The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults

A Multicenter, US Domestic and International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains the current PACTG P1006 protocol, which is comprised of the following documents, presented in reverse chronological order:

Clarification Memorandum #1, dated 06 September 2005
Protocol Version 4.0, dated 02 May 2005
The following serves as Clarification Memo #1 for PACTG P1006, “The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults”, Version 4.0, dated May 2, 2005.

The following changes were made to standardize the immediate specimen handling language and clarify the sample processing procedures for P1006, and to provide consistency regarding the Hepatitis A vaccination at the week 100 study visit.

1. Please make the changes in the third paragraph, Section 5.1 (pg. 24) to reflect those made in the corrected Appendix I paragraph related to the week 100 visit.


3. The Standard Method is to be used for the quantitative HIV-1 PCR assay.

Please file with your protocol documents. The Version 4.0 Laboratory Processing Chart (LPC) for PACTG P1006 will reflect these changes and should be available shortly.

This information will be added to the next version of the protocol. Please contact the protocol team at actg.teamp1006@fstrf.org if you have any questions.

This Clarification Memo and the corrected Appendices will be available shortly from the P1006 Protocol Specific Web Page, under current protocol related documents. Access the Pediatric ACTG Website ([http://pactg.s-3.com](http://pactg.s-3.com)). The username is: pactg and the password is: cure (all lower case).

Thank you for your participation in PACTG P1006.

The P1006 Protocol Team
APPENDIX I (Cont.)-CORRECTED

1. Stored Sample (pre-enrollment) for newly diagnosed HIV-infected subjects for possible future enrollment and for other individuals who need to start or change therapy before entry. The pre-enrollment stored sample is 3 mL blood in an EDTA (purple top) tube. Plasma should be stored from this sample. The plasma sample will remain at the clinic or local processing lab until it is tested, or destroyed at one month.

2. Physical exam (height, weight, vital signs, symptoms).

3. Immunizations are required within 2 weeks of scheduled visits. All patients will be monitored for one hour immediately following the immunization. Telephone contact will be made within 24 to 48 hours after the immunization to evaluate any vaccine related complications. If there are any > Grade 3 adverse reactions, the patient should be directed to return to the clinic for further evaluations.

4. DTaP will be given to children < 7. Subjects < 7 years who cannot receive vaccine with a pertussis component will receive DT-pediatric. Td will be given to children and young adults ≥7 years at week 8.

5. Laboratory evaluations can be performed within 2 weeks of scheduled visits.


7. Chemistries (indirect bilirubin, direct bilirubin, AST, ALT, electrolytes glucose, BUN, creatinine, amylase, cholesterol).

8. To be stored for future analysis. See Appendix III-B.


10. Serology for hepatitis A only at screen. May be done at a local laboratory. For insufficient blood draws, priorities are as follows:

   1. LPA
   2. Hepatitis A Serology
   3. Lymphocyte subsets

**Subjects who were enrolled in version 3.0 of the study and have not completed the week 100 visit by the time version 4.0 is implemented, will be re-consented (in accordance with IRB procedures), if they agree to receive the hepatitis A vaccination at week 100. The subject will then be registered through the SDAC/DMC system into Step 2. A new prescription, with a new SID number, will be generated for the pharmacist. Subjects should complete their assigned Group 1 or Group 2 immunizations and receive the additional hepatitis A Vaccination at week 100.

NOTE: Sites should inform the team whether CD4 values are being obtained at a PICL or other certified laboratory. Sites may obtain CD4 values at either laboratory, but should remain consistent and use the same laboratory throughout the course of the study.
### APPENDIX III-A-CORRECTED

### QUANTITATIVE PLASMA HIV-1 RNA PCR-STANDARD METHOD

| VIROLOGY |
|-----------------|-----------------|-----------------|-----------------|
| **ASSAY REQUIREMENT** | **SPECIMEN COLLECTION** | **COLLECTION CONTAINER** | **IMMEDIATE SPECIMEN HANDLING** |
| Plasma | 3 mL blood collected by venipuncture | 3 mL Tripotassium EDTA Vacutainer™ tube (purple top) | • Gently invert tubes several times to mix. Do not shake. |
| | | | • Label **primary** specimen with SID#, PID#, study visit week, date and time of collection, specimen type. |
| | | | • Specimen should be kept at room temperature (18–24°C) and processed as **soon** as possible. |

**SPECIMEN PROCESSING:**

A. Plasma - Draw 3 mL of blood into a 3 mL draw EDTA (purple top tube). This tube should be processed as soon as possible. Process plasma using ACTG standard method: spin blood at 800 x g for 10 minutes, remove plasma, then re-spin plasma at 800 x g for 10 minutes. Freeze 2 x 0.5 mL aliquots at −70°C. Ship 1 x 0.5 mL real-time to an ACTG laboratory certified (i.e. participates in VQA QC/QA program) to do Quantitative Plasma HIV-1 RNA PCR assay. Store the remaining aliquot. All specimens must be logged into the LDMS by the processing laboratory and labeled with an LDMS generated standard ACTG label. LDMS code: BLD/EDT/PL2.

**ALIQUOTS:** 0.5 mL x 2

**DESIGNATED LABORATORY/CONTACT PERSON:** ACTG laboratory certified (i.e. participates in VQA QC/QA program) to do the Quantitative Plasma HIV-1 RNA PCR assay (Standard Method).

**SHIPPING:** Ship 1 x 0.5 mL aliquot real time to (designated laboratory); store pre-enrollment plasma aliquots for 1 month, if applicable.

**OTHER INSTRUCTIONS:** None.
APPENDIX III-B-CORRECTED

PBMC AND PLASMA STORAGE

<table>
<thead>
<tr>
<th>VIROLOGY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSAY REQUIREMENT</strong></td>
<td><strong>SPECIMEN COLLECTION</strong></td>
</tr>
<tr>
<td>PBMC and plasma storage for future analysis</td>
<td>3 mL blood collected by venipuncture</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SPECIMEN PROCESSING: PBMCs are separated from red blood cells and neutrophils by density centrifugation on Ficoll-Hypaque. Cells should be frozen using the ACTG Immunology Consensus Method for PBMC cryopreservation. Process plasma using the ACTG standard method. Store 2 x 0.5 mL plasma. Store both plasma and PBMCs at the processing lab. All specimens must be logged into the LDMS by the processing laboratory and labeled with an LDMS generated standard ACTG label. LDMS code: BLD/ACD/CEL/DMS; BLD/ACD/PL2

ALIQUOTS: PBMC: 2 (2 x 10⁶ cells); PLASMA: 0.5 mL x 2

LABORATORY/CONTACT PERSON: NA

SHIPPING: Future shipment to the repository, if required, will be made upon request.

OTHER INSTRUCTIONS: Store PBMCs and plasma at the processing laboratory.
### IMMUNOLOGY

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Serum             | 3 mL blood collected by venipuncture | Sterile Vacutainer™ Tubes (red top) | - Place tube in a rack and allow blood to clot. Do not mix or shake.  
- Label primary specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
- Specimen should be processed by the local lab as soon as possible after collection |

### SPECIMEN PROCESSING INSTRUCTIONS:

Separate serum into two equal size aliquots. Freeze the aliquots in -20°C freezer until shipment is requested. All specimens must be logged into the LDMS by the processing laboratory and labeled with an LDMS generated standard ACTG label. LDMS codes: BLD/NON/SER

### DESIGNATED LABORATORY/CONTACT PERSON:

LDMS Lab 134, Patricia Defechereux, Ph.D., UCSF Pediatric Immunology Core Lab, Room HSE 301, 505 Parnassus Avenue, San Francisco, CA 94143. Phone: (415) 476-3993; Fax: (415) 476-5795. E-mail: defechep@peds.ucsf.edu

### SHIPPING:

On dry ice, in batches, priority overnight, upon request.

### 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.  
* DO NOT send specimens on Fridays or the day before a legal holiday.
## ADVANCED FLOW CYTOMETRY

### IMMUNOLOGY

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Whole Blood       | 1 mL blood collected by venipuncture | Tripotassium EDTA Vacutainer™ tubes (purple top) | • Gently invert tubes several times to mix. Do not shake.  
• Label **primary** specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
• Specimen **should be shipped priority overnight to the designated PICL.** |

### FLOW CYTOMETRY PANEL:

- **FITC (Green)**
  - CD3
  - CD45RA

- **PE/RD (Orange)**
  - CD45RO
  - CD62L

- **CY-5/PER-CP(RED)**
  - CD4

### PROCESSING INSTRUCTIONS: None.

### DESIGNATED LABORATORY/CONTACT PERSON: Sites will be assigned to a Pediatric Immunology Core Lab (PICL).

### SHIPPING: Room temperature, priority overnight.

### 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 IV-C-CORRECTED

## LPA FOR TETANUS TOXOID, CANDIDA, AND HEPATITIS A

## IMMUNOLOGY

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Whole blood       | 4 mL blood collected by venipuncture | Heparinized (green top) | • Gently invert tubes several times to mix. Do not shake.  
• Label **primary** specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
• Specimen **should be shipped priority overnight to the designated PICL.** |

### PROCESSING INSTRUCTIONS: None

### DESIGNATED LABORATORY/CONTACT PERSON: Sites will be assigned to a Pediatric Immunology Core Laboratory (PICL).

### SHIPPING: Room temperature, priority overnight.

### 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.
THE EFFECTS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON THE RECOVERY OF IMMUNE FUNCTION IN HIV-INFECTED CHILDREN AND YOUNG ADULTS

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:
Aventis-Pasteur
GlaxoSmithKline Pharmaceuticals

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Version 4.0
Final
May 02, 2005
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All questions concerning this protocol should be sent via e-mail to actg.teamp1006@fstrf.org. Remember to include the subject's PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1006@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call (301) 897-1707. For Serious Adverse Experience (SAE) Reporting questions, e-mail RCCSafetyOffice@tech-res.com or call 1-800-537-9979. To order study vaccines, call the Clinical Research Products Management center at (301) 294-0741. For enrollment or randomization questions call the Data Management Center (DMC) at (716) 834-0900 ext. 7226.

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SUMMARY OF CHANGES FOR PACTG P1006, VERSION 4.0

PACTG P1006: THE EFFECTS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON THE RECOVERY OF IMMUNE FUNCTION IN HIV-INFECTED CHILDREN AND YOUNG ADULTS

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

1. The Team Roster has been updated.

2. An additional hepatitis A vaccination booster has been added at week 100 for those subjects who have not yet reached week 100 of the study upon implementation of this amendment.

3. Accrual goals for version 4.0 have been defined in the Study Design Section (3.0).

4. Inclusion criteria have been modified/expanded to allow for the enrollment of subjects through 24 years of age.

5. Study duration has been increased so that those subjects who receive an additional hepatitis A vaccine booster at week 100 will have an additional physical exam, assessment of HIV-related symptoms, hematology, chemistry, hepatitis A serology, and LPA done at week 104.

6. An additional secondary objective has been added to assess whether or not an additional hepatitis A vaccination (booster) at week 100 will result in an increase in antibody.

7. Preliminary Findings (section 1.3) have been added to the protocol, based on analyses conducted from the results obtained in versions 1.0, 2.0, and 3.0 of the protocol.

8. The Study Design (section 3.0), Statistical Considerations (section 8.0), and Appendix I (Schedule of Evaluations) have been updated to include the additional hepatitis A vaccine booster at week 100 and the additional study visit at week 104.

9. Original entry criteria, based on laboratory evaluations, have been highlighted in the Study Design section (3.0) to ensure that subjects do not continue on study if they do not meet certain necessary criteria.

10. T-20 has been included as another option in HAART regimens in the Study Design (section 3.0), Enrollment of Subjects (section 4.0), and Study Treatment (section 5.0).
SUMMARY OF CHANGES (Cont.)

11. The exclusion criteria (section 4.2) have been updated to allow pregnant females to remain on study if they become pregnant subsequent to receiving all vaccinations.

12. The Allowed Medications/Therapies section (4.3) has been updated to allow for routine childhood immunizations while on study.

13. The Drug Regimens, Administration, and Duration section (5.1) has been updated to include a change in number of days for notification of the site pharmacist regarding the acquisition of vaccine (DTaP and DT-pediatric).

14. The Enrollment Procedures (section 4.5) and Study Treatment (section 5.0) have been updated to include instructions for Step 2 for subjects who have not yet reached week 100 of the protocol (on version 3.0) when version 4.0 is implemented.

15. The Reporting Requirements section (7.1) has been updated to include the most recent contact information for the RCC Safety Office.

16. A new reference has been added to the References section (12.0).

17. Appendix I has been updated to include evaluations in the case of premature discontinuation. The Sample Informed Consent (SIC) has also been updated to include a Premature Discontinuation section.

18. Reference to the qualitative HIV culture has been removed from Appendix I.

19. A note has been added to Appendix I asking sites to inform the team as to whether they will be using a PICL laboratory, or other certified laboratory, in order to obtain CD4 values.

20. Lymphocyte subsets have been added to Appendix I (Schedule of Evaluations). In the amendment, the CD4% will be completed from the lymphocyte subsets.

21. References to qualitative PBMC microcultures have been removed from the protocol. The former Appendix III-B (qualitative microcultures) has been removed.

22. Updated designated laboratory contacts have been added to Appendix IV-A and IV-B.

23. Appendix IV-B has been updated to clarify information, as presented in a Clarification Memo dated 2/27/04.
SUMMARY OF CHANGES (Cont.)

24. Changes to the SIC include the following:

- You/your child has been added throughout the SIC since this protocol will now include subjects through 24 years of age.
- NIH has been identified as the protocol sponsor.
- An additional objective has been included in the Purpose section.
- The Procedures section has been updated to include the additional hepatitis A vaccine booster at week 100, with an additional follow-up visit at week 104.
- Additional blood volumes have been added to the Procedures section.
- Estimated lengths of study visits have been added to the Procedures section.
- Information regarding vaccines provided outside of this study has been included in the Procedures section.
- Procedures for Premature Discontinuation have been added to the SIC.
- Information about the storage of specimens for NIAID sites and NICHD sites has been included in the SIC. Separate NICHD stored specimen information for NICHD sites has been added as Appendix VII.
- A section was included informing subjects of the procedures for finding out their test results.
- A feeling of lightheadedness was included as a risk related to blood draws.
- Clarification regarding procedures to be followed if a subject becomes pregnant during the study has been added to the Pregnancy section.
- A section that includes “Other Information” has been added to the SIC.
- Information regarding the Certificate of Confidentiality has been added to the Confidentiality section.
SCHEMA

THE EFFECTS OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON THE RECOVERY OF IMMUNE FUNCTION IN HIV-INFECTED CHILDREN AND YOUNG ADULTS

DESIGN: A randomized, comparative, response study with long-term follow-up

SAMPLE SIZE: Enroll approximately 125 subjects; follow 90 virologic responders (defined as either having a $\geq 0.75$ log decrease or becoming undetectable in plasma HIV RNA copy number 1 month after initiation of highly active antiretroviral therapy [HAART]); approximately 45 in each of two groups.

POPULATION: HIV-infected, severely immunosuppressed (CD4% <15%) children and young adults aged 2-24 years who are initiating an open-label HAART regimen. Both HAART naïve and experienced individuals are eligible for the study. The only requirement for subjects already receiving HAART is that 2 new drugs (including at least 1 PI or NNRTI) be initiated. These could be added to or substituted for previous drugs used in the therapy of HAART-experienced patients.

REGIMEN:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Four Week Visit</th>
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<tbody>
<tr>
<td>Initiation of HAART</td>
<td></td>
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<tr>
<td>Entry Viral Load (VL)</td>
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<tr>
<td>Randomization</td>
<td></td>
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<tr>
<td>Group 1* VL at one month</td>
<td>Responders $\rightarrow$ Vaccination</td>
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<tr>
<td></td>
<td>Non-responders $\rightarrow$ Off Study</td>
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<tr>
<td>Group 2* VL at one month</td>
<td>Responders $\rightarrow$ Vaccination</td>
</tr>
<tr>
<td></td>
<td>Non-responders $\rightarrow$ Off Study</td>
</tr>
</tbody>
</table>

*Eligibility to continue to four week visit determined by entry evaluation results of CD4% $< 15\%$ and no $> $ Grade 3 laboratory or clinical toxicities.

Subjects will be randomly assigned to one of two vaccine groups. In Group 1, subjects will receive tetanus toxoid immunizations at 8, 16, and 24 weeks and hepatitis A vaccinations at 32, 40, and 48 weeks. In Group 2, subjects will receive hepatitis A vaccinations at 8, 16, and 24 weeks and tetanus toxoid immunizations at 32, 40, and 48 weeks. In version 4.0, both groups will
receive an additional hepatitis A vaccination at week 100. Subjects who were enrolled in version 3.0 and have not completed the week 100 visit will be re-consented to version 4.0 if they agree to receive the hepatitis A vaccination at week 100.

NOTE: Tetanus toxoid immunizations will be administered as DTaP, DT-pediatric, or Td.

STUDY DURATION: The total duration of the study will be 104 weeks from entry to end for all subjects who have not yet reached week 100 of the study prior to the initiation of version 4.0 and who agree to receive a booster dose of hepatitis A at week 100. Subjects will be on treatment (vaccines) from week 8 to week 100 (no vaccines will be administered between weeks 48 and 100) followed by a final post immunization visit at week 104 for subjects who receive the additional dose of vaccine. An interim review will be conducted after the first 30 virologic responders have been on study for 6 months.

OBJECTIVES:

Primary

1. To assess the ability of newly derived CD4 T cells to spontaneously develop lymphoproliferative responses to a recall antigen, tetanus toxoid, or to develop responses after booster vaccinations with tetanus vaccine.

2. To assess the ability to develop protective antibody responses to a T cell dependent antigen using a primary series of hepatitis A vaccinations.

3. To measure the durability of any response beyond the last vaccination.

Secondary

1. To measure CD4 T cell percentage at baseline and at the time of vaccination(s) and to correlate these with the establishment of immune responses.

2. To study the correlation of the establishment of phenotypic "naive" and "memory" T cells at baseline and the time of vaccination(s) with the establishment of immune responses.

3. To assess the ability of newly-derived CD4 T cells to develop spontaneous cell-mediated immune responses to an environmental antigen, candida.
4. To assess the ability to develop lymphoproliferative responses to T cell-dependent antigen, hepatitis A.

5. To assess whether the recovery of functional immunity is seen early or late after HAART.

6. To measure the HIV plasma copy number at baseline, the time of vaccination(s), and at the study completion (104 weeks) and to correlate these with the establishment of immune responses.

7. To assess the safety of giving multiple immunizations with FDA licensed vaccines to HIV-infected children and young adults.

8. To assess whether a hepatitis A vaccination booster at week 100 will result in an increase in hepatitis A antibody.
INTRODUCTION

1.1 Background

HIV-1 infected children treated with multiple potent antiretrovirals have experienced a significant increase in CD4 T cells after the initiation of highly active antiretroviral therapy (HAART). Although researchers are aware there are several changes in the immune function following HAART, no large published studies have delineated the dynamics of immune recovery in HIV-infected children.

Adults treated with HAART have had mean increases of 250 CD4 T cells/μL and the return of some T-cell mediated responses to recall antigens (1). This return of functional memory T cells may be due to the fact that the majority of the replenished T cells are of the "memory" phenotype, perhaps elicited by proliferation of peripherally distributed T cells, and presumably independent of recent thymic education (2). This increase in memory CD4 T cells is similar to that seen in adult cancer chemotherapy patients who have a recovery of exclusively memory cells after T cell depletion (3). In addition, Connors et al. reported that the phenotype of T cells regenerated after the initiation of HAART depends on the types of T cells present before therapy despite robust increases in CD4 cell counts (4).

The role of the independent thymic pathway in the regeneration of the immune system to a near normal level post-HAART seen in adults may not coincide with the process occurring in children. In contrast, the age dependent thymopoietic pathway may be the catalyst for the regeneration of a normal and sustainable diversity of CD4 T cell repertoire. Thymic enlargement during HAART treatment was recently observed in a small study of HIV-infected children suggesting an active role of the thymus in this population (5). Understanding the pathogenesis of T cell recovery in HIV-infected children and to what extent there is restoration in the ability of the immune system to respond to recall and neo-antigens will impact on the clinical management and ultimately on the survival of these patients. These findings will define the role of vaccines and chemoprophylaxis in disease prevention in these patients.

A recent study of nine children with advanced HIV disease reported a median increase of 499 cells/mm$^3$ after a few months of HAART (6). Whether the increase in CD4 counts in this population of children translates in a complete functional immune recovery is not known. Increases of primarily CD45RA CD4 T (naïve) cells were seen months after the initiation of HAART even in children whose baseline value was <100 CD4 cells/μL. Responses to a recall antigen, such as tetanus toxoid (TT), were seen in 3 of 6 children studied 9 months following the initiation of HAART.
Similarly, in a pilot study at New York University Medical Center, 25 pediatric patients with advanced HIV disease initiated HAART. The mean age at the start of therapy was 9.6 years (7). Four patients were rapid progressors, infants who developed severe immune compromise in the first year of life and were started on protease inhibitor (PI) combination therapy just before or just after their second birthday. The other 21 patients were relatively slow progressors with a more gradual depletion of CD4 cells, and an average age at onset of PI therapy of 10.25 years. Duration of therapy ranged from 9 to 23 months with a mean of 16.4 months. No side effects reported were severe enough to warrant discontinuation of or change in therapy. Baseline mean CD4% was 2.3% (range 0 to 6%) corresponding to a mean CD4 count of 24 cells/μL (range 0 to 160). Peak changes in CD4% and CD4 count were 19% (median with 25-75 percentile range of 1.8-27 and mean of 19.6 +/- 11 with range 0 to 40 and 430 cells/μL; median with 25-75 percentile range of 238-928; mean of 638+-509 with range 0 to 2240 cells/μL), respectively. The baseline mean RNA level was 256,500 copies/mL (range 600 to 1,875,600 copies/mL). Analysis of post-treatment CD4% for each individual patient showed that the peak CD4 count was achieved, on average, at day 305 of therapy. When analyzed relative to baseline CD4 at 1 to 3 months, 6 months and 12 months post-treatment, the change in CD4% was highly statistically significant at each evaluation. By contrast, the same analysis for the change in HIV-1 RNA level was significant only up to 6 months post-treatment, implying that CD4 response to therapy lasts much longer than viral load response. Hutton et al. reported similar increases in CD4 number (mean 539) in a cohort of severely immunosuppressed children after initiating HAART despite increases in HIV-1 RNA levels (8).

In the pilot study, fourteen children had lymphoproliferative (LP) and immunophenotypic responses analyzed. The average age was 8.9 years (range 2-14 years). Subjects chosen for LP responses were those with the greatest increases in CD4 cells (average CD4% of 27%). Approximately 62% of the reconstituted CD4 T cells were CD45RA/CD62L double positive cells. No subjects had positive diphtheria or tetanus LP responses nine months after initiation of therapy. Positive LP candida responses were seen in 5 of 14 patients and all 5 responders had a decrease in viral load, even if transient. No LP responses were seen if no decrease in viral load was documented.

These preliminary data support the assumptions that 1) children with severe immunodepletion will develop significant numbers of CD4 T cells (particularly those of a naive phenotype) for 1-2 years after initiating HAART; 2) the recovery of T cells is dependent on a significant decrease in viral load in the first 3 months of therapy but not on the sustained inhibition of viral replication after 6 months of therapy; 3) the spontaneous recovery of immunologic responses will not occur due
to the clonal deletion of memory T cells; and 4) newly acquired CD4 T cells can develop responses to antigens encountered.

A multi-center study powered to examine the phenotype and function of T cells regenerated post-HAART initiation is needed to further assess several assumptions supported by the preliminary data.

1.2 Study Rationale

HIV-1 infected children initiating HAART have shown significant inhibition of HIV growth and significant increases in T cell counts. It is not known to what extent an increase in CD4 count in this population of children translates to a complete functional immune recovery. Partial recovery of CD4+ T cell function has been reported in adults who have demonstrated new lymphoproliferative responses to several antigens (i.e. tetanus, CMV) after virologic response to HAART (1,2,9). The longevity of the return of CD4+ T cell function corresponds to the degree and length of HIV viral suppression.

HIV-1 infected children have demonstrated poor serological responses to routine childhood immunization(s) (10,11). Hepatitis A vaccine is not routinely administered in the United States. Guidelines from various health organizations recommend vaccines primarily for all persons who are at high risk for infection. The prevalence of hepatitis A in the pediatric HIV population is unknown and is most likely age dependent. Increased co-infection between hepatitis A and HIV has been reported in the HIV adult literature (12) accentuating the need for prevention.

Highly immunogenic hepatitis A vaccines have been recently licensed in the United States. There is a paucity of data regarding hepatitis A seroconversion and cell mediated immunity (CMI) after vaccination in the pediatric HIV-infected population. The rate of seroconversion in HIV-infected adults vaccinated against hepatitis A ranged from 75% to 80% (13-16). Most importantly, among the severely immunodeficient patients (CD4 <100/µL) only 25% responded with protective levels of antibody to the vaccine (13). The antibody titers were much lower in those patients as compared to non-HIV infected controls. A recent study of CMI after hepatitis A vaccination in 42 healthy adults reported that all subjects vaccinated showed a hepatitis A virus (HAV)-specific LPA response at 2 weeks after the first vaccine dose which was maintained for a one year period after the 6 month booster dose (17). Such data are not available for HIV-infected children.

This study will examine the phenotype of T cells regenerated post-HAART initiation and assess function by evaluating T cell responses to neoantigens and recall antigens. One specific question to be addressed will be whether recovery of immunologic function in children occurs early in therapy when an increase in
Peripheral memory T cells is likely to occur. Alternatively, memory T cell clones may not be expanded from the periphery but thymus-derived naive T cells can be newly educated to become memory cells. In order to further dissect function, cell-mediated immune responses to an environmental antigen (Candida), a recall antigen (tetanus), and a primary immunogen (hepatitis A) will be tested. The ability of T cells to respond *de novo* will be assessed by challenging the cells with a T-dependent antigen (hepatitis A). While the recommended regimens for the Havrix® hepatitis A vaccine, manufactured by GlaxoSmithKline Pharmaceuticals, are 0, 1, and 6 months of 360 EL.U. or 0 and 6 months of 720 EL.U., the regimens are modified in this study. Subjects will receive a three-dose schedule at 0, 2, and 4 months of 360 EL.U (i.e. at weeks 32, 40, and 48 for Group 1 and weeks 8, 16, and 24 for Group 2). This schedule will be used to facilitate patient and laboratory evaluations. Since the response to hepatitis A vaccine has resulted in low titers of antibody (see section 1.3) all newly enrolled subjects, and those who have not yet reached week 100 of the study by the time version 4.0 is ready for implementation, will receive an additional hepatitis A booster at week 100 if they agree to do so.

B cell responses to T-dependent antigens will also be assessed as individuals treated with HAART have been shown to develop an increase in B cells (CD19) twelve weeks after treatment initiation, as well as the previously described T cell changes. These studies will elucidate if it is better to immunize patients on HAART when viral load is low, or when CD4 cell count is high, and correlate the function of T cells with the phenotypes of cells regenerated.

1.3 Preliminary Findings from P1006 (based on data available in October 2003)

Of 53 subjects enrolled, 32 were virologic responders and eligible to continue on study past week four. Overall, median CD4% increased from 7% at baseline to 15% at 24 weeks and 17% at 48 weeks. Median HIV log RNA decreased from 5 at baseline to 2.6 at 24 and 48 weeks. Lymphoproliferative responses to tetanus were seen in 50% and 27% in Groups 1 and 2, respectively. Lymphoproliferative responses to hepatitis A were seen in 25% and 21% in Groups 1 and 2, respectively. Serologic responses to tetanus were seen in both groups after three immunizations with tetanus toxoid. Antibody responses to hepatitis A were seen more often than lymphoproliferative responses, but were of very low titer (18).
2.0 STUDY OBJECTIVES

2.1 Primary

2.11 To assess the ability of newly derived CD4 T cells to spontaneously develop lymphoproliferative responses to a recall antigen, tetanus toxoid, or to develop responses after booster vaccinations with tetanus vaccine.

2.12 To assess the ability to develop protective antibody responses to a T cell dependent antigen using a primary series of hepatitis A vaccinations.

2.13 To measure the durability of any response beyond the last vaccination.

2.2 Secondary

2.21 To measure CD4 T cell percentage at baseline and at the time of vaccination(s) and to correlate these with the establishment of immune responses.

2.22 To study the correlation of the establishment of phenotypic "naive" and "memory" T cells at baseline and the time of vaccination(s) with the establishment of immune responses.

2.23 To assess the ability of newly-derived CD4 T cells to develop spontaneous cell-mediated immune responses to an environmental antigen, candida.

2.24 To assess the ability to develop lymphoproliferative responses to T cell-dependent antigen, hepatitis A.

2.25 To assess whether the recovery of functional immunity is seen early or late after HAART.

2.26 To measure the HIV plasma copy number at baseline, the time of vaccination(s), and at the study completion (104 weeks) and to correlate these with the establishment of immune responses.

2.27 To assess the safety of giving multiple immunizations with FDA licensed vaccines to HIV-infected children and young adults.

2.28 To assess whether a hepatitis A vaccination booster at week 100 will result in an increase in hepatitis A antibody.
3.0 STUDY DESIGN

This is a randomized, comparative, response study of immune reconstitution in approximately 90 severely immunosuppressed HIV-infected children and young adults aged 2 to 24 years who are initiating open-label HAART (HAART is defined as ≥ 3 antiretrovirals from at least 2 of the available therapeutic classes, i.e., NRTI, NNRTI, PI). The total duration of the study will be 104 weeks from study entry to study end for subjects who agree to receive a booster dose of hepatitis A vaccine at week 100. All eligible subjects will be on treatment (vaccines) from week 8 to week 100 (no vaccine will be administered between weeks 48 and 100), followed by a final post-immunization visit at week 104 (see Appendix I, Schedule of Evaluations) for subjects who receive the additional dose of vaccine. Subjects who were enrolled in version 3.0 of the study and have not completed the week 100 visit by the time version 4.0 is implemented, will be re-consented to version 4.0 if they agree to receive the hepatitis A vaccination at week 100; if so, they will be registered to step 2 of the study and will receive a new SID number for the new prescription. The rest of the subjects, including new subjects enrolled under version 4.0, will not enter step 2 and will just continue on their schedule. Those subjects who do not wish to receive the additional dose of hepatitis A will complete the study at week 100.

Both HAART naive and experienced individuals are eligible to enroll in the study. Subjects are eligible if HAART is initiated or altered within 2 weeks prior to entry, although they should optimally start or change therapy at entry. The only requirement for subjects already receiving HAART is that 2 new drugs (including at least 1 PI or NNRTI) be initiated. These could be added to or substituted for previous drugs used in therapy of these HAART-experienced patients. Subjects will be randomized into two groups at entry. T-20 (enfuvirtide, Fuzeon®) may also be initiated as an option for subjects who are not naïve to nucleoside analogues as part of their previous HAART regimens.

NOTE:
Laboratory evaluations done at entry must confirm the following for subjects to continue in the study: 1) CD4% of < 15%; 2) absence of ≥ Grade 3 clinical or laboratory toxicity (defined by the Division of AIDS [DAIDS] Toxicity Table for Grading Severity of Pediatric (> 3 Months of Age) Adverse Experiences, April 1, 1994); and 3) absence of ≥ Grade 3 hemoglobin or absolute neutrophil count after treatment with EPO or G-CSF/GM-CSF. If these criteria are not met, subjects will NOT continue in the study.

A viral load will be taken either at study entry, or at the time of initiation of or change in HAART regimen. One month after entry a second viral load will be taken. Only those subjects with virologic suppression defined as ≥ 0.75 log decrease or becoming undetectable in plasma HIV RNA copy (responders) will continue on the study. Subjects who do not experience a ≥ 0.75 log decrease or who fail to become undetectable in plasma HIV RNA copy (non-responders) will NOT be continued on study and will not be
followed in this study. However, subjects may be re-enrolled to the study for the following reasons: 1) subjects were non-adherent to medication regimen and are now deemed likely to succeed with therapy; 2) subjects are to be switched to a new antiretroviral regimen that site physicians/nurses believe will result in greater success in suppressing their virus.

An interim review will be conducted after the first 30 virologic responders have been on study for 6 months.

Individuals newly diagnosed with HIV infection (who may not be ready to make the decision to enroll in a research study), and other individuals who need to start or change their therapy before entry may consent to having a sample of blood drawn, which can be stored for up to one month (Appendix VI). If these individuals agree to enroll in the study within two weeks of starting or changing their HAART regimen, this stored specimen will be used as the baseline for evaluating viral load changes.

In Group 1, approximately 45 subjects will receive tetanus toxoid (as DTaP, DT-pediatric, or Td) immunizations at 8, 16, and 24 weeks and hepatitis A vaccinations at 32, 40, and 48 weeks. In Group 2, approximately 45 subjects will receive hepatitis A vaccinations at 8, 16, and 24 weeks and tetanus toxoid (as DTaP, DT-pediatric, or Td) immunizations at 32, 40, and 48 weeks. Both groups will receive a hepatitis A booster vaccine at week 100 on study. Immunizations are required within 2 weeks of scheduled visits. Serologic responses will be assessed one month after the first and third vaccination. Blood for lymphoproliferative studies will be drawn at baseline, 4 weeks, and 1 month after the first and final tetanus vaccination. The lymphoproliferative responses to Candida and hepatitis A will be measured concomitantly (see Appendix I, Schedule of Evaluations).

Blood samples will be collected from subjects when initiating HAART (week/month 0) and at time intervals designed to establish the lag time of immune recovery and identify the phenotype of T cells at baseline and over time. Because the rate of T cell recovery is gradual and variable, increases of cells may be seen as early as one month with temporal differences of isoforms but may be delayed for several months. Hence, a long-term follow-up is necessary.

Evaluation of immune reconstitution will be based on CD4 T cell rise, phenotype, and function as well as a significant virologic suppression (defined as a ≥ 0.75 log decrease or becoming undetectable in plasma HIV RNA copy number). A sustained response will be determined by maintaining the HIV RNA copy number at ≥ 0.75 log below the baseline level or remaining undetectable for the duration of the study. An increase of 150 CD4+ cells (or 10% CD4+ cells) from baseline will be considered an adequate response. T cell function will be measured by 1) LPA to assess the ability to respond to environmental antigen (Candida) and 2) serologic and LPA kinetics to recall and neoantigens (tetanus toxoid and hepatitis A) after immunization. Responses will be correlated with the
frequency of phenotypic memory and naive cells.

PBMCs will be stored for possible future analysis of new measures of thymic recovery such as TCR DNA excision circles.

CELL MEDIATED RESPONSES

Quantitative responses to recall, environmental, and neoantigens, tetanus toxoid (TT), Candida, and hepatitis A, respectively, will be done at study entry and at designated times to determine whether changes in viral load and/or CD4 counts account for recall and primary immune responses. Tetanus toxoid will be used to monitor the survival of memory cells derived from some distant immunization/antigenic encounter. Response to Candida may point to the ability to mount a de novo memory response in the newly acquired CD4 T cells. The responses will be monitored over time using qualitative criteria (i.e. a stimulation index of ≥ 3 as positive). Immune reconstitution will be further studied among the children and young adults who show a lymphoproliferative response to tetanus toxoid after a single study immunization versus 2-3 immunizations.

HUMORAL RESPONSE

The ability of B cells to respond to a T-dependent antigen (hepatitis A) will be evaluated by measuring increased protective antibody levels after a series of hepatitis A vaccines and by comparing antibody titers between the group vaccinated early and the group that has not yet received the hepatitis A vaccination.

ACCRUAL GOALS FOR VERSION 4.0

The team will monitor version 4.0 of the protocol very closely (monthly) in regards to accrual. For accrual goals to be met, the protocol team would like to enroll and retain an average of at least three subjects per month under version 4.0. With the expansion of the inclusion criteria, to include subjects through the age of 24 years, it is expected that these accrual goals will easily be met. The team will re-evaluate accrual within six months after version 4.0 has been open at the sites; if accrual goals are not met, the team will submit accrual results of the first six months to CSRC for discussion.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria:

4.11 Ages 2 to 24 years

4.12 Laboratory evidence of HIV-1 infection as demonstrated by: Two positive viral tests (antibody, culture, quantitative or qualitative PCR, p24
antigen, or ICD p24 antigen) on two different specimens. HIV antibody tests must be determined by a federally licensed ELISA. One of the two positive HIV antibody tests must be confirmed by any of the confirmatory tests (Western Blot or IFA). If two viral tests (other than HIV antibody) performed at a non-ACTG certified laboratory prior to entry are positive, subjects may be enrolled and a specimen sent at or before entry to an ACTG certified laboratory for culture.

4.13 Subjects initiating **HAART** of at least three drugs, including two new drugs to which the subject is naive. One of the drugs to which the subject is naive must be a protease inhibitor or a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz. Combinations of highly effective drugs are encouraged. **T-20 may also be initiated as an option for subjects who are not naïve to nucleoside analogues as part of their previous HAART regimens.**

4.14 Subjects who have received immunomodulator therapy as part of perinatal clinical trials or in trials for HIV-exposed infants are eligible.

4.15 Parent or legal guardian able and willing to provide signed informed consent.

4.2 **Exclusion Criteria:**

4.21 Presence of active opportunistic and/or bacterial infection at the time of enrollment.

4.22 Concurrent use of IVIG or use of IVIG within 6 months prior to study entry.

4.23 Current diagnosis of malignancy.

4.24 Pregnancy (females of childbearing potential must be screened for possible pregnancy). **Note: Pregnant females will be allowed to remain on study and complete all applicable study visits/evaluations if they become pregnant subsequent to receiving all vaccinations.**

4.25 Immunity to hepatitis A by routine serology.

4.26 Children **and young adults** currently receiving hydroxyurea.

4.27 Previous ≥ Grade 3 adverse event to a tetanus toxoid-containing vaccine.

4.28 Previous allergic reaction to a tetanus toxoid-containing vaccine.
4.3 Allowed Medications/Therapies

4.31 Opportunistic infection prophylaxis will be allowed.

4.32 EPO and/or G-CSF/GM-CSF are allowed.

4.33 Routine childhood immunizations are allowed. DT or DTaP, received as part of this protocol, will be allowed to count as required booster doses if the study inoculations are received during the appropriate window, as specified by the harmonized AAP/ACIP childhood immunization schedule.

4.4 Disallowed Medications/Therapies

IVIG, IL-2, steroids and other experimental immune modalities or immunosuppressive medications.

4.5 Enrollment Procedures

4.51 Eligible subjects will be enrolled when HAART is initiated or changed within 2 weeks prior to entry. Subjects will be randomized at entry. All eligible subjects will be on treatment (vaccines) from week 8 to week 100 (no vaccine will be administered between weeks 48 and 100), followed by a final post-immunization visit at week 104 (see Appendix I, Schedule of Evaluations). Subjects who were enrolled in version 3.0 of the study and have not completed the week 100 visit by the time version 4.0 is implemented, will be re-consented to version 4.0 if they agree to receive the hepatitis A vaccination at week 100; if so, they will be registered to step 2 of the study and will receive a new SID number for the new prescription. The rest of the subjects, including new subjects enrolled under version 4.0, will not enter step 2 and will just continue on their schedule.

NOTE: For subjects to remain in this study, entry evaluations must confirm that subjects CD4% is < 15% and that subjects do not have ≥ Grade 3 clinical or laboratory toxicity as defined by the Division of AIDS (DAIDS) Toxicity Table for Grading Severity of Pediatric (> 3 Months of Age) Adverse Experiences, April 1, 1994. Subjects must also not have a ≥ Grade 3 for hemoglobin or absolute neutrophil count after treatment with EPO or G-CSF/GM-CSF.

4.52 A baseline viral load will be obtained at entry. One month after study entry, a second viral load will be obtained to determine if a ≥ 0.75 log drop
in viral load or an undetectable level has been achieved. Those subjects who experience this > 0.75 log drop or become undetectable (responders) will receive the first immunization at the 8 week visit. Those subjects who fail to achieve ≥ 0.75 log drop or fail to become undetectable in viral load after one month of therapy (non-responders) will NOT continue to be followed in this study. However, subjects who meet the criteria (Section 3.0, Study Design) will be allowed to re-enroll in the protocol. Re-enrollment can take place within 2 weeks of reinstituting antiretroviral therapy.

4.53 Re-enrolled subjects will sign the re-enrollment signature page of the Sample Informed Consent Form (Appendix V). Subjects will then proceed to entry/screening visit (Schedule of Evaluations, Appendix I). These subjects will require the ≥0.75 log decrease or becoming undetectable in plasma HIV RNA by the week 4 visit after re-enrollment to continue in the study.

4.54 Individuals newly diagnosed with HIV infection who may not be ready to make the decision to enroll in a research study, and other individuals who need to start or change their therapy before entry may consent to having a sample of blood drawn, which can be stored for up to one month (Appendix VI). After one month this blood sample will be destroyed. If these individuals agree to enroll in the study within two weeks of starting or changing their HAART regimen, this stored specimen will be used as the baseline for evaluating viral load changes. At that point, subjects who wish to enroll and meet inclusion criteria may enter the study.

4.6 Co-enrollment Guidelines

Subjects may co-enroll to PACTG 219C or subsequent versions of 219.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

Subjects must be receiving HAART as chosen by their primary care provider. Subjects must be initiating HAART of at least 3 drugs, including 2 new drugs to which the subject is naive. One of the drugs to which the subject is naive must be a protease inhibitor or a potent NNRTI such as efavirenz. T-20 may also be initiated as an option for subjects who are not naive to nucleoside analogues as part of their previous HAART regimens. Combinations of highly effective drugs are encouraged. No antiretroviral study drugs will be administered or supplied as part of this study. All subjects will be monitored for one hour.
Immediately following the immunization. Telephone contact will be made within 24 to 48 hours after the immunization to evaluate any vaccine-related complications. If there are any grade 3 adverse reactions, the subject should be directed to return to the clinic for further evaluations.

In Version 4.0, an additional hepatitis A vaccination has been added at week 100 for subjects in both Groups 1 and 2.

Subjects who were enrolled in version 3.0 of the study, and have not completed the week 100 visit by the time version 4.0 is implemented will be re-consented to version 4.0 if they agree to receive the hepatitis A vaccination at week 100. If so, they will be registered through the SDAC/DMC system into Step 2. A new prescription, with a new SID number, will be generated for the pharmacist. Subjects should complete their assigned Group 1 or Group 2 immunizations and receive the additional hepatitis Vaccination at week 100.

- Group 1 immunizations:
  DTaP (Td or DT-pediatric)* 0.5 mL IM at 8, 16, and 24 weeks then
  Hepatitis A Vaccine 360 EL.U./0.25 mL IM at 32, 40, 48, and 100 weeks.

- Group 2 immunizations:
  Hepatitis A Vaccine 360 EL.U./0.25 mL IM at 8, 16, 24, and 100 weeks then
  DTaP (Td or DT-pediatric)* 0.5 mL IM at 32, 40, and 48 weeks.

*NOTE:

- Subjects less than 7 years of age at week 8 will receive DTaP (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed). Study personnel must notify the site pharmacist 21 working days in advance if a subject needs to receive DTaP.

  NOTE: Subjects less than 7 years of age at week 8 who cannot receive vaccine with a pertussis component will receive DT-pediatric. Study personnel must notify the site pharmacist 21 working days in advance if a subject needs to receive DT-pediatric.

- Subjects greater than or equal to 7 years of age at week 8 will receive Td (Tetanus and Diphtheria Toxoids Adsorbed for adults and children 7 years of age and older).

For all vaccines shake the vial/syringe well to resuspend the contents before withdrawal and before use. Administer by intramuscular injection. Vaccines
administered must be recorded in the subject’s permanent medical record in accordance with the National Childhood Vaccine Injury Act. Vaccines must also be recorded on the CRF.

5.2 Drug Dispensing

Study agents provided in multi-dose vials should be dispensed in accordance to site regulations for multi-dose vials and in a manner that will assure accountability of the study agent.

5.3 Drug Formulation

Hepatitis A vaccine inactivated IM suspension (HAVRIX®) 720 EL.U./0.5 mL. The dose to be administered in this study is 360 EL.U (0.25 mL). Store the Hepatitis A Vaccine between 2-8°C (36-46°F). Do not freeze; do not use if product has been frozen. Return to the CRPMC.

Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP, Tripedia®) IM suspension in syringes or vials. Store between 2-8°C (36-46°F). Do not freeze; do not use if product has been frozen. Return to the CRPMC. Each 0.5 mL dose contains 6.7 Lf units of diphtheria toxoid, 5 Lf units of tetanus toxoid and 46.8 mcg of pertussis antigens.

Tetanus and Diphtheria Toxoids Adsorbed, for adult use (Td) IM suspension in syringes or vials. Each 0.5 mL dose of Td is formulated to contain 5 Lf units of tetanus toxoid and 2 Lf units of diphtheria toxoid. Do not freeze; do not use if product has been frozen. Return to the CRPMC. Store refrigerated, away from freezer compartment, at 2-8°C (36-46°F).

Diphtheria and Tetanus Toxoids Adsorbed (DT-pediatric) IM suspension in syringes or vials. Each 0.5 mL dose of DT-pediatric is formulated to contain 5 Lf units of tetanus toxoid and 6.7 Lf units of diphtheria toxoid. Do not freeze; do not use if product has been frozen. Return to the CRPMC. Store refrigerated, away from freezer compartment, at 2-8°C (36-46°F).

NOTE: The amount of tetanus toxoid in all products provided for this study will be 5 Lf units per 0.5 mL. The amount of diphtheria toxoid may vary slightly depending on the manufacturer. All products are commercially available and approved for use in children.

5.4 Drug Supply, Distribution, and Pharmacy

Hepatitis A Vaccine (Havrix®) will be provided by GlaxoSmithKline Pharmaceuticals.
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP, Acel-Imune®), Tetanus and Diphtheria Toxoids Adsorbed, Purogenated® (Td), and Diphtheria and Tetanus Toxoids Adsorbed (DT-pediatric) were provided by Wyeth-Ayerst Laboratories for Version 1.0 and Version 2.0 until the study agents provided expired. (Wyeth-Ayerst Laboratories discontinued manufacturing these products.) Subsequently, Aventis-Pasteur has been and will be providing these agents as Tripedia®, Tetanus and Diphtheria Toxoids Adsorbed for adult use and Diphtheria and Tetanus Toxoids Adsorbed for pediatric use.

Study agents will be available through the NIAID Clinical Research Products Management Center. The ACTU pharmacist can obtain the study agents for this protocol by following the instructions in the manual "Pharmacy Guidelines and Instructions for AIDS Clinical Trials Group" in the section on Investigational Agent Control.

The NIAID Clinical Research Products Management Center will not provide HAART, syringes, or supplies for administration of vaccines as part of this study.

The ACTU pharmacist is required to maintain complete records of all study medication received from the NIAID Clinical Research Products Management Center and subsequently dispensed. All unused study medication must be returned to the NIAID Clinical Research Products Management Center 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 Group", in the section on Investigational Agent Control.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

Appendix II, Vaccine-Related Toxicities Occurring Within 48 Hours of Vaccination, will be used for grading vaccine toxicity. A ≥ Grade 3 adverse reaction requires a clinic visit within 12 hours of the event (see 6.31). Management of adverse vaccine reactions < Grade 3 is left to the discretion of the site clinicians/primary care providers.

Management of HAART toxicities associated with drug therapies is left to the discretion of the site clinicians/primary care providers.

6.2 Study Management Plan

Although subjects are encouraged to maintain initial antiretroviral regimens, changes in HAART regimens will be allowed after discussion with the protocol
team. The protocol team guidelines for changing HAART include the following: 1) an increase in plasma HIV RNA level which exceeds 50,000 copies/mL or 2) if subject's peak CD4% drops by more than one quarter, demonstrated after two consecutive evaluations done within two weeks of each other. If a change occurs, the protocol team must be informed. New HAART regimens must comply with the study treatment criteria.

6.3 Criteria for Treatment Discontinuation

6.31 Treatment discontinuation will be allowed if subject is not able to be vaccinated due to vaccine-related toxicities ≥ Grade 3, as defined in Appendix II or for any other reasons after discussion with protocol team.

6.32 Vaccine discontinuation will occur if there is discontinuation of HAART. Discontinuation of HAART for any reasons including toxicities (defined by the Division of AIDS (DAIDS) Toxicity Table for Grading Severity of Pediatric Adverse Experiences for Children ≥3 months of age [April 1, 1994]) should be discussed with the protocol team.

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

7.1 Reporting Requirements

Serious Adverse Experience (SAE) Forms for study intervention related events should be submitted to the DAIDS Regulatory Compliance Center (RCC) Safety Office as described in the SAE Reporting Manual, dated August 1, 1998. The RCC Safety Office can be reached at RCCSafetyOffice@tech-res.com. This protocol follows intensive reporting requirements, as described.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This study will evaluate the immune reconstitution in severely immunosuppressed HIV-infected children and young adults aged 2 to 24 years who are initiating open-label HAART. The subjects will be randomized into two groups. Entry evaluations must confirm a CD4% of < 15% and the absence of ≥ Grade 3 clinical or laboratory toxicities in order for subjects to remain in the study. One month after study entry, subjects must achieve a ≥ 0.75 log drop or become undetectable in plasma HIV RNA copy number relative to their baseline sample (taken at initiation of or change in HAART regimen) to continue on the study. Non-responders (those who do not experience a ≥ 0.75 log decrease or who fail to
become undetectable in plasma HIV RNA copy one month after study entry) will NOT be followed in the study. See Section 3.0, Study Design, regarding possible re-enrollment opportunity for qualifying subjects. In Group 1, eligible subjects will receive tetanus toxoid immunizations at 8, 16, and 24 weeks and hepatitis A vaccinations at 32, 40, 48, and 100 weeks. In Group 2, eligible subjects will receive hepatitis A vaccinations at 8, 16, 24, and 100 weeks and tetanus toxoid immunizations at 32, 40, and 48 weeks. Serologic and lymphoproliferative responses will be measured. The analyses related to the primary objectives will be performed on data from the first six months after the initiation of vaccine treatment, before the crossover in the vaccine administration.

The first group will provide data for studying the response to a recall antigen (tetanus). The second group will provide data for measuring the primary response to a de novo antigen (hepatitis A), and also for studying spontaneous recovery of response to tetanus, following HAART. The response to an environmental antigen (Candida) will be assessed as well, along with the relative effects of early versus late vaccination and the durability of any response beyond the last vaccination.

When the first 30 virologic responders reach 6 months on the study, a preliminary analysis of the data will be performed. If the results of this investigation answer all of the scientific questions associated with the primary objectives of the study, the team will evaluate the potential benefits of closing accrual to the study.

8.2 **Endpoints**

8.2.1 **Primary Endpoints:**

- A Stimulation Index (SI) of ≥ 3 on at least 2 occasions will be the criterion for an LPA response to tetanus, positive or negative.

- Hepatitis A:
  Positive serologic response.

- Tetanus:
  Four fold-increase over baseline in antibody titers.

**Primary Response Variables:**

- SI to tetanus on the LPA assay.

- Antibody titers for tetanus and hepatitis A.
8.22 Secondary Endpoints:

- A Stimulation Index (SI) of $\geq 3$ on at least two occasions will be the criterion for an LPA response to hepatitis A and Candida.

- Increase in CD4 T cell percentage and/or absolute CD4 number of 10\% and 150 cells/ml over baseline, respectively.

- Presence of $\geq$ Grade 3 toxicities attributable to vaccination.

Secondary Response Variables:

- SI to hepatitis A and Candida on the LPA.

8.3 Sample Size and Analysis:

Spontaneous return of function:

The group that does not receive tetanus vaccine during the first 6 months of the study will provide data for studying spontaneous recovery of function, following HAART. The analyses will consist of paired t-tests, comparing baseline with 2-month and 6-month log-transformed SI values of tetanus LPA for this group. Sample size calculations are based on the assumption that a 3 fold improvement over baseline is the minimum change which would be considered clinically important. These calculations indicate that a sample of 22 patients would be needed to provide 80\% power to detect such a change, given the variability in the LPA assay. Additional analyses will assess change over time in terms of the response criteria defined above, using the McNemar test.

[NOTE: The group needed for this analysis will be a subgroup of the larger study sample, which will also include children and young adults whose spontaneous recovery of response to tetanus cannot be measured, since they will receive tetanus vaccine during the first 6 months.]

Response to Recall Antigen:

The response to a recall antigen will be assessed by comparing the 2-month tetanus LPA of the group which, at that time point, will have received a single tetanus booster with that of the other group, which will not yet have been boosted with tetanus. The extent to which patients are responding to tetanus as a recall antigen should be reflected in this group difference.

The data will be analyzed in terms of log (10) transformed SI, with statistical significance assessed by means of a t-test (or a Wilcoxon test, if the data are not normally distributed). Assuming that a 3 fold difference is the minimal effect
considered to be clinically important, samples of 41 patients per group will be needed to provide 80% power to detect such a difference.

Additional analyses of the 2-month tetanus LPA data, dichotomized in terms of the LPA response criteria defined above, will assess lymphoproliferation to tetanus, using a chi-square test.

The validity of this analysis rests upon the assumption that administration of the hepatitis vaccine to the group not receiving tetanus will neither enhance nor diminish the tetanus LPA response. This assumption must be true, for the group receiving hepatitis A during the first 6 months is to serve as an unbiased control for the group vaccinated with tetanus during this time period.

Primary Response to Vaccination:

The primary response to a new vaccination will be examined by comparing the 6-month serologic response rate of the group receiving hepatitis A vaccine during that time period with that of the group which has not yet been treated with this vaccine. The statistical significance of group differences will be examined by means of a chi square test. Sample size calculations were based upon the assumption that the response rate in the unvaccinated group will be no greater than 10% and that the minimal effect which would be of clinical importance would be an increase to a 35% response rate in the vaccinated group. These calculations indicate that samples of 40 patients per group would be needed to provide 80% power to detect a true effect of this magnitude.

Overall Sample Size:

The calculations reviewed above indicate that 40-41 responder patients per group will be required to power the study for its primary objectives. Allowing for 10% attrition, this indicates that samples of 45 patients per group, or a total sample of 90 patients should be accrued to the study. The study is not powered to stratify the sample into subgroups, based upon factors such as virologic and immunologic response, and to test whether each of these subgroups meets the primary objectives.

Analyses relating to secondary objectives:

The study design will provide data for examining the role of virologic and immunologic response to therapy in predicting the 3 forms of immune function described in the primary objectives. Thus, the extent to which immune function depends upon RNA reduction, CD4 rebound and the distribution of memory versus naive T cells will be examined, using regression models with these factors,
as well as study group, as predictors. The effects of demographic factors including age, ethnicity, and gender will also be assessed in these models.

The relative effects of early versus late vaccination will be addressed by comparing the 12 month data from the group vaccinated during the first 6 months of the study to those of the group vaccinated during months 7 to 12. Another further comparison will be made between the 6 month data from the former group and the 12 month data from the latter, to test the strength of response immediately after the last booster. For tetanus, the primary data will be LPA, and the analyses will consist of t-tests (or Wilcoxon tests, depending on the distribution of the data). For hepatitis A, the primary data will be binary classifications of serologic response, and the primary analyses will be chi-square tests.

LPA response to hepatitis A and candida will be analyzed in terms of log (10) transformed SI, with statistical significance assessed by means of a t-test (or a Wilcoxon test, if the data are not normally distributed). Additional analyses of the data, dichotomized in terms of the LPA response criteria defined above, will assess lymphoproliferation to these antigens, using Chi-square tests. The study is not powered for analysis of secondary objectives. Thus, failure to find statistically significant results on some of these analyses may be due to inadequate sample size, rather than the absence of clinically important effects.

Although the study treatments are well established vaccines, the rate of Grade 3 and 4 toxicities will be closely monitored and reported in descriptive analyses. The following table presents 95% confidence limits around potential rates of such toxicities.

<table>
<thead>
<tr>
<th>Proportion of Patients Exhibiting Toxicity</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>.0 (0/90)</td>
<td>.000</td>
</tr>
<tr>
<td>.1 (9/90)</td>
<td>.047</td>
</tr>
<tr>
<td>.2 (18/90)</td>
<td>.123</td>
</tr>
<tr>
<td>.3 (27/90)</td>
<td>.208</td>
</tr>
</tbody>
</table>
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 and the informed consent documents (Appendices V, VI, VII) and any subsequent modifications will be reviewed and approved by the Institutional Review Board or Ethics Committee responsible for oversight of the study. Written informed consent will be obtained from the subject (or parent or legal guardian 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 associated with the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number only to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, or the NIAID.

9.3 Study Discontinuation

The study may be discontinued at any time by the FDA, NIAID, pharmaceutical sponsors, 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 blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 650 for diagnostic specimens. Please refer to individual carrier guidelines (e.g., FedEx, Airborne) for specific instructions.
12.0 REFERENCES


## APPENDIX I
### SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Pre-enrollment Stored Sample¹</th>
<th>SCREENING ENTRY/INITIATION OF HAART/RE-ENROLLMENT</th>
<th>ON TREATMENT: STUDY WEEK/VISIT</th>
<th>Post Immunization Visits</th>
<th>Premature Discontinuation</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Assessment of HIV-Related Symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IMMUNIZATION³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tetanus toxoid⁴</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hepatitis A</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>tetanus toxoid⁴</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LABORATORY EVALUATIONS⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology⁶ (CBC) (purple top)</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Chemistries⁷ (red top)</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BETA HGB (Serum/Urine)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX I (Cont.)

#### SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Pre-enrollment Stored Sample</th>
<th>SCREENING ENTRY/INITIATION OF HAART/RE-ENROLLMENT</th>
<th>ON TREATMENT: STUDY WEEK/VISIT</th>
<th>Post Immunization Visits</th>
<th>Premature Discontinuation</th>
<th>LAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIROLOGY (REFER TO APPENDIX III)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative HIV RNA (purple top)</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>PBMC storage (yellow top)</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>IMMUNOLOGY (REFER TO APPENDIX IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A and TT (Tetanus Toxoid)</td>
<td>3 mL&lt;sup&gt;10&lt;/sup&gt;</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>Serology (red top)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced Flow Cytometry (purple top)</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>LPA (TT, Candida, hep A) (green top)</td>
<td>4 mL</td>
<td>4 mL</td>
<td>4 mL</td>
<td>4 mL</td>
<td>4 mL</td>
<td>4 mL</td>
</tr>
<tr>
<td>Lymphocyte Subsets - Routine</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Total Blood Volume</td>
<td>3 mL</td>
<td>18 mL</td>
<td>11 mL</td>
<td>7 mL</td>
<td>7 mL</td>
<td>11 mL</td>
</tr>
</tbody>
</table>

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APPENDIX I (Cont.)

1. Stored Sample (pre-enrollment) for newly diagnosed HIV-infected subjects for possible future enrollment and for other individuals who need to start or change therapy before entry. This sample will be destroyed after one month.
2. Physical exam (height, weight, vital signs, symptoms).
3. Immunizations are required within 2 weeks of scheduled visits. All patients will be monitored for one hour immediately following the immunization. Telephone contact will be made within 24 to 48 hours after the immunization to evaluate any vaccine related complications. If there are any ≥ Grade 3 adverse reactions, the patient should be directed to return to the clinic for further evaluations.
4. DTaP will be given to children < 7. Subjects < 7 years who cannot receive vaccine with a pertussis component will receive DT-pediatric. Td will be given to children and young adults ≥7 years at week 8.
5. Laboratory evaluations can be performed within 2 weeks of scheduled visits.
7. Chemistries (indirect bilirubin, direct bilirubin, AST, ALT, electrolytes glucose, BUN, creatinine, amylase, cholesterol).
8. To be stored for future analysis.
10. Serology for hepatitis A only at screen. May be done at a local laboratory.

For insufficient blood draws priorities are as follows:
1. LPA
2. Hepatitis A Serology
3. Lymphocyte subsets

**Subjects who were enrolled in version 3.0 of the study and have not completed the week 100 visit by the time version 4.0 is implemented, will be re-consented to version 4.0 if they agree to receive the hepatitis A vaccination at week 100; if so, they will be registered to step 2 of the study and will receive a new SID number for the new prescription. The rest of the subjects, including new subjects enrolled under version 4.0, will not enter step 2 and will just continue on their schedule. Subjects who have not yet reached week 100 but do not wish to receive an additional
hepatitis A booster at this time point will still be asked to come in for a final study follow-up visit and end their study participation at week 100.

NOTE: Sites should inform the team whether CD4 values are being obtained at a PICL or other certified laboratory. Sites may obtain CD4 values at either laboratory, but should remain consistent and use the same laboratory throughout the course of the study.
## APPENDIX II

**SUPPLEMENTAL TABLE: VACCINE-RELATED TOXICITIES OCCURRING WITHIN 48 HOURS OF VACCINATION**

<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>Erythema: diameter (mm) of skin redness at the site of injection</td>
<td>Present but &lt; 10 cm</td>
<td>(\geq 10 \text{ cm but } &lt; 50% \text{ of the extremity})</td>
<td>(\geq 50% \text{ of the extremity})</td>
<td></td>
</tr>
<tr>
<td>Induration: diameter (mm) of palpable hardness of the skin at the site of injection</td>
<td>Present but &lt; 10 cm</td>
<td>(\geq 10 \text{ cm but } &lt; 50% \text{ of the extremity})</td>
<td>(\geq 50% \text{ of the extremity})</td>
<td></td>
</tr>
<tr>
<td>Pain: at site of injection</td>
<td>Crying or protest to touch</td>
<td>Crying on movement of site - not touching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever: rectal temperature</td>
<td>(\geq 100.4,\text{°F but } &lt; 103,\text{°F})</td>
<td>(\geq 103,\text{°F but } # 105,\text{°F})</td>
<td>(&gt; 105,\text{°F})</td>
<td></td>
</tr>
<tr>
<td>Fatigue/weakness/malaise/myalgie</td>
<td>Transient, no limit on ADL, no therapy needed</td>
<td>Mild to moderate ADL (no intervention needed)</td>
<td>Marked impact on ADL requiring medical intervention</td>
<td>Completely disabling requiring hospitalization</td>
</tr>
<tr>
<td>Irritableness: subjective parent report</td>
<td>Irritable or fussy, but otherwise normal routine</td>
<td>More crying than usual, not on normal routine</td>
<td>Prolonged crying, refuses to play/smile with parent/guardian</td>
<td>Inconsolable crying (\geq 3) hours, unusual high pitched crying/screaming</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Mild lethargy, irritability, sleeps through a feeding; headache (no treatment)</td>
<td>Moderate lethargy, irritability, needs to be awakened for feedings; headache required non-narcotic analgesic</td>
<td>Somnolent, needs to be stimulated to take feedings; narcotic for headache</td>
<td>Comatose</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, moist desquamation.</td>
</tr>
</tbody>
</table>

* \(\geq\) Grade 3 adverse reactions require a clinic visit within 12 hours of the event.
APPENDIX III-A
QUANTITATIVE PLASMA HIV-1 RNA PCR

<table>
<thead>
<tr>
<th>ASSAY REQUIREMENT</th>
<th>SPECIMEN COLLECTION</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Plasma            | 3 mL blood collected by venipuncture | 3 mL Tripotassium (purple top) Vacutainer™ tube | • Gently invert tubes several times to mix. Do not shake.  
• Label specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
• Specimen should be kept at room temperature (18–24° C) and processed as rapidly as possible, ideally within 6 hours. |

SPECIMEN PROCESSING:
A. Plasma - Draw 3 mL of blood into a 3 mL draw EDTA (purple top tube). This tube should be processed as quickly as possible, preferably within <6 hours.

ALIQUOTS: 0.5 mL x 2

DESIGNATED LABORATORY/CONTACT PERSON: Not applicable

SHIPPING: Real time

OTHER INSTRUCTIONS: ACTG laboratory certified to do the Quantitative Plasma HIV-1 RNA PCR assay.
# APPENDIX III-B

## PBMC STORAGE

<table>
<thead>
<tr>
<th>VIROLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSAY REQUIREMENT</strong></td>
</tr>
<tr>
<td><strong>SPECIMEN COLLECTION</strong></td>
</tr>
<tr>
<td><strong>COLLECTION CONTAINER</strong></td>
</tr>
<tr>
<td><strong>IMMEDIATE SPECIMEN HANDLING</strong></td>
</tr>
<tr>
<td>PBMC</td>
</tr>
<tr>
<td>3 mL blood collected by venipuncture</td>
</tr>
<tr>
<td>ACD Vacutainer™ tube</td>
</tr>
<tr>
<td>• Gently invert tubes several times to mix. Do not shake.</td>
</tr>
<tr>
<td>• Specimen should be identified as to patient ID#, study ID#, site ID#, visit ID#, date and time of collection, and type of specimen.</td>
</tr>
<tr>
<td>• Specimen should be kept at room temperature (18°-24°C) and processed within 1 hour of collection.</td>
</tr>
<tr>
<td>SPECIMEN PROCESSING:</td>
</tr>
<tr>
<td>PBMC are separated from red blood cells and neutrophils by density centrifugation on Ficoll-Hypaque. Cells should be frozen using the ACTG Immunology Consensus Method for PBMC cryopreservation.</td>
</tr>
<tr>
<td>ALIQUOTS: 2 x 10⁶/1 mL x 2</td>
</tr>
<tr>
<td>LABORATORY/CONTACT PERSON: NA</td>
</tr>
<tr>
<td>SHIPPING: NA</td>
</tr>
<tr>
<td>OTHER INSTRUCTIONS: Store PBMCs at the local laboratories.</td>
</tr>
</tbody>
</table>
# APPENDIX IV-A

**HEPATITIS A AND TETANUS TOXOID SEROLOGY**

<table>
<thead>
<tr>
<th>IMMUNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSAY REQUIREMENT</strong></td>
</tr>
</tbody>
</table>
| Serum | 3 mL blood collected by venipuncture | Sterile Vacutainer™ Tubes (red top) | • Place tube in a rack and allow blood to clot. Do not mix or shake.  
• Label specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
• Specimen must be processed immediately upon collection. |

**PROCESSING INSTRUCTIONS:** Separate serum and aliquot into two 1-mL aliquots. If less than 2 mL of serum is obtained, divide it equally into two aliquots. Freeze the aliquots in -20°C freezer until shipment.

**DESIGNATED LABORATORY/CONTACT PERSON:** **LDMS Lab 134, Patricia Defechereux, Ph.D., UCSF Pediatric Immunology Core Lab, Room HSE 301, 505 Parnassus Avenue, San Francisco, CA 94143. Phone: (415) 476-3993 Fax: (415) 476-5795**

**SHIPPING:** On dry ice, in batches, priority overnight.

**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.

*DO NOT send specimens on Fridays or the day before a legal holiday.*
APPENDIX IV-B

ADVANCED FLOW CYTOMETRY

<table>
<thead>
<tr>
<th>IMMUNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSAY REQUIREMENT</td>
</tr>
</tbody>
</table>
| Whole Blood | 1 mL blood collected by venipuncture | Tripotassium EDTA Vacutainer™ tubes (purple top) | • Gently invert tubes several times to mix. Do not shake.  
  • Label specimen with SID#, PID#, study visit week, date and time of collection, specimen type.  
  • Specimen must be processed immediately upon collection. |

FLOW CYTOMETRY PANEL:

<table>
<thead>
<tr>
<th>FITC (Green)</th>
<th>PE/RD (Orange)</th>
<th>CY-5/PER-CP(RED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>CD45RO</td>
<td>CD4</td>
</tr>
<tr>
<td>CD45RA</td>
<td>CD62L</td>
<td>CD4</td>
</tr>
</tbody>
</table>

Key:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>fluorescein</td>
<td>isothiocyanate</td>
<td>indodicarbocyanine</td>
<td>peridin chlorophyll protein</td>
<td>helper T lymphocyte</td>
<td>memory T lymphocyte</td>
<td>mature T lymphocyte</td>
</tr>
<tr>
<td>PC:</td>
<td>RD:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phycoerythrin</td>
<td>red dye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD62L</td>
<td>CD645RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PROCESSING INSTRUCTIONS: None.

DESIGNATED LABORATORY/CONTACT PERSON: Sites will be assigned to a Pediatric Immunology Core Lab (PICL).

SHIPPING: Room temperature, priority overnight.

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 IV-C

LPA FOR TETANUS TOXOID, CANDIDA, AND HEPATITIS A

<table>
<thead>
<tr>
<th>IMMUNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSAY REQUIREMENT</td>
</tr>
<tr>
<td>Whole blood</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

PROCESSING INSTRUCTIONS: None

DESIGNATED LABORATORY/CONTACT PERSON: Sites will be assigned to a Pediatric Immunology Core Laboratory.

SHIPPING: Room temperature, priority overnight.

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

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

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

NOTE FROM OPRR (OFFICE OF PROTECTION AGAINST RESEARCH RISKS) TO SITES
ENROLLING SUBJECTS IN THIS STUDY:

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

TITLE OF CLINICAL TRIAL: PACTG P1006, Version 4.0, dated May 02, 2005: The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults

PRINCIPAL INVESTIGATOR: PHONE:

INFORMED CONSENT

You are/your child is being asked to take part in the research study named above because you are/your child is infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. This study is sponsored by the United States (U.S.) National Institutes of Health (NIH). This is a study to see how well your/your child's ability to fight infection is responding to a drug combination for the treatment of HIV infection. Before you can decide whether or not to take part/allow your child to take part in this study, we would like to explain the purpose of the study, how it may help you/your child, any risks to you/your child, and what is expected of you/your child.

YOUR PARTICIPATION IS VOLUNTARY

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

Before you learn about the study, it is important that you know the following:

- You/your child's participation is entirely voluntary;
- You may decide not to take part/allow your child to take part or to withdraw/withdraw your
child from the study at any time without losing the benefits of your/your child's routine medical care.

PURPOSE OF STUDY

HIV damages the immune system (the body’s natural defense system against viruses) by infecting many different types of blood cells in the body. Some of the infected cells are supposed to protect the body from disease by helping to fight infections, such as HIV. When these cells become infected, they are not able to fight infections and eventually the cells die. As a result, your/your child's immune system gets weak.

When you/your child take(s) a combination of drugs for the treatment of HIV infection (HAART), the virus is not able to multiply (or grow) as quickly and the cells of the immune system can help fight infection. The purpose of the study is to tell how many of your/your child's immune cells return. The purpose of this study is also to see how quickly those immune cells that are able to fight both new and old infections return. This study will also look at the amount of HIV in your/your child's blood while you are/your child is on HAART. Finally, this study will look at the safety of giving multiple vaccinations to HIV-infected children and young adults. In order to study your/your child's immune system, you/your child will receive two different vaccines which are approved by the FDA for children.

PROCEDURES

Your primary care physician has already discussed starting you/your child on a combination of drugs for the treatment of HIV infection. Because you are/your child is starting a new drug combination, you/your child may be eligible to enroll in this study. The study will last for about 104 weeks and will include approximately 90 patients.

Entry

If you are/your child is eligible for this study you/your child will be enrolled. The following procedures will be done when you/your child enter(s) the study:

- **You/your** child will have a physical exam.
- About 4 teaspoons of blood will be drawn to determine the amount of HIV in the blood, to determine if you have/your child has a hepatitis A infection, and for other routine tests. You will be informed of the amount of HIV in your/your child's blood when these results are available.
- **You/your** child will give a urine sample.
- If you are/your child is female and able to become pregnant, you/she will have a blood or
urine test performed to test for pregnancy. If a blood test is performed, less than 1 teaspoon of blood will be collected.

This study visit will last approximately 30-45 minutes.

Your child's entry laboratory results must confirm a CD4% (percent of cells that are involved in protecting your body against viral infections) of less than 15%. Additionally, you may have no serious clinical or laboratory toxicities (substances that are harmful to your child’s body) in order for you to continue in this study. If the laboratory results do not confirm these requirements, then you will not continue in the study and will not be given any vaccinations. In addition, if you have a positive Hepatitis A test at entry, you will not be eligible to participate in this study. Your child may have received prior tetanus vaccines. You will be able to receive all routine childhood immunizations while on study.

One month after entry, at week 4, you will return to the clinic. If the amount of HIV in your child's blood has decreased by 6 times or has become undetectable since the first test, you will continue to be part of the study. If the amount of HIV in your child's blood has not decreased by 6 times or has not become undetectable since the first visit, you will not be part of the study or be given any vaccinations. However, if your child's physician determines that you may be eligible to re-enroll in this study, the information in this consent form will be discussed with you again. You will be asked to sign a re-enrollment consent page. The requirement for decrease in viral load (amount of HIV in your child's blood) stated above will be required at the week 4 visit after re-entry to continue in the study or to be given any vaccinations.

On Study

If you are part of the study, you must come to the clinic 12 times during the next 96 weeks (approximately 2 years) at weeks 8, 12, 16, 24, 28, 32, 36, 40, 48, 52, 76, and 100. The following procedures will be done at these times:

- **You will have a physical exam.**
- During 9 of these visits, **about 3 teaspoons** of blood will be drawn to determine the amount of HIV in the blood and for other routine tests. You will be informed of the amount of HIV in your child's blood when these results are available. During 2 of these visits, **about 4 teaspoons** of blood will be drawn for the same purposes.
- During 7 visits, you will be immunized (receive vaccine). In total, you will receive 4 hepatitis A immunizations (3, if you do not agree to a 4th dose of hepatitis A vaccine) and 3 tetanus immunizations intramuscularly (injected into the muscle). All vaccines are approved for children. You will be randomly assigned (placed in a study group by chance, like flipping a coin). Half of the
participants on this study will first receive 3 hepatitis A vaccines (at weeks 8, 16, and 24) and then 3 tetanus vaccines (at weeks 32, 40, and 48) over the course of one year. The other half of the participants on this study will first receive 3 tetanus vaccines (at weeks 8, 16, and 24) and then 3 hepatitis A vaccines (at weeks 32, 40, and 48) over the course of one year. If you/your child agree(s), you/your child will receive a final hepatitis A vaccine at week 100. If you have/your child has been in the study for a while and you/your child chooses not to receive the final hepatitis A vaccine at week 100, you/your child will still be asked to come into the clinic for a final study visit at week 100.

The hepatitis A vaccine is FDA approved and used to help prevent you/your child from becoming infected with hepatitis A, a viral infection of the liver. You/your child can become infected with hepatitis A by eating infected food or drinking infected water. In this study you/your child will receive hepatitis A vaccinations at slightly different times than the FDA approved regimen.

The tetanus vaccination (in combination with diphtheria toxoid (dt) or in combination with diphtheria toxoid and acellular pertussis [D'TaP]) is to help prevent you/your child from becoming infected with tetanus (and diphtheria or pertussis), a disease caused by a bacteria.

Each study visit will last approximately 30-45 minutes. In addition, after you/your child receive(s) a vaccine, you/your child will be asked to stay in the clinic for 1 hour to monitor for any vaccine related complications. Within 24-48 hours after the immunization, you/your child will receive a telephone call from site personnel to discuss any vaccine-related complications.

Follow-Up After Last Immunization

After receiving all your/your child’s vaccines, you/your child will come to the clinic for a final follow-up visit at week 104, after the last hepatitis A vaccine is received. This study visit will last approximately 30-45 minutes. The purpose of this and earlier visits that follow immunizations is to determine how long immunity (resistance to a specific disease), acquired as a result of immunization, will last. If you do/your child does not agree to receive the last hepatitis A vaccine, you/your child will come to the clinic for a final follow-up visit at week 100.

- You/your child will have a physical exam.
- During the final follow-up visit, about 3 teaspoons (about 4 teaspoons if the final follow-up visit is at week 100) of blood will be drawn to determine the amount of HIV in the blood, to see if the immune cells are working well to fight infection, and for routine tests. You will be informed of the amount of HIV in your/your child's blood when the results are available.
APPENDIX V (Cont.)

While on study and on follow-up, a total of about 35 teaspoons of blood may be collected from you/your child if you/your child complete(s) all study visits.

Premature Discontinuation

If you/your child stops taking part in this study before week 100 you/your child will be asked to have the following evaluations:

- A physical exam.
- About 2 teaspoons of blood will be drawn to determine the amount of HIV in the blood and for other routine tests.

You should tell your/your child's nurse or doctor before you/your child take(s) any non-study medications or enroll(s) in other clinical trials.

FINDING OUT THE TEST RESULTS

Site staff will review the results of your/your child’s tests (including blood and urine tests) at each study visit, or as soon as they become available.

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. Less than 1 teaspoon 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
APPENDIX V (Cont.)

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 study 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, all possible efforts will be made to destroy your/your child’s samples.

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 study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your/your child’s consent.

RISKS RELATED TO VACCINES

You/your child may experience an allergic reaction to either of the 2 vaccinations used in this study. This may include a rash, redness, swelling, fever, pain, drowsiness, weakness, seizures, or other serious side effects. Following the vaccinations, you/your child may also have a brief increase in the amount of HIV in your/your child’s blood. The amount of HIV usually returns to the same amount present before the vaccination without any associated problems.

RISKS RELATED TO BLOOD DRAWS

The risks of drawing blood include discomfort, bleeding or bruising where the needle enters the body, a feeling of lightheadedness and, in rare cases, fainting or infection.
APPENDIX V (Cont.)

PREGNANCY

It is not known if the drug or drug combinations in this study harm unborn babies. Tests in pregnant animals do show some risk. If you are/your child is having sex that could lead to pregnancy, you/your child must agree not to become pregnant or make a woman pregnant.

Because of the risk involved, you/your child or your/your child’s partner must use two methods of birth control that you discuss with the study staff. You/your child may choose two of the birth control methods listed below.

- Hormonal birth control drugs that prevent pregnancy given by pills, shots or placed on or 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/your child must have a pregnancy test before you/your child enter(s) this study. The test must be negative. If you think you/your child may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you/your child about your/your child’s choices. You/your child will be allowed to stay on study if you/she becomes pregnant after all of the vaccines have been given. You/your child will just be asked to complete the rest of the scheduled visits/evaluations.

BREAST FEEDING

Women who are breast-feeding their baby may not join the study.

Taking antiretroviral drug(s) does not guarantee that you/your child will decrease the risk of passing HIV through your/your child’s breast-milk to your/your child’s baby. In addition, it is unknown whether antiretroviral drugs pass through the breast-milk and produce bad effects in the infant.

The effects of a vaccine passing through the breast-milk are also unknown. Receiving a vaccine does not guarantee that you/your child will decrease the risk of passing HIV through breast-milk to your/your child’s baby.
APPENDIX V (Cont.)

BENEFITS

The vaccines you/your child will receive are beneficial in preventing infection with hepatitis A, tetanus, diphtheria, and/or pertussis. You/your child and others may benefit in the future from the information that will be learned in this study.

OTHER INFORMATION

The information and knowledge that comes out of doing this study 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 study 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.

NEW FINDINGS

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

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

You/your child may be removed from the study without your consent for the following reasons:

- the investigator decides that continuing in the study would be harmful to you/your child;
- you/your child need(s) a treatment not allowed on this study;
- you are/your child is unable to keep appointments or take study drugs as instructed;
- you have/your child has a bad reaction to a vaccine or drug combination;
- you/your child become(s) pregnant;
- the study is canceled by the Food and Drug Administration (FDA), the National Institute of Allergy and Infectious Diseases (NIAID), or the pharmaceutical companies supplying study treatment; and/or
- other administrative reasons.
COSTS TO YOU/YOUR CHILD

You will not be charged for any study-related visits/appointments. Any medical costs for your/your child's treatment outside this study and/or any anti-HIV drug taken by you/your child will be charged to you or your/your child's insurance company. The vaccines given to you/your child in this study are supplied as part of the study. You/your child will not receive any money for being in this study.

ALTERNATIVES

The alternative to participating and taking the vaccines offered in this study is to not participate in the study. However, you/your child may take one or more of the FDA approved anti-HIV drugs available by prescription by your child’s doctor, in the absence of the vaccinations offered in this study.

CONFIDENTIALITY

Your/your child's research records will be confidential to the extent permitted by law. You/your child will be identified by a code, and personal information from your/your child's records will not be released without your written permission. You/your child will not be personally identified in any publication about this study. However, your/your child's records may be reviewed, under guidelines of the Federal Privacy Act, by the U.S. Food and Drug Administration; the National Institute of Allergy and Infectious Diseases, the Office for Human Research Protections (OHRP), the Division of AIDS; and study monitors.

To help us protect your/your child’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of health. With this Certificate, the researchers cannot be forced to disclose information that may identify 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 United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the 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, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.
APPENDIX V (Cont.)

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 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.

RESEARCH-RELATED INJURY

If you are/your child is injured as a result of being in this study, the ________ (name of the clinic) will give you/your child immediate necessary treatment for the 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 the U.S. NIH.

PROBLEMS OR QUESTIONS

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

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

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

OR

Volunteer's legal guardian
or representative

Legal Guardian's Signature
Date

OR

Witness' Name
(typed or printed)
Witness' Signature
Date

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

The Division of AIDS strongly encourages a witness for the subject's signature.
APPENDIX V (Cont.)

RE-ENROLLMENT CONSENT SIGNATURE PAGE

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

<table>
<thead>
<tr>
<th>Volunteer’s Name (typed or printed)</th>
<th>Volunteer’s Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Volunteer’s Legal Guardian</th>
<th>Legal Guardian’s Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Witness Name</th>
<th>Witness’s Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

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

The Division of AIDS strongly encourages a witness for the subject’s signature.
APPENDIX VI

SAMPLE INFORMED CONSENT FOR STORAGE OF SPECIMENS OBTAINED PRE-ENROLLMENT FOR POSSIBLE PARTICIPATION IN A DAIDS-SPONSORED RESEARCH TRIAL

TITLE OF CLINICAL TRIAL: P1006, VERSION 4.0, dated May 02, 2005: The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults

PRINCIPAL INVESTIGATOR:

INTRODUCTION

You are/your child is infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS. You/your child will start treatment to control the HIV infection. Once we get to know you/your child better, you/your child may qualify to enroll in a childhood HIV research study. This study may require a blood sample from you/your child before treatment for HIV is started or changed. You are/your child is being asked to give a blood sample today. We will store this sample just in case you/your child can participate in a research study within the next month. If you/your child qualifies to participate in the research study, we will explain the study to you and ask you/your child to agree to participate.

YOUR PARTICIPATION IS VOLUNTARY

If you agree to participate and/or allow your child to take part, you will be asked to sign this consent form. You will be given a copy to keep. It is important that you know that your/your child's participation is entirely voluntary and that you may decide not to participate/allow your child to participate without losing the benefits of your/your child's routine medical care.

PURPOSE OF STORAGE OF BLOOD SAMPLE

We do not know today if you/your child will qualify to participate in the HIV research study. We will take less than a teaspoon full of blood from a vein today and store it for one month. If you agree to participate/let your child participate in the HIV research study, the stored blood will be used only for blood tests to see how much HIV virus is in your/your child's blood. This blood sample will be destroyed after one month.

If you do/your child does enroll in the study, you will sign another consent form with more information about the study at a later date.
APPENDIX VI (Cont.)

PROCEDURE

If you decide to/allow your child to have blood drawn, and you sign this consent form, the following procedure will be done:
- About 1/2 teaspoon of blood will be drawn from you/your child.

RISKS RELATED TO BLOOD DRAWS

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

BENEFITS

The stored blood sample will be of no immediate benefit to you/your child, but may be used within one month to see if you are/your child is eligible for the above research study.

COSTS TO YOU

There will be no costs to you/your child for allowing this sample to be stored.

CONFIDENTIALITY

In order to keep your/your child’s information private, your/your child’s samples will be labeled with a code that can only be traced back to your/your child’s research clinic. Your/your child’s personal information (name, address, phone number) will be protected by the research clinic. Every effort will be made to keep your/your child’s personal information confidential, but we cannot guarantee absolute confidentiality. Your/your child’s personal information may be disclosed if required by law.

To help us protect your/your child’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of health. With this Certificate, the researchers cannot be forced to disclose information that may identify 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 United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).
APPENDIX VI (Cont.)

People who may review your/your child’s records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, 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 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.
Please read carefully the statement below and think about your/your child’s choice.

I agree to have a sample (blood) stored for one month pending decision for my/my child’s participation in P1006.

_____ Yes
_____ No

__________________________                    ______________________________
Participant’s Name                      Participant’s Signature                   Date

__________________________                    ______________________________
Participant’s Legal Guardian            Legal Guardian’s Signature                  Date

__________________________                   _______________________________
Study Staff Conducting Consent Discussion  Study Staff Signature                  Date

__________________________                   _______________________________
Witness’s Name (As appropriate)            Witness’s Signature                  Date
APPENDIX VII

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 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 VII (Cont.)

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?

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 “The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults,” you are/your child is being asked to have some blood and urine 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 VII (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>
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<tbody>
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<td>Parent or Legal Guardian Signature</td>
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<tbody>
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<td>Participant Signature</td>
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</table>
APPENDIX VII (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/your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your/your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your/your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your/your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

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

Risks: The specimens would be collected as part of your/your child’s study visits. 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 |
APPENDIX VII (Cont.)

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).

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

________________________________________  ____________________________  __________
Parent or Legal Guardian Signature         Witness Signature             Date
FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD)

YOUTH FACT SHEET

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 VII (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 “The Effects of Highly Active Antiretroviral Therapy (HAART) on the Recovery of Immune Function in HIV-Infected Children and Young Adults,” you are being asked to have some blood and urine 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.

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APPENDIX VII (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