WESTAT PROCEDURES MANUAL

FOR

ACTG PROTOCOL 185

VERSION 5.0

SEPTEMBER 1997

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF EXHIBITS

1. BACKGROUND AND STUDY RATIONALE

With an increasing shift in the epidemiologic features of human immunodeficiency virus (HIV) infection toward populations in which heterosexual activity and/or injection drug use predominate as modes of transmission (1), prevention of HIV transmission to women and of vertical transmission from mother to child have become urgent public health priorities.

The annual incidence of AIDS among children and women of childbearing age in the U.S. has been increasing every year for most racial/ethnic groups. HIV infection numbers among the 10 leading causes of death for U.S. children aged one through four years.(2) Vertical transmission accounts for almost 90 percent of AIDS in U.S. children.(3) As of 1990, estimates of the number of children with HIV infection in the United States ranged from 5,000 to 10,000.(4) A national population-based HIV seroprevalence survey has provided an estimate that there were approximately 7,000 births to HIV-infected women in the United States during 1991; assuming a 30 percent rate of HIV transmission from mother to child, this translates to 2,100 infected infants born annually.(5)

Synthesis of available data on the timing of vertical transmission suggests that intrauterine transmission may account for an estimated 20-30 percent of observed cases of vertically acquired HIV infection and that more commonly, HIV is probably transmitted around the time of birth (70-80%), analogous to vertical transmission of hepatitis B virus. Breast feeding as a mode of transmission is possible, but seemingly rare (6).

HIVIG is a preparation of highly purified human immune globulin containing high titers of antibody to HIV structural proteins with considerable functional activity in virus neutralization, and antibody dependent cytotoxicity assays (7). This intravenous IgG solution (HIVIG) is prepared from plasma of multiple HIV seropositive donors selected according to strict clinical and biological criteria.

Preliminary efficacy in man has been evaluated by measuring HIV antibody levels and the infectivity of patient plasma for normal stimulated lymphocytes, as an index of circulating infectious virus. In six HIV antigen positive patients, antigenemia disappeared during treatment with HIVIG. Plasma culture was positive in nine patients at study entry.

Circulating HIV was neutralized in three of 13 specimens (23%) following low dose (50 mg/kg) HIVIG and six of 11 specimens (55%) following high dose (200 mg/kg) HIVIG (8). These results suggest a dose-dependent capacity of HIVIG to neutralize circulating infectious HIV. Similar results were obtained in several studies of symptomatic HIV adults treated with HIVIG preparations (9-13) and in one child with AIDS who received passive immunotherapy with a HIVIG preparation (14).

This study will evaluate the hypothesis that in HIV-infected pregnant women receiving oral ZDV for medical indications, HIVIG administered monthly beginning at 20-30 weeks gestation in combination with intravenous ZDV intrapartum, together with a single newborn dose of HIVIG within 12 hours after birth in combination with six weeks of newborn oral ZDV, reduces vertical HIV transmission compared with IVIG administered identically as a control agent.

1.1 References

1. Centers for Disease Control. Update: Acquired immunodeficiency syndrome - United States, 1981-1990. Morbidity and Mortality Weekly Report 1991; 40(22):357-69.

2. Centers for Disease Control. Morbidity and Mortality Weekly Report 39(SS-3):23-30.

3. Centers for Disease Control. HIV/AIDS surveillance report, 1995; 7 (No. 2): 1-38.

4. Institute of Medicine, Hardy, L.M. (ed.): HIV Screening of Pregnant Women and Newborns. National Academy Press, Washington, DC, 1991.

5. Gwinn, M., Wasser, S., Fleming, P., et al. Increasing prevalence of HIV infection among childbearing women, United States, 1989-1991. IX International Conference on AIDS, 1993, Berlin, Germany. Abst. PO-C16-2990.

6. Van de Perre, P., LePage, P., Hornsy, J., and Dabis, F. Mother to infant transmission of human immunodeficiency virus by breast milk: presumed innocent or presumed guilty? Clin. Inf. Dis. 1992; 15:502-507.

7. Cummins, L.M., Weinholt, K.J., Matthews, T.J., et al. Preparation and characterization of an intravenous solutionof IgG from human immunodeficiency virus-seropositive donors. Blood 1991; 77:1111-1117.

8. Rhame, F.S., Goodroad, R.N., Cummins, L.M., et al. Safety and pharmacokinetics of human immunodeficiency virus immune globulin in persons with acquired immunodeficiency syndrome. (unpublished).

9. Jackson, G.G., Rubenic, M., Knigge, M., et al. Passive immunoneutralization of HIV patients with advanced AIDS. Lancet 1989; 2:647-51.

10. Karpas, A., Hill, F., Youle, M., et al. Effects of passive immunization in patients with AIDS related complex and AIDS. Proc Natl Acad Sci USA 1988; 85:9234-7.

11. Osther, K., Wilk, A., Black, F., et al. PASS HIV-1 treatment of patients with HIV-1 infection. A preliminary report of a Phase 1 trial of hyperimmune porcine immunoglobulin to HIV-1. AIDS 1992; 6:1457-1464.

12. Levy, J. and Youvan, T. Efficacy and safety of passive hyperimmune therapy in HIV disease: Results of a 12-month study. IX International Conference on AIDS, 1993, Berlin, Germany. Abst. PO-B28-2129.

13. Lefreve, J.J., Vittecoq, D., and the French Passive Immunotherapy Collaborative Study Group. Passive immunotherapy in AIDS: Results of a double-blind randomized phase II study. The First National Conference on Human Retroviruses and Related Infections, 1993, Washington DC, Abst. L-12.

14. Wong, V.K., Gillette, S.G., Roth, M.J., Miles, S., Stiehm, E.R. Passive immunotherapy in a child with acquired immunodeficiency syndrome. Pediatr. Infect. Dis. J. 1993: 12:947-951.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the effect of combination therapy with HIVIG and ZDV compared to IVIG and ZDV on the incidence of HIV infection in infants born to HIV-infected women who are receiving ZDV for medical indications.

2.2 Secondary Objective

- Establish the pharmacokinetics of the HIVIG preparation by measuring quantitative p24 antibody pre- and post- infusion in a small subset of pregnant women and in their newborns.
- Evaluate maternal virologic and immunologic factors involved in HIV transmission from mother to infant, and the influence of HIVIG on these parameters, as follows:
  - Compare HIV plasma viremia and quantitative cell culture, p24 antigenemia, and CD4 cell counts between transmitting and non-transmitting mothers.
  - Evaluate the role of HIV antibody in vertical transmission by measuring quantitative anti-p24 antibody, V3 loop antibody, and neutralizing antibody in transmitting and nontransmitting women and in their infants.
  - Evaluate ZDV genotypic/phenotypic resistance in selected mother-infant viral isolates.
- Compare other methods for detection of HIV including polymerase chain reaction (PCR) detection of HIV DNA and placental HIV RNA in situ hybridization to HIV culture as methods of early diagnosis of HIV infection in infants born to HIV-infected women.
- Evaluate the response of selected laboratory markers of HIV infection (plasma viremia and cell culture, p24 antigen, CD4 count), and HIV-associated symptoms during pregnancy through 78 weeks (18 months) postpartum in women receiving HIVIG compared to women receiving IVIG.
- Evaluate the safety and tolerance of HIVIG when administered in combination with ZDV to pregnant HIV-infected women.
- Evaluate the safety and tolerance of HIVIG when administered in combination with ZDV to infants with perinatal HIV exposure.

3. STUDY DESIGN

This is a Phase III, multicenter, double blind, randomized, controlled trial to evaluate the efficacy, safety, and tolerance of the combination of HIV hyperimmune globulin (HIVIG) and ZDV versus combination therapy of IVIG and ZDV for the reduction of vertical HIV transmission in HIV-infected pregnant women who are receiving ZDV during pregnancy for medical indications.

3.1 Study Population

- HIV-infected pregnant women who are between 20 and 30 weeks gestation, who are receiving ZDV during their pregnancy for medical indications.
- Pre-entry CD4 count $\leq 500/mm^3$

Note: An estimated one-half of the women will have pre-entry CD4 < $200/mm^3$ and/or ZDV treatment duration of $\geq$ 6 months.

3.2 Estimated Sample Size

A total of 800 women (720 evaluable women-infant pairs)

3.3 Stratification

- Pre-entry CD4 count < $200/mm^3$ or $\geq 200/mm^3$,
- Antiretroviral therapy initiation prior to or after conception, and
- Geographic region of study center.

3.4 Randomization

HIV-infected women who are between 20 and 30 weeks gestation and receiving antiretroviral therapy will be randomized to one of the following medication regimens:

Arm	Pregnancy	Intrapartum	Newborn
1	HIVIG	ZDV	HIVIG + ZDV
2	IVIG	ZDV	IVIG + ZDV

3.5 Dose and Treatment Period

Women:	HIVIG or IVIG:	200 mg/kg IV every 28 days
	Intrapartum ZDV:	Loading dose 2.0 mg/kg IV, followed by 1.0 mg/kg/hr continuous infusion
Infant:	HIVIG or IVIG:	200 mg/kg IV within 12 hours of birth
	ZDV Syrup:	2.0 mg/kg PO q6h, birth to week 6

3.6 Endpoint

Definitive HIV infection status in the infant. This is defined by either:

- Children of any age who have one (1) or more confirmed positive HIV viral cultures (blood or CSF),

OR

- Children $\geq$ 18 months of age, without confirmed positive culture who have $\geq$ 2 federally licensed positive screening tests for HIV antibody, one obtained no earlier than 18 months of age, and none obtained earlier than 15 months of age. These must be confirmed by an accepted FDA approved confirmatory test.

4. PROTOCOL IMPLEMENTATION

4.1 Site Implementation Plan

The site implementation plan is a required component for **initial** site registration in perinatal studies. The site plan should be completed, and two copies should be sent to Westat for processing.

The site plan will initially be reviewed by Westat. Questions will be addressed to the principal investigator if there is an immediate need for additional information. A review meeting with a site implementation plan committee will be held, and after review, the site will be contacted by the Protocol Manager. After final approval has been obtained, sites will be notified in writing that authorization to participate in ACTG Protocol 185 has been given. This authorization is required to complete site registration.

All sites must complete Parts I and II of Protocol 185 Site Implementation Plan (Exhibit 4-1).

- Send two copies to:

  Jean Whitehouse, B.S.
  Westat, Inc.
  1650 Research Blvd., Room WB 452
  Rockville, MD 20850

If there are questions or concerns about this process, contact Jean Whitehouse at (301) 738-8331.

4.2 Site Registration

Before patients may be enrolled into the ACTG Protocol 185, the site must become registered. All clinical ACTG sites (NICHD and NIAID) and each delivery site desiring participation in the protocol will submit the following documents to Westat:

- A Site Implementation Plan (for initial site registration);

- Completed Westat Site Registration Form (3 pages) for ACTG Protocol 185 (Exhibit 4-2);
- IRB approval letter which clearly identifies the version number of the protocol, bears the signature of the IRB chair; and includes the site's IRB OPRR approved MPA (Multiple Project Assurance) or CPA (Cooperative Project Assurance) numbers.
- Copy of IRB approved informed consent form(s) (also clearly stating the version number of the protocol) accompanied by a completed consent form checklist;
- Signed original FDA Form 1572, Department of Health and Human Services Statement of Investigator for each institution requiring IRB approval (Exhibit 4-3);
- NICHD sites must submit two separate FDA 1572 forms; one for the pediatric IoR and a second for the obstetric IoR;
- CVs for all pediatric and obstetric investigators involved with the study and listed on the FDA Form 1572 (CVs must be updated within the last year);
- Normal reference ranges for laboratory assays to be performed at the site for women and infants (i.e., hematology, chemistry, urinary creatinine clearance). If using Harriet Lane normal reference ranges, it should be noted;
- Current laboratory certification for local laboratory by CAP.

Note: A copy of all materials submitted for site registration must be maintained in a separate file at the site. Site registration documents must be accessible to site monitors for review.

Site registration documents will be reviewed in detail by the site registration coordinator. The site will be notified if any items are missing or incomplete. When the required documents have been received and determined to be complete and accurate, Westat will send written notification to the site acknowledging registration. This letter will approve implementation of the protocol. The original acknowledgment letter will be sent to the principal investigator, with copies to the study coordinator, site pharmacist, the NIAID drug repository, the NHLBI specimen repository, and the FDA. NICHD sites may order PID logs from Westat. NIAID study coordinators will continue to use the existing FSTRF system for obtaining additional PIDs for study use. A Study Identification Number (SID) list, the Drug Supply Statement and instructions for ordering drug from the drug repository will be included with the site pharmacist's notification for both NICHD and NIAID sites.

Exhibit 4-1. Site Implementation Plan

Part I
ACTG 076 Checklist Adapted for ACTG 185

The following items need to be addressed prior to receiving final approval for initiating ACTG Protocol 185. If and when you identify problems in the course of completing this checklist, specify how and when you expect the problems to be overcome. Please feel free to call Jean Whitehouse (301-738-8331) if you have any questions about the checklist and the drug distribution plan.

There are 5 separate clinical areas in which this protocol will be conducted: prenatal clinic, labor and delivery, postpartum clinic, nursery, and pediatric clinic. In addition, the baby will be medicated at home by the mother or guardian following discharge from the hospital.

Address each category (e.g., communication) on the checklist making sure you cover all 6 areas where the protocol will be conducted.

I. General Issues

A. Communication

1. Who is the person with overall responsibility for ACTG 185?

2. Identify the ACTG/NICHD personnel who are responsible for providing contact to each of the 5 clinical areas and the mother (guardian) at home.

3. What percentage of time are you allocating for each person you have identified as participating in ACTG 185?

4. Will 24-hour coverage by ACTG/NICHD staff be provided for all the clinical areas? How will this be accomplished?

5. Who have you identified as contacts in the 5 clinical areas?

6. Describe the communication plan between all the clinical areas and the ACTU contact personnel; identify all responsible persons.

7. Describe the arrangements made for the mother (guardian) to use if the baby experiences problems/adverse events at home.

Exhibit 4-1. Site Implementation Plan (continued)

8. How will the mother and baby be identified as participants in ACTG Protocol 185?

9. What responsibilities does the mother have in alerting the labor/delivery staff about her status as a Protocol 185 patient?

B. Recordkeeping

1. The following forms must be completed for all the clinical areas prior to implementation of this trial: Form 1572, curriculum vitae, IRB approval, HHC approval (in NYC only) and HHS assistance.

2. Describe the recordkeeping system, i.e., the required regulatory documents for site registration, the procedure for updating required forms, the location of the consent forms at all clinical areas, the case report forms and the source documents.

3. All records or copies of records needed for documentation of ACTG 185 must be at the ACTU for monitoring.

4. Describe the process by which serious adverse events are reported. Outline the persons to be contacted and the paper flow of the reports. All Adverse Events Reports must be sent to Westat.

C. Training

1. Identify the personnel responsible for training staff (full and part-time) for ACTG 185. Describe the plan for training staff for Protocol 185.

2. The following documents will be needed at the clinical areas:

- Name(s) and telephone/beeper numbers of key contact(s) at ACTU/NICHD
- Current version of protocol
- Flow sheets pertaining to care provided (optional)
- IRB approved informed consent for mother and baby; paternal consent is also required if available
- Specific CRFs needed at each clinical area and the required evaluations needed to be obtained.
- Drug transfer sheet (to be supplied by DAIDS pharmacist)
- Investigational drug accountability log (standard form used by ACTU pharmacist)

- Adverse event reporting forms
- Mother's history, prenatal records, current medical records
- Baby's hospital record and medication diary (for home care)
- Standing orders (as needed)
- Copy of ACTG 185 implementation plan for each clinical area

3. Describe the process by which the parent (guardian) will be trained in the administration of study drug and documentation of all doses given.

4. Describe the process by which the parent (guardian) will be trained to identify adverse events in the baby.

D. Laboratory

1. Have the lab normals been obtained for maternal and infant subjects? What are the arrangements for obtaining lab samples? Are the necessary lab supplies present for drawing blood and for storage? Do samples need to be shipped and are shipping supplies accessible?

II. Drug Distribution Plan

Maternal Study Drug

Prenatal intravenous HIVIG/IVIG

Intrapartal intravenous ZDV

Infant Study Drug

At birth – Intravenous HIVIG/IVIG

Birth - 6 weeks ZDV

Exhibit 4-1. Site Implementation Plan (continued)

The ACTU pharmacist with the study coordinator will outline a detailed plan for preparation and distribution of the maternal and infant study drug at each site for the DAIDS. This plan will address the initial drug supplies to all patient care/drug distribution sites as well as resupply at Weeks 1, 2, 3, etc. This will be coordinated between the study coordinator and the ACTU pharmacist. If there is to be non-ACTU pharmacy support for this protocol, this support must be specified in the drug distribution plan submitted to the DAIDS. Even though non-ACTU pharmacies may be used, it is the ACTU pharmacist who has the ultimate responsibility for the distribution of the study drug, maintenance of the blind, and assuring the completion of all study drug records. In all cases, only the ACTU pharmacist will have access to the SID list.

A. Describe the overall plan for the safe, reliable, and responsible distribution of study drug(s) from ALL patient care or drug dispensing sites.

   The plan should include provisions for secure storage of the study drug(s), names of specific persons responsible for the handling and distribution of study drug, access to study drug dosing information, and communication with the ACTU pharmacist.

B. Describe in detail the exact procedures for dispensing the study drug(s) including the exact location that the study drug(s) will be stored in the following situations:

   - Maternal prenatal intravenous HIVIG/IVIG
   - Maternal intrapartum intravenous ZDV
   - Newborn intravenous HIVIG/IVIG
   - Newborn (NPO) intravenous ZDV
   - Newborn ZDV syrup

C. Name the person responsible in each clinical area for each of the following procedures:

   - Receipt and secure storage of study drug
   - Dispensing of the study drug to the patient
   - Documentation of the study drug in the investigational drug accountability log
   - Return of unused study drug to the ACTU pharmacist

D. Describe the procedures for preparation of the intravenous investigational study drug

E. Describe the procedures in calculating dosages and labeling study drugs for maternal and infant subjects.

F. Describe the plan for 24-hour pharmacy support for Protocol ACTG 185

- Will non-ACTU pharmacists at the delivery site institution be provided information concerning the drug and Protocol 185 in the event the ACTU pharmacist cannot be reached?
- Are non-ACTU pharmacists thoroughly informed and knowledgeable with the protocol, the blinded study drug dosage forms that are specific to the protocol, study drug dosing information, and the preparation of investigational intravenous study drug?

NOTE: If there is to be non-ACTU pharmacy support, give the exact name and address of the institution, and the name of the Director of the Pharmacy Department.
Provide assurance to the DAIDS that the pharmacy director is in concurrence with the above drug distribution plan.

Provide assurance that any non-ACTU pharmacist who will be involved with the dispensing of study drug and/or in the preparation of the intravenous study drug, has read the protocol and is knowledgeable of the dosage forms of study drug that are to be used in this protocol, and are familiar with all study drug dosing calculations.

G. Who will contact the ACTU pharmacist when:

- A patient is admitted to Labor and Delivery?
- When patient's medication supply needs to be replenished or returned?
- When an emergency unblinding needs to be done?

H. Based on the information supplied above, provide to the NICHD/NIAID a COMPLETE STEP-BY-STEP EXAMPLE describing how an actual mother/infant pair will receive study drugs in all settings, from initial enrollment until study completion. Include all patient care/drug distribution sites and all persons who have been designated to prepare and dispense study drug to this mother/infant.

Exhibit 4-1. Site Implementation Plan (continued)

Part II
ACTG 185 Site Implementation Requirements

I. Infusion of Study Drug

A. Prenatal Infusions

An infusion of the study drug must be administered to the patient for 1-3 hours every 4 weeks. Prompt access (<10 minutes) to obstetrical staff, and to external fetal monitoring must be available in the event of occurrences of adverse events.

- Describe the facility, noting location of infusion visit and access to fetal monitor.
- Include a description of staff who will administer the drug and who will respond to adverse events.

B. Intrapartum Infusions

Intravenous ZDV is to be administered to all study women throughout labor.

- Describe the staff and facilities for administering intrapartum ZDV infusions.
- Describe the pharmacy staff coverage (24 hour) for dispensing the drug.

C. Neonatal Infusions

Within 12 hours after birth, a 2-3 hour IV study drug infusion should be administered to all study infants.

- Describe the staff and facilities for administering neonatal infusions.
- Describe the pharmacy staff coverage (24 hour) for dispensing the drug.

Exhibit 4-1. Site Implementation Plan (continued)

II. On-site Virology Specimen Processing

Whole blood specimens must be processed promptly, separating cells and plasma.

A. Describe the process by which specimen processing will occur. Specimens must be centrifuged, sterilely aliquotted, frozen and stored at -70 degrees Centigrade within 6 hours of phlebotomy.

- Include a description of the staff, including night/weekend coverage for processing maternal intrapartum and infant birth samples.
- Include methods of communication between the clinical area and the laboratory and the storage facilities.

B. Frozen specimens must be shipped at specified intervals to a designated lab and/or repository.

- Include the procedure for shipping specimens to the repository.
- List the virology laboratory and the contact person at the lab (with telephone numbers).

III. On-site Pathology Specimen Processing

Placental specimens for HIV-RNA in situ hybridization must be processed promptly after delivery. Within one hour after delivery, the pathologist must examine, section, and begin RNase-free paraformaldehyde fixation of the placenta. Storage of the specimen must be in ethanol at 4 degrees Centigrade prior to shipping to a designated lab.

If the site is interested in participating in this aspect of the protocol:

A. Describe the process of obtaining the placental specimen.

B. Describe the pathologists involvement, and coverage for night/weekend deliveries.

C. Estimate the number of specimens anticipated to be collected for the study.

Exhibit 4-1. Site Implementation Plan (continued)

IV. Justification for Exemption

Patients who are enrolled in more than one study may have competing requirements for blood drawing.

A. Indicate if there are any competing studies being conducted at your institution.

B. If an exemption from certain components of Protocol 185 should be considered for your site, document in detail, using Appendix XVI of the Protocol, competing requirements for blood samples from patients, otherwise eligible for ACTG 185.

C. List potential solutions, if available.

Exhibit 4-2. Westat Site Registration Form

ACTG 185 (01 Nov 96)

WESTAT SITE REGISTRATION FORM

ACTG Protocol 185

This form must be completed for initial site registration and each submission of IRB approval for updated versions of the protocol. You may reproduce this form on a copier.

Questions concerning required site registration materials should be directed to Westat via e-mail to Kramer.Shirley or Armstrong.Linda.

Please check item(s) included with this form:

Investigator of Record: _____

Institution: _____ Code: |__|__|__|__|

|__| Site implementation plan

|__| IRB letter of approval

Protocol version number: _____

Date of IRB approval: _____

|__| IRB-approved consent form

|__| Informed consent checklist

|__| FDA form 1572*

|__| CVs* for principal investigator and all sub-investigators listed on 1572

|__| Laboratory normals for women/infants

|__| Laboratory Certification by CAP*

*Must be updated annually.

_____ _____

Signature of Study Coordinator/Investigator Date

Exhibit 4-2. Westat Site Registration Form (continued)

ACTG 185 (01 Nov 96)

SITE PERSONNEL INFORMATION

Please complete the following information.

_____ OB Investigator Name Mailing address: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet:	_____ PEDS Investigator Name Mailing address: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet:
_____ OB Study Coordinator Name Mailing address: (Please indicate room no.) _____ _____ _____ Is this the address where forms and other information should be sent ☐ YES ☐ NO If no, where should these materials be sent? Attn: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet:	_____ PEDS Study Coordinator Name Mailing address: (Please indicate room no.) _____ _____ _____ Is this the address where forms and other information should be sent ☐ YES ☐ NO If no, where should these materials be sent? Attn: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet:

Exhibit 4-2. Westat Site Registration Form (continued)

ACTG 185 (01 Nov 96)

SITE PERSONNEL INFORMATION

Please complete the following information.

_____ Virology Laboratory Contact Mailing address: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet: E-Mail Logon: _____	_____ Flow Cytometry Laboratory Contact Mailing address: _____ _____ _____ PHONE: ( ) FAX: ( ) Internet: E-Mail Logon: _____
_____ Study Pharmacist's Name _____ _____ _____ PHONE: ( ) FAX: ( ) Internet: E-Mail Logon: _____	Preferred E-Mail Logon for Clinical Personnel _____ ACTG FSTRF LOGON

SEND COMPLETE PACKET TO:

Westat
Site Registration WB426
1650 Research Boulevard
Rockville, MD 20850

Exhibit 4-3. DHHS Statement of Investigator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions of reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: December 31, 1999
See OMB Statement on Reverse

Note: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator Form FDA 1572 (21 CFR 312.53(c))

NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED:

[X] CURRICULUM VITAE [ ] OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g. research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (1/97) PREVIOUS EDITION IS OBSOLETE Page 1 of 2

Exhibit 4-3. DHHS Statement of Investigator (continued)

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:
   [ ] FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

   [ ] FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

   [X] NOT APPLICABLE

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.

   Attach curriculum vitae or other statement of qualifications as described in Section 2.

3. Attach protocol outline as described in Section 8.

4. Sign and date below.

5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).
   INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR	11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 84 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer
Reduction Project (09100-0014)
Humphrey Building, Room 531-H
200 Independence Avenue, S. W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a Paperwork collection of information unless it displays a currently valid OMB control number

Please DO NOT RETURN this application to this address.

4.3 Shipment of Study Drug

Following site registration, the site pharmacist will receive an investigator's brochure pertaining to the study drug, the Study Identification (SID) list, a drug supply statement, instructions for ordering the drug supply, and a supply of HIVIG/IVIG Pharmacy Records with instructions.

The site pharmacist can obtain study drugs, (HIVIG, IVIG, intravenous ZDV, and oral ZDV for the infant) by faxing orders to the repository contractor McKesson Bioservices. The FAX number is (301) 294-2905. The repository is open from 8:30 a.m. to 5:00 p.m. Eastern Standard Time, Monday through Friday, and the routine shipping hours are between 9:00 a.m. and 4:00 p.m. Drug orders are usually processed and shipped the same day that the orders are received with the expectation that the drugs should arrive at the site within 2 working days. Routine drug orders are not shipped on weekends.

Specific information about ordering drugs from the repository, recording of drug accountability and returning drugs to the repository, etc. is found in the Pharmacy Guidelines and Instructions for AIDS Clinical Trials Group Manual. NICHD sites may obtain a copy of the manual from Westat. NIAID sites may obtain a copy of the manual from the Pharmaceutical and Regulatory Affairs Branch.

The HIVIG/IVIG Pharmacy Record (Exhibit 4-4) must be completed by the pharmacist and sent directly to Westat, Attention: Ann Wolters, R.Ph., <u>each</u> time a study infusion is prepared.

- The site study coordinator must <u>not</u> receive a copy of these forms.
- Direct all questions concerning the form to Dennis DeRycke at (800) 825-4844.

ACTG Protocol 185

HIVIG/IVIG PHARMACY RECORD

PID: |__|__| |__|__|__|__| |__|	Date Prepared Infusion: |__|__| |__|__| |__|__| (m m d d y y)
SID: |1|8|5| |__|__|__|__| |__|	Institution Code: |__|__|__|__|

1. Was the infusion dispensed to this patient prepared from vials from more than 1 lot?..... (1-Yes, 2-No) |__|

2. List lot # of all vials used to prepare this infusion:

   a. Lot #: _____ Dispensed: |__\|__\|__\| . |__\|__\| ml
   b. Lot #: _____ Dispensed: |__\|__\|__\| . |__\|__\| ml
   c. Lot #: _____ Dispensed: |__\|__\|__\| . |__\|__\| ml
   d. Lot #: _____ Dispensed: |__\|__\|__\| . |__\|__\| ml
   e. Lot #: _____ Dispensed: |__\|__\|__\| . |__\|__\| ml

3. Total amount of HIVIG or IVIG dispensed: |__\|__\|__\| . |__\|__\| ml

   If total volume of the infusion is greater than the amount of study drug dispensed, complete question 4.

4. Total volume dispensed: |__\|__\|__\| . |__\|__\| ml
   Diluent used: _____

5. Remarks: _____

   _____

_____
Signature of Pharmacist

Send Original Form To:

Westat, Inc.
Attention: Ann Wolters, WB 427
1650 Research Blvd.
Rockville, Maryland 20850

Exhibit 4-4. ACTG Protocol 185 HIVIG/IVIG Pharmacy Record (continued)

INSTRUCTION FOR THE COMPLETION OF

ACTG PROTOCOL 185

HIVIG/IVIG PHARMACY RECORD

The pharmacokinetics substudy will test serum and plasma samples for antibodies that are present in the HIVIG/IVIG preparations. In order to capture all of the information required for data analysis of the pharmacokinetic assays, it will be necessary to identify lots used in study patients participating in ACTG Protocol 185. To identify lots used for the infusions without unblinding the study staff, the site pharmacist must collect additional information for the ACTG Protocol 185.

In the future it may be necessary to use more than one lot of study drug. This may have some implications for the final analysis of the product's effectiveness. Enclosed is a form to record the following information: patient PID and SID, date the infusion was prepared, the lot number(s), the amount of each lot used in the preparation of the infusion, and the total amount of product used in the preparation of the infusion, and the total amount of product used in the infusion.

Please complete the enclosed ACTG Protocol 185 HIVIG/IVIG Pharmacy Record as the infusions are dispensed to the study patients. Within 2 weeks after preparation of the infusion, please send the completed form to:

Ann Wolters, R.Ph.
Westat, Inc.
WB 42F
1650 Research Blvd.
Rockville, MD 20850

To avoid the possibility of unblinding study staff, please do not give the completed form to the site study staff for mailing. Use the mailing labels included in the pharmacy packet. If additional forms or labels are needed, contact Dennis De Rycke at (800) 825-4844.

Thank you for your assistance. If there are questions about this procedure, contact Dennis De Rycke at (800) 825-4844.

4.4 Enrollment

Once a site has received confirmation for registration for Protocol 185, the following should occur:

- Randomization Questionnaires, Case Report Form (CRF) notebooks, Virology notebooks, and an Appendices Manual will be sent from Westat.
- The site pharmacist may order the initial drug supply.
- Study staff may begin scheduling patients who appear to satisfy the inclusion/exclusion criteria.

The initial visit will consist of assigning one of the sequential Patient Identification (PID) numbers to the potential study candidate, reviewing the informed consent and screening the patient for eligibility. If additional PID numbers are needed, NICHD sites should contact their Westat data manager. NIAID sites should follow their standard procedure for obtaining additional PID numbers.

4.5 Informed Consent

An IRB-approved consent form must be signed by all women enrolled in the study. The mother will provide written informed consent for herself and her infant's participation in the study. The father's written informed consent for the participation of the infant is required at the time the mother provides consent (Exhibit 4-5, 4-6). A reasonable attempt should be made to contact the father. If the father cannot be contacted, the effort taken to contact the father should be documented in the medical record. Each center should consult with its IRB to determine if an additional consent form must be signed for the infant after birth.

- If, during the course of the study, the legal guardian of the infant changes, the original infant consent form is no longer valid. The new legal guardian must sign another consent form.
- A separate consent form, specific to the Pharmacokinetic Sampling Substudy or a consent form which includes specific information pertaining to the Pharmacokinetic Sampling Substudy must be signed when either the woman or the infant participates in the Pharmacokinetic Sampling Substudy (only at selected sites).

Exhibit 4-5. Paternal Consent Information

ACTG 185

PATERNAL CONSENT INFORMATION

Federal Regulations: Federal regulations concerning research activities directed toward pregnant women as subjects and toward fetuses in utero as subjects are defined in 45 CFR: section 46.207 and 46.208 (sections are enclosed). Such research studies may be conducted when the purpose of the activity is to meet the health needs of the mother and/or fetus and the risks to the fetus are minimized or are already minimal. In either case, mother and father must be legally competent and provide informed consent. Informed consent from the father, in the case of research directed toward fetuses, need not be secured when (1) his identity or whereabouts cannot be reasonably ascertained; 2) he is not reasonably available; or 3) the pregnancy resulted from rape.

The language of the regulations may require interpretation of "reasonable availability." The NIH Office for Protection from Research Risks (OPRR) has indicated that the local IRB should provide guidance to investigators to assist in determining when a father is or is not "reasonably available."

OPRR has provided examples of some situations in which a father is customarily judged NOT to be "reasonably available." These include situations in which 1) paternity is uncertain (it is not necessary for the IRB or investigator to establish paternity); 2) the father's whereabouts cannot be readily ascertained; 3) the father does not acknowledge that he is the father of the fetus; or 4) the father has assumed no responsibility for the pregnancy and has manifested no interest in or has denied responsibility for the well-being of the fetus. In the last case, it may be sufficient for an investigator to obtain a statement to this effect from the mother, and no further assessment of the facts is required.

In all cases where the investigators determine that a father is not "reasonably available", the reasons must be documented by the investigator as part of the research record. Investigators should consult with their IRB in cases where applicability of the requirement for paternal consent is unclear.

Research Protocol ACTG 185: ACTG 185, section 6.1 inclusion criteria, bullet 11 states that the father of the fetus (if available after reasonable attempt to contact him) must provide informed consent. Appendix XXIII Sample Informed Consent provides statements concerning the father as follows: 1) introduction: the father of the baby may refuse to give consent and this would prevent the mother's participation in the study; 2) circumstances for withdrawal from study: if the father of the baby withdraws consent for the mother's participation in the study, and 3) signature: a specific line for the father's signature for informed consent is provided with a signature line for the witness and the dates informed consent is signed.

Example of a Situation: In situations in which requiring paternal consent would breech maternal confidentiality (disclosure of HIV status), which in turn could result in significant harm (physical abuse) to the woman, investigators should NOT do anything that might jeopardize the health or safety of a potential subject. However, by providing the patient with an opportunity to participate in a study which requires that the eligible patient must be HIV-infected, it should be noted that there is a risk of disclosing maternal HIV infection status to anyone else who becomes aware that the women is participating in the study, including the putative father of the fetus. In the event that some unforeseen harm came to the fetus as a result of a pregnant women's participation in the study and a legitimately concerned father came forward to ask why he had not been notified, the investigator, institution, and sponsor can not respond acceptably unless careful attention has been paid to, and documentation made of, the existence of a situation where waiver of the requirement for paternal consent is permissible. It is recommended that the maternal patient should NOT be considered a candidate for a research study such as ACTG 185, when disclosure of the very condition which is the reason for studying her may bring her harm, and at the same time when applicable human subjects research protection regulations require consent by the father of the fetus.

Exhibit 4-6. 45 Code of Federal Regulations Section 46

46.207 Activities directed toward pregnant women as subjects

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

46.208 Activities directed toward fetuses in utero as subjects

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

All IRB approved consent forms must comply with federal regulations as stated in 45 CFR 46, 46.116. Any modifications to the information contained in the section on risks must be justified in writing by the IoR and approved by the IRB. All the components of informed consent are listed on the Consent Form Checklist and will assist in assuring compliance with these requirements. (Exhibit 4-7)

Samples of informed consent forms (English and Spanish) are contained in Appendices XXIIIa, XXIIIb: Sample Informed Consent and Appendix XXII. Sample Informed Consent for Special Pharmacokinetic Studies of the protocol.

Exhibit 4-7. Components of Informed Consent

COMPONENTS OF INFORMED CONSENT

_____ Invitation to participate in study.

_____ Assurance that subject has the right to refuse to participate and that withdrawal will not place the subject in jeopardy nor will it involve penalty or loss of benefits.

_____ Explanation of the purpose of the study.

_____ Explanation of study procedures (as they relate to subjects) including identification of experimental procedures.

_____ Description of potential risks, discomforts, inconvenience, or threats to dignity involved in study as well as the expected duration of the subjects participation.

_____ Description of potential benefits of participation in the study for the subjects or others.

_____ Description of compensation to be expected, whether monetary or otherwise (if applicable); including medical treatment for injury due to this research.

_____ Disclosure of available alternatives (if applicable).

_____ Assurance of confidentiality.

_____ Identification of the contact person to answer questions.

_____ Clear, unambiguous and appropriate language for subjects age, education, etc., has been utilized.

_____ Concluding statement noting that the subject indicated by signature (or, in certain studies, return of completed questionnaire) that he/she read the information and has decided to participate.

_____ Statement that the sponsor will not provide compensation in case of injury resulting from participation (if required by the particular agency).

_____ Statement that procedure may involve risks which are currently unforeseeable (if applicable).

_____ Description of circumstances under which the subject's participation may be terminated, if any, as well as the consequences of a subject's decision to withdraw (if applicable).

_____ Description of additional costs to the subject (if any).

_____ Statement that new findings from the research which relate to the subject's willingness to participate will be provided to the subject (if applicable).

_____ Approximate total volumes of blood to be drawn.

_____ Paternal Consent.

Signature _____ Date: _____

4.6 Pre-entry/Screening Period

The purpose of the pre-entry period is to determine if the woman meets the eligibility criteria for the study.

The consent form must be signed prior to pre-entry screening and randomization.

- Clinical and laboratory tests used for screening must be performed within twenty eight days prior to randomization. (For example, if the first test used to screen the patient for study eligibility is April 1st, the patient must have completed all required laboratory tests and evaluations and be randomized by April 28th).

- If a patient completes screening, but does not meet eligibility requirements or refuses to consent to study participation, Form 18509: Ineligibility/Nonparticipation Log must be completed and sent to Westat.

4.7 Randomization Questionnaire

The randomization questionnaire is used to verify the eligibility of the patient. When all the results of the pre-entry evaluations are obtained, the randomization questionnaire is completed. If the woman is determined to be eligible, she may be randomized.

NICHD sites should direct questions about completing the form or about a patient's eligibility to their assigned Westat study manager. For NIAID sites, these questions should be directed to the protocol manager via E-mail, WHITEHOUSE.JEAN@karloff.fstrf.org.

4.8 Randomization

All completed randomization questionnaires from NIAID and NICHD sites must be sent by FAX to Westat for review of patient eligibility and randomization. Randomization questionnaires must be received at Westat by 3 p.m. EST in order for a patient to be randomized the same day.

The following steps are required to complete the patient randomization process:

- Contact the project phone at (800) 825-4844 to leave a message informing Westat that an enrollment questionnaire is being faxed.
- FAX the completed enrollment questionnaire to (301) 517-4188 or (301) 738-8379 Attention: Dennis DeRycke.
- The patient will be randomized at Westat.
- If the information meets the eligibility criteria and is verified, the woman will be assigned a Study Identification (SID) number generated by the randomization computer program.

OR

- If the eligibility criteria is not met, the study coordinator will be contacted by phone to verify information submitted.
- When the patient is successfully randomized, the study coordinator at the clinical site will be informed of the SID number by telephone. A contact person and telephone number must be included on the randomization questionnaire. The site will receive, by FAX, a copy of the PID and SID numbers. The patient will also be registered in the FSTRF system by Westat.

All waivers for enrollment of women who do not meet the eligibility requirements must be submitted in writing at the time of randomization. This may be accomplished by faxing a copy of the waiver with the Randomization Questionnaire. See Study Management section in the protocol for instructions related to the requesting waivers for randomization exemptions.

The study coordinator will give this SID number to the site pharmacist so that the pharmacist will be able to identify the woman's treatment group assignment by referring to the Pharmacy SID list. The Pharmacist is the only staff member not blinded to the woman's and infant's treatment group. The infant will receive the same drug as the mother. Likewise, each infant of a multiple birth will receive the same study drug as the mother.

After a woman is randomized, a calendar of anticipated study visit dates and PID/SID labels will be generated upon receipt of the faxed Form 18500: Entry Report. Labels with the infant's PID and SID and a calendar of anticipated study visits for the infant and

woman will be sent to the site upon receipt of the faxed Form 18511: Intrapartum Record. Additional labels may be requested by E-mail or included on a shipping request form.

4.9 Entry Visit

The entry visit must take place within 72 hours of randomization. It is composed of clinical evaluations, laboratory tests, and the initiation of study treatment.

4.10 Study Visits

The study visit schedule for the mother is described in detail in Section 5.4 in this manual. The study visit schedule for the infant is described in detail in Section 6.2.

4.11 Data Collection and Maintenance

A Case Report Form (CRF) notebook will be provided for each woman and each infant enrolled. The CRF notebook contains all of the forms necessary for data collection. The forms are organized in the CRF notebook according to week of visit. At the beginning of each visit section there is a menu, or a list of the forms required for that visit, based upon the protocol list of clinical and laboratory evaluations. These menus only reflect the forms required for the visit. They should not be used as a guide of evaluations required for the study visit.

For each form, it is essential that items on the header be completed correctly since these items are critical for database recordkeeping and tracking.

- The labels with printed PID and SID numbers should be placed in the designated location of the header.
- Record the date, paying careful attention to the date requested (date of visit, date of exam, date of specimen, etc.).
- Record the study visit number.

- Record the sequence number. The sequence number will always be "1" unless more than one of the same form is being submitted for the same visit number, on the same date of visit.

- Record the institution code.

Additional Tips for Accurate Completion of Forms:

1. Each form is numbered and has a name descriptive of the type of data being collected.

2. The instructions on each form will guide you through completion, and will direct you to a PRN form if it is needed.

3. Dates are recorded according to the following rules:

   a. Dates are recorded as month / day / year.

   b. If you do not know the year of an event, record "-1" in the entire date

   c. If you do not know the month but you know the year, record the midpoint of the year, i.e., 07/01/94.

   d. If you do not know the day of an event, record the midpoint of the month, i.e., 05/15/92.

   e. If you do not know the day and the month, but know the season and the year, record the following:

Spring	04/01/92
Summer	07/01/92
Fall	10/01/92
Winter	01/01/92

4. Data items must be completed as specified on the forms:

   a. Do not enter results with more digits or decimal places than are provided on the form.

   b. Enter results in units designated.

   c. Use leading/trailing zeros to fill the unused spaces if the number of spaces provided is larger than necessary to record the data.

   d. If a given procedure on a form was not completed, not required or lost or unobtainable for whatever reason, record "-1" (unless otherwise specified on the form).

e. NEVER use zeros to designate missing data or items not done.

f. Values recorded that fall out of the acceptable range for a certain test will be verified during data retrieval.

g. Do not use white-out to make a change on the case report form. Cross out the incorrect entry with a single line, write in the correct entry next to it and initial and date the correction.

h. Complete the form header even if the test was not done (i.e., patient did not keep appointment, specimen clotted, etc.). Complete Form 18553: Clinical Case Review Form to explain procedures or evaluations not performed.

i. Use a black felt tip or ball point pen to fill out the forms. These photocopy more clearly and are easier to read.

5. Patient names are not permitted on any study forms.

Once sites actually begin to record data on the forms, it is expected that questions will arise. NIAID sites should address questions via E-mail to the protocol manager, Jean Whitehouse. NICHD sites should contact their study manager at Westat.

4.12 Sending Forms to Westat

Each site should designate one day each week to mail completed forms to Westat. The forms should be carefully reviewed for accuracy and completeness and photocopied.

- Send the originals to Westat; retain the photocopied forms and insert into the CRF notebook.
- The menu which is located at the beginning of each visit section, should be photocopied and will serve as a transmittal form for all forms sent to Westat.
  - Indicate the forms being sent by placing an "X" in the appropriate box for each form ("T"= Transmitted, "P" = Pending, or "NR" = Not Required).
  - Apply the PID/SID to the top right hand corner of the menu page.
- If amended or additional information needs to be included in a form previously sent to Westat, complete a duplicate form, highlight the new data, write "UPDATE" in red at the top of the form, and send to Westat with a copy of the menu for the study visit update.

4.13 Data Retrieval

Data retrieval refers to the process of correcting inconsistencies in previously reported information or obtaining missing or additional information not included on the forms sent to Westat.

Data retrieval will be accomplished via telephone or FAX communication with the study coordinator. Procedures for automated data retrieval are described in Chapter 12. The information contained in the forms in the CRF notebook and the forms at Westat must be identical. Changes made to the form by the study coordinator and the Westat study manager must follow these guidelines:

- Draw a single line through the original entry
- Record the correct information
- Initial and date the correction

4.14 Site Monitoring

Site visits will be conducted at least three times a year. The purpose of the site visit is to:

- Verify that a signed informed consent is on file for every study participant.
- Verify eligibility criteria with source documentation.
- Review a sample of CRF notebooks to verify test results with source documentation, and determine the accuracy of all reporting.
- Confirm that all regulatory documentation is on file (for example, IRB approval letter, FDA Form 1572, etc.).
- Confirm that the study drug is being stored and accounted for per ACTG pharmacy regulations.
- Review the PID logbook.

Sites must maintain a "shadow" file containing hard copies of results of laboratory and diagnostic tests for each of the study visits.

In addition, a pharmacy audit will take place once per year to update the pharmacy plan and review in detail the drug accountability records.

The Clinical Site Monitoring Group (CSMG) will provide site monitoring for NIAID sites. Westat study managers will provide site monitoring for NICHD sites.

4.15 Study Management and Contacts

When questions arise, it is helpful to know to whom they should be addressed. The following list serves as a resource to guide the flow of questions that are expected.

AER Questions..... Send an E-mail message to ARMSTRONG.LINDA@karloff.fstrf.org or KRAMER.SHIRLEY@karloff.fstrf.org or call 1-800-825-4844.

Copies of Protocol... Send an E-mail message to WHITEHOUSE.JEAN@karloff.fstrf.org.

Management Questions, NON-EMERGENT ..... Exemptions Co-enrollment Concomitant Medications Toxicity Management Clinical Medical Management	Send an email message to ACTG.TEAM185 @karloff.fstrf.org and state PID and SID #s, brief relevant history, date of expected randomization, if applicable. If team does not respond in a timely manner for **non-emergent** questions, contact the following individuals:

Protocol Co-Chairs: Dr. Richard Stiehm at (310) 825-6481 (office) or Dr. Jack Lambert at (410) 706-4613.

Medical Officer - Dr. Lynne Mofenson at (301) 496-7339; Medical Officer - Dr. Mary Glenn Fowler at (301) 496-6177; Project Officer - Dr. George Nemo at (301) 435-0075.

If the non-emergent response needed concerns obstetrics contact Dr. Rhoda Sperling at (212) 241-7639.

Management Questions, EMERGENT	Contact should be made by telephone, and directed to the appropriate individuals:

Emergency obstetrical questions - Dr. Rhoda Sperling at (212) 241-7639 (office)/(212) 401-9374 (beeper). If Dr. Sperling is not available, call Dr. Lynne Mofenson at (301) 496-7339 (office)/(301) 236-9319 (home).

Emergency pediatric questions - Dr. Richard Stiehm at (310) 825-6481 (office)/(310) 451-2681 (home)/(310) 825-6301, #03021 (beeper) or Dr. John Lambert at (410) 706-4613 (office)/(410) 792-3189 (beeper)/(410) 997-8228 (home). If Drs. Stiehm or Lambert are unavailable, call Dr. Lynne Mofenson at (301) 496-7339 (office)/(301) 236-9319 (home).

Miscellaneous Questions..... Inclusion/Exclusion Schedule of Evaluations Case Report Forms Requesting Waivers for Randomization Transfers and Delinquencies Data Management Topics	Send an E-mail message to ACTG.TEAM185@karloff.fstrf.org (ATTN: Study Manager Jean Whitehouse) Give detailed description of question, PID and SID, if referring to a specific patient.
Order Study Drug	Call the Clinical Research Proudcts Repository: McKesson Bioservices Repository: John Ferinde, R.Ph. or Brian Myers, R.Ph. (301) 294-0741.
Pharmacy Questions ..... Study Drug Study Drug Dose Supplies Records Returns	NIAID Sites: Call Lynette Purdue, Pharm,. D. at the Pharmaceutical and Regulatory Affairs Branch (301) 496-8213. NICHD Sites: Call your Westat study manager.
Randomization Problems/Questions ..... SID lists	Call the Westat Randomization Desk at 1-800-852-4844, or Dennis DeRycke at (301) 738-8348
Site Registration Questions	Send E-mail message to ARMSTRONG.LINDA@karloff.fstrf.org or KRAMER.SHIRLEY@karloff.fstrf.org
Shipping/Repository Questions	Call McKesson Bioservices Repository: Steve Lindenfelser (301) 340-1620 FAX: (301) 340-9245

5. MANAGEMENT OF WOMEN

5.1 Informed Consent

The mother will provide written informed consent for her own participation and that of the infant. The father's written informed consent for the participation of the infant is required at the time the mother provides informed consent. A reasonable attempt should be made to contact the father. If a father refuses to give informed consent, the mother will be denied participation in the protocol. If, after a reasonable attempt the father cannot be contacted, it should be documented in the patient progress note. In this case the mother and infant can participate in the study.

5.2 Patient Selection

5.2.1 Inclusion Criteria for Women

To be considered eligible for enrollment in ACTG Protocol 185, a woman must meet the entry criteria listed below:

- Evidence of HIV infection documented by an EIA with an appropriate confirmatory test, positive p24 antigen, or positive viral culture (blood or CSF). Source documentation is required for the virology test(s) which confirms HIV infection.
- On ZDV therapy during current pregnancy*

*Note: Women receiving antiretroviral therapy other than ZDV at pre-entry must receive an exemption from the ACTG 185 Team prior to randomization of a patient.

- Pre-entry CD4 count $\leq 500/mm^3$*

*Note: Source documentation is required for all CD4 counts.

- An estimated gestational age of at least 20 weeks, 0 days and no later than 30 weeks, 6 days based on sonogram results compatible with the gestational age (biparietal diameter or crown-rump length) or menstrual history confirmed by first pelvic examination.

- The following laboratory values within 28 days prior to randomization:

  - Hemoglobin ≥ 8.0 gm/dl

  - Serum creatinine ≤ 1.5 mg/dl OR eight-hour urine creatinine clearance > 70 ml/min*

*Note: **An 8 hour urine creatinine clearance is not required for pre-entry, but must be done if the patient's pre-entry serum creatinine is > 1.5 mg/dl.**

  - Urine protein < 2+ by dipstick OR < 4 gm protein in a 24-hour urine collection.*

*Note: **A 24 hour urine for protein is not required for pre-entry, but must be done if the patient's pre-entry urine protein is ≥ 2+.**

- Availability of venous access (placement of a central line or Hickman catheter placement is not indicated for study purposes). However if a central line or Hickman is in place, it may be used to administer HIVIG/IVIG or intravenous ZDV.

- At least ≥ 13 years of age or IRB local age of consent, whichever is higher.

- Women who intend to carry this pregnancy to term.

- Willing to be followed by a participating center for the duration of the study.

- Able to provide informed consent.

- The father of the fetus, if available after a reasonable attempt to contact him, must also provide informed consent.

5.2.2 Exclusion Criteria for Women

Women who meet any of the following criteria will be excluded from study participation:

- Evidence of pre-existing fetal anomalies which may result in a high probability that the fetus-infant will not survive to the end of the study period. Examples include: anencephaly, renal agenesis, or Potter's syndrome.

- Chorionic villous sampling (CVS) or percutaneous umbilical blood sampling (PUBS) occurring in this pregnancy prior to study entry or anticipated to be medically indicated during this pregnancy.

- Illnesses associated with excessive protein loss, as delineated below:
  - Illnesses associated with chronic diarrhea with no documented weight gain in a 3-month period during pregnancy.
  - Illnesses associated with severe proteinuria (protein ≥ 4 gm protein in a 24-hour urine collection).
- Pre-existing conditions such as hypogammaglobulinemia or immune thrombocytopenia which are felt to require IVIG therapy.
- Receipt of anti-HIV vaccines or passive immunotherapy with HIVIG or IVIG (prior to randomization) during this pregnancy.
- Receipt of investigational antiretroviral agents during this pregnancy prior to study entry (e.g., rCD4, CD4-IgG); receipt of didanosine (ddI), stavudine (d4T), lamivudine (3TC), nevirapine (NVP), or zalcitabine (ddC) during the pregnancy prior to entry requires protocol chair approval for entry.
- Multiple gestation > 24 weeks by sonogram.
- Severe preeclampsia (HELLP syndrome: hypertension, elevated liver enzymes, and low platelets) as defined by blood pressure 140/90 on two or more occasions more than 6 hours apart, proteinuria at least 5 gm in a 24-hour urine collection, and one or more of the following:
  - Oliguria (< 100 cc in 4 hours);
  - Epigastric or right upper quadrant pain;
  - Platelet count < 80,000 cells/mm^3;
  - SGPT ≥ 3 times baseline;
  - Cerebral or visual disturbances such as altered consciousness, headache, scotomata, or blurred vision;
  - Pulmonary edema or cyanosis;
  - Eclampsia.
- When the proportion of women with pre-entry CD4 + count ≥200/mm^3 AND less than 6 months ZDV use reaches 50 percent of the total study population, enrollment into this group may be restricted. No such enrollment restriction will be applied to women with CD4 + pre-entry counts <200/mm^3 or women with 6 months or more of prior ZDV use.

- Receipt of protease inhibitors during the current pregnancy (e.g., saquinavir, ritonavir, indinavir, etc.).

- Prior enrollment to ACTG 185.

5.3 Randomization

Study patients will be stratified by geographic region of the study center, CD4 count obtained during the pre-entry/screening period, and whether ZDV therapy began prior to or after conception. Pregnant women will be randomized to one of two treatment groups:

Group 1:

- Pregnant woman - **HIVIG** 200 mg/kg will be administered intravenously every 28 days until labor.

  An intravenous loading dose of **ZDV**, 2.0 mg/kg, is administered over one hour, followed by a continuous infusion of ZDV at 1.0 mg/kg/hr during the intrapartum period.

- Infant - **HIVIG** 200 mg/kg (total dose) will be administered intravenously within 12 hours of delivery.

  As soon as the infant is tolerating p.o. fluids, oral **ZDV** 2.0 mg/kg every six hours for six weeks will begin. Intravenous ZDV (1.5 mg/kg q 6 hr) may be administered if the infant remains NPO.

Group 2:

- **IVIG** will replace **HIVIG** in the above regimen.

5.4 Structure of Visits

Women will be seen to receive and monitor study drug infusions every 4 weeks until delivery, during labor and delivery, and for evaluation at 6, 12, 26, 48, and 78 weeks postpartum. Followup of women beyond the immediate postpartum period allows for additional data collection on safety and the effect of HIVIG on disease progression. Antepartum visits should be scheduled every 28 days, +/- 7 days (21-48 day range). Visits will be numbered sequentially, beginning with the pre-entry visit as follows:

Pre-entry	always visit 0
Entry (1st infusion)	always visit 1
Infusion visits	always visits 2-6
L & D	always visit 10
PP wk 6	always visit 11
PP wk 12	always visit 12
PP wk 26	always visit 13
PP wk 48	always visit 14
PP wk 78	always visit 15

A pre-printed calendar providing a projected schedule of visits for the HIVIG/IVIG infusions will be generated for each woman enrolled on study. It is obtained by faxing a completed Entry Report, Form 18500, immediately after the entry visit.

A minimum of three HIVIG/IVIG infusions are to be administered to each woman. The number of infusions administered will vary depending on the patient's week of gestation at entry. For example, a woman who is at 20 weeks gestation at entry should be scheduled to receive 5 HIVIG/IVIG infusions. A woman who is 28 weeks gestation at entry should be scheduled to receive 3 HIVIG/IVIG infusions. If it becomes difficult to administer this number of infusions due to noncompliance or other factors, the study manager should be contacted for advice in scheduling visits.

5.5 Late Visits/ Missed Visits

5.5.1 Prenatal Visits

Late visit: If a patient misses a scheduled appointment, she should be seen at the earliest possible date, and the HIVIG/IVIG infusion should be administered at that time. A study visit/infusion which occurs > 35 days after the last study visit/infusion is considered a late study visit. If the study visit is late and occurs > 7 days prior to the next scheduled study visit, the clinical and laboratory procedures should be performed and the infusion should be administered. The next study visit should occur as scheduled. (It is possible the woman could return to the clinic in eight days for the next infusion and clinical assessments).

Missed visits: If a patient's return to clinic for infusions is > 49 days after the previous study visit, the patient will be considered to have missed a visit. The study manager must be consulted for directions on scheduling appropriate clinical and laboratory evaluations.

5.5.2 Intrapartum Visit

Within 1 week of the delivery of the infant, the study coordinator must send the following information by E-mail to ACTG.TEAM185:

- PID of mother and infant;
- Site of birth;
- Date and time of birth; type of delivery;
- Sex of the infant;
- Height, weight, and gestational age of the infant;
- Apgar scores;
- Status of mother and infant;
- Administration of HIVIG/IVIG infusion to infant;
- Number of HIVIG/IVIG infusions the mother received;
- Study drug administered during intrapartum period;
- Complications;
- Any other pertinent information.

If a patient delivers her baby in a place other than the scheduled study site, the study coordinator must obtain the hospital records for the labor and delivery and complete the case report forms.

5.5.3 Postpartum Period

If the 6-week postpartum visit (study visit 11) is > 3 weeks (21 days) late, the clinical and laboratory evaluations required for the 12-week postpartum visit (study visit 12) should be done. In this case, study visit 11 will be considered missed, and the evaluations required for study visit 12 should be completed.

If study visit 12 is > 4 weeks (42 days) late, the visit will be considered a missed visit. The patient should be seen again for the 26 weeks postpartum visit (study visit 13).

If study visit 13 is > 4 weeks (28 days) late, the visit will be considered a missed visit. The patient should be seen again for the 48 weeks postpartum visit (study visit 14). If study visit 14 is > 4 weeks (28 days) late, the visit will be considered a missed visit. The patient should be seen for her final visit at 78 weeks postpartum (study visit 15). If study visit 15 is > 4 weeks (28 days) late, the visit will be considered a missed visit, and Form 18538: Off study should be completed.

5.6 Pre-entry/Screening Period

Pre-entry is defined as 28 days prior to randomization. Entry is defined as the date of study drug initiation (HIVIG/IVIG) and must begin within 72 hours of randomization. Designated pre-entry clinical and laboratory evaluations are outlined in Exhibit 5-1, Schedule of Evaluations: Women.

5.7 Clinical Evaluations

Exhibit 5-1, Schedule of Evaluations: Women lists the evaluations required for each maternal study visit. A complete medical history obtained at pre-entry will include documentation of previous pregnancy outcomes and a maternal medical (including STD) and behavioral history. These pre-entry findings are documented on several forms:

5.7.1 Form 18501: OB Intake History. Demographic data, obstetrical history, and prenatal antiretroviral treatment information is recorded on this form.

APPENDIX I

SCHEDULE OF EVALUATIONS: WOMEN

		ANTEPARTUM							L & D	POSTPARTUM		
Study Week	Pre-Entry	Entry 1	4	8	12	16	Intra-Partum	Week 6	Week 12	Week 26	Week 48	Week 78
Infusion		1	2	3	4	5	ZDV					
Visit Number	0	1	2	3	4	5	10	11	12	13	14	15
OB Hx	x											
Sono	x											
EIA/WB	x											
Chem	x											
U/A	x	x	x	x	x	x						
History	x	x	x	x	x	x	x	x	x	x	x	x
PE	x	x	x	x	x	x	x	x	x	x		
OB PE	x	x	x	x	x	x	x	x	x	x		
HIV Sx	x	x	x	x	x	x	x	x	x	x	x	x
Infusion Record		x	x	x	x	x						
STD	x[1]											
Labs must be drawn pre-infusion unless specified												
Hematology	x	x		x						x	x	x
HIV Culture*		x		x			x			x		
Lymphocyte Subsets	x	x		x						x	x	x
Cells/Plasma Storage[2]	x	x		x			x		x	x	x	x

[1]Neisseria gonorrhoeae, Chlamydia trachomatis, and Treponema pallidum (STS).
[2]See Appendix XVI for specimen collection processing storage, and shipping requirements. Includes serial ICD p24 antigen determinations at NICHD central laboratory.
*Quantitative HIV PBMC Micro-culture.

5.7.2 **Form 18502: STD Testing.** Only STD testing required by ACTG 185 should be recorded on this form.

5.7.3 **Form 18503: Obstetrical Ultrasound.** A sonogram is required only during the pre-entry period (within 28 days of randomization).

Note: A woman with an estimated gestational age of 18 weeks based on a sonogram done two weeks prior to the scheduled date of randomization satisfies the criterion that the estimated gestational ages be at least 20 weeks and no later than 30 weeks at the time of randomization.

5.7.4 **Form 18505: Behavioral History.** This form records the use of tobacco, alcohol, and drugs during the pregnancy and is completed at pre-entry and at delivery.

5.7.5 **Form 18509: Ineligibility/Non-Participation Log.** The Ineligibility/Non-Participation Log, Form 18509, is completed for each patient screened for ACTG 185 who is found to be ineligible or declines participation in the study.

Clinical assessments are documented in the following forms which are given in order of form number:

5.7.6 **Form 18504: Vital Signs.** Vital signs are obtained at every visit beginning with the pre-entry visits. At each antepartum study visit that a HIVIG/IVIG infusion is given, vital signs and weight should be recorded on Form 18525: Infusion Record. If a HIVIG/IVIG infusion is not given at an antepartum study visit, the vital signs should be recorded on form 18504: Vital signs.

5.7.7 **Form 18506: HIV Assessment/Maternal.** This form, completed at pre-entry and each study visit, documents any <u>newly</u> identified ACTG 185-targeted diagnoses, physician exam findings and signs and symptoms. All HIV-related diagnoses must also be recorded on Form 18529: Diagnoses, and all HIV-associated signs and symptoms must be recorded on Form 18528: Signs and Symptoms.

5.7.8 **Form 18507: Urinalysis.** During the prenatal period, a urinalysis form must be completed for each study visit and the results recorded on Form 18507: Urinalysis. Urine specimens must be sent to a certified laboratory for analysis for this study. In the event a urinalysis cannot be obtained, a dipstick result may be used as long as it is documented in the medical record.

5.7.9 **Form 18508: Procedures or Conditions Complicating Pregnancy.** This form is completed at each prenatal study visit and at delivery and documents conditions complicating the pregnancy. Any reportable grade toxicity or signs and symptoms that may possibly be related to study treatment should also be reported on Form 18540: Toxicity/Adverse Experience Report.

5.7.10 **Form 18510: Antepartum Infusion Summary.** This form, completed at delivery, must be faxed to Westat. It documents the number of HIVIG/IVIG infusions given to the mother during the study.

5.7.11 **Form 18520: Patient Status.** This form is completed at each study visit including each missed visit.

5.7.12 **Form 18521: Registration.** This form contains identifying information and must be kept confidential and placed in a secure area. Do not place in the CRF Notebook. Do not send to Westat.

5.7.13 **Form 18522: Physical Exam.** A complete physical examination is performed at each study visit. All abnormal findings should be recorded on Form 18528: Signs/Symptoms or Form 18529: Diagnoses.

5.7.14 **Form 18527: Blood Products.** This form should be completed at each study visit and should document any blood products the mother receives.

5.7.15 **Form 18528: Signs/Symptoms.** Complete this form at each study visit and report only those signs and symptoms that are NOT associated with a diagnosis recorded on the Diagnoses form. Do not report laboratory abnormalities. Any signs/symptoms related to protocol treatment, HIV and protocol treatment, or those signs/symptoms that you are unable to judge the relationship to protocol treatment must be reported on Form 18540: Toxicity/Adverse Experience Report.

5.7.16 **Form 18529: Diagnoses.** This form should be completed at each study visit and should reflect abnormalities that are reported on Form 18522: Physical Exam or Form 18506: HIV Assessment-Maternal.

Any diagnosis thought to be related to protocol treatment must also be recorded on Form 18540: Toxicity/Adverse Experience Report.

Intrapartum Treatment: Intravenous ZDV

When labor begins, an intravenous loading dose of ZDV, 2.0 mg/kg, is administered over 1 hour, followed by a continuous infusion of ZDV at 1.0 mg/kg/hr for the duration of the intrapartum period, until the cord is clamped. If the anticipated time to delivery is short, and there is concern that the woman will not receive the loading dose, the infusion may be given over one-half hour. Instructions for the administration of intravenous ZDV are as follows:

- The dose of intravenous ZDV is to be **calculated based on the woman's weight on the day of the infusion**.
- Intravenous ZDV must be diluted with 5% dextrose solution and administered within 8 hours if stored at room temperature or 24 hours if refrigerated at 2-8 degrees Celsius. The diluted drug does not need to be protected from the light.
- Intravenous ZDV should not be mixed with any other fluids or medications. A separate intravenous line should be used for the administration of ZDV.
- All women receive an intrapartum infusion of ZDV, regardless of the time of the last dose of oral ZDV, or whether the ZDV dose during the pregnancy was modified or discontinued, unless the investigator determines the infusion to be contraindicated. In this case, the study chair should be contacted prior to the anticipated delivery date.
- If women are admitted for elective Cesarean section, at least 4 hours of ZDV infusion (loading dose plus an additional three hours of continuous infusion dosage) is desirable.
- Women admitted for induction of labor will have the ZDV infusion started at the time induction begins.
- Women who receive intravenous ZDV during premature or false labor and are subsequently discharged and still pregnant, should resume their pre-existing oral ZDV regimen. They should resume oral ZDV no sooner than four hours after the infusion was stopped.

5.7.17 **Form 18524: Infusion Record (IV ZDV)-Maternal.** Information related to the ZDV infusion should be recorded on this form.

Antepartum Therapy: HIVIG/IVIG

Reminder: For this protocol, the intravenous HIVIG/IVIG taken by the pregnant women is categorized as a study drug. Study drug therapy must begin within 72 hours of randomization.

HIVIG 200 mg/kg or IVIG 200 mg/kg will be administered by intravenous infusion every 28 days until labor. Women will not receive HIVIG/IVIG infusions after delivery. Instructions for the administration of HIVIG/IVIG are as follows:

- The dose of HIVIG or IVIG is to be calculated based on the women's weight **on the day of the infusion.**
- The study drug should not be mixed with any other fluids or medications. The infusion should be piggybacked to 5% dextrose and water in the event that it needs to be stopped.
- The infusion should be started at a rate of 0.02 ml/kg body weight per minute for the first 30 minutes. If well tolerated, the rate may be gradually increased to the maximum recommended dose of 0.08 ml/kg body weight per minute. This pattern should be followed with every HIVIG/IVIG infusion.
- Vital signs should be monitored prior to starting the infusion, midway through the infusion and immediately post infusion. Auscultation for fetal heart sounds should be done at the beginning, middle, and completion of the infusion.
- Exhibit 5-2, Guidelines for Toxicity Management for HIVIG/IVIG: Women provides suggested treatments for patients who experience reactions to the HIVIG/IVIG infusion.
- Severe allergic reactions such as exfoliative erythroderma or anaphylaxis will result in permanent discontinuation of HIVIG/IVIG.

A preprinted calendar providing a projected schedule of visits for the HIVIG/IVIG infusions will be generated for each woman enrolled in the study. The total number of infusions must be recorded on Form 18510: Antepartum Infusion Summary. This form should be submitted to Westat when **all** HIVIG/IVIG infusions have been completed, and after the mother has delivered.

APPENDIX X

GUIDELINES FOR TOXICITY MANAGEMENT OF HIVIG/IVIG: WOMEN

	Level I*	Level II*	Level III
Cardiovascular			
Tachycardia	HR 1.1 - 1.3 x baseline	HR 1.4 - 1.6 x baseline	HR > 1.6 baseline
Arrhythmia	Occasional, asymptomatic	Continuous, < 1 per min., and asymptomatic	Continuous, > 1 per min., or symptomatic
Hypotension (Systolic)	BP 10 - 20 mm Hg below baseline	BP 21 - 40 mm Hg below baseline	BP > 40 mm Hg below baseline
Hypertension (Systolic)	BP 10 - 20 mm HG over baseline asymptomatic	BP 21 - 40 mm Hg over baseline	BP > 40 mm Hg over baseline
Allergic	Chest tightness, transient or local rash, mild itching	Tachypnea 1.3 - 2 x baseline, wheeze, cough, diffuse rash or urticaria, mod. itching	Bronchospasm, tachypnea > 2 x baseline, severe generalized rash or urticaria, ** anaphylaxis**
Systemic			
Fever	37.7 - 38.4°C	38.5 - 39.4°C	Temp > 39.4°C
Chills	Mild	Intermittent shaking	Continuous, cold, clammy
Headache	Slight	Moderate	Severe
Other pain	Backache, other mild complaint	Moderate joint pain or backache	Severe pain anywhere
G.I.	Nausea, no vomiting	Occasional vomiting	Continuous vomiting with or without dehydration
Suggested TX	Slow infusion rate by 50% or to initial rate; may give ASA and benedryl.	D/C infusion, keep IV in, give APAP or ASA, benadryl; if sx subside, restart in 30 min.; use fetal monitor and monitor next visit.	Treat as necessary; D/C Rx for day; use fetal monitor; check with study chair prior to reinstituting Rx.**

* If the patient has experienced a Level I or II toxicity previously, premedicate with Benadryl (50 mg.) and ASA (650 mg.) or Acetaminophen (650 mg.) 1 hour prior to next infusion

** Severe allergic reaction such as exfoliative erythroderma or anaphylaxis will result in permanent D/C of the study drug.

5.7.18 **Form 18525: Infusion Record.** More detailed information pertaining to the infusion of HIVIG/IVIG is recorded on Form 18525: Infusion Record. This form is sent to Westat following each infusion with the other case report forms specific to the study visit. If a grade 2, 3, 4, or 5 adverse event occurs that is believed to be related to the HIVIG/IVIG, during or after the completion of the infusion, Form 18540: Toxicity/Adverse Experience Report should be completed.

Toxicity Management of HIVIG/IVIG

Usually, adverse reactions to HIVIG/IVIG are directly related to the rate at which the drug is infused. Reactions are usually mild, although rarely, serious symptoms may develop. Appendix X: Guidelines for Toxicity Management of HIVIG/IVIG Toxicity: Women, provides a list of expected adverse events which may be related to the HIVIG/IVIG infusion. The events are categorized as: Level I - mild; Level II - moderate; and Level III - severe. This chart is to be used as guidance for clinically managing adverse reactions and should not be confused with Appendix XII: Table for Grading Severity of Adverse Experiences (Women), which assigns grades for reporting adverse events to the Adverse Event Reporting Office at Westat. In the event of a level III reaction, the infusion should be discontinued immediately, treatment necessary to manage the reaction administered, and fetal well-being monitored. No subsequent infusions should be administered without prior approval from the study chair. See Chapter 7 for Adverse Event Reporting guidelines.

Permanent Discontinuation of HIVIG/IVIG

Criteria for HIVIG/IVIG discontinuation:

- Severe allergic reaction to the infusion such as exfoliative erythroderma, anaphylaxis or vascular collapse, or a clinical condition which the on-site physician believes is incompatible with life.
- At the request of the patient, investigator, Food and Drug Administration, pharmaceutical company or IND sponsor.
- Severe preeclampsia (HELLP) syndrome as defined by blood pressure of 140/90 on two or more occasions more than six hours apart, proteinuria at least 5 gm in a 24-hour urine collection, and one or more of the following:
  - Oliguria (< 100 cc in four hours);

- Epigastric or right upper quadrant pain;
- Platelet count < 80,000 cells/mm^3;
- SGPT ≥ 3 times baseline;
- Cerebral or visual disturbances such as altered consciousness, headache, scotomata, or blurred vision;
- Pulmonary edema or cyanosis; and/or
- Eclampsia.

- Disseminated intravascular coagulation.
- Fetal death or detection of a fetal anomaly which may result in a high probability that the fetus-infant will not survive to the end of the study period. Examples include anencephaly, renal agenesis or Potters syndrome.
- If the pregnant woman required discontinuation of the study drug, her infant should receive the study drug unless the investigator determines the infant infusion of HIVIG/IVIG is contraindicated.

Women who discontinue HIVIG/IVIG for any reason will continue to be followed through postpartum week 78.

5.7.19 **Form 18537: Permanent Discontinuation of Protocol Treatment** should be completed when a woman is permanently discontinued from protocol drug treatment (HIVIG/IVIG and IV ZDV) prior to completion of the treatment period. This form must be completed at study visit 10.

Concurrent Medications and Treatments

5.7.20 **Form 18526: Concomitant Medications.** All prescriptions and non-prescription medications (other than ZDV and HIVIG/IVIG) received by the woman during pregnancy, labor, and post delivery should be recorded on Form 18526: Concomitant Medications. At entry, list all medications that were taken during the current pregnancy. This includes medications that were started during this pregnancy prior to the study entry, whether stopped or not. New medications are those that were started after the last evaluation. Ongoing medications are those that were reported at the last evaluation, and were not stopped at the last evaluation.

- Women may receive all medications/treatments as required for the obstetrical management of HIV-infected women.

- It is permissible for a woman to discontinue oral ZDV due to intolerance or disease progression, and begin a different antiretroviral medication, such as ddI or ddC. The site must contact protocol co-chairs by team e-mail (ACTG.Team185@karloff.fstrf.org) for approal. Anti-HIV vaccines and passive immunotherapy with HIVIG/IVIG (outside of the study) are not permissible.

- Protease inhibitors are not permitted until after delivery (Visit 10).

- Drugs that are metabolized by hepatic glucuronidation may alter the ZDV metabolism and should be used with caution.

- Acyclovir for chronic suppressive therapy, ketoconazole, INH, and antibiotics are permissible concurrent medications.

- Prophylaxis for PCP is recommended according to current practice guidelines.

- All blood products are entered on Form 18527: Blood Products.

5.8 Laboratory Evaluations

The schedule of laboratory evaluations required at each study visit is displayed in Appendix I, Schedule of Evaluations: Women. Appendix XVI: Specimen Collection, Processing, and Storage Procedures, located in the protocol, contains the laboratory procedures for obtaining, processing, storing, and analyzing blood specimens required by the protocol.

At site registration, each study coordinator will be sent three mother/infant sets of Virology Specimen Tracking notebooks. A set consists of a Virology Specimen Tracking notebook for both the mother and the infant. Each notebook is divided by study visit. Within each study visit are study specific barcode labels, located in brown envelopes, and Specimen Tracking Forms. **Use the same Virology Specimen Tracking notebook set for a mother/infant pair for the entire study.**

The specimen collection schedules and procedures are outlined in Appendix XVI: Specimen Collection, Processing, and Storage Procedures. All of the virology specimens will be collected in yellow top (ACD) tubes in 2.6 ml or 8.5 ml draw volumes. Prior to specimen

collection, all yellow top tubes must be labeled with the PID/SID numbers, and date and time of collection.

Study visit-specific, pre-printed bar code labels are provided in Virology Specimen Tracking notebooks for each patient for labeling the aliquot derived from processing the yellow top tubes. If a yellow top tube is sent to an off-site ACTG certified virology laboratory for processing, the bar code labels for the aliquots obtained from processing the yellow top tube must accompany the specimen to the lab. When an on-site ACTG-certified laboratory prepares aliquots from the yellow top tubes, each of the aliquots must be labeled with a barcode label before it is stored and shipped monthly to McKesson Bioservices, the central repository.

NOTE: **Antepartum visit blood samples must be drawn PRIOR to the HIVIG/IVIG infusion. Intrapartum blood samples should be drawn prior to ZDV infusion.**

The day that the study visit is scheduled may be contingent upon the laboratory shipping and processing guidelines provided by the site's designated laboratory. Sites that will be sending specimens to Quest Diagnostics should note that Quest Diagnostics will receive specimens Tuesday through Friday except on national holidays. The specimens should be shipped Monday through Thursday. It is important to keep this in mind if clinic patients are routinely seen on Fridays. Other ACTG approved laboratories may have similar restrictions. An arrangement for receipt, processing, and temporary storage of all (prenatal, intrapartum, neonatal, and post delivery) laboratory specimens must be made with ACTG approved laboratories prior to the initiation of this study. Receipt of specimens on the weekend related to labor and delivery must be arranged with Quest Diagnostics.

5.8.1 **Form 18530: Hematology.** A CBC with differential (machine is the preferred method) and platelet count is required at pre-entry and study visits 1, 3, 13, 14, and 15. The differential includes polys, bands, lymphocytes, monocytes, eosinophils, basophils, and atypical lymphocytes. The CBC with differential may be processed at the site's local laboratory or the ACTG-certified flow cytometry laboratory. Results of both lab tests will be sent to the site within 24 hours.

5.8.2 **Form 18531: Chemistries, LFTs.** BUN, creatinine, SGOT, SGPT, total and direct bilirubin, alkaline phosphatase, and electrolytes are required only at pre-entry. The specimen for chemistries is processed at the site's local lab. Results are reported on Form 18531: Chemistries, LFTs.

5.8.3 **Form 18532: Immunologic Studies/Lymphocytic Subsets.** A specimen for lymphocyte subsets should always be drawn whenever blood is drawn for a CBC. Lymphocyte subsets include total and percent CD3, CD4, CD8, CD19, and CD4/CD8 ratio. The lymphocyte subsets will be processed at an ACTG-certified flow cytometry lab affiliated with the site, not at the site's local lab. NICHD sites will send their specimens to the Quest Diagnostics. NIAID sites will send these specimens to their designated ACTG certified flow cytometry laboratory. Results of both lab tests will be sent to the site within 24 hours.

5.8.4 **Form 18533: Serology.** EIA and appropriate confirmatory test (e.g., Western Blot, IFA, etc.) are performed at pre-entry only, and processed at the site's local laboratory, unlike the other retrovirologic evaluations described below. Results are recorded on Form 18533: Serology.

5.8.5 **Form 18534: Specimen Tracking Form.** A Specimen Tracking form (Form 18534) must be completed for all study visits that include virology yellow top ACD tube draws. The tracking form links the specimen to the patient and collects information on the processing of the specimen. A study visit-specific, pre-printed Specimen Tracking form barcode label must be affixed to the tracking form. The specimen source ID (the last 3 digits on the top number of the barcode) on the pre-printed tracking form barcode label should be identical to the specimen source ID on the barcode label for the processed specimen.

If all the virology yellow top tubes for one study are processed in the laboratory, only one Specimen Tracking Form is needed. If, for a study visit, the virology specimens are processed in two different laboratories, each set of specimens must have a Specimen Tracking Form accompany it to the laboratory, therefore, two Specimen Tracking Forms are needed.

Virology specimen collection schedules and procedures are outlined in the protocol in Appendix XVI: Specimen Processing Collection and Storage Procedures.

Rapid Processed Plasma

Rapid processed plasma for storage will be collected, processed, and frozen within six hours of collection at study visits 0 (pre-entry), 1 (entry), 3, 10, 12, 13, 14, and 15. The

plasma aliquots will be stored frozen and shipped monthly to McKesson Bioservices, the central repository.

HIV Quantitative Culture

HIV quantitative cultures are required at study visits 1 (entry), 3, 10, and 13. The HIV quantitative cultures are processed at a certified ACTG virology lab. Each site must arrange for the lab to send hard copy culture results. Place a copy of this lab report in the CRF notebook for source documentation.

If the culture is positive, the laboratory will save and freeze isolates. These isolates will be shipped monthly to McKesson Bioservices, the central repository.

Cell/Plasma Storage

Required at study visits 0 (pre-entry), 1 (entry), 3, 10, 12, 13, 14, and 15, the aliquots will be stored frozen and shipped monthly to McKesson Bioservices, the central repository.

5.9 Other Evaluations

5.9.1 **Form 18535: Patient Progress Note.** At each study visit, this form is used to record any pertinent information regarding the patient's progress. It should be filed in the CRF notebook.

Do not send this form to Westat.

5.9.2 **Form 18536: Missed Visit.** Complete this form if the patient fails to keep an appointment. Form 18520: Patient Status should also be completed with each missed visit. A missed visit is defined as the following:

- If it has been > 49 days since the previous infusion (antepartum);
- If the 6-week postpartum visit (study visit 11) is > 3 weeks late;
- If study visit 12 > 4 weeks late;

- If study visit 13 > 4 weeks late;
- If study visit 14 > 4 weeks late; or
- If study visit 15 > 4 weeks late.

5.9.3 **Form 18537: Permanent Discontinuation of Protocol Treatment.** Complete this form when a woman has permanently discontinued HIVIG/IVIG and IV ZDV, usually at study visit 10. If circumstances necessitate that the woman discontinue treatment at an earlier point in the study, complete Form 18537.

5.9.4 **Form 18538: Off Study.** This form is completed when a woman is permanently discontinued from all study followup. A woman is considered off study when all followup is discontinued prior to the completion of the protocol required period of observation. These circumstances include:

- Death;
- Parent/legal guardian refuses all further contact;
- Unable to contact patient after repeated attempts; or
- Inadvertent enrollment.

This form must be completed at study visit 15 and should accompany all other forms for the visit. If a patient is lost to followup, and is taken off study prior to completion of the study, Form 18520: Patient Status, Form 18536: Missed Visit, and Form 18537: Permanent Discontinuation of Protocol Treatment (if before study visit 10) must accompany Form 18538: Off Study.

5.9.5 **Form 18539: Cause of Death.** If a patient dies while on study or during, the followup study period, the center must contact Westat within 24 hours. Form 18539: Cause of Death is completed and sent to Westat as soon as possible. An Adverse Event Report (AER) Form 18540 must also be completed (see Chapter 7). An AER form must also be completed in the event that a patient dies within 3 months of going off study. All required forms submitted after a death (Forms 18539 and 18540) which occurred after being off study, should be completed with the study visit recorded as "95."

5.9.6 **Form 18540: Toxicity/Adverse Experience Report.** Refer to Chapter 7 Managing Toxicities/Adverse Experience: Woman and Infants.

5.9.7 **Form 18546: Treatment Record (Antiretroviral) Maternal.** This form should be completed for each study visit, and should include each antiretroviral agent that the patient receives.

Antepartum Therapy: Oral ZDV

Reminder: For this protocol, the oral ZDV taken by pregnant women is not considered a study drug. However, intravenous ZDV administered during labor to the woman is categorized as a study drug.

All pregnant women who are enrolled in this study must be receiving antiretroviral therapy for medical indications according to obstetrical standards of care. Medical management of antiretroviral therapy and dose adjustment for toxicity are at the discretion of the patient's physician and should be consistent with currently recommended guidelines.

Women who have antiretroviral therapy discontinued after study entry for medical indications such as toxicity or disease progression may remain on study. These women may receive a different antiretroviral agent during the antepartum period at the discretion of their physician and upon notification of the Protocol co-chairs (ACTG.Team185@karloff.fstrf.org). Pregnant women who have discontinued oral ZDV will receive the intrapartum ZDV infusion, unless the investigator determines the infusion to be contraindicated. This decision must be discussed with the protocol chair prior to the anticipated delivery date. Similarly, pregnant women who are taking a different antiretroviral agent will receive the intrapartum ZDV infusion, unless contraindicated.

5.9.8 **Form 18553: Clinical Case Report Form.** This optional form is used to record confounding co-morbidities, laboratory abnormalities or inconsistent data which require further explanation.

5.9.9 **Form 18555: Baseline Antiretroviral History.** This form should be completed at pre-entry and should document all antiretroviral drugs the woman has taken previously or is taking currently.

5.9.10 **Form 18556: Delivery Followup.** This form is completed at study visit 10 and provides additional information about the intrapartum period.

6. MANAGEMENT OF INFANTS

6.1 Informed Consent

The mother will provide written informed consent for the infant's participation in the study. The father's written informed consent for the participation of the infant is required at the time the mother provides informed consent. A reasonable attempt should be made to contact the father. If the father is not available, it must be noted in the medical record. In this case, the infant may participate in the study.

Each center should consult its IRB for guidance regarding the need for an additional consent form after birth.

If a new legal guardian assumes custody of a child enrolled in the study, the original consent form is no longer valid. The new legal guardian must sign a new copy of the consent form.

6.2 Structure of Visits

Infants will be seen for toxicity monitoring and/or evaluation for evidence of HIV infection at birth (day 1/newborn), weeks 1, 2, 6, and 12, 16, 20, 24, 36, 48, 60, and a final evaluation at week 78 (18 months). Long term followup of infected and uninfected infants will occur through co-enrollment in ACTG 219.

Visits will be numbered sequentially, beginning with the newborn evaluation visit, as follows:

Study Week	Study Visit #	Visit Window
Birth (Day 1/Newborn)	visit 1	--
1 week visit	visit 2	+/- 1 day
2 week visit	visit 3	+/- 2 days
6 week visit	visit 4	+/- 1 week
12 week visit	visit 5	+/- 1 week
16 week visit	visit 6	+/- 1 week

20 week visit	visit 7	+/- 1 week
24 week visit	visit 8	+/- 1 week
36 week visit	visit 9	+/- 4 weeks
48 week visit	visit 10	+/- 4 weeks
60 week visit	visit 11	+/- 4 weeks
78 week visit	visit 20	+/- 4 weeks

A pre-printed calendar providing a projected schedule of visits will be sent by Westat as soon as Form 18511: Intrapartum Record has been received. The schedule of study visits must be adhered to as closely as possible. The term "study week" reflects the actual number of weeks since the infant's date of birth. It is expected that study visit 8 (study week 24) will occur exactly 24 weeks after the infant's date of birth. If study visit 7 (study week 20), is 10 days late, study visit 8 should still be scheduled for study week 24 based upon the infant's date of birth, not on the date of study visit 7.

For example: An infant is born on January 1, 1994. The entry visit (#1) was held 11 hours later on January 2 when the infant received the HIVIG/IVIG infusion. Study Visit 2 will be scheduled 1 week after birth (January 8). Study visit 8 will be scheduled 24 weeks after the January 1st birth, and be conducted on June 17, 1994.

If at any time during the study, it becomes difficult to determine which study visit should be designated due to a missed visit or poor compliance, contact the Westat protocol manager for instructions.

6.3 Intrapartum Assessment

Form 18511: Intrapartum Record

Information concerning the delivery of the infant(s) is recorded on Form 18511: Intrapartum Record. A separate form should be completed for each infant in the event of multiple births. This form must be faxed to Westat after which a patient specific calendar of expected study visit dates will be generated and mailed to the site. If an infant is delivered at a non-study hospital, the records from the delivery site must be obtained and case report forms, except for the infusion record, must be completed.

6.4 Placenta HIV RNA

At selected sites, a placental biopsy to detect HIV-RNA will be obtained. Biopsy analysis will be performed at the pathology laboratory at Baylor University. Sites interested in participating in this aspect of the study must be approved during the site implementation plan review.

The placenta specimen must be obtained, examined, and the fixation process begun within 1 hour after birth. This will maximize the preservation of RNA in placental tissue. Once the fixation process has been completed, the specimen should be refrigerated at 4°C until final shipment to Baylor. Before the specimen is shipped, the Baylor pathology department must be contacted at (713) 770-2250. The specimen should be placed in a small plastic container, and does not require refrigeration for shipment.

The RNase-free paraformaldehyde is stable for only 1-2 weeks at 4°C. Aliquots may be frozen at -20°C indefinitely and thawed as needed. For instructions about tissue fixation and shipping, refer to Appendix XVII: Placental Biopsy Preparation and Shipment located in the protocol.

6.4.1 Form 18512: Placenta Pathology

Record the infant's PID and SID on this form. The form is to be completed by the pathologist who prepares the specimen for shipment to Baylor.

6.5 Clinical Evaluations

Exhibit 6-1, Schedule of Evaluations: Infants provide the schedule of required clinical evaluations. Infants will be evaluated at birth (day 1/newborn) and at weeks 1, 2, 6, 12, 16, 20, 24, 36, 48, 60, and 78. For infants who reach an endpoint (confirmed HIV quantitative culture) prior to the final study visit, a brief summary followup assessment, including vital status will be done every 3 months. This may be done by telephone. Findings will be documented on Form 18517: Pediatric Followup. All infants, regardless of HIV infection status, will return for the final study visit at week 78.

6.5.1 Pediatric Vital Signs

Growth measurements and vital signs are obtained at every study visit. At birth, they are recorded on Form 18513: Newborn Exam. Beginning with study visit 2, and thereafter, vital signs and growth measurements are recorded on Form 18514: Pediatric Vital Signs. These guidelines should be followed:

- Weight may be recorded in grams, kilograms, or pounds. Whichever unit of measurement is chosen must be used throughout study participation. A balanced infant/pediatric scale must be used, and the patient should be undressed. Remember that with shoes/without shoes, winter clothing/summer clothing, dressed/undressed will affect the measurement. Be consistent.

- Height or length may be measured in centimeters or inches. Whichever unit of measurement is used, it must remain constant throughout the child's enrollment. The child should not be wearing shoes or a hat when the measurement is taken. Each site should develop a standard for measuring children of a defined age, i.e., lying down or standing.

- Head circumference is recorded in centimeters. The measuring tape should be placed over the largest diameter of the head from the forehead to the occipital area.

- Temperature may be recorded in either Centigrade or Fahrenheit. Include the route or method.

- Measure pulse and respirations for a full minute.

APPENDIX II

SCHEDULE OF EVALUATIONS: INFANTS

Study week number	Cord	Newborn	Wk 1	Wk 2	Wk 6	Wk 12	Wk 16	Wk 20	Wk 24	Wk 36	Wk 48	Wk 60	Wk 78 (18 mo.)	Confirmatory Culture[c]
Study visit number	1	1	2	3	4	5	6	7	8	9	10	11	20 Final	
CLINICAL:														
Gest age		x												
Physical		x	x	x	x	x	x	x	x	x	x	x	x	
HIV Sx Assess		x	x	x	x	x	x	x	x	x	x	x	x	
LAB:														
CBC, 5-part diff. platelets		x[b]	x	x	x	x			x					
SGPT/SGOT	x	or x[b]		x	x									
Ig's	x				x	x								
Lymph subsets					x	x			x					
EIA-WB												x[e]	x[e]	
Quant HIV PBMC Micro-culture		x[a,d]			x[a]				x[a]		x[a]			x
Cells/Plasma Storage	x	x[d]		x	x	x	x		x		x	x[e]		x

a. If positive, HIV culture (confirmatory culture) must be drawn.
b. Prior to initiation of ZDV therapy.
c. Will be assigned same visit number as most recent visit.
d. Prior to initiation of the HIVIG/IVIG infusion, and ZDV therapy.
e. If positive and no prior positive culture, a confirmatory culture must be drawn.

6.5.2 Form 18513: Newborn Exam

Measurements and vital signs obtained at birth are recorded on Form 18513: Newborn Exam. If any congenital anomalies are identified, they must also be reported on Form 18540: Toxicity/Adverse Event Report and either Form 18528: Signs/Symptoms or Form 18529: Diagnoses.

6.5.3 Form 18514: Vital Signs (Pediatric)

Growth measurements and vital signs are obtained at each study visit and recorded on Form 18514: Vital Signs.

6.5.4 Form 18515: HIV Assessment/Pediatric

Form 18515: HIV Assessment/Pediatric contains documentation of the infant's HIV status including the 185 HIV-related diagnoses and signs/symptoms. Be sure to record any **newly** identified HIV-related diagnoses on Form 18529: Diagnoses and any **newly** identified HIV-related signs and symptoms on Form 18528: Signs/Symptoms.

Example: If an infant presents with splenomegaly, this finding is recorded on Form 18528: Signs/Symptoms. If an infant presents with oral candidiasis, this finding is recorded on Form 18529: Diagnoses; "oral ulcer" does NOT have to be recorded on the Signs/Symptoms form.

Each sign/symptom and diagnosis recorded on these forms must have a code. Codes for signs/symptoms and diagnoses are listed in the Appendices Notebook.

6.5.5 Form 18516: Quantitative Immunoglobulin Levels

At birth* and study visits 4 and 5, quantitative IgG, IgA, and IgM are required. The specimen for immunoglobulins is processed at the site's local lab.

***Note: The birth specimen for quantitative IgG, IgA, and IgM may be obtained from cord blood. If cord blood is obtained for this test, a specimen from the newborn is not required.**

Form 18516: Quantitative Immunoglobin Levels documents the results of these laboratory tests.

6.5.6 Form 18518: Birth Order

Complete Form 18518: Birth Order at birth for every infant. In the event of a multiple birth, assign the lowest numeric PID to the infant born first, the next PID to the infant born second, etc.

6.5.7 Form 18519: Phototherapy/Exchange Transfusion

This form should be completed at study visits 2 and 3 only.

If an infant has an elevated bilirubin or jaundice, it should be reported on Form 18540: Toxicity/Adverse Experience Report and Form 18528: Signs/Symptoms or Form 18529: Diagnoses.

6.5.8 Form 18520: Patient Status

This form is completed at each visit including each missed visit.

6.5.9 Form 18521: Registration

This form contains identifying information and must be kept confidential and placed in a secure area. Do not place in the CRF Notebook. Do not send to Westat.

6.5.10 Form 18522: Physical Examination

A complete physical examination is performed at every study visit. Form 18522: Physical Exam contains documentation of the physical findings. Abnormal physical findings are recorded on Form 18528: Signs/Symptoms and Form 18529: Diagnoses. Form 18528: Signs/Symptoms is completed only for those signs/symptoms documented in the physical exam that are not associated with a diagnosis recorded on the Diagnoses form.

6.6 Study Endpoint

Acceptable endpoint criteria are laboratory evidence of HIV infection demonstrated by:

- Children of any age: One (1) or more **confirmed** positive HIV viral cultures (blood or CSF). Following a first positive HIV culture, a repeat culture should be performed before discontinuation of further interim required study visits. All infants must complete study visits through week 6, regardless of HIV infection status
- Children $\geq$ 18 months old without **confirmed** positive HIV culture: $\geq$ 2 federally licensed positive screening tests for HIV antibody, one no earlier than 18 months, and none earlier than 15 months of age. These must be confirmed by an accepted FDA approved confirmatory test.

Children who meet the study endpoint for HIV infection prior to the final study visit are not considered to be off study. All infants must complete study visits through week 6 (study visit 4), regardless of HIV infection status. Beyond this point in time, children who meet criteria for study endpoint must be followed at 3 month intervals. For example, if the child meets study endpoint at study visit 4, followup should be conducted on an every 3 month basis after study visit 4. All followup for these children may be done by telephone. At study week 78 (study visit 20), all children should be seen for the final protocol evaluation.

Infants with documented HIV infection may co-enroll in other pediatric investigational treatment protocols.

6.6.1 Form 18517: Pediatric Followup

This form is used to record information gathered on children who have reached study endpoint.

6.7 Medication Management

Reminder: For this protocol, the HIVIG/IVIG infusion and ZDV received by the infant are considered to be study drugs.

6.7.1 Infant Eligibility: HIVIG/IVIG

The infant study drug (HIVIG or IVIG) will match the maternal study drug. Each infant of a multiple birth will receive the study drug according to the mother's randomized drug assignment. If the maternal study administration of HIVIG/IVIG is discontinued, the infant should still be administered the study drug unless the investigator determines the infusion to be contraindicated. Decisions to omit the infant infusion must be approved by the protocol chair prior to the anticipated delivery date.

6.7.2 HIVIG/IVIG Therapy

Reminder: Laboratory specimens must be obtained prior to administration of HIVIG/IVIG, however the infusion may be given prior to reviewing the laboratory results.

A total dose of 200 mg/kg of HIVIG/IVIG will be administered intravenously to the infant. Instructions for the administration of HIVIG/IVIG are as follows:

- As soon as the newborn infant has stabilized, HIVIG/IVIG should be administered. For maximal efficacy, the study drug should be administered within 12 hours after birth. However, if not administered within 12 hours, the study drug should be administered as soon as possible.
- The study drug should not be mixed with any other fluids or medications. The infusion should be piggybacked to 5% dextrose and water in the event that it needs to be stopped.
- The infusion should be started at a rate of 0.01 ml/kg/min. This can be doubled at 15-minute intervals if no adverse effects are observed to a maximum rate of 0.08 ml/kg/min.
- Caution should be taken with the administration of study drug in the presence of cardiopulmonary disease, due to the potential for fluid overload. A slower rate of infusion or dividing the total dose into multiple infusions within a 12-hour period may be used.
- Vital signs should be monitored prior to starting the infusion, midway through the infusion and immediately post infusion.
- Guidelines for the clinical management of HIVIG/IVIG infusion reactions are located in Exhibit 6-2, Guidelines for Toxicity Management of HIVIG/IVIG: Infants.
- A severe allergic reaction such as exfoliative erythroderma or anaphylaxis will result in permanent discontinuation of HIVIG/IVIG.

Exhibit 6-2. Guidelines for Toxicity Management of HIVIG/IVIG: Infants

APPENDIX XI

GUIDELINES FOR TOXICITY MANAGEMENT OF HIVIG/IVIG: INFANTS

	Level I	Level II	Level III
Cardiovascular			
Tachycardia	HR 1.1 - 1.3 x baseline	HR 1.4 - 1.6 x baseline	HR > 1.6 baseline
Arrhythmia	Occasional, asymptomatic	Continuous, < 1 per min., and asymptomatic	Continuous, > 1 per min., or symptomatic
Hypotension	MAP+ 5-10 mm Hg below baseline	MAP+ 10.1 - 15 mm Hg below baseline	MAP+ > 15 mm Hg below baseline
Hypertension	MAP+ 5-10 mm Hg over baseline	MAP+ 10.1 - 15 mm Hg over baseline	MAP+ > 15 mm Hg over baseline
Allergic	Slight flushing	Tachypnea 1.3 - 2 x baseline, wheeze, cough, localized rash or urticaria, generalized flushing	Tachypnea > 2 x baseline, retractions, decreased breath sounds, broncho-spasms, severe rash or urticaria, anaphylaxis*
Systemic			
Temperature	37.2 - 38.0°C	38.1 - 39.9°C	Temp > 39.9°C or <35.8°C
Chills	Mild	Intermittent shaking	Continuous, cold, clammy
Gastro-intestinal		Transient vomiting	Vomiting
Suggested TX	Slow infusion rate by 50% or to initial rate;	D/C infusion, keep IV in, give Benadryl (1-2 mg/kg); if sx subside restart in 30 min.	Treat as necessary; D/C Rx; check with study chair prior to completing infusion.*

* A severe allergic reaction such as anaphylaxis will result in permanent discontinuation of the study drug.
\+ Mean Arterial Pressure = Calculation:

$$MAP = \frac{S - D}{3} + D$$

or

$$MAP \frac{2D + S}{3}$$

6.7.3 Form 18525: Infusion Record (HIVIG/IVIG)

Information pertaining to the infusion of HIVIG/IVIG is recorded on Form 18525: Infusion Record. If a grade 1, 2, 3, 4, or 5 adverse event occurs that is believed to be related to the HIVIG/IVIG during or after the completion of the infusion, Form 18540: Toxicity/Adverse Experience Report should be completed.

6.7.4 Infant Eligibility: ZDV

Reminder: Laboratory specimens must be obtained and results must be reviewed PRIOR to administration of ZDV.

Infants will begin ZDV therapy unless any one of the following conditions exist:

- A clinical condition which the on-site pediatrician believes is incompatible with life;
- Infants with the following laboratory values:
  - ANC < 750/mm^3,
  - Hemoglobin < 8.0 gm/dl (transfusions are allowed),
  - Platelets < 50,000/mm^3,
  - Hyperbilirubinemia requiring exchange transfusion (does not include phototherapy), or
  - SGPT > 5 X upper limit of age-adjusted normal;
- Parent/guardian not available to give informed consent, if necessary.

An infant that does not begin ZDV due to one of the clinical or laboratory abnormalities noted above will be monitored at regular intervals corresponding to the study visit schedule. Form 18545: Treatment Record must be completed to provide the reason for omission of ZDV therapy.

6.7.5 ZDV Therapy: Inpatient

The duration of ZDV therapy is 6 weeks, and during this period the infant will be monitored for toxicity and compliance. Infants will begin treatment with ZDV syrup at 2.0 mg/kg (0.2 ml/kg) every 6 hours as soon as they are able to tolerate liquids by mouth and within 24 hours of birth. It is recommended that 30 ml amber plastic bottles be used to dispense the initial ZDV. Oral syringes with calibration to 0.01 ml will be needed to administer the ZDV. ZDV may be held for a maximum of 48 hours for infants who cannot tolerate oral medication. Intravenous ZDV should be initiated if oral ZDV cannot be given. Intravenous ZDV is administered at 1.5 mg/kg and infused over a 30 minute period, every 6 hours. Intravenous ZDV should not be mixed with any other fluids or medications. It should be administered through a separate peripheral IV line. Umbilical arterial or venous lines should not be used.

6.7.6 Form 18545: Treatment Record (ZDV) - Infant

Information related to the route of administration, compliance, and dose modification are recorded on Form 18545: Treatment Record (ZDV) - Infant.

6.7.7 ZDV Therapy: Outpatient

Oral ZDV will be provided in 240 ml opaque plastic bottles with childproof caps. It should be stored at room temperature and protected from light. It is recommended that 30 ml amber plastic bottles be used to dispense the initial therapy supply. It is expected that caregivers will require clear and specific instructions to insure that the infant is being given the correct dose, and that the study medication is being stored under the proper conditions. Written instructions and a medication diary should be provided. A sample Parent/Guardian Instruction Sheet is provided in Exhibit 6-3, ZDV Administration Instructions for Parents/Guardians.

The infant should be weighed at each study visit and the dose of ZDV should be calculated based on the current weight. Refer to Section 6.5.1 for guidelines on obtaining accurate weights. If there is greater than a 10 percent difference in the infant's calculated dose, the

dose will be adjusted. A ZDV Dosing Table for Infants is provided in Exhibit 6-4, ZDV Dosing Table - Infants . Empty or unused medication bottles must be returned by the parent/guardian at each study visit (weeks 1, 2, and 6). These bottles must be discarded according to ACTG Pharmacy Procedure.

Exhibit 6-3. Administration Instructions for Parents/Guardians

APPENDIX VI

ZDV ADMINISTRATION INSTRUCTIONS FOR PARENTS/GUARDIANS

1. Give your baby the medicine every six hours.

2. Draw up the medicine in the syringe as you were shown in the hospital. Give the amount of medicine your nurse or doctor told you to give. Clean the syringe after you give your baby the medicine. Each syringe can be used again after it is taken apart and rinsed in water.

   DO NOT CHANGE THE AMOUNT OF MEDICINE UNLESS YOU HAVE BEEN INSTRUCTED TO BY YOUR DOCTOR OR NURSE.

3. Do not give the medicine to anyone else.

4. Keep all of the medicine bottles even if they are empty. Bring all bottles (empty and full) to each clinic visit. If you do not bring the bottles back to the clinic, we cannot give you more medicine.

5. Keep your appointment at the clinic.

6. Keep the medicine at room temperature. It should not be kept in the refrigerator.

7. Other medications may cause your baby to have a bad reaction if you mix the study drug with other medicines. Do not give your baby other medicines without talking to your nurse or doctor at the clinic.

8. Call the clinic to report any problems or changes in behavior you think the baby is having.

9. What to do if the baby spits up some of the medicine:

   - If the baby only spits up a little, do not worry.

   - If the baby throws up a lot, check to see when you gave the medicine to the baby.

     - Has it been less than 1 hour since you gave the medicine? IF YES, then give the same amount of medicine again.

     - Has it been more than 1 hour since you gave the medicine? IF YES, then DO NOT give the medicine again. Wait until the next scheduled time you are supported to give the medicine.

If you have any questions, or if your baby gets sick, or if you need more medicine or supplies for your baby, call the clinic and ask for _____. Leave a message, if he/she is not there. He/she will call you right back.

TELEPHONE: _____

Exhibit 6-4. ZDV Dosing Table - Infants

APPENDIX V

ZDV DOSING TABLE - INFANTS

Weights for infants and Corresponding Dose in Milliliters

Weight in Grams	Kg	Dose in ml (2 mg/kg)
1500 - 1625	1.500 - 1.625	0.30
1626 - 1874	1.626 - 1.874	0.35
1875 - 2125	1.875 - 2.125	0.40
2126 - 2374	2.126 - 2.374	0.45
2375 - 2625	2.375 - 2.625	0.50
2626 - 2874	2.626 - 2.874	0.55
2875 - 3125	2.875 - 3.125	0.60
3126 - 3374	3.126 - 3.374	0.65
3375 - 3625	3.375 - 3.625	0.70
3626 - 3874	3.626 - 3.874	0.75
3875 - 4125	3.875 - 4.125	0.80
4126 - 4374	4.126 - 4.374	0.85
4375 - 4624	4.375 - 4.624	0.90

WEIGHT CONVERSION:
Weight in ounces x 28.35 = Weight in Grams (gm)

$$\frac{\text{Weight in grams}}{1000} = \text{Weight in kg}$$

DOSE CALCULATION:
Weight in kg x 2 mg/kg = DOSE in mg

$$\frac{\text{Dose in mg}}{10\ \text{mg/ml}} = \text{Dose in ml (round off to nearest 0.05 ml)}$$

Example:
Infant weights 4 lb. 8 oz., or 72 oz.

72 oz. x 28.35 = 2,041 gm

$\frac{2041}{1000} = 2.041$ kg

2.041 kg x 2 mg/kg = 4.082 mg

$\frac{4.082\ \text{mg}}{10\ \text{mg/ml}}$ = 0.408 ml or 0.4 ml when rounded to the nearest 0.05 ml

6.7.8 Form 18526: Concomitant Medications

Concurrent Medications and Treatments

Note: An infant may not receive any other antiretroviral drug while receiving the ZDV study treatment during the first 6 weeks of life.

All prescription and non-prescription medications received by the infant should be recorded on Form 18526: Concomitant Medications. New medications are those that were started after the last evaluation. Ongoing medications are those that were reported at the last evaluation and continued to the current evaluation. All blood products are entered on Form 18527: Blood Products.

Guidelines for concurrent medications and treatments:

- Medications for drug withdrawal (i.e., phenobarbital, chlorpromazine, tincture of opium, paregoric, valium) are permissible.
- Infants may receive all medications/treatments as medically indicated for the medical management of an HIV-exposed infant (i.e., hepatitis B vaccine, syphilis treatment, PCP prophylaxis).
- Antiretroviral therapy is NOT permitted after the initial 6 weeks of ZDV unless the infant satisfies the study endpoint criterion for definitive HIV infection.
- Drugs that are metabolized by hepatic glucuronidation may alter the ZDV metabolism and should be used with caution. Acetaminophen is allowed.
- Infants should be immunized according to current recommendations of the Immunization Practices Advisory Committee.

6.7.9 Form 18527: Blood Products

This form is completed at each study visit and reports the administration of any blood products.

6.8 Clinical Abnormalities

6.8.1 Form 18528: Signs/Symptoms

Complete this form at each study visit and report only those signs and symptoms that are not associated with a diagnosis recorded on the Diagnoses form. This form should reflect abnormalities that are recorded on Form 18522: Physical Exam and Form 18515: HIV Assessment (Pediatric).

Any signs or symptoms related to protocol treatment, HIV and protocol treatment, or those signs/symptoms that you are unable to judge the relationship to protocol treatment must also be recorded on Form 18540: Toxicity/Adverse Experience Report.

6.8.2 Form 18529: Diagnoses

This form should be completed at each study visit and should reflect abnormalities reported on Form 18522: Physical Exam or Form 18515: HIV Assessment (Pediatric).

Any diagnosis thought to be related to protocol treatment must also be recorded on Form 18540: Toxicity/Adverse Experience Report.

6.9 Laboratory Evaluations

The schedule of laboratory evaluations required at each study visit is also displayed in Appendix II: Schedule of Evaluations: Infants. Appendix XVI: Specimen Collection, Processing, and Storage Procedures contains the laboratory procedures for obtaining, processing, storing and analyzing blood specimens required by the protocol. Appendix XVI is located in the protocol and in every Virology Tracking Notebook.

Note: The day that the study visit is scheduled may be contingent upon laboratory shipping and processing guidelines provided by the site's designated laboratory. Sites that will be sending specimens to Quest Diagnostics should note that Quest Diagnostics will receive specimens Tuesday through Friday except for national holidays. The

specimens should be shipped Monday through Thursday. It is important to keep this in mind if clinic patients are routinely seen on Fridays. Other ACTG approved laboratories may have similar restrictions. An arrangement for receipt, processing, and temporary storage of all (prenatal, intrapartum, neonatal, and post delivery) laboratory specimens must be made with ACTG approved laboratories prior to the initiation of this study. Receipt of specimens on the weekend related to labor and delivery must be arranged with Quest Diagnostics.

6.9.1 Form 18530: Hematology

A CBC with differential and platelet count are required at birth* (study visit 1) from newborn blood, and at study visits 2, 3, 4, 5, and 8. The differential (machine is preferred) should consist of polys, bands, lymphocytes, monocytes, eosinophils, basophils, and atypical lymphocytes.

***Note: The CBC specimen may NOT be obtained from cord blood.**

As noted in Table 4 of Appendix XVI: Specimen Collection, Processing, and Storage Procedures, the CBC is to be processed at the site's local lab, unless a specimen is obtained for lymphocyte subsets, in which case, both the CBC and lymphocyte subset specimens will be processed at the ACTG flow cytometry lab affiliated with the site.

NICHD sites will send the specimens for CBC with differential and lymphocyte subset analysis to Quest Diagnostics. Arrangements must be made with Quest Diagnostics for those deliveries that occur on weekends or holidays. NIAID sites will send the specimens to their designated ACTG certified flow cytometry laboratory. When the specimens have been processed at a flow cytometry lab, the results of the lab tests will be sent to the site. Results of CBCs should be received in a timely manner in order to assess for toxicities.

6.9.2 Form 18531: Chemistries, LFT's

Evaluation of SGOT and SGPT is required at birth*, and at study visits 3 and 4. They are processed at the site's local lab, and the results of the SGOT and SGPT are recorded on Form 18531: Chemistries/LFTs.

***Note: The birth specimen for SGOT and SGPT may be obtained from cord blood. If the specimen is not obtained from cord blood, a newborn specimen must be drawn.**

6.9.3 Form 18532: Immunologic Studies/Lymphocyte Subsets

Lymphocyte subsets include total and percent CD3, CD4, CD8, CD19, and CD4/CD8 ratio and are required at study visits 4, 5, and 8. NICHD sites will send the specimens for CBC with differential and lymphocyte subset analysis to Quest Diagnostics. NIAID sites will send the specimens to their designated ACTG certified flow cytometry laboratory. When the specimens have been processed at a flow cytometry lab, the results of the lab tests will be sent to the site.

6.9.4 EIA and Confirmatory Test

Form 18533: Serology

An EIA is required at study visit 11 and 20. A Western Blot or an appropriate confirmatory test must be obtained if the EIA is positive. These specimens are processed at the site's local lab. Results are recorded on Form 18533: Serology.

Note: A confirmatory HIV quantitative culture must be performed at an ACTG certified virology laboratory to confirm a previous study-related positive HIV quantitative culture, or, at ≥ 15 months, a positive EIA/WB in an infant with no previous positive culture. See Appendix XVI (Section C.2.C *Confirmatory Culture*) for further instructions for confirmatory culture collection.

6.9.5 Virology Assays

At site registration, each study coordinator will be sent three mother/infant sets of Virology Specimen Tracking notebooks. A set consists of a Virology Specimen Tracking notebook for both the mother and the infant. Each notebook is divided by study visit. Within each study visit are study specific bar code labels, located in brown envelopes, and Specimen Tracking Forms. **Use the same Virology Specimen Tracking notebook set for a mother/infant pair for the entire study.**

The specimen collection schedules and procedures are outlined in Appendix XVI: Specimen Collection, Processing and Storage Procedures. All of the virology specimens will be collected in yellow top (ACD) tubes in 2.6 ml or 8.5 ml draw volumes. Prior to specimen collection, all yellow top tubes must be labeled with the PID/SID numbers, date and time of collection.

Study visit-specific, pre-printed bar code labels are provided in Virology Specimen Tracking notebooks for labeling the aliquots derived from processing the yellow top tubes. If a yellow top tube is sent to an off-site ACTG certified virology laboratory for processing, the bar code labels for the aliquots obtained from processing the yellow top tube must accompany the specimen to the lab. When an on-site ACTG certified laboratory prepares aliquots from the yellow top tubes, each of the aliquots must be labeled with a barcode label before it is stored and shipped monthly to McKesson Bioservices, the central repository.

6.9.6 Form 18534: Specimen Tracking

A Specimen Tracking Form, (Form 18534), must be completed for all study visits which include virology yellow top ACD tube draws. The tracking form links the specimen to the patient and collects information on the processing of the specimen. A study visit specific, pre-printed Specimen Tracking Form barcode label must be affixed to the tracking form. The specimen source ID (the last 3 digits on the top number of the barcode) on the pre-printed

tracking form barcode label should be identical to the specimen source ID on the pre-printed barcode label for the specimen.

If all the virology yellow top tubes for one study visit are processed in one laboratory, only one Specimen Tracking Form is needed. If, for a study visit, the virology specimens are processed in two different laboratories, each set of specimens must have a Specimen Tracking Form accompany it to the laboratory, therefore two Specimen Tracking Forms are needed.

6.9.7 HIV Quantitative Culture

An HIV quantitative culture is required at study visits 1 (cord blood unacceptable), 4, 8, 10 and for confirmatory culture. The HIV quantitative cultures are processed at a certified ACTG virology lab. Each site must arrange for the lab to send hard copy results of the culture back to the site. Place a copy of this lab report in the CRF notebook for source documentation.

If the culture is positive, the laboratory will save and freeze isolates. These isolates will be shipped monthly to McKesson Bioservices, the central repository. If the culture is positive, a confirmatory HIV quantitative culture must be performed.

Once a child has demonstrated a confirmed positive HIV culture, the study endpoint has been reached.

6.9.8 Cell/Plasma Storage

Cell/Plasma storage is required at study visits 1 (cord & infant blood), 3, 4, 5, 6, 8, 10, 11 and for confirmatory culture visits. The aliquots will be stored frozen and shipped monthly to McKesson Bioservices, the central repository.

6.10 Form 18535: Patient Progress Note

At each study visit this form is used to record any pertinent information regarding the patient's progress. It should be filed in the CRF Notebook.

Do not send this form to Westat.

6.11 Missed Visit

Form 18536: Missed Visit

If an infant does not keep an appointment for a visit during the window periods, the visit will be considered a missed visit. NICHD sites should contact their Westat study manager for guidance if the visit missed included procedures that are only performed occasionally (i.e., lymphocyte subsets). NIAID sites should contact Jean Whitehouse via E-mail.

If the supply of study medication is depleted because the child has missed a scheduled visit, a new supply of study drug may not be dispensed until laboratory safety tests are performed (i.e., hematology, chemistry).

Form 18520: Patient Status should be completed and sent with Form 18536: Missed Visit.

6.12 Management of Toxicities

Reminder: Elevated MCV will not be considered a reportable adverse event in infants.

6.12.1 HIVIG/IVIG Toxicity Management

Usually, adverse reactions to HIVIG/IVIG are directly related to the rate at which the drug is infused. Reactions are usually mild, although rarely, serious symptoms may

develop. See Appendix XI: Guidelines for Toxicity Management of HIVIG/IVIG: Infant, for a list of expected adverse events which may be related to the HIVIG/IVIG infusion. The events are categorized as: Level 1 - mild, Level II - moderate, Level III - severe. This chart should be used as a guide for clinically managing adverse events during the infusion of HIVIG/IVIG and should not be confused with Appendix XIII: Recommendations for Grading of Acute and Subacute Toxic Effects: Children, which assigns grades for reporting adverse events to the Adverse Event Reporting Office at Westat.

6.12.2 Criteria for HIVIG/IVIG Discontinuation

The following reasons warrant permanent discontinuation of the newborn HIVIG/IVIG therapy:

- Severe allergic reaction to the infusion such as exfoliative erythroderma, anaphylaxis, or vascular collapse or a clinical condition which the on-site pediatrician believes is incompatible with life.
- At the request of the parent or guardian, pediatrician, investigator, Food and Drug Administration, pharmaceutical company or IND sponsor.

6.12.3 ZDV Toxicity Management

The administration of ZDV will remain constant during the 6 weeks of therapy, unless the infant develops a toxicity that warrants permanent discontinuation. There are no dose reduction schedules for ZDV.

Form 18537: Permanent Discontinuation of Protocol Treatment should be completed when a patient is permanently discontinued from protocol drug treatment prior to completion of the treatment period.

6.12.4 Criteria for ZDV Discontinuation

ZDV therapy will be discontinued during the six-week course for any of the following reasons:

- An immediate life-threatening or clinical condition which the on-site pediatrician believes is incompatible with life.
- Infants with the following laboratory values which have been repeated to assure validity:
  - ANC < 750/mm^3,
  - Hemoglobin < 8.0 gm/dl (transfusions are allowed),
  - Platelets < 50,000/mm^3,
  - Hyperbilirubinemia requiring exchange transfusion (does not include phototherapy),
  - SGPT > 5 X upper limit of age-adjusted normal.
- Grade III toxicity (as detailed in Appendix XIII: Recommendations for Grading of Acute and Subacute Toxic Effects: Children other than the defined laboratory values noted above. Elevated MCV will not be considered a reportable adverse event.
- Severe allergic reaction such as exfoliative erythroderma, anaphylaxis, or vascular collapse.
- At the request of the parent, legal guardian, investigator, Food and Drug Administration, pharmaceutical company, or IND sponsor.

6.12.5 Form 18537: Permanent Discontinuation of Protocol Treatment

Form 18537: Permanent Discontinuation of Protocol Treatment is to be completed when an infant permanently discontinues protocol drug treatment (HIVIG/IVIG and ZDV). This form must be completed at study visit 4.

6.13 Off Study

A child is considered off study when contact is terminated prior to completion of the protocol required period of observation. These circumstances include:

- Death,

- Parent/Legal guardian refuses all further contact,
- Unable to contact parent/legal guardian after repeated attempts, or
- Inadvertent enrollment.

6.13.1 Form 18538: Off Study

Form 18538: Off Study is completed when an infant is permanently discontinued from all study followup. This form must be completed at study visit 20.

6.13.2 Form 18539: Cause of Death

If a child dies while on study, the center must contact Westat within 24 hours so that the Division of AIDS and the FDA may be notified of the death. Form 18539: Cause of Death must be completed and sent to Westat as soon as possible. A Toxicity/Adverse Experience Report Form 18540 must be completed in the event the child dies while on study therapy or within 3 months of going off study. In the event a child dies after going off study, all required forms should be completed with the study visit recorded as "95."

Form 18540: Toxicity/Adverse Experience Report

Refer to Chapter 7 Managing Toxicities/Adverse Experiences: Women and Infants.

6.14 Virology Cultures

6.14.1 Form 18543: Virology Culture Report

Complete this form for all positive ACTG 185 study related HIV quantitative cultures and for all confirmatory cultures.

6.14.2 Form 18544: Unscheduled Virology Tests

Form 18544: Unscheduled Virology Test must be completed whenever virology testing occurs outside of the protocol prescribed study visit schedule. If a positive HIV culture is obtained for clinical or laboratory suspicion of HIV by a non-ACTG certified laboratory, the results must be confirmed by an ACTG certified laboratory. All virology culture results, including confirmatory culture results obtained from the ACTG certified laboratory, must be submitted on Form 18543: Virology Culture Report. To report virology testing after going off study (to confirm HIV status), complete Form 18544: Unscheduled Virology Test with the study visit recorded as "95."

6.15 Form 18553: Clinical Case Review Form

This optional form is used to record confounding co-morbidities, laboratory abnormalities, or inconsistent data which require further explanation.

7. MANAGING TOXICITIES/ADVERSE EXPERIENCES: WOMEN AND INFANTS

Adverse experiences are expected or unexpected untoward events that occur during the course of the study. For this protocol, the rating used for clinical management of the study drug is NOT the same as that used for adverse event reporting. Appendix XII: Table for Grading Severity of Adverse Experiences: Women, is used to determine the grade of an adverse event for reporting purposes for women. Appendix XIII: Recommendations for Grading of Acute and Subacute Toxic Effects: Children, is used to determine the grade of an adverse event for reporting purposes for infants. The reporting procedures required for specific grades are outlined in Section 7.2.

7.1 Toxicities/Adverse Experience Reporting Requirements

- The prompt reporting of toxicities/adverse experiences to the Westat AER coordinator is the responsibility of each investigator.
- All toxicities/adverse experiences (regardless of grade) for infants are reported on Form 18540: Toxicity/Adverse Experience Report. Toxicities of grades 2-5 are reported on Form 18540: Toxicity/Adverse Experience Report for the mothers.
- Form 18540 is required through study visit 12 for a woman and at study visits 1 through 6 for the infant.
- Elevated MCV in an infant will not be considered a reportable adverse event.
- All deaths while on study, regardless of association with study drug(s), must be reported on Form 18540: Toxicity/Adverse Experience Report.
- For patients off drug:

  a. Report deaths that occur within 3 months of going off study. If there is any possibility that the study therapy may have contributed to the patient's death, notify by phone, within 24 hours;

  b. Report other toxicities/adverse experiences which occur within 8 weeks and meet the reporting requirements noted in Section 7.2.

- All overdoses must be reported regardless of outcome, even if toxic effects were not observed.

- If a toxicity/adverse event resolves or improves to a non-reportable level, and then recurs, another report is required.

- **Intercurrent illnesses** are illnesses (except deaths) that are DEFINITELY NOT related to study drug and are otherwise documented in the CRF and the patient's record; they should not be reported on Form 18540.

- **Progression of disease** that is DEFINITELY NOT related to drug treatment is not an adverse experience, and should not be reported on Form 18540.

- Form 18540 should NOT be completed for patients **hospitalized**, unless the hospitalization is a result of the adverse event.

- In addition to the required Form 18540, the routine, required case report forms should be completed, whether the adverse experience is noted during a routine scheduled visit or as part of an unscheduled visit.

- Adverse experiences should always be reported to the Institutional Review Board.

- Investigators may be asked to provide additional information if necessary. Continued failure to report adverse experiences in a timely and accurate manner, or failure to supply information requested regarding particular adverse experiences, may result in suspension of the investigator's clinical research privileges in this study.

- If a health care worker experiences an adverse event related to the administration or handling of study therapy, it should be reported on the AER form for health care workers (Form HCW-AER) and submitted to the AER coordinator at Westat.

- When amended or additional information needs to be included in a form already sent to Westat, a duplicate form should be sent with "update" written at the top and the new data highlighted.

- All AER (18540) forms must be signed by the physician. The physician is the only person who should determine the relationship of the adverse event to study treatment.

7.2 Toxicity/Adverse Experience Reporting Requirements for Clinical Sites

Expected		**WOMEN**
Grade 2		Send Form 18540 with CRFs for specific study visit
Grade 3		Send Form 18540 with CRFs for specific study visit
Grade 4:	not immediately life-threatening	Send Form 18540 within five days
Grade 4 & 5:	immediately life-threatening	*Deaths and immediately life-threatening events which could possibly be related to study drug use, must be reported by phone (1-800-825-4844) within 24 hours and Form 18540 sent within 3 days.
Unexpected		
Grade 2		Send Form 18540 with CRFs for specific study visit
Grade 3		Send Form 18540 within 5 days.
Grade 4 & 5		*Deaths and immediately life-threatening events which could possibly be related to study drug use, must be reported by phone (1-800-825-4844) within 24 hours and Form 18540 sent within 3 days.
Expected		**INFANTS**
Grade 1 and 2		Send Form 18540 with CRFs for specific study visit
Grade 3		Send Form 18540 within five days
Grade 4:	not immediately life-threatening	Send Form 18540 within five days
Grade 4 & 5:	immediately life-threatening	*Deaths and immediately life-threatening events which could possibly be related to study drug use, must be reported by phone (1-800-825-4844) within 24 hours and Form 18540 sent within 3 days.

Unexpected Grade 1 and 2	**INFANTS** Send Form 18540 with CRFs for specific study visit.
Grade 3	Send Form 18540 within five days.
Grade 4 & 5	*Deaths and immediately life threatening events which could possibly be related to study drug use, must be reported by phone (1-800-825-4844) within 24 hours and Form 18540 sent within 3 days.
For patients off study:	Report on AER form, deaths which occur within 3 months of going off study. If there is any possibility that the study therapy may have contributed to the patient's death, notify by phone, within 24 hours. In the header information code visit "95" for off study
For patients off study drug:	Report other adverse experiences/toxicities which occur within 8 weeks and meet reporting requirements. Any adverse experiences/toxicities which occur after 8 weeks off study drug which could possibly be related to study drug, should be reported.

All overdoses must be reported irrespective of outcome, even if toxic effects were not observed. An AER report must be sent within 5 days for all congenital anomalies, regardless of grade.

Toxicity/Adverse Experience Reports which are not mailed with routine required CRFs for a given study visit should be mailed to:

Adverse Experience Report: WB 427
Westat, Inc.
1650 Research Boulevard
Rockville, Maryland 20850

7.3 Telephone Reporting for Adverse Experiences

Grade 5 events and immediately life threatening grade 4 events (expected and unexpected) for adults and infants must be reported by telephone (to the AER coordinator at Westat) within 24 hours of identification of the event.

All telephone reports must be left on the AER Hotline number **(1-800-825-4844)**. Reports will be recorded. The AER office will contact the individual making the report if additional information is required. Information needed for a phone report include:

- Date and time of report
- Clinical site
- Protocol number
- Patient and study identification number
- Description and grade level of event
- Date of onset of event
- Current status of patient
- Medications and dose at time of event
- Current management of study therapy
- Relationship to study therapy (none, possible, definite)
- Name and phone number of person reporting the event.

An AER form must be completed and submitted to Westat within 3 days of identification of the event. Include all relevant CRFs including Signs/Symptoms, Diagnosis, Laboratory, and Concomitant Medication forms.

8. PHARMACOKINETICS STUDY FOR SELECTED SITES

A Pharmacokinetics (PK) Study, nested in ACTG Protocol 185, will be conducted at nine selected sites. PK sampling will be performed on up to 50 mother-infant pairs first enrolled in the study. Each woman should receive at least 3 infusions prior to delivery. It is anticipated that both the woman and her infant will enroll in the PK study. However, an infant whose mother was not involved in the PK study is permitted to enroll with the parent/guardian's consent. An informed consent form specific for the Pharmacokinetics Study must be signed by all participating women. The father's written informed consent must also be obtained if he is reasonably available. If the father is not available, a note must be made in the medical record. The infant can then be enrolled in the study.

Evaluation of the pharmacokinetics of serum and plasma samples will consist of quantitative measurements of p24 antibodies, immunoglobulins, and antibody to a non-HIV antigen (i.e., rubella or CMV). All of the samples will be coded, and investigators will be blinded as to the treatment that the patient received. The serum pharmacokinetics sample analysis will be performed after each infusion draw series (baseline or 1 hour through 28 day post infusion draw). The samples will be sent to McKesson Bioservices Repository for processing. The real time serum analysis will be done at Quest Diagnostics. The plasma specimens will be frozen and saved for future assays of antiviral activity. Data analysis will be coordinated by the National Heart, Lung and Blood Institute (NHLBI), Westat, and the University of Minnesota.

HIVIG Pharmacokinetics (Appendix VII of the protocol) outlines the schedule of the PK serum and plasma sampling for both the woman and the infant, and includes the requirements for laboratory processing at the site.

All PK specimens must be obtained by peripheral venipuncture in a serum separator tube (SST) with polymer gel and silica activator (red-gray top tube for serum specimens), and in a acid-citrate-dextrose (ACD) anticoagulant (yellow top) tube for plasma specimens. Every attempt to collect the specified volume at the stated time should be made.

Information collected during the PK Study is recorded on Form 18523: Pharmacokinetics Study for each draw and then sent to Westat in a separate mailing. See Instructions for Completing Form 18523: Pharmacokinetic Study.

8.1 Pharmacokinetic Supplies

The following supplies will be provided to participating sites by McKesson Bioservices:

- Preprinted specimen sample bar code labels;
- Specimen collection tubes (red-gray and yellow top tubes);
- Sterile polypropylene 1.5 ml vials for transporting refrigerated serum specimens;
- Sterile 1.5 ml freezer vials for transporting frozen plasma specimens;
- Shipping supplies;
- Shipping labels; and
- Shipping containers.

All sites participating in the PK study will initially receive adequate supplies and shipping containers for two mother-infant pairs. Shipping containers will be returned to the site to be reused. Contact Steve Lindenfelser of McKesson Bioservices at (301) 340-1620 or FAX # (301) 340-9245 for any questions related to the supplies or shipping for the PK Study.

8.2 Shipping Instruction

All PK samples will be shipped to McKesson Bioservices Corporation. All refrigerated serum specimens must be shipped within 24 hours of collection. All frozen plasma specimens related to an infusion should be processed and stored until the 28 day post infusion specimen is frozen. All plasma specimens obtained for a given infusion must be shipped monthly to the repository.

Ship all PK specimens using an overnight commercial courier to:

Attention: Steve Lindenfelser
McKesson Bioservices Corp.
685 Lofstrand Lane
Rockville, MD 20850

Prior to shipping refrigerated serum specimens, contact Steve Lindenfelser at (301) 340-1620 to inform him of the anticipated receipt date and time. Prior to shipping frozen plasma specimens, FAX a copy of Form 18542: Shipping and Receipt to Steve Lindenfelser FAX # (301) 340-9245.

The guideline for the packaging requirements and shipping etiologic agents are described in Appendix XVIII: Regulations for Shipping Etiologic Agents - Completing the Dangerous Goods Airbill (Federal Express), located in the protocol.

8.3 PK Collection Guidelines

The patient's weight (women in kilograms and infants in grams) must be obtained each time a PK specimen is obtained, except when 2 scheduled draws occur on the same day (i.e., at baseline and 1 hour post infusion, or 28 day post infusion and 1 hour post infusion).

An outline of the scheduled PK specimens to be collected for an infusion for a woman and an infant is located in Appendix VII: HIVIG Pharmacokinetics and Section 13.0 Pharmacokinetic Study of the protocol.

9. TRANSFER OF PATIENTS

Patients may wish to relocate while participating in the ACTG 185 study. The transfer may be a "permanent" transfer in which the patient moves from one locale to another or a "brief" transfer in which a patient temporarily relocates in another area (vacation) or goes to another ACTU for a specific visit such as labor and delivery. It is expected that these patients will remain on study and receive uninterrupted study drug treatment and medical attention during these circumstances. The following transfer procedures are to be used for all patients to provide continuity for the patient in the study. The procedures are the DAIDS policies and procedures for the adult and pediatric ACTG with specific Westat information inserted for contact personnel and Westat Transfer Information Protocol 185 Form.

Permanent or temporary transfers require that the receiving site have IRB approval for Protocol ACTG 185 and the informed consent document. The receiving site must be site-registered for conducting ACTG 185.

9.1 Initiation of Permanent Transfer

The originating ACTU contacts the ACTU where the patient requests to go. The ACTU of origin determines from the potential receiving unit (1) whether it is conducting the protocols in which the patient is enrolled, and (2) that it is willing to accept the patient. If an ACTU site is not known in a particular geographic location, please contact the study manager at Westat by E-mail or by telephone to determine a potential receiving ACTU for transfer.

NOTE: A patient cannot transfer to an ACTU that does not conduct ACTG 185.

Once the proposed receiving ACTU agrees to accept the patient, the originating ACTU should take the following steps:

- Receive written confirmation from the receiving ACTU that it is participating in protocol 185 and willing to accept the patient.
- Notify the Study Team via E-mail (ACTG.Team185@Karloff.fstrf.org) at least 14 days in advance of the transfer.

- Complete the following checklist information and send it to the receiving ACTU and Study Team via E-mail.

  Patient related information:

  a. PID/SID numbers

  b. Originating ACTU site number

  c. Receiving ACTU site number

  d. Reason for transfer request

  e. Name of contact person at the originating ACTU who requested the transfer

  f. Name of person who agreed to accept patient at the receiving ACTU

  g. Brief medical history

  h. Name of the original pharmacist and the date the receiving pharmacist was contacted by him/her.

  Study-related Information

  a. Date of registration/randomization

  b. Date of initiation of study therapy

  c. Study drug status and dose, and any dose reductions

  d. Brief protocol history:

     1. HIV status

     2. Toxicities

     3. Compliance on protocol

     4. Disease progression

     5. Estimated date of confinement (prenatal)

  e. Date of the last scheduled study visit and study visit number at the originating clinic, and expected date and study visit number at the receiving clinic including time (if appropriate), address of the clinic, and contact. Indicate if the patient or the originating site will be scheduling the appointment with the receiving site.

The Westat Data Manager will supply information to the originating and receiving ACTUs regarding current delinquencies, outstanding edit failures, and queries for the patient. All problems with data collected at the originating site must be resolved by the originating site.

9.2 Implementation of the Transfer

The following steps should be taken only after the originating ACTU site has supplied all the required information and the receiving site has agreed to accept the patient.

The originating site should:

- Complete and send to Westat all original completed Case Report Forms up to and including the last visit.
- Verify, clarify, and/or rectify any pending problems with data corrections or edits before the transfer occurs.
- Photocopy all CRFs to retain a copy for the originating ACTU site's records and send a copy to the receiving ACTU site. Send copies of all pertinent source document records to the receiving ACTU site, such as Elisa, Western Blot, medical history, etc.
- Send the original Case Report Form notebook and original Virology notebooks by Federal Express to the receiving ACTU contact person who will be responsible for the patient when the transfer to the new ACTU is complete.
- Complete the Westat Patient Transfer Information Protocol 185 Form and forward it to the Westat Data Manager: Dennis DeRycke, Fax: (301) 517-4188.
- Request the originating site's pharmacist to:

  a. Contact the pharmacist at the receiving site and discuss the patient's protocol and drug history.

  b. Send the following information by confidential mailing to the receiving pharmacist:

     1) Patient's PID/SID number

     2) Patient's current week on study.

3) Last date and amount of drug received by patient.

4) Copy of the pharmacist's Prescription List page that includes patient's SID and treatment assignment.

5) Date and time of patient's appointment at the receiving ACTU

c. If a patient is still receiving study drug, notify the Westat Pharmacist of the transfer. The pharmacist is Ann Wolters, telephone: (301) 738-8342.

- Provide patient with the name and address of the receiving ACTU site, date and time for the first appointment, and the contact person at the new site.

The receiving site should:

- Review the materials (completed CRFs, CRF notebook, and Virology notebook) to determine completeness. Request clarification from the originating site if there are any problems. The receiving ACTU site may reschedule the patient visit if the requested documentation from the originating site is incomplete.

- Notify the originating ACTU site when it receives the required documentation. The Study Coordinator should also notify Westat of the first appointment at the receiving site.

9.3 Conclusion of the Transfer

ORIGINAL SITES WILL BE REQUESTED TO RESOLVE DATA COLLECTION PROBLEMS FOR VISITS WHICH OCCURRED AT THE SITE.

- When all outstanding corrections and delinquencies have been forwarded to Westat, the originating ACTU site should notify the receiving site and the Westat Data Manager via E-mail (DeRycke.Dennis).

- The receiving ACTU site shall have the patient SIGN the pertinent consent form approved by the receiving site's IRB.

- Once the patient has been seen at the new ACTU, the receiving site protocol nurse or Study Coordinator must notify the Westat Data Manager via E-mail of the date of the visit so the current site status change can be made to the database. This action transfers responsibility for followup from the originating site to the receiving site. The Westat Data Manager will notify SDAC of the patient transfer via E-mail.

a. If the patient does not continue care at the new ACTU site (does not keep appointments(s)), the originating site will retain responsibility for the attempted followup and complete the forms to remove the patient from the study.

b. If the patient does not keep the appointment(s) at the new ACTU site, the receiving site should return the CRF and Virology notebooks by registered mail to the originating ACTU site and notify the Westat Study Manager.

- If the patient transfers again, or returns to the original ACTU site, this procedure must be repeated.

9.4 Unscheduled Transfer of a Patient

If a patient arrives at an ACTU site without prior notice, the receiving site should alert the originating ACTU site and the Study Team. The originating site will be requested by Westat Data Manager to initiate the transfer process as previously described.

9.5 Brief (Temporary) Transfer of a Patient

A brief transfer is one in which the patient will be away from the originating ACTU site for no more than two scheduled visits and less than six months, Examples would include patient transfer relating to vacation or transferring to a subunit for labor and delivery.

- The originating ACTU site will contact the closest ACTU to the patient's new destination and arrange for the patient to receive the prescribed medical care and laboratory tests.

- The originating ACTU site will provide a packet of information containing CRFs for the transfer visits, barcodes for virology tests and a request (signed by the study physician) for any laboratory tests required during the transfer period. The CRF will not be photocopied or sent to the receiving site.

- The receiving ACTU site will send all laboratory test results back to the originating ACTU site.

- The pharmacist at the originating ACTU will issue the appropriate drug supply for the period of transfer. This period is not to exceed what would be required for the interval surrounding no more than two scheduled visits and not to exceed a six-month supply. The pharmacist at the originating ACTU

site will contact the pharmacist at the receiving ACTU to discuss receipt and administration of study drug. The receiving site, when necessary, will modify the patient's dosage according to protocol requirements. If drug is needed other than what has been supplied, the receiving site will contact the pharmacist at the original site and the study drug will be sent from the original site's pharmacy to the receiving site's pharmacy. For any study drug infusions, the pharmacist at the receiving ACTU will send the completed pharmacy forms to Westat c/o Ann Wolters, WB 427, 1650 Research Boulevard, Rockville, Maryland 20850, Fax number (301) 517-4188. A copy of the documentation of study drug ordered, dispensed, and given at the brief transfer site must be sent to the original pharmacist for their accountability records.

- The originating ACTU site will be responsible for contacting personnel at the brief transfer site about obtaining all the clinical/laboratory evaluation requirements for the visit(s) conducted during the brief transfer.

9.6 Transfer to a Non-ACTU Site

The procedure for permanent or brief transfer does not apply to patients transferring to a non-ACTU site. Investigational drugs MAY NOT be shipped to a non-ACTU site without prior approval from the sponsor, NHLBI.

If a patient experiences labor and delivery at a non-ACTU unit and returns for followup care to the original ACTU site, obtain a copy of the medical chart to complete the appropriate case report forms. All case report forms for the L&D visit will use the original ACTU site as the institutional code for data forms. Notify Westat if L&D occurs at a non-ACTU site.

Exhibit 9-1. Transfer Information

PROTOCOL 185 FORM

PLEASE FILL OUT THE FOLLOWING INFORMATION WHEN REPORTING A TRANSFER TO DENNIS DERYCKE. THIS INFORMATION IS NEEDED IN THE DATABASE BEFORE FORMS CAN BE ENTERED, AND FOR THE DELINQUENCY CHECK.

Protocol: _____ PID #: _____ SID #: _____

Old Subunit	Last Visit Old Subunit Date	Study Visit	New Subunit	First Visit New Subunit Date	Study Visit
_____	_____	_____	_____	_____	_____

FAX

TO: Dennis DeRycke
Westat Data Manager ACTG 185
WB 427

FAX: (301) 517-4188

FROM: _____

_____

_____

TELEPHONE: _____

10. DAIDS POLICIES AND PROCEDURES FOR ACTG LOST-TO-FOLLOW-UP (LFU) GUIDELINES AND STANDARD OPERATING PROCEDURES

ACTG 185

Retention: A patient's successful completion of the protocol-defined period of observation, by not becoming lost-to-follow-up or prematurely self withdrawing from study medications. (For ACTG 185, this would include the study required visits as treatment is for a limited period in the protocol.)

Missed Visits: A patient's failure to appear for a scheduled protocol-directed visit. A missed visit should be recorded in a source document and entered in the database if a patient is not seen at the ACTU for a scheduled protocol visit and if more than 50% of the time has elapsed between this visit and the next scheduled visit.

Non-compliance: Patients are considered non-compliant if protocol visits or evaluations are chronically or frequently misses and/or the patient is not compliant with study medications (does not take a significant percent of medication) over an extended period of time as defined by the protocol.

Self-Withdrawal: Patient's refusal to continue with protocol and take study medication, relocation without transfer, and/or decision to seek alternative therapy.

Lost-to-follow-up (LFU): Patient's refusal to communicate with study staff in any context and the patient's lack of further participation in the study after repeated attempts. The site is unable to contact patient by phone, mail, primary care physician, next of kin, home visits, or emergency contact numbers after repeated attempts. Patients will be considered "confirmed LFU" when the Off-Study Form is entered into the database indicating that the patient is lost.

Phase II/III Study: Three consecutive missed visits have occurred or a period of 9 months has elapsed since any contact with the patient is considered to be LFU. This includes contact by telephone or information from another source.

ACTG 185 Patient Compliance: Women - compliance for HIVIG/IVIG infusions will be assessed by deviation from visit schedule. A deviation from the 28 day infusion visit schedule is permitted but not desirable. Infants - compliance for infant 6 week ZDV therapy will be assessed by return of all empty or unused medication bottles at each clinic visit. Windows of visits for infants: ± 1 day from the scheduled visit for week 1, ± 2 days for the week 2 visit; ± 1 week for visits at week 6 through 24, and ± 4 weeks for visits at week 36 through 78. The convention for the window period for visit completion for women (not specified in the protocol) is ± 2 weeks during the antepartum period, labor and delivery is not considered missed, ± 2 weeks at postpartum week 6 through 26, and ± 4 weeks at week 48 through 78.

11. CLOSURE TO ACCRUAL

On March 25, 1997 new enrollment and HIVIG/IVIG infusions were discontinued for ACTG 185.

The following recommendations made by the ACTG 185 Data and Safety Monitoring Board (DSMB) on March 21, 1997 were approved by the ACTG Pediatric Executive Committee on March 24, 1997:

- Discontinue new enrollment to ACTG 185.
- Unblind study participants to their randomized treatment assignments.
- Continue to provide intrapartum and newborn zidovudine study treatment to all enrolled patients.
- Discontinue further HIVIG or IVIG infusions for all currently enrolled women and infants.
- Continue study follow-up of all enrolled patients according to the current ACTG 185 protocol schedule of evaluations.
- Provide extended follow-up of all women and infants enrolled in ACTG 185 beyond the 18-month duration of protocol follow-up. Infants should be followed through enrollment into ACTG 219, and a mechanism for extended follow-up of women should be identified.

The following steps were taken for all patients who are participating or have participated in this study.

A. PATIENT MANAGEMENT

All patients who are currently enrolled in this study were contacted by the Principal Investigator and arranged for an appointment to discuss the results of this study with their physicians.

For patients who have completed follow-up, every effort should have been made to contact them and share with them the preliminary results of the first ACTG 185 efficacy analysis.

An "unblinding" list of patient treatment assignments was sent by the ACTG 185 coordinating center at Westat to the Study Coordinator and Principal Investigators. This was available on Wednesday, March 26, 1997, and was sent by express mail to the Study Coordinator at all participating units. The Study Coordinator shared this list with the Site Pharmacist. The HIVIG/IVIG treatment assignments for all subjects were unblinded.

All currently enrolled patients should continue to receive intrapartum maternal intravenous zidovudine study treatment and newborn oral zidovudine study treatment according to the protocol.

After discussion of the new information provided in the accompanying documents, patients currently on study who have not completed their course of study immunoglobulin were informed that they will not receive further maternal or infant infusions of HIVIG or IVIG as part of the study.

All currently enrolled patients were informed that, with their continuing consent, their ongoing study follow-up will continue according to the current protocol schedule of evaluations until 18 months postpartum in women and 18 months of age in infants.

B. PATIENT FOLLOW-UP

Women will continue to be followed according to the schedule of evaluations outlined in the current protocol (monthly during pregnancy, at labor and delivery, and at 6, 12, 26, 48, and 78 weeks postpartum). Infants will be followed according to the schedule of evaluations outlined in the protocol, until 18 months of age.

Coenrollment of infants into ACTG 219 ("Pediatric Late Outcomes Protocol"), should be strongly encouraged.

C. CASE REPORT FORM INSTRUCTIONS

Use the ACTG 185 Form 18535 (Patient Progress Note) to document efforts at patient notification, discussion with patient of new information from the preliminary first efficacy analysis, continuing consent for ongoing study follow-up and continuation of maternal intrapartum and newborn study ZDV according to the current protocol. For patients who have not completed their study HIVIG/IVIG treatment document patient understanding regarding discontinuation of study HIVIG/IVIG.

For patients who have not already completed their full course of study HIVIG or IVIG, continue to complete the Infusion Record (HIVIG/IVIG) Form 18525 for all scheduled HIVIG/IVIG infusions (prenatal and newborn). Complete Question #1 of Form 18525 using the "2-no" response, and indicate the reason as "sponsor request". As before, complete Form 18537 (Permanent Discontinuation of Protocol Treatment) at Study Visit #10 (labor and delivery) for women and at Study Visit #4 (6 weeks) for infants. Complete Question #1 of Form 18537 for HIVIG/IVIG discontinuation using the code "08" (at the request of investigator/sponsor) response, and put in the date that HIVIG/IVIG was discontinued.

Note that intrapartum ZDV infusions for all enrolled women, and newborn ZDV for all infants from birth to six weeks, are still to be given according to the study protocol. Use zidovudine from the pharmacy's ACTG investigational drug supply, and complete all relevant study case report forms (e.g., Form 18524 [Infusion Record (IV ZDV) - Maternal], Form 18545 [Treatment Record (ZDV) - Infant]).

Please note also when completing Form 18540 (Toxicity/Adverse Experience Reporting) that particular attention must be paid to which study drug the toxicity is being attributed since HIVIG/IVIG will no longer be given to patients on study.

D. INSTRUCTION FOR PHARMACISTS

As a reminder of ACTG policy, the pharmacist cannot dispense any ACTG 185 study drug for purposes or situations other than those specified by the protocol.

1. Zidovudine (ZDV) Study Drug

   All women and infants will continue to receive ZDV as specified in the protocol, section 8.1.2, section 8.3.2 and section 8.3.4. Ordering, drug accountability, preparation, and dispensing of ZDV will be conducted according to the instructions in the protocol and per DAIDS Pharmacy Guidelines.

2. HIVIG/IVIG Study Drug

Dispensing and administration of HIVIG or IVIG was stopped as of 12:00 noon EST on Tuesday, March 25, 1997. Completed HIVIG/IVIG Pharmacy Records for all study subjects who have received HIVIG or IVIG study drugs should have been sent before April 30, 1997 to:

Ann Wolters, RPh
Westat, Inc.
WB 42F - Protocol 185
1650 Research Blvd.
Rockville, MD, 20850

All remaining HIVIG and IVIG study drug supplies for ACTG 185 should be returned to the repository following the guidelines for the return of investigational drug in the DAIDS Pharmacy Manual, Section III - 7,8. Additional information is contained in the Pharmacy Manual distributed to the pharmacist for ACTG 185. All HIVIG/IVIG glass bottles should be packed in such a way as to prevent breakage. Three to four ice packs can be included to keep the package cool but should NOT be in direct contact with the glass bottles, to prevent the liquid study drug from freezing. During the winter season, the bottles can be packed and shipped at room temperature.

E. SITE REGISTRATION

All sites conducting follow-up of ACTG 185 woman and infant patients must be site registered for version 5.0 of ACTG 185 to assure compliance with federal regulations for the conduct of clinical research studies.

F. IRB NOTIFICATION

All IRBs must be notified as soon as possible, that patient enrollment to ACTG 185 closed effective March 25, 1997. IRBs should also be told that the patients currently enrolled will continue to receive study zidovudine according to the protocol, and those patients who have not completed their course of study immunoglobulin will not receive further HIVIG or IVIG. Also, all patients will continue to be followed according to the current protocol schedule of evaluations (18 months postpartum for women and 18 months of age for infants).

The sample patient letters should also be submitted for IRB review before it is distributed. (Exhibits 11-1, 11-2, and 11-3.)

Exhibit 11-1. Sample patient letter for patient's currently on Study HIVIG/IVIG treatment

Note: Please review these model letters, modify as necessary, and use for your patients.

DATE: March 24, 1997
FROM: ACTG Protocol 185 Study Team
SUBJ: ACTG 185 Discontinuation of New Enrollment
TO: ACTG 185 Participants Currently On Study HIVIG/IVIG Treatment

Dear ACTG 185 Participant:

As you know, ACTG 185 was designed to see if HIV hyperimmune globulin (HIVIG), compared with standard intravenous immune globulin (IVIG), reduced transmission of HIV from women to their babies, when added to standard zidovudine (ZDV) preventive treatment. Another purpose of the study was to evaluate the safety of HIVIG when given to pregnant women and to their newborn babies. Information collected in this study has been checked by researchers regularly to look at the progress of the study. As a result of the most recent review of this information, it was decided not to enroll any more patients. Stopping enrollment does not mean that the study has stopped.

We would like to share with you several important reasons why we made the decision to stop adding new patients. At this time, information on up to 379 babies who had at least one test for HIV was reviewed to see how many became infected. Only 15 babies were identified as being HIV infected. The overall rate of HIV infection transmitted from mother to infant was very low, only about 5%, and was no different whether patients received HIVIG or IVIG. This rate is even lower than the 8% seen with ZDV in ACTG 076, where only women with milder or earlier HIV disease were studied, and it is much less than the 15% baseline rate that was projected when ACTG 185 was designed.

While it is a welcome finding, the cause of the decrease in the overall transmission rate is not known. In order to keep enrolling new patients to be able to answer the study question with the 800 women and babies that the study was designed for, the transmission rate now would need to be at least 7.5%. Since the rate of HIV transmission was much lower than expected, many more than 800 patients would be needed to answer the study's main question. Because this would take too long, it was decided to stop enrolling new patients. This means the study will not be able to say whether HIVIG reduces HIV transmission. However, there are still important questions about the safety of HIVIG, about factors involved in HIV transmission from mother to baby, and about early diagnosis of HIV in babies that the study can still try to answer. So patients who are already enrolled will be asked to continue on the study.

Exhibit 11-1. Sample patient letter for patient's currently on Study HIVIG/IVIG treatment (continued)

Both HIVIG and IVIG when given as used in the study seem to be fairly safe. Mothers and babies receiving HIVIG or IVIG have had very few side effects from the HIVIG or IVIG. The side effects that a few experienced included vomiting, chills, fever, pain, and/or shortness of breath while they were getting or shortly after they were given HIVIG or IVIG. Since HIVIG is an investigational drug, women and infants already enrolled on the study are strongly encouraged to continue follow-up to see whether there are any other side effects.

Your doctors and nurses will discuss the study results with you. It is recommended that you stay on the study ZDV treatment because it is part of an approved treatment for HIV infected pregnant women to reduce the risk of transmitting HIV to their babies. The ZDV study treatment included as part of the protocol (intravenous ZDV during labor and delivery for women and oral ZDV for 6 weeks for babies) will continue to be provided by the ACTG 185 study.

You will not receive further HIVIG or IVIG treatments for you or your baby as part of the study.

To continue to study the safety of the study drugs and to study other aspects of transmission of HIV infection to babies and methods for early diagnosis of HIV infection in babies, we ask that you continue all of your study visits and tests as outlined in the protocol. This means that you should return for all of your remaining visits (monthly during pregnancy, at labor and delivery, and then at 6 weeks, 12 weeks, 6 months, 12 months, and 18 months after delivery). Your infant should return for all scheduled study visits until 18 months of age. This will provide continuing care and will provide you with information about your health and the health and HIV status of your baby.

It is still not known what if any late side effects there may be for pregnant women and newborns taking the study medications (ZDV and HIVIG or IVIG). It is important for us to follow all ACTG 185 patients. If your baby is not already enrolled in ACTG 219 ("Pediatric Late Outcomes Protocol"), we encourage you to discuss that study with your baby's doctor or nurse. ACTG 219 is a study that will look for any side effects that might show up later in your child's life that might relate to any study treatments that you received while pregnant or that your baby received. Your child can be followed in ACTG 219 until age 21 years. We will continue to try to make sure that you receive the best available medical care and that continued follow-up will be available to you after you complete your participation in ACTG 185.

We would like to thank you for taking part in the ACTG 185 study and for helping us increase our understanding of how transmission of HIV from mother to infant can be prevented.

Sincerely,

E. Richard Stiehm, M.D., Protocol Chair
John S. Lambert, M.D., Protocol Chair
for the ACTG Protocol 185 Study Team

Exhibit 11-2. Sample letter for patient's who have completed Study HIVIG/IVIG treatment

DATE: March 24, 1997
FROM: ACTG Protocol 185 Study Team
SUBJ: ACTG 185 Discontinuation of New Enrollment
TO: ACTG 185 Participants Who Have Completed Study HIVIG/IVIG Treatment

Dear ACTG 185 Participant:

As you know, ACTG 185 was designed to see if HIV hyperimmune globulin (HIVIG), compared with standard intravenous immune globulin (IVIG), reduced transmission of HIV from women to their babies, when added to standard ZDV preventive treatment. Another purpose of the study was to evaluate the safety of HIVIG when given to pregnant women and to their newborn babies. Information collected in this study has been checked by researchers regularly to look at the progress of the study. As a result of the most recent review of this information, it was decided not to enroll any more patients. Stopping enrollment does not mean that the study has stopped.

We would like to share with you several important reasons why we made the decision to stop adding new patients. At this time, information on up to 379 babies who had at least one test for HIV was reviewed to see how many became infected. Only 15 babies were identified as being HIV infected. The overall rate of HIV infection transmitted from mother to infant was very low, only about 5%, and was no different whether patients received HIVIG or IVIG. This rate is even lower than the 8% seen with ZDV in ACTG 076, where only women with milder or earlier HIV disease were studied, and it is much less than the 15% baseline rate that was projected when ACTG 185 was designed.

While it is a welcome finding, the cause of the decrease in the overall transmission rate is not known. In order to keep enrolling new patients to be able to answer the study question with the 800 women and babies that the study was designed for, the transmission rate now would need to be at least 7.5%. Since the rate of HIV transmission was much lower than expected, many more than 800 patients would be needed to answer the study's main question. Because this would take too long, it was decided to stop enrolling new patients. This means the study will not be able to say whether HIVIG reduces HIV transmission. However, there are still important questions about the safety of HIVIG, about factors involved in HIV transmission from mother to baby, and about early diagnosis of HIV in babies that the study can still try to answer. So patients who are already enrolled will be asked to continue on the study.

Both HIVIG and IVIG when given as used in the study seem to be fairly safe. Mothers and babies receiving HIVIG or IVIG have had very few side effects from the HIVIG or IVIG. The side effects that a few experienced included vomiting, chills, fever, pain, and shortness of breath while they were getting or shortly after they were given HIVIG or IVIG. Since HIVIG is an investigational drug, women and infants already enrolled on the study are strongly encouraged to continue follow-up to see whether there are any other side effects.

Exhibit 11-2. Sample letter for patient's who have completed Study HIVIG/IVIG treatment (continued)

Your doctors and nurses will discuss the study results with you. If you have not already finished it, it is recommended that you stay on the study ZDV treatment because it is part of an approved treatment for HIV infected pregnant women to reduce the risk of transmitting HIV to their babies. The ZDV study treatment included as part of the protocol (intravenous ZDV during labor and delivery for women and oral ZDV for 6 weeks for babies) will continue to be provided by the ACTG 185 study.

To continue to study the safety of the study drugs and to study other aspects of transmission of HIV infection to babies and methods for early diagnosis of HIV infection in babies, we ask that you continue all of your study visits and tests as outlined in the protocol. This means that you should return for all of your remaining visits (monthly during pregnancy, at labor and delivery, and then at 6 weeks, 12 weeks, 6 months, 12 months, and 18 months after delivery). Your infant should return for all scheduled study visits until 18 months of age. This will provide continuing care and will provide you with information about your health and the health and HIV status of your baby.

It is still not known what if any late side effects there may be for pregnant women and newborns taking the study medications (ZDV and HIVIG or IVIG). It is important for us to follow all ACTG 185 patients. If your baby is not already enrolled in ACTG 219 ("Pediatric Late Outcomes Protocol"), we encourage you to discuss that study with your baby's doctor or nurse. ACTG 219 is a study that will look for any side effects that might show up later in your child's life that might relate to any study treatments that you received while pregnant or that your baby received. Your child can be followed in ACTG 219 until age 21 years. We will continue to try to make sure that you receive the best available medical care and that continued follow-up will be available to you after you complete your participation in ACTG 185.

We would like again to thank you for taking part in the ACTG 185 study and for helping us to increase our understanding of how transmission of HIV from mother to infant can be prevented.

Sincerely,

E. Richard Stiehm, M.D., Protocol Chair
John S. Lambert, M.D., Protocol Chair
for the ACTG Protocol 185 Study Team

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185

WHAT IS PEDIATRIC ACTG PROTOCOL 185?

Pediatric AIDS Clinical Trial Group (PACTG) Protocol 185 is a randomized, double-blind, controlled clinical trial, designed to evaluate whether hyperimmune anti-HIV immunoglobulin (HIVIG), an immunoglobulin containing high levels of antibodies to HIV, administered to HIV-infected pregnant women and their infants receiving zidovudine (AZT) could reduce the rate of HIV transmission from mother to infant. All women and their newborns received standard AZT therapy. In addition to AZT, women and their infants received either HIVIG or standard intravenous immunoglobulin (IVIG) that contains no antibodies to HIV. The study also evaluated the safety of HIVIG when administered to pregnant women and to their infants within 12-24 hours of birth.

WHO SPONSORED THIS STUDY?

PACTG Protocol 185 was conducted by the Pediatric AIDS Clinical Trials Group funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy and Infectious Diseases (NIAID). The study was a collaborative effort between three Institutes of the National Institutes of Health: the National Heart, Blood, and Lung Institute (NHLBI), NICHD and NIAID. The study was co-chaired by Dr. John Lambert from the Institute of Human Virology at the University of Maryland, Baltimore, Maryland and Dr. E. Richard Stiehm from the University of California Medical Center, Los Angeles, California. Glaxo Wellcome provided AZT for the study. IVIG was acquired from Bayer Pharmaceuticals, West Haven, Connecticut, and HIVIG was acquired from NABI, Boca Raton, Florida.

WHEN AND WHERE WAS THE STUDY CONDUCTED?

Study enrollment opened in October 1993. The study was conducted at 45 centers in the United States; 12 are NICHD-funded sites and 33 are NIAID-funded sites of the Pediatric ACTG.

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185 (continued)

WHO PARTICIPATED IN THE STUDY?

The study enrolled HIV-infected pregnant women who required antiretroviral therapy for their own health needs and who had a CD4+ lymphocyte count less than or equal to 500 cells/mm^3. The women entered the study between 20 and 30 weeks of their pregnancy. As of 12/23/96, the data-freeze date for the PACTG 185 Data and Safety Monitoring Board (DSMB) meeting, 455 women had enrolled, 395 women had delivered 402 liveborn infants, and one or more HIV culture results were available on 379 infants.

The population of women enrolled in PACTG 185 differs from those enrolled in PACTG 076, the 1994 clinical trial that demonstrated that administration of AZT to infected pregnant women and their newborns reduces perinatal transmission by two-thirds. All women enrolled in PACTG 076 had CD4+ lymphocyte counts above 200 cells/mm^3, did not require antiretroviral therapy for their own health, and had little or no prior therapy with AZT. The women enrolled in PACTG 185 had more advanced disease requiring antiretroviral therapy, lower CD4+ lymphocyte counts, and many had received AZT before becoming pregnant.

WHY WAS PACTG 185 CONDUCTED?

Mother-to-child transmission of HIV accounts for the vast majority of HIV infection in infants and children worldwide. As of December 1996, 7,629 cases of pediatric AIDS have been reported in the U.S.; of these children, 4,406 have died. AIDS is currently the seventh leading cause of death in the U.S. for children between one and fourteen years of age; in New York State, it is the leading cause of death for African-American children between one to four years old and second leading cause of death for Hispanic children of the same age. It is estimated that in addition to those children living with AIDS, there are approximately 10,000 other children infected with HIV who have not yet developed AIDS. Furthermore, approximately 7,000 infants are born to HIV-infected women each year in the U.S. Not all infants born to infected women become infected. Perinatal HIV transmission rates vary in different regions and different patient populations. The overall transmission rate in the U.S. is approximately

23% without AZT treatment. When AZT treatment is given to relatively healthy pregnant women and their infants in the first 6 weeks of life, the overall transmission rate is decreased to approximately 8%. Because the women enrolled in PACTG 185 were sicker than those in PACTG 076, it was hypothesized that even with AZT therapy the rates of perinatal transmission could be as high as 15%. It was felt that the combination of HIVIG with AZT might further decrease the risk of transmission in this group of symptomatic infected women.

WHAT WAS THE RATIONALE FOR THE TREATMENT REGIMEN IN PACTG 185?

Although AZT has been shown to reduce the rate of perinatal transmission to approximately 8% in HIV-infected women who are healthy, little to no data existed on the safety or efficacy of AZT in HIV-infected women with more advanced disease and/or prior antiretroviral use. In hepatitis B virus infection, another viral infection that can be transmitted from mother to infant, the use of an immunoglobulin preparation with high concentrations of antibody to hepatitis B has been shown to reduce the risk of perinatal hepatitis B transmission. It was postulated that the combination of HIVIG and AZT would provide further reduction in transmission from women with advanced HIV disease than might be observed with AZT alone.

HIVIG contains high concentrations of HIV-specific antibodies. It is prepared from the plasma of healthy HIV-infected individuals and undergoes extensive processing to inactivate any HIV present in the product (the product is negative for HIV on culture and DNA and RNA polymerase chain reaction). It was hypothesized that by providing high levels of anti-HIV antibody, virus in the mother would be neutralized and prevented from crossing the placenta to the baby, and that the presence of antibody in the infant at birth and during the first few weeks of life would neutralize any virus that crossed to the infant and thereby prevent infection of infant T-cells. The selection of the proposed comparison treatment arm (IVIG) was designed to control for any potential nonspecific beneficial immunoglobulin effect (not related to the presence of HIV antibodies) of HIVIG on study outcome.

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185 (continued)

WHAT WAS THE DESIGN OF THE STUDY?

Eligible women were stratified according to the baseline CD4+ cell count as below or greater than or equal to 200 cells/mm^3; AZT therapy first started prior to or during the current pregnancy; and geographic region of the study center. The women were randomized to either receive HIVIG (200 mg/kg) infusions every 28 days during the pregnancy or IVIG infusions given identically. The infants received the same HIVIG or IVIG study drug as the mother in a dose of 200 mg/kg within 12 hours of birth.

Additionally, women in both HIVIG and IVIG treatment groups received the PACTG 076 AZT regimen that is currently the standard of care for the purpose reducing perinatal HIV transmission. All women received AZT prescribed for them during pregnancy and intravenous AZT during labor and delivery (loading dose 2.0 mg/kg followed by 1.0 mg/kg/hour continuous infusion until delivery). Additionally, all infants received AZT syrup, 2 mg/kg by mouth every six hours, beginning 8 - 12 hours after birth and continued for six weeks.

The ability of HIVIG to reduce the rate of HIV transmission in infants born to HIV-infected mothers was evaluated by comparing the rate of HIV infection at 6 months of age in infants born to mothers who had received HIVIG to that observed in those who had received IVIG.

HOW WAS HIV INFECTION DETECTED IN THE INFANTS?

All infants were checked for evidence of HIV infection by HIV cultures at birth and at study weeks 6, 24, and 48. A positive viral culture was confirmed by a secondary HIV infection assay such as a quantitative culture and/or DNA PCR. Infants were also tested for HIV antibodies at 18 months.

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185 (continued)

WHAT IS THE DSMB?

To avoid bias in study results, large clinical trials are conducted so that the investigators and participants do not know the emerging results of the study. The Data and Safety Monitoring Board (DSMB) was an independent panel of experts appointed by the director of NHLBI. The DSMB reviews interim data of the ongoing trial at set intervals during the course of the study. This review ensures that study participants are not being harmed because of toxicity or because one treatment regimen is significantly superior to the other, and ensures that the study will be able to answer the question it was designed to address. For example, if the assumptions made to determine the number of study participants necessary for the trial is in error, the DSMB makes recommendations to remedy the situation either by changing the number of patients that will be enrolled in the trial or by ceasing enrollment into the trial.

WHY WAS ENROLLMENT INTO THE STUDY DISCONTINUED?

As of December 1996, one or more HIV culture results were available on 379 infants; these results were the basis for the Kaplan-Meier estimates of transmission. Fifteen infants were determined to be HIV-infected. All infected infants were identified by 6 months of age.

The estimated overall rate of mother-to-child HIV transmission rate was an unexpectedly low 4.8% (95% confidence interval 2.4% to 7.1%). This transmission rate was well below the anticipated transmission rate on which the initial power and sample size calculations were based. The study was designed to be able to detect a 50% reduction in the risk of transmission with HIVIG if the transmission rate in the control IVIG group was over 15%. The estimated transmission rate by treatment group was 4.7% (95% confidence interval, 1.2%-8.2%) in HIVIG recipients and 4.8% (95% confidence interval, 1.5%-8.2%) in IVIG recipients. Under the present study design, the chance of obtaining significant results with the current sample size is only about 29%.

The DSMB determined that it would require a substantial increase (over a doubling) in the number of women enrolled into the study to meet the initial guidelines of this study. Given the unexpectedly low rate of transmission in this study and the low power to detect a treatment difference under the current study design, the DSMB recommended that enrollment into the study be discontinued, and that all patients currently on study continue to be followed as per the current protocol.

WHAT ARE THE IMPLICATIONS OF PACTG 185 REGARDING THE EFFICACY OF AZT TO REDUCE PERINATAL TRANSMISSION?

PACTG 076 demonstrated that AZT could reduce the risk of perinatal transmission by nearly 70% from infected women who had CD4+ cell count greater than 200/mm^3, had minimal symptoms, did not require antiretroviral therapy for maternal health indications, and had little to no prior AZT therapy. Transmission was reduced from 22.6% in the placebo group to 7.6% in AZT recipients. However, the efficacy of ZDV for reducing transmission among women with more advanced disease and/or prior ZDV use and, if efficacy was observed in this population of women, the extent of such reduction was undefined.

The data from PACTG 185 not only confirms the efficacy of AZT for reduction of perinatal transmission, as originally demonstrated in PACTG 076, but extends this efficacy to women with more advanced disease and prior ZDV use. In PACTG 076, all women had CD4+ cell counts greater than or equal to 200/mm^3 and only 19 women (4.6%) had received any AZT prior to the current pregnancy. In contrast, in PACTG 185, 23% had baseline CD4+ cell counts under 200/mm^3 and 21% of women had received AZT prior to as well as during the current pregnancy.

The results from PACTG 185 are consistent with accumulating information from other studies in the United States. For example, in North Carolina, mother-to-child transmission rates have decreased from 21% in 1993 to 6% in 1996 with use of AZT; in New York City, rates have similarly decreased to 5% for infected women who have received the antenatal, intrapartum and newborn AZT regimen. Additionally, in France, transmission rates have decreased from 14% prior to the use of AZT to 5% in women receiving AZT.

HOW OLD WERE THE WOMEN IN THE TRIAL, WHAT WERE THEIR CD4+ CELL COUNTS AND WHAT WAS THEIR HISTORY OF PRIOR AZT USE?

The average age of the women who participated in the trial was 26 years old. The average CD4+ cell count at study entry was 293 cells/mm^3. Twenty-three percent of women had CD4+ cell counts under 200 cells/mm^3. Twenty-one percent of women had received AZT prior to as well as during their current pregnancy.

WHAT WERE THE ETHNIC BACKGROUNDS OF THE WOMEN ENROLLED?

Of the women enrolled, 52% were African-American, 35% Hispanic/Latina, 13% were White/non-Hispanic, and 1% Other. The ethnic and racial distribution of the trial participants is comparable to that in the population of HIV-infected women in the U.S.

WERE SIGNIFICANT SIDE EFFECTS SEEN IN THE MOTHER THAT COULD BE ASSOCIATED WITH HIVIG USE?

Few toxicities were reported as being related to treatment, and those that were reported were common side-effects associated with receipt of intravenous immunoglobulin product infusions, such as chills, headache, and back pain. Only 4 women (1%) required discontinuation of study drug infusions, 2 in each treatment arm.

WERE SIGNIFICANT SIDE EFFECTS SEEN IN THE INFANTS THAT COULD BE ASSOCIATED WITH HIVIG USE?

Very few toxicities were reported as being related to the HIVIG/IVIG infusions, and no infant required that study drug infusions be discontinued due to toxicity.

WERE SIGNIFICANT SIDE EFFECTS SEEN IN THE INFANTS THAT COULD BE ASSOCIATED WITH AZT USE?

Overall, AZT was well tolerated. During the six weeks of treatment, the most common side effects reported for both treatment groups were low hemoglobin (anemia) and low white blood cells (neutropenia). Severe (grade 3 or 4) anemia was reported in <0.5% of infants and severe (grade 3 or 4) neutropenia in approximately 4%.

HAVE ANY WOMEN OR INFANTS IN THE STUDY DIED?

Three women died during the study, 2 in the HIVIG and 1 in the IVIG group. Deaths were due to HIV disease progression: HIV encephalopathy with aspiration pneumonia; *P. carinii* pneumonia; and end-stage dialysis-dependent renal disease with pneumonia. None of the deaths were felt to be treatment-related.

Six infants died during the study, 2 in the HIVIG and 4 in the IVIG group. Deaths in the HIVIG study arm were due to perinatal asphyxia with severe hypoxic ischemia and renal dysgenesis with multiorgan failure. Deaths in the IVIG study arm were due to sudden infant death syndrome; prematurity; necrotizing enterocolitis and prematurity; and a stillbirth (maternal diabetes mellitus). None of the deaths were felt to be treatment-related, and in two of the deaths no study HIVIG/IVIG or AZT had been administered to the infant.

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185 (continued)

WHAT HAPPENED TO THE WOMEN AFTER THEY DELIVERED?

The mother's health was initially monitored for six months after delivery. As of June 1995, the follow-up of maternal patients was extended through 18 months to evaluate longer-term safety and whether there were any influence of HIVIG on disease progression. Co-enrollment by women who have completed the treatment portion of the protocol (through labor and delivery) was permitted in other investigational treatment studies. In the women evaluated to date there has not been any difference noted in viral load by treatment group.

HOW WILL THE MANAGEMENT OF MOTHERS AND THEIR INFANTS WHO ARE NOW IN THE STUDY CHANGE?

All participants will be informed of the study results and informed of the study treatment they received during the trial. HIVIG or IVIG study drug infusions will be discontinued for all currently enrolled women and infants. All pregnant women will continue to receive AZT during labor and delivery and 6 weeks of AZT will be provided for their infant. Data will continue to be collected as outlined in the protocol. This means that all women will be seen monthly during pregnancy and at 6 and 12 weeks, 6 months, 12 months and 18 months postpartum. Infants will be followed on study for 18 months.

Although there were no short-term serious toxicities to either women or infants observed in PACTG 185, there is no information regarding any long-term effects on the infants or mothers treated in this study. PACTG 219 is a protocol that is evaluating long-term effects of intrauterine exposure to antiretroviral drugs on PACTG perinatal protocols, and enrollment into this protocol will be offered and strongly encouraged for all PACTG 185 infants. Long-term follow-up is recommended for all infants exposed to antiretroviral treatments *in utero* or as newborns.

Exhibit 11-3. Questions and Answers about Pediatric ACTG Protocol 185 (continued)

DO THE STUDY RESULTS MEAN THAT HIVIG WAS NOT EFFECTIVE IN REDUCING PERINATAL TRANSMISSION?

The data from PACTG 185 will not be able to definitively answer the question regarding the ability of HIVIG to reduce perinatal transmission because of the unexpectedly low transmission rate in the study. Because almost all HIV-infected women in the United States will be receiving antiretroviral therapy during pregnancy, it will not be possible to address the role of HIVIG in reducing perinatal transmission in a timely fashion. In areas of the world in which antiretroviral therapy may not be available, it is possible that passive immunization may provide some benefit, and further study in appropriate settings is warranted.

WHAT DOES THIS MEAN FOR ALL PREGNANT HIV-INFECTED WOMEN?

The PACTG 185 results provide important additional support to the existing Public Health Service recommendations that all pregnant women enter prenatal care early and be offered HIV testing. All HIV-infected pregnant women should be offered the PACTG 076 ZDV regimen of antenatal, intrapartum and neonatal ZDV for the purpose of reducing transmission risk, and the now standard AZT regimen should be a part of whatever treatment an infected woman receives during pregnancy for her own health.

General information about HIV disease, testing or treatment options may be obtained from your health care provider, your local and state health departments or by calling any of the national organizations such as the following:

- National AIDS Information Hotline (1-800-342-AIDS)
- National AIDS Information Clearinghouse (1-800-458-5231)
- National Pediatric HIV Resource Center (1-800-362-0071)
- HIV/AIDS Treatment Information Services (1-800-448-0440)

12. AUTOMATED DATA RETRIEVAL

In June 1997, the process of data retrieval was automated for ACTG 185. Exhibit 12-1 lists the procedures by which all sites should make correction to CRFs. Exhibit 12-2 is a checklist that each site should review before returning data retrieval to Westat.

Exhibit 12-1. ACTG Auto Data Retrieval Procedures for Sites (Revised 8/20/97)

1. Edits will be run each week on forms for ACTG 185.

2. Edits will be processed electronically and a printed copy of all errors will be produced. Errors will print out one error per page and will look similar to the Data Retrieval (DR) sheets (or query sheets) sites have been receiving from Westat to date.

3. DR sheets will be forwarded by Dennis DeRycke to the sites via FAX or FedEx. If the DR is urgent, your Westat study manager will forward the DR to you directly.

4. Sites will receive one DR sheet for each error.

5. At the top of the DR sheet, it will state whether the DR is urgent. Urgent DR should be responded to as soon as possible (within 2-3 calendar days of receipt of the DR). Routine DR will just say DR at the top of the DR sheet. Routine DR should be responded to within 7 calendar days of receipt of the DR.

6. On each DR sheet, there will be identifying information (i.e., Form #, PID, SV #, Visit Date, center #, Westat study manager name, etc.). It will also list the question text for the specific question being edited, the value entered in that question field, and the error message explaining the problem. There may be some extra comments or clarification entered for specific error messages if we feel more explanation is needed.

7. Each DR sheet has a solution area and a designated space to enter your name (printed) or initials, and the date. Signature is no longer required.

8. Respond to the DR by completing the solution area of each DR sheet. Please enter what needs to be done to correct the error. If data changes are required, you can simply state "see update" or "update attached".

9. If the data being questioned on the DR sheet is verified as correct, then please write, "Data correct. Override", in the solution area of the DR sheet.

10. Print your name or enter your initials in the 'Site Contact Person' field, and enter the date on each DR sheet. Signature is no longer required.

11. If data changes are being made, you must attach a copy of the entire updated form (all pages) to the DR sheet. If you are verifying the data as correct and are requesting an override, you do not need to attach a copy of the case report form to the DR sheet.