memory will depend upon the sample sizes of vaccine-eligible subjects accrued to each stratum, table 5 provides 95% CIs around potential rates of immunologic memory, assuming a range of potential sample sizes.
TABLE 5. Sample Size Within a Given Stratum

<table>
<thead>
<tr>
<th>Rate of immunologic memory (Upper, Lower 95% Confidence Limits)</th>
<th>10</th>
<th>30</th>
<th>50</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>.10</td>
<td>(.003,.45)</td>
<td>(.02,.27)</td>
<td>(.03,.22)</td>
<td>(.04,.20)</td>
</tr>
<tr>
<td>.30</td>
<td>(.07,.65)</td>
<td>(.15,.49)</td>
<td>(.18,.45)</td>
<td>(.20,.42)</td>
</tr>
<tr>
<td>.50</td>
<td>(.19,.81)</td>
<td>(.31,.69)</td>
<td>(.36,.64)</td>
<td>(.38,.62)</td>
</tr>
<tr>
<td>.70</td>
<td>(.35,.93)</td>
<td>(.51,.85)</td>
<td>(.55,.82)</td>
<td>(.58,.80)</td>
</tr>
<tr>
<td>.90</td>
<td>(.55,.997)</td>
<td>(.73,.98)</td>
<td>(.78,.97)</td>
<td>(.80,.96)</td>
</tr>
</tbody>
</table>

For example, the first entry indicates that, with a sample size of 10 vaccine-eligible subjects within a stratum, a rate of immunologic memory of .10 (1/10) would estimate the population rate as falling somewhere within a 95% CI which extends from a rate of .003 to a rate of .45. Table 5 indicates that rates within Groups 2-4 may be estimated with reasonable precision, if the sample sizes anticipated by the protocol team are actually accrued.

Enrollment must be completed by January 18, 2006 to allow for the completion of study visits prior to the discontinuation of the PACTG.

8.5 Monitoring

Toxicity reviews will be performed during monthly team calls and accrual will be monitored. A safety analysis will be done at the conclusion of P1061s to identify any unusual or excess rates of adverse effects that may occur following the administration of booster doses of the P1061s study vaccines.

8.6 Analysis

Primary:

- AEs:

Based upon the P1024 data, low rates of Grade 3 or 4 AEs are anticipated. The rates which are observed will be reported for each immunologic stratum and will be bounded by 95% CIs. Likewise, the rates of such events, which have been
attributed to the study vaccines, will be calculated for each immunologic stratum, along with 95% CIs.

- **Immunology:**

The primary immunologic hypotheses for this substudy are the following:

1. Some, but not all, HIV-infected children who received two doses of PCV and one dose of PPV while on HAART, will have evidence of pneumococcal type-specific immunologic memory.

2. Some, but not all, HIV-infected children who received a booster dose of HBV vaccine while on HAART, will have evidence of hepatitis B-specific immunologic memory.

3. Some, but not all, HIV-infected children who received a booster dose of MMR vaccine while on HAART, will have evidence of measles-specific immunologic memory.

These hypotheses will be addressed by calculating 95% CIs around the rates, within each immunologic stratum, of immunologic memory (using the criteria defined in Section 8.22). The response criteria are defined in terms of a four-fold increase of Ab concentration between day 0 and day 7, seropositivity on day 0, and/or seropositivity on day 7. Responses fulfilling these criteria are not likely to occur in the absence of immunologic memory. Estimation of these response rates comprises the primary analyses for this study.

Further analyses will consist of logistic regression models, with rates of immunologic memory (yes/no) to each vaccine (and serotype) as outcomes, and with stratification factors (immunologic and age) as predictors. The main effects of these models will test whether response rates vary significantly as a function of these factors. Interaction terms will be introduced to test whether the effects of immunologic strata vary as a function of age.

**Secondary:**

Secondary immunologic hypotheses include the following:

1. Both PCV and PPV will boost Ab levels to vaccine-containing serotypes in HIV-infected children who received two doses of PCV, followed by one dose of PPV, while on HAART.
This hypothesis will be addressed by calculating CIs around the rates of secondary (anamnestic) responses (4-fold rise in Ab concentration between day 0 [booster dose] and day 7) and the rates of conversion from seronegative to seropositive between day 0 and day 7 for each pneumococcal serotype tested, following a PCV booster dose versus a PPV booster dose. Four-fold rises and/or conversion from seronegative to seropositive between day 0 and day 7 will be interpreted as indications of the ability of the vaccines to stimulate memory cells to boost Ab levels. Although the study is not powered to compare the effects of PCV with those of PPV, the geometric mean titers (GMCs) of the groups receiving these two vaccines will be compared by means of t-tests performed for each serotype. Only unexpectedly strong differences would result in statistically significant differences.

2. Factors that correlate with memory responses to vaccines will include CD4% (nadir, at P1024 study entry, and at P1061s screen/entry), HIV-1 RNA (peak, at P1024 study entry, and at P1061s screen/entry), age, duration of HAART, and change in antiretroviral therapy due to virologic failure (between the end of the P1024 vaccination period and P1061s screen/entry).

Subjects with evidence of immunologic memory to each vaccine and serotype will be compared with subjects lacking evidence of memory, with respect to the variables listed above. For continuous variables, statistical tests will consist of t-tests (in cases in which the data can be assumed to be normally distributed) or Wilcoxon sum ranks tests (in cases where this assumption does not appear to be justified). With categorical variables, statistical tests will consist of chi-squared tests, if the sample size is adequate; or Fisher’s exact tests, if the sample size is too small to meet the assumptions of the chi-squared test.

3. Some, but not all, HIV-infected children who lack immunologic memory to PCV, PPV, HBV, and MMR vaccines received while on HAART will have evidence of primary responses to booster doses of these vaccines.

Secondary analyses will calculate rates and 95% CIs of primary responses to P1061s booster vaccinations (using the criteria defined in Section 8.22). Subjects with primary responses will be interpreted as having de novo responses to study vaccines, under the assumption that the failure to detect seropositivity at day 0 or a response at day 7 is an indication of lack of development of, or loss of, memory cells following P1024 vaccination. Further analyses will consist of logistic regression models, with rates of primary responses (yes/no) to each vaccine (and serotype) as outcomes, and with stratification factors (immunologic and age) as predictors. The main effects of these models will test whether response rates vary significantly as a function of these factors. Interaction terms will be introduced to test whether the effects of immunologic strata vary as a function of age.
Additional analyses will focus on the detection of potential indicators of immunologic memory, other than the criteria defined in Section 8.22 (e.g., pneumococcal high avidity Ab, immunogen-specific memory B cells, and measles cell-mediated immune responses). Data measuring these types of responses will be presented descriptively and correlated with the indicators of immunologic memory specified in Section 8.22.

9.0 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.

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix V), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee (EC) responsible for oversight of the 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 legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent document 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 resigns the consent. The plan should follow all IRB, local, and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 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/parent/legal guardian, except as necessary for monitoring by the FDA, the
pharmaceutical sponsor, NIAID, the site IRB, the Office for Human Research Protection (OHRP), or the sponsor’s designee.

9.3 Study Discontinuation

The study may be discontinued at any time by the FDA, NIAID, pharmaceutical sponsors, the site IRB, or other government agencies, as part of their duties to ensure that research subjects are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

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

11.0 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 650 for Diagnostic Specimens. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.
12.0 REFERENCES


(53) Chan CY, Lee SD, Tsai YT, Lo KJ. Booster response to recombinant yeast-derived hepatitis B vaccine in vaccinees whose anti-HBs responses were initially elicited by a plasma-derived vaccine. Vaccine 1991; 9(10):765-767.


Ref Type: Abstract


# APPENDIX I
## SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen/Entry&lt;sup&gt;16&lt;/sup&gt;</th>
<th>On Treatment: Study Day/Visit</th>
<th>Premature Study Discontinuation&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
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</tr>
<tr>
<td>History&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>X</td>
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<tr>
<td>Physical exam&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Assessment of HIV-related symptoms&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>X</td>
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<td>IMMUNIZATIONS&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>PCV&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>M-M-R®&lt;sup&gt;6&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>HBV&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td>LABORATORY EVALUATIONS</td>
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<tr>
<td>Hematology (purple top)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
<td></td>
</tr>
<tr>
<td>Chemistries (red top)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
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</tr>
<tr>
<td>Beta HCG (urine)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>VIROLOGY (see Appendix III)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HIV RNA (purple top)</td>
<td>2mL</td>
<td></td>
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<td>PACTG-Certified Virology Core Lab</td>
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<tr>
<td>IMMUNOLOGY (see Appendix IV)</td>
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<tr>
<td>Lymphocyte subsets (purple top)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1mL</td>
<td></td>
<td></td>
<td>ACTG-Certified Flow Lab</td>
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</tbody>
</table>
### APPENDIX I (Cont.)

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen/Entry&lt;sup&gt;16&lt;/sup&gt;</th>
<th>On Treatment: Study Day/Visit&lt;sup&gt;17&lt;/sup&gt;</th>
<th>Premature Study Discontinuation&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green top/Heparinized Tube: PBMCs for measles cell-mediated immunity&lt;sup&gt;12&lt;/sup&gt;</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>Measles CMI and serology: CDC</td>
</tr>
<tr>
<td>Plasma for measles serology (0.5 mL)&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>Plasma for pneumococcal serology (1 mL)&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td>Pneumococcal serology: Boston University</td>
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<tr>
<td>Plasma for hepatitis B serology (1 mL)&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis B serology: UCSF</td>
</tr>
<tr>
<td>Store remaining plasma&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Stored plasma: Assigned Core Lab</td>
</tr>
<tr>
<td>Green top/Heparinized Tube: Store PBMCs&lt;sup&gt;15&lt;/sup&gt;</td>
<td>10 mL</td>
<td>10 mL</td>
<td>10 mL</td>
<td>Stored PBMCs: Assigned Core Lab</td>
</tr>
<tr>
<td>Store plasma&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Stored plasma: Assigned Core Lab</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL)</td>
<td>20 mL</td>
<td>15 mL</td>
<td>17 mL</td>
<td>17 mL</td>
</tr>
</tbody>
</table>
APPENDIX I (Cont.)

1. History – at the screen/entry visit, record pneumococcal (PCV, PPV), measles, and Hepatitis B vaccinations since the week 16 P1024 visit; record proven pneumococcal, measles, and hepatitis B infections since the week 16 P1024 visit; record new diagnoses since the week 96 P1024 visit; record antiretroviral history since the P1024 entry visit (and reasons for changes in antiretroviral therapy); and record current medications (antiretrovirals and others). At subsequent visits, record any vaccine-related complications; new diagnoses; changes in medications and indications for changes in medications; and symptoms present since the preceding study visits.

2. Physical Exam - weight, vital signs [temperature, blood pressure, pulse, and respiratory rate] at all visits. At the screen/entry visit: examination of skin, lungs, joints, muscles, general neurologic/mental state, and other systems, as appropriate, for intercurrent history. At subsequent visits: targeted exam evaluating anatomic sites at which immunizations were administered at the screen/entry visit and signs/symptoms suggestive of vaccine-related toxicities (see Appendix II).

3. Assessment of HIV-related symptoms – record current symptoms.

4. Subjects will receive up to a total of three vaccinations at screen/entry. Parents/guardians or, when age-appropriate, subjects will complete a diary of vaccine-related events for three days after screen/entry. Additionally, they will be asked to record any symptoms that develop beyond day 3 in the diary. All subjects will be monitored for one hour, immediately following vaccinations. Telephone contact will be made by study staff three days (+/- 1 day) after the first study visit and, for subjects receiving MMR vaccine, 21 days (+/- 1 day) after the first study visit, to evaluate for any vaccine-related complications. Additionally, parents/guardians will be advised to call clinic staff if they are concerned about any signs or symptoms their children are having, or if any symptom appears severe.

5. Subjects will either be immunized with PCV or PPV, not both. Neither PCV nor PPV should be administered if the subject either (a) did not receive two doses of PCV plus one dose of PPV in P1024; or (b) has received PCV or PPV since the conclusion of the P1024 vaccination period.

6. MMR®II should be administered only to subjects, all of whom will be ≥ 6 years at screen/entry, who previously received the P1024 dose of MMR vaccine and for whom the two preceding, consecutive, lymphocyte subset measurements indicate a CD4% ≥15% and an absolute CD4 cell count of ≥200/mm³. MMR will not be administered, if the subject (a) did not receive one dose of MMR vaccine in P1024; (b) has received MMR since the conclusion of the P1024 vaccination period; or (c) has had proven measles infection since the end of the P1024 vaccination period.

7. HBV vaccine will not be administered if the subject (a) did not receive one dose of HBV vaccine in P1024; (b) has received HBV vaccine since the conclusion of the P1024 vaccination period; or (c) has had a documented history of previous, or current, acute or chronic HBV infection.

8. Hematology - Complete blood count (CBC), cell differential, platelet count must be obtained within the preceding 90 days of the screen/entry visit; if results are abnormal, or not available, these tests should be repeated at the screen/entry visit. Repeat CBC, cell differential, and platelet count are required at the day 28 visit and at the premature study discontinuation visit.
APPENDIX I (Cont.)

9. Chemistries - Total bilirubin, direct bilirubin, ALT, and creatinine must be obtained within the preceding 90 days of the screen/entry visit; if results are abnormal, or not available, these tests should be repeated at the screen/entry visit. Repeat total bilirubin, direct bilirubin, ALT, and creatinine are required at the day 28 visit and at the premature study discontinuation visit.

10. Beta HCG (urine) - Females of childbearing potential will be given a pregnancy test at the screen/entry visit or within seven days prior to receiving M-M-R®II vaccine. A negative result must be known prior to the administration of study vaccines.

11. Lymphocyte subsets - Basic lymphocyte phenotyping including CD3/CD4, CD3/CD8, CD19 will be performed. Tests are to be performed locally in an ACTG certified flow lab, according to its standard sample requirements (usually 3 mL purple top K3 EDTA tube).

12. Measles serology (Plaque Reduction Neutralization) and Cell-Mediated Immunity Assay (lymphocyte proliferation assay) – will be measured only in children who received MMR in P1024, have not received MMR since the conclusion of the P1024 vaccination period, and who have not had documented measles infection since the conclusion of the P1024 vaccination period. For cell-mediated immunity assay, use PACTG cryopreservation protocol: collect 5 mL blood in heparin-containing tube and send to PICL at room temperature overnight. PBMCs are separated and cryopreserved at PICL per PACTG Immunology website consensus protocol (using Mr. Frosty freezing chambers). Cells are frozen at 5-10 x 10⁶ PBMC/vial.

13. Pneumococcal serology – ELISA (serotypes 1, 6B, 14, 19F, 23F, 7, 22, 15) and Avidity Assay – will be measured only in children who received two doses of PCV and one dose of PPV in P1024 and who have not received PCV or PPV since the conclusion of the P1024 vaccination period.

14. Hepatitis B serology - ELISA antibody (Ab) will be measured only in children who received HBV vaccine in P1024, have not received HBV vaccine since the conclusion of the P1024 vaccination period, and who do not have previous or current acute or chronic HBV infection.

15. Stored PBMCs/plasma – Plasma is to be stored and frozen (for retesting or replacement of specimens, as needed, and for additional serologic assays of immunologic memory, as they become available, e.g., Hepatitis B Avidity ELISA); PBMCs are to be stored and frozen for hepatitis B, measles, and pneumococcal memory B cell assays. PBMCs are to be separated and frozen using PACTG cryopreservation protocol: site should collect 10 mL blood in heparin-containing tube and send to PICL at room temperature overnight. PBMCs are separated and cryopreserved at PICL per PACTG Immunology website consensus protocol (using Mr. Frosty freezing chambers). Cells should be frozen at 5-10 x 10⁶ PBMC/vial.

16. The screen/entry (1st) visit should occur by January 18, 2006.

17. The 2nd study visit should follow the screen/entry visit by 7 (± 2) days.

18. The 3rd study visit should follow the screen/entry visit by 28 (± 4) days.

19. Subjects who discontinue treatment, but remain on study, should complete all evaluations at each of the regularly scheduled visits. Subjects who are to discontinue study participation should complete the evaluations listed in this column at their off-study visit.
APPENDIX I (Cont.)

For insufficient blood draws, priorities are as follows:

Visit 1
1. CBC, differential, platelet count (if abnormal within the preceding 90 days or are not available)
   Total bilirubin, direct bilirubin, ALT, creatinine (if abnormal within the preceding 90 days or are not available)
   Basic lymphocyte phenotyping (CD3/CD4, CD3/CD8, CD19)
   Quantitative plasma HIV-1 RNA PCR
   Green top/heparin tube (5 mL): Plasma for Pneumococcal serology (IgG ELISA and IgG Avidity ELISA)
      Plasma for Measles serology (plaque reduction neutralization)
      Plasma for Hepatitis B serology (surface Ab ELISA)
      PBMCs for measles cell-mediated immunity
   
   Subtotal = 10 mL

2. Green top/heparin tube (10 mL): Store PBMCs
   Store plasma

Visit 2
1. Green top/heparin tube (5 mL): Plasma for Pneumococcal serology (IgG ELISA and IgG Avidity ELISA)
   Plasma for Measles serology (plaque reduction neutralization)
   Plasma for Hepatitis B serology (surface Ab ELISA)
   PBMCs for measles cell-mediated immunity

2. Green top/heparin tube (10 mL): Store PBMCs
   Store plasma

Visit 3
1. CBC, differential, platelet count – purple top – 1 mL
   Total bilirubin, direct bilirubin, ALT, creatinine – red top – 1 mL
   Green top/heparin tube (5 mL): Plasma for Pneumococcal serology (IgG ELISA and IgG Avidity ELISA)
      Plasma for Measles serology (plaque reduction neutralization)
      Plasma for Hepatitis B serology (surface Ab ELISA)
      PBMCs for measles cell-mediated immunity
   
   Subtotal = 7 mL

2. Green top/heparin tube (10 mL): Store PBMCs
   Store plasma
## APPENDIX II

**SUPPLEMENTAL TOXICITY TABLE - VACCINE-RELATED TOXICITIES AND TIMETABLE FOR REACTIONS**

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3*</th>
<th>GRADE 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema: diameter (mm) of skin redness at the site of injection</strong></td>
<td>Present but &lt; 25 mm (size of a quarter)</td>
<td>≥ 25mm but &lt; 50% of the extremity</td>
<td>≥ 50% of the extremity</td>
<td></td>
</tr>
<tr>
<td><strong>Induration: diameter (mm) of palpable hardness of the skin at the site of injection</strong></td>
<td>Present but &lt; 25 mm (size of a quarter)</td>
<td>≥ 25mm but &lt; 50% of the extremity</td>
<td>≥ 50% of the extremity</td>
<td></td>
</tr>
<tr>
<td><strong>Pain: subjective report from child (or parent if child is too young)</strong></td>
<td>Mild tenderness at injection site</td>
<td>Moderate pain without limitation of usual activities</td>
<td>Pain must be judged to be severe and require analgesics &gt; 4 hours after immunization, or it must be severe and limit usual activities. If pain is not judged to be severe, it should NOT be considered Grade 3 (even if analgesics are given &gt; 4 hours after immunization).</td>
<td>Severe pain not responding to analgesics</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Injection site only</td>
<td>Generalized, &lt; 50% body surface</td>
<td>Generalized, ≥ 50% body surface</td>
<td>Hemorrhagic</td>
</tr>
<tr>
<td><strong>Abscess (sterile or bacterial)</strong></td>
<td></td>
<td>1</td>
<td>&gt; 1</td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>≥ 100.4°F but &lt; 103°F</td>
<td>≥ 103°F but &lt; 105°F</td>
<td>&gt; 105°F</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue/weakness/malaise/anorexia</strong></td>
<td>Transient, no limit on Activities of Daily Living (ADL), no therapy needed</td>
<td>Mild to moderate impact on ADL &lt; 48 hours (no intervention needed)</td>
<td>&gt; 48 hours or marked impact on ADL requiring medical intervention</td>
<td>Completely disabling requiring hospitalization</td>
</tr>
</tbody>
</table>
APPENDIX II (Cont.)

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3*</th>
<th>GRADE 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability/Headache</td>
<td>Irritable, but otherwise normal routine; headache [no treatment]</td>
<td>More crying than usual and not on normal routine; headache requiring non-narcotic analgesia</td>
<td>Prolonged crying, Refuses to play/smile with parent/guardian; narcotic required for headache</td>
<td>Inconsolable crying ≥ 3 hours, unusual high-pitched crying/screaming; headache requiring hospitalization</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Mild lethargy</td>
<td>Moderate lethargy</td>
<td>Somnolent</td>
<td>Comatose</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Transient arthralgia, myalgia; no limits on ADL</td>
<td>Mild-moderate arthralgia, myalgia &lt; 48 hrs; mild impact on ADL</td>
<td>&gt; 48 hrs or severe; marked impact on ADL</td>
<td>Arthritis or myositis</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td>one seizure</td>
<td>Multiple seizures</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>Transient rash</td>
<td>Persistent, diffuse rash</td>
<td>mild urticaria, bronchospasm requiring therapy</td>
<td>Severe urticaria, anaphylaxis, angioedema within 48 hours of vaccination; exfoliative dermatitis, Stevens-Johnson Syndrome or erythema multiforme</td>
</tr>
</tbody>
</table>

* ≥ Grade 3 adverse reactions require a clinic visit within 48 hours of the event.

1. PCV, PPV, HBV -7 days; M-M-R®II -28 days, or severe, unexplained toxicity regardless of timing.
### APPENDIX III

**Virology Collection and Shipping Instructions**

**ASSAY:** QUANTITATIVE PLASMA HIV-1 RNA PCR (Roche Amplicor Assay- Ultrasensitive) Test Code: HIVRNARU

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Plasma            | Minimum of 2.0 mL blood collected by venipuncture | 3.0 mL Tripottasium EDTA Vacutainer® (Purple top tube) | • Gently invert tubes several times to mix. Do not shake.  
• Label primary specimens with patient ID, protocol, site, visit, date and time of collection, specimen type, anticoagulant.  
• Specimen should be kept at room temperature (18°C-24°C) and processed within 4-6 hours of collection. |

**SPECIMEN PROCESSING:**
- Centrifuge blood at 800 x g for 10 minutes at 18°C-24°C.
- Transfer plasma to a centrifuge tube; re-centrifuge at 800 x g for 10 minutes to completely remove platelets and cell debris.
- If plasma is not to be tested within 30 minutes of separation, aliquot at least 2 x 0.6 mL plasma into sterile, labeled cryovial. Log specimens into the LDMS and label aliquots with standard ACTG labels. Store at -60°C to -80°C until samples are shipped to PACTG certified laboratory.

To minimize RNA degradation, all plasma samples must be processed and stored at -70°C within 48 hours of collection. Although the required processing time has been increased from 4-6 hours to 48 hours, sites are encouraged to continue to process HIV-1 RNA samples as soon as possible.

**ALIQUOTS:** At least 2 aliquots of 0.6 mL each.

**DESIGNATED LABORATORY:** All HIV RNA assays will be done at a PACTG certified virology laboratory.

**SHIPPING:**
1. RNA assays will be run real time.
2. All virology specimens will be shipped to an assigned PACTG Virology Core Laboratory. All sites must provide the name, phone number, fax number and e-mail address of the persons responsible for on-site storage and shipping of samples.

**OTHER INSTRUCTIONS:** The Roche AMPLICOR Ultrasensitive assay is to be used for HIV RNA.
# APPENDIX IV

## IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Plasma for Pneumococcal, Measles & Hepatitis Ab EIA assays. & PBMCs for Measles CMI | **5 mL Na Heparin blood collected by venipuncture.** | (1) 5 mL and (1) 10 mL Na Heparin Vacutainer® tubes (green top) | • Hold blood at room temperature until processed.  
  • Label primary specimens with patient ID, protocol, site, visit, date and time of collection, specimen type.  
  • Ship both tubes ambient to the assigned PICL by overnight courier. Restrict blood collections to Monday through Wednesday if possible. Specimens must be received by the PICL within 24 hours of being drawn. |
| Plasma and PBMC Storage                        | **10 mL Na Heparin blood collected by venipuncture.** |                      |                             |

**PROCESSING INSTRUCTIONS** for Core Laboratories: Collect plasma by centrifugation and aliquot plasmas as described below, log specimens into the LDMS and label aliquots with standard ACTG labels, and store frozen at -20°C or less until shipped. Prepare PBMCs by Ficoll gradient centrifugation and use PACTG consensus cryopreservation protocol for cell storage in vapor phase liquid nitrogen. Log specimens into the LDMS and label aliquots with standard ACTG labels.

- **From 5 mL Na Heparin Tube:** Pneumococcal Serology: Prepare at least 2 (preferably 3) x 250 µL aliquots in cryovials. 
  Measles Serology: Prepare 4 x 100 µL aliquots in cryovials. 
  Hepatitis B Serology: Prepare 2 x 0.5 mL aliquots in cryovials. 
  Measles CMI Studies (LPA): Prepare 5-10 x 10⁶ PBMC aliquots. 
  Store Additional plasma in 0.5 mL plasma/aliquots. Store plasmas at assigned PICL until called for by P1061s team.

- **From 10 mL Na Heparin Tube:** Stored Plasma: Prepare 10 or more plasma aliquots @ 0.5 mL/cryovial. Store plasmas at assigned PICL until called for by P1061s team. 
  Stored PBMC Aliquots: Aliquot all recovered cells in 5-10x10⁶ PBMCs/0.5 mL aliquots. Store cells at assigned PICL until requested.

**SHIPPING:** Whole blood samples collected at protocol sites are to be shipped overnight to their assigned PICL. Frozen plasma samples will be batch-shipped (monthly) to sites described below. Cells for Measles CMI studies will be shipped monthly to Dr. Bellini’s lab at CDC. Stored Samples: Batch shipping will be arranged for each aliquot by study team and coordinated by FSTRF. PBMCs for memory cell assays will be shipped to UMass when requested by the P1061s team.
<table>
<thead>
<tr>
<th>LABORATORY SHIPPING ADDRESSES/CONTACT PERSON</th>
<th>Pneumococcal Serological Studies</th>
<th>Measles Serologies and CMI Assay</th>
<th>Hepatitis B Serologies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole Blood Samples:</strong></td>
<td>Maxwell Finland Laboratory for Infectious Diseases</td>
<td>William J. Bellini, Ph.D.</td>
<td>Patricia Defechereux, Ph.D., Pediatric Immunology Core Lab, Room HSE 301, 505 Parnassus Avenue, San Francisco, CA 94143</td>
</tr>
<tr>
<td>Immunology core lab assignments:</td>
<td>774 Albany Street</td>
<td>c/o D.A.S.H.</td>
<td>(415) 476-3993</td>
</tr>
<tr>
<td><a href="http://pactg.s-3.com/members/labassgn0100.htm">http://pactg.s-3.com/members/labassgn0100.htm</a></td>
<td>5th Floor, ELISA Lab</td>
<td>Measles Virus Section, Group 81</td>
<td>Fax: (415) 476-5795</td>
</tr>
<tr>
<td>Immunology core lab contacts:</td>
<td>Boston, MA 02118</td>
<td>Mailstop C-22</td>
<td>E-mail: <a href="mailto:defechep@peds.ucsf.edu">defechep@peds.ucsf.edu</a></td>
</tr>
<tr>
<td></td>
<td>(617) 414-7407</td>
<td>1600 Clifton Road, N.E.</td>
<td></td>
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<tr>
<td></td>
<td>Fax: (617) 414-5806</td>
<td>Atlanta, GA 30333</td>
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<tr>
<td></td>
<td>E-mail: <a href="mailto:jbowden@bu.edu">jbowden@bu.edu</a></td>
<td></td>
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<tr>
<td></td>
<td>LDMS lab code: 222</td>
<td></td>
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<tr>
<td>Memory Cell Assays:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Linda Lambrecht</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Immunology Laboratory</td>
<td></td>
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<tr>
<td>University Of Massachusetts Medical School</td>
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<td></td>
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<tr>
<td>373 Plantation Street, Suite 318</td>
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<td></td>
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<tr>
<td>Worcester, MA 01605</td>
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<tr>
<td>(508) 856-2760</td>
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<tr>
<td>Fax: (508) 856-5500</td>
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<tr>
<td>E-mail: <a href="mailto:Linda.lambrecht@umassmed.edu">Linda.lambrecht@umassmed.edu</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDMS lab code: 036</td>
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</tr>
</tbody>
</table>

**OTHER INSTRUCTIONS:** A fax or email must go to the core lab each time a sample is sent. This message must include the PID# of the subject whose samples are being shipped, and the Federal Express tracking number of the shipment. Send the message on the day the lab is drawn. *DO NOT send specimens on Fridays or the day before a legal holiday.*
APPENDIX V

PACTG SAMPLE INFORMED CONSENT TEMPLATE

DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)
SAMPLE INFORMED CONSENT
For protocol:
PACTG P1061S “EVALUATION OF IMMUNOLOGIC MEMORY FOLLOWING
PNEUMOCOCCAL, HEPATITIS B, AND MEASLES VACCINATION IN HIV-INFECTED
CHILDREN TREATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)”
Version 1.0, dated _________

SHORT TITLE FOR THE STUDY: Evaluation of Immunologic Memory in HIV-Infected Children Treated with HAART.

INTRODUCTION

You are/your child is being asked to take part in the research substudy named above because you are/your child is infected with Human Immunodeficiency Virus (HIV), the virus that causes AIDS. This substudy is sponsored by the National Institutes of Health (NIH). The doctor in charge of this substudy at this site is: (insert name of Principal Investigator).

You are/your child is eligible to participate in this substudy because you/your child participated in P1024, “Evaluation of the Immunogenicity of Pneumococcal Conjugate Vaccine and Routine Pediatric Immunizations in HIV-Infected Children Treated with Highly Active Antiretroviral Therapy (HAART).” P1024 was a study to see how well the following vaccines can help you/your child fight different types of infection: Pneumococcal Conjugate Vaccine (PCV), Pneumococcal Polysaccharide Vaccine (PPV), Measles-Mumps-Rubella Vaccine (M-M-R®II), Diphtheria-Tetanus-Pertussis Vaccine (DTaP) and Hepatitis B Vaccine (HBV).

This substudy will look at whether or not you have/your child has developed “immunologic memory” from the vaccines received in P1024 (whether you/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection). This substudy will check if you are/your child is still protected from the following: pneumococcal infection, measles, and/or hepatitis B virus. This substudy will not look at your/your child’s immunologic protection against pertussis.

This substudy will look at whether you/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection by giving you/your child additional (booster)
doses of Pneumococcal Conjugate Vaccine (PCV) or Pneumococcal Polysaccharide Vaccine (PPV); Measles-Mumps-Rubella Vaccine (M-M-R®II); and Hepatitis B Vaccine (HBV) and looking at blood tests that test for responses to these vaccines. You/your child will not receive a booster dose of Diphtheria-Tetanus-Pertussis Vaccine (DTaP) as part of this substudy.

Before you can decide whether or not to take part or allow your child to take part in this substudy, we would like to explain the purpose of the substudy, how it may help you/your child, any risks to you/your child, and what is expected of you/your child.

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

WHY IS THIS SUBSTUDY BEING DONE

The purpose of this substudy is to determine whether HIV-infected children on HAART produce protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection. The vaccines that were previously given to you/your child as part of P1024 included: 2 doses of PCV, followed by 1 dose of PPV; 1 dose of MMR; 1 dose of HBV; and 1 dose of DTaP (however, DTaP will not be given to you/your child as part of this substudy). Since these vaccines offer protection to both HIV-uninfected and HIV-infected children against pneumococcal infection (PPV/PCV), measles (MMR), and hepatitis B virus (HBV), it is important to study whether additional doses of vaccine given 3-4 years after the initial doses are needed to continue to protect children further. PCV is not FDA-approved for use in children greater than 9 years of age, but has been used safely in studies in older children, including in P1024, which you/your child participated in.

This substudy will also look at whether an additional vaccine dose of PCV will work better or worse than an additional dose of PPV vaccine in protecting you/your child from pneumococcal infection.

Additionally, this substudy will look at other factors, not related to vaccine, which may make you/your child more or less likely to be protected by previous vaccine doses. These factors include CD4% (number of cells in the blood that fight infection); HIV viral load (amount of HIV in the bloodstream); age; amount of time on HAART; and if HAART medication was changed because it was not working so well.

This substudy will also look at how safe additional doses of PCV, PPV, HBV, and MMR are in HIV-infected children.

Finally, this substudy will look at how effective additional doses of these vaccines are in helping HIV-infected children to be protected from pneumococcal infection, measles, and hepatitis B virus infection if the initial doses were not able to produce protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection.
WHAT DO I/DOES MY CHILD HAVE TO DO IF I/HE/SHE IS IN THIS SUBSTUDY?

If you are/your child is eligible for this substudy, you/your child will be assigned to your/your child’s original P1024 stratification group, based on your/your child’s lowest CD4% and your/your child’s CD4% at P1024 screen/entry. You/your child will have a physical exam. In addition, site staff will review symptoms, medication history, and medical history with you/your child. About 4 teaspoons of blood will be drawn from you/your child to determine the amount of HIV in the blood, to check routine blood counts and chemistries, and to test antibody levels (substances in the blood that destroy or make bacteria and toxins non-harmful) against pneumococcus, measles, and hepatitis B virus. Some of your/your child’s blood will also be stored for future tests of a similar kind (that also look at whether or not you have/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection). If you are/your child is female and able to become pregnant, a urine test will be performed to test for pregnancy.

At this visit, you/your child will receive 1 dose of either PCV or PPV vaccine. You/your child will be randomized (assigned by chance, like flipping a coin with an equal (50:50) chance of receiving either vaccine) in a 1:1 ratio, meaning that half of the children will receive PPV and half of the children will receive PCV vaccine); 1 dose of HBV; and 1 dose of MMR.

You/your child must remain in the clinic for observation for 1 hour immediately following the vaccinations. This study visit will take about 90 minutes (1 ½ hours). You/your child will be asked to complete a diary of any side effects from any of the vaccines for 3 days after the screen/entry visit. You/your child will also be asked to record in the diary any side effects that occur beyond 3 days. Telephone contact will be made about 3 days after the screen/entry visit and also at 21 days after the screen/entry visit for children receiving MMR. You will also be instructed to call the clinic if you are concerned about any symptoms you are/your child is having, or if any symptoms seem severe.

If you/your child have had an allergic reaction or another severe reaction to one of the study vaccines, you/your child will not receive that vaccine in this substudy. If you have/your child has received additional doses of any of the vaccines that will be given in this substudy after receiving these vaccines in P1024, you/your child will not be given another dose of that vaccine. You/your child will still get additional doses of the other vaccine(s). If you/your child did not receive the pneumococcal, hepatitis, or measles vaccines during the P1024 study, you/your child will not receive those vaccines in this substudy. In addition, if you have/your child has been diagnosed with either hepatitis B virus or measles since receiving the P1024 vaccines, you/your child will not receive additional doses of those vaccines. If the two most recent blood tests to measure the number of cells that fight infection do not show that your/your child’s CD4% is at least 15% and that your/your child’s CD4 count is at least 200/mm3, you/your child will not receive the measles vaccine.

On Study
You/your child will come back for study visits on days 7 and 28. On the day 7 visit, you/your child will have a limited physical exam. In addition, site staff will review symptoms, medication history, and medical history with you/your child. About 3 teaspoons of blood will be drawn from you/your child to test antibody levels against pneumococcus, measles, and hepatitis B virus. Some of your/your child’s blood will also be stored for future, similar tests (that also look at whether or not you have/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection).

On the day 28 visit, you/your child will have a limited physical exam. In addition, site staff will review symptoms, medication history, and medical history with you/your child. About 3 to 3 ½ teaspoons of blood will be drawn from you/your child to check routine blood counts and chemistries, and to test antibody levels against pneumococcus, measles, and hepatitis B virus. Some of your/your child’s blood will also be stored for future, similar tests (that also look at whether or not you have/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection).

These visits will take about 30 minutes (1/2 hour) to complete.

You will be informed of the results of your/your child’s blood tests.

**Early/Premature Discontinuation**

If you/your child stop(s) taking part in the substudy treatment (discontinuation of vaccinations) during the screen/entry visit, you/your child will be asked to come back for your/your child’s regularly scheduled visits at day 7 and day 28 and complete all substudy evaluations.

If you/your child stop(s) taking part in the substudy after the screen/entry visit, you/your child will be asked to come to the clinic for a final substudy visit. At this visit, you/your child will have a physical exam. In addition, site staff will review symptoms, medication history, and medical history with you/your child. About 3 to 3 ½ teaspoons of blood will be drawn from you/your child to check routine blood counts and chemistries, and to test antibody levels against pneumococcus, measles, and hepatitis B virus. Some of your/your child’s blood will also be stored for future, similar tests (that also look at whether or not you have/your child has developed protective cells that remember how to fight pneumococcal, measles, and hepatitis B infection).

**OTHER INFORMATION:**

The information and knowledge that comes out of doing this substudy may be used for other research related to HIV disease and approved by the PACTG. The summaries and conclusions about the different things looked at by this substudy may be used in designing future research studies about vaccinations and HIV disease that are similar to the problems studied in this research. No individual information in the PACTG study records will be looked at or used for this purpose.
STORAGE OF BLOOD SAMPLES

FOR NIAID SITES:

Some of your/your child’s blood will be taken and stored (with usual protectors of identity) and used for future PACTG-approved, HIV-related research. About 6 teaspoons (from the total of the 3 visits) of your/your child’s blood will be taken for this purpose.

Your/your child’s samples will be stored at a special laboratory facility where only approved researchers will have access to them. People who work at the facility will also have access to your/your child’s samples to keep track of them, but these people won’t have information that directly identifies you/your child. Your/your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your/your child’s regular doctor with the results of studies done using your/your child’s stored samples. This is because research studies are often done with experimental procedures, and results of such studies should not be used to make decisions about your/your child’s medical care. If the researchers decide that the result of a certain study provides important information for your/your child’s medical care, then your/your child’s study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your/your child’s address or phone number.

You may decide that you do not want your/your child’s samples stored for future research studies. You/your child can still participate in this substudy even if you make this decision.

You may withdraw your consent for the storage and use of your/your child’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

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

I agree to allow my/my child’s blood samples to be stored for use in future PACTG-approved, HIV-related research studies.

__________ Yes __________ No __________ Initials __________ Date

FOR NICHD SITES:
Some of your/your child’s blood specimens collected as part of this substudy will be stored for testing at a later date as part of this substudy. There is a separate consent form to explain this and get your/your child’s consent.

HOW MANY CHILDREN WILL TAKE PART IN THIS SUBSTUDY?

About 149-224 children will take part in this substudy.

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

You/your child will be in this substudy for about 28 days.

RISKS AND/OR DISCOMFORTS

You/your child previously received all of the vaccines that will be given in this substudy. Common reactions that can occur after receiving any of the vaccines given in this substudy include skin redness, pain, and swelling at the site of injection. You/your child may also experience mild to moderate fever after one or more of the vaccines given in this substudy. Sometimes, reactions to vaccines can happen more often in people who have received the same vaccines before. Serious, though rare, side effects that can occur with any of the vaccines in this substudy include severe allergic reactions that include skin rash, hives, itching, difficulty breathing, hoarseness or wheezing, fast heart beat and shock. Side effects that generally occur only with a particular vaccine given in this substudy are listed below.

HBV – This vaccine may cause some of the common reactions listed above.

MMR - This vaccine can cause mild rash, temporary low platelet counts (and a risk of bleeding), swelling of the glands in the cheeks or neck, and temporary arthritis (pain, swelling, or stiffness in the joints). Rarely, other severe problems that can occur after a child receives MMR vaccine include deafness, long-term seizures, lowered consciousness or coma, and permanent brain damage. It is not certain whether these serious and rare problems are caused by the vaccine.

PPV - This vaccine can cause muscle aches.

PCV - This vaccine can cause soreness in the limb where the vaccine is given. On some occasions, there have been reports of apnea, particularly when given with other vaccines, including hepatitis B and MMR. In many of the cases, children had pre-existing conditions that may have led to this side effect.

While these are not all the possible side effects of these vaccines, they are the more serious or common ones with a known or possible relationship. Reactions to PCV, PPV and HBV usually occur within 7 days of immunization and reactions to M-M-R® II usually occur within 28 days of immunization. There may be other risks that we don’t know about yet. You will be monitored for any other reactions in the clinic after each vaccination.
If you have/your child has questions concerning the safety of the vaccines administered during this substudy, please ask the medical staff at your site. The study staff will give you/your child Vaccine Information Statements issued by the Centers for Disease Control (CDC).

Risks Related to Blood Draw

The risks of drawing blood include discomfort, bleeding or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

PREGNANCY

It is not known if the vaccines given in this substudy can harm unborn babies. If you are/your child is having sex that could lead to you/her becoming pregnant, you/she must agree not to become pregnant.

Because of the risk involved, you/your child must use two methods of birth control that you discuss with the study staff. You/your child must continue to use both methods until 3 months after your last vaccine in this substudy. You may choose two of the birth control methods listed below:

- Hormonal birth control drugs that prevent pregnancy given by pills, shots or placed under the skin
- Male or female condoms with, or without, a cream or gel that kills sperm
- Diaphragm or cervical cap with a cream or gel that kills sperm
- Intrauterine device (IUD)

If you/your child can become pregnant, you/she must have a pregnancy test before entering this substudy. The test must be negative. If you think you/your child may be pregnant at any time during the substudy, tell your study staff right away. The study staff will talk to you about your/her choices.

BREAST-FEEDING

Women who are breastfeeding their baby may not join the substudy.

ARE THERE BENEFITS TO TAKING PART IN THIS SUBSTUDY?

Taking part in this substudy may further protect you/your child from becoming infected with pneumococcus infection, measles, and hepatitis B virus, but no guarantee can be made. You/your child may receive no benefit from this substudy. However, knowledge gained from this substudy may in the future help others who have HIV infection.

WHAT ARE THE REASONS WHY YOU/YOUR CHILD MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR/YOUR CHILD'S CONSENT?
You/your child may have to have vaccinations stopped or be totally withdrawn from the substudy without your/your child's consent for the following reasons:

- the investigator or your/your child's doctor decides that receiving additional vaccines or continuing in the substudy would be harmful to you/your child;
- you/your child need(s) a treatment not allowed on this substudy;
- you are/your child is unable to keep appointments or take substudy vaccines as instructed;
- you have/your child has a bad side effect from a substudy vaccine;
- you/your child become(s) pregnant;
- you are/your child is unable to remain on combination therapy for HIV infection
- the substudy is cancelled by the Food and Drug Administration (FDA), the National Institute of Allergy and Infectious Diseases (NIAID), the site’s Institutional Review Board (an IRB is a committee that watches over the safety and rights of research subjects) or the pharmaceutical company(ies) supplying substudy treatment; and/or
- other administrative reasons.

WHAT OTHER CHOICE DO I/DOES MY CHILD HAVE BESIDES THIS SUBSTUDY?

Instead of being in this substudy, you have/your child has the choice of:

- receiving the vaccines from your/your child’s clinician;
- volunteering for another study;
- not receiving any vaccinations;
- not participating in any study.

Before you decide to take part in this substudy or allow your child to take part in this substudy, your/your child’s doctor will give you information about the benefits and risks of the alternative treatments that may be appropriate for you/your child.

WHAT ARE THE COSTS TO ME?

Taking part in this substudy may lead to added costs to you or to your and/or your child’s insurance company. In some cases it is possible that your/your child’s insurance company will not pay for these costs because your child is taking part in a research study. You will be responsible for claims that are refused by your/your child’s insurance company.

WHAT ABOUT CONFIDENTIALITY?

Your/your child’s name will not be recorded as part of this substudy. Only a coded number will be used. All records will be kept in a locked cabinet and only study staff will have access to your/your child’s information.
To help us protect your/your child’s privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, 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/your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the U.S. Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

People who may review your/your child’s records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, NIH, study staff, study monitors, the pharmaceutical companies, and their designees.

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

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your/your child’s consent, information that would identify you/your child as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your child, or others.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?

If you are/your child is injured as a result of being in this substudy, you/your child will be given immediate necessary treatment for your/your child’s injuries. The cost for this treatment will be charged to you or your/your child’s 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 through this institution or through the NIH. You will not be giving up any of your/your child’s legal rights by signing this consent form.

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

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

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

For questions about this substudy or a research-related injury, 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
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/let your child take part in this substudy, 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              Study Staff Signature and Date
Consent Discussion (print)

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

__________________________     _____________________________________
Father’s Name         Father’s Signature and Date
(As appropriate)
APPENDIX VI

FACT SHEET AND TEMPLATE CONSENT FORM FOR SPECIMEN STORAGE 
at Repositories funded by the National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET

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

Why have a repository?

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

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

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

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

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

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and
APPENDIX VI (Cont.)

coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my/my child’s specimens?

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

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

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

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

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

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

What type of research will be done with my/my child’s specimens?
APPENDIX VI (Cont.)

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 “Evaluation of Immunologic Memory Following Pneumococcal, Hepatitis B, and Measles Vaccination in HIV-Infected Children Treated with Highly Active Antiretroviral Therapy (HAART),” you are/your child is being asked to have some blood and plasma taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your/your child’s time in this NICHD sponsored Study.

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

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

TEMPLATE CONSENT FORM

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

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

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

Risks: The specimens would be collected as part of your/your child’s study visits. Risks related to blood draws include discomfort, bleeding or bruising where the needle enters the body, and in rare cases, fainting or infection. Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test.

<table>
<thead>
<tr>
<th>I give permission for the use of my/my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent or Legal Guardian Signature</td>
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</table>

<table>
<thead>
<tr>
<th>I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Signature</td>
</tr>
</tbody>
</table>
What are the special HIV-related studies that can be done with the repository specimens?

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

Benefits: There are no direct benefits to 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. Risks related to blood draws include discomfort, bleeding or bruising where the needle enters the body, and in rare cases, fainting or infection. Once in the repository, there are few risks. Your/your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your/your child’s genetic makeup.

I give permission for the use of my/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/your child’s samples, contact (Study personnel) at (phone).

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

<table>
<thead>
<tr>
<th>I refuse to have any specimen collected from me/my child stored in the repository.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent or Legal Guardian Signature   Witness Signature   Date</td>
</tr>
</tbody>
</table>
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

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 new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study has ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your rights are being protected.

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.
APPENDIX VI (Cont.)

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 sponsored Study has to be reviewed by a special committee of people known as an Institutional Review board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you 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 new 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 consent 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 “Evaluation of Immunologic Memory Following Pneumococcal, Hepatitis B, and Measles Vaccination in HIV-Infected Children Treated with Highly Active
ANTIRETROVIRAL THERAPY (HAART),” you are being asked to have some blood and plasma 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. Risks related to blood draws include discomfort, bleeding or bruising where the needle enters the body, and in rare cases, fainting or infection. 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 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
APPENDIX VI (Cont.)

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. Risks related to blood draws include discomfort, bleeding or bruising where the needle enters the body, and in rare cases, fainting or infection. 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 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 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).

I refuse to have any specimen collected for storage in the repository.

Participant Signature ___________________________ Witness Signature ___________________________ Date ________________