ACTG 185

A Phase III Randomized, Double Blind, Controlled Study of the Use of HIVIG for the Prevention of Maternal-Fetal HIV Transmission in Pregnant Women and Newborns Receiving Zidovudine (ZDV)

Sponsored By:

National Heart, Lung, and Blood Institute
National Institute of Child Health and Human Development
National Institute of Allergy and Infectious Diseases

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VERSION 5.0
November 1, 1996
FINAL

ACTG PROTOCOL 185

PROTOCOL LISTS OF CHANGES

(VERSION 5.0, November 1, 1996)

1. **Instructions for completing the site implementation plan for ACTG Protocol 185.**

   ADDED:

   ACTG 076 Checklist adapted for ACTG 185.

2. **Study Management**

   Names and telephone number of persons to contact were updated.

3. **Footnote References and Section 21.0 - References.**

   DELETED:

   References 2, 114, 117, 112-129, 136, and 144.

   ADDED:

   New references of 2, 114, 115, 117-123, 129, 142, 144, and 145 were added and footnotes reference were formatted to be in sequential order.

4. **Section 1.3. Study Population**

   READ:

   HIV-infected pregnant women who are receiving ZDV during their pregnancy for medical indications (i.e., have pre-entry CD4 count $\leq$500/mm^3). One-half or more will have pre-entry CD4 $\leq$200/mm^3 and/or ZDV treatment duration of 6 months or more.

   CHANGED TO READ:

   HIV-infected pregnant women who are receiving ZDV during their pregnancy for medical indications (i.e., have pre-entry CD4 count $\leq$500/mm^3). **An estimated** one-half or more, will have pre-entry CD4 **<200/mm^3** and/or ZDV treatment duration of 6 months or more.

Protocol List of Changes

5. **Section 2.0. Protocol Team Members**

Addresses and telephone numbers of team members were updated.

6. **Section 3.1. Epidemiology**

READ:

With an increasing shift in the epidemiologic features of human immunodeficiency virus (HIV) infection toward populations in which heterosexual activity and/or intravenous 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.

As of October 1993, 43,019 cumulative cases of acquired immunodeficiency syndrome (AIDS) in women have been reported to the Centers for Disease Control (CDC); in 49 percent of women, intravenous drug use is reported as the route of HIV exposure, and in an additional 37 percent heterosexual contact is reported as the route of HIV exposure (2). The majority of these women are of childbearing age. Cumulatively, 4,906 cases of pediatric AIDS cases have been reported. The extent of AIDS and HIV infection in the pediatric population, where HIV is predominately acquired by vertical transmission from mother to infant, is clearly linked to the prevalence of HIV infection in women of childbearing age.

CHANGED TO READ:

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.

As of **December 1995, 71,818** cumulative cases of acquired immunodeficiency syndrome (AIDS) in women have been reported to the Centers for Disease Control (CDC). **In 47** percent of women, **injection** drug use is reported as the route of HIV exposure, and in an additional 37 percent heterosexual contact is reported as the route of HIV exposure (2). The majority of these women are of childbearing age. Cumulatively, **6,948** cases of pediatric AIDS cases have been reported. The extent of AIDS and HIV infection in the pediatric population, where HIV is predominately acquired by vertical transmission from mother to infant, is clearly linked to the prevalence of HIV infection in women of childbearing age.

7. **Section 3.3.1. Safety and Pharmacokinetics of ZDV in Pregnancy**

READ:

Comprehensive data regarding the use of ZDV is contained in the Burroughs-Wellcome Investigator's Brochure. Additional information on ZDV pharmacokinetics in HIV-infected pregnant women and their infants and on clinical experience with ZDV in HIV-infected pregnant women is contained in ACTG Protocol 076 (52).

CHANGED TO READ:

Comprehensive data regarding the use of ZDV is contained in the **Glaxo** Wellcome Investigator's Brochure **and package insert**. Additional information on ZDV pharmacokinetics in HIV-infected pregnant women and their infants and on clinical experience with ZDV in HIV-infected pregnant women is contained in ACTG Protocol 076 (52).

8. **Section 3.4.1. Preparation and Antibody Content**

2nd Paragraph

READ:

The preparation of HIVIG includes multiple steps to inactivate HIV including treatment of the plasma with solvent/detergent, and fractionating the IgG by Cohn-Oncley alcohol precipitation and ion exchange chromatography. The final 5 percent solution of HIVIG contains 98 percent monomeric IgG.

CHANGED TO READ:

The preparation of HIVIG includes multiple steps to inactivate **and/or partition** HIV including treatment of the plasma with solvent/detergent, and fractionating the IgG by Cohn-Oncley alcohol precipitation and ion exchange chromatography. The final 5 percent solution of HIVIG contains 98 percent monomeric IgG.

9. **Section 3.6. Diagnosis of HIV in Newborns**

READ:

The diagnosis of vertically transmitted HIV infection in infants is complicated by difficulties unique to this age group. In newborns and young infants, transplacentally acquired maternal IgG antibody renders unreliable the standard HIV-specific antibody detection enzyme immunoassay or immunoblot assays used to establish the laboratory diagnosis of HIV infection in older children and adults. In the absence of clinical evidence of HIV infection in infants and children under 15 months of age, diagnosis of HIV infection requires the identification of virus in blood or tissues, confirmed by culture or other laboratory detection methods (114).

Definitive laboratory diagnosis of HIV infection by viral culture is the accepted reference standard (115). The practical utility of viral culture is limited by the complex, time-consuming, and resource intensive nature of currently available techniques (116). Sample volume limitations in small infants impose an additional restriction on the use of standard techniques for viral culture.

As developments in therapeutic research provide possibilities for early prophylaxis against secondary infectious complications of HIV (117, 118) and begin to provide prospects for early treatment with specific antiretroviral agents (119-121), the need becomes more pressing to

develop capabilities to distinguish infected from uninfected perinatally exposed, seropositive infants. Additionally, early ability to detect vertically transmitted HIV infection would facilitate the evaluation of agents designed to interrupt transmission. Through early diagnosis, benefits could accrue also in the complex and difficult decision-making process faced by state and local child welfare/protective services agencies with regard to foster care placement or adoptive services for infants in need, as well as in easing the psychological burden of waiting, anxiety, and uncertainty that the present inability to provide timely and accurate ascertainment of infant infection status imposes on parents and other caregivers.

No single, fully standardized laboratory test is currently available that can provide reliable, early identification of all HIV-infected infants. A major limitation in laboratory diagnosis of HIV in early infancy appears to be the sporadic presence of virus as detected by standard culture techniques before age 12 weeks. A number of new methods hold promise as practical means to identify infection in the newborn infant or within the first months of life. These include polymerase chain reaction (PCR) detection of HIV DNA, and HIV-specific IgA assays (116). However, the evaluation of these methods has been limited to studies which included only small numbers of infants (122-129). Importantly, the effect of maternal and/or neonatal antiretroviral therapy on the sensitivity of these research tests has not been evaluated in any of these reports.

Thus, the present study proposes to include as a nested substudy the prospective evaluation of PCR and anti-HIV IgA for early diagnosis of HIV infection as compared with viral culture in this unique population of infants, all of whom have received antiretroviral therapy via maternal and neonatal administration of ZDV. Because the purpose of the early diagnosis substudy will be to evaluate the use of these research diagnostic methods for HIV detection, the results of the PCR and anti-HIV IgA early diagnosis assays will not be used routinely to define infection status. In addition, because the implication of such linked PCR and anti-HIV IgA assays will be unclear until infection status as determined by serial viral culture and clinical follow-up is established, linked results will not be used for routine clinical management and will not be made available prematurely.

Additionally, placental samples, when available, will be evaluated for the presence of HIV RNA, both to evaluate the utility of this technique for the early diagnosis of HIV as well as the implications of positive findings for the timing of vertical transmission.

CHANGED TO READ:

1st Paragraph

The diagnosis of vertically transmitted HIV infection in infants is complicated by difficulties unique to this age group. In newborns and young infants, transplacentally acquired maternal IgG antibody renders unreliable the standard HIV-specific antibody detection enzyme immunoassay or immunoblot assays used to establish the laboratory diagnosis of HIV infection in older children and adults. In the absence of clinical evidence of HIV infection in infants and children under **18** months of age, diagnosis of HIV infection requires **direct detection of virus or viral components in blood or tissues by HIV culture, viral nucleic acid detection methods such as polymerase chain reaction, or HIV p24 antigen assays (114).**

Protocol List of Changes

2nd Paragraph - Added

Advances in viral detection assay development and performances have made it possible to diagnose HIV infection in nearly all HIV-infected infants by 4-6 months of age (115).

3rd Paragraph

Definitive laboratory diagnosis of HIV infection by viral culture is the accepted reference standard (116). **Although sensitivity of HIV culture is 50% or lower during the first week after birth, it increases to >90% by age 3 months and to nearly 100% by 6 months of age (117-119).**

Subsequent paragraphs were deleted. ADDED:

The performance of serial viral culture for diagnosis of HIV infection has been evaluated in prospective cohort studies. Sensitivity of a single culture is approximately 90% at ages from 1-6 months, with positive and negative predictive values 97-98%. When cultures are obtained at two separate ages from 1-6 months, at least one of any two cultures is positive in 95-100% of infected infants. The specificity of negative cultures obtained at two separate ages after one month is 99-100% for establishing the absence of HIV infection (117, 120).

With repeated sampling, the cumulative probability of first detecting a positive culture in an infected infant exceeds 95% beginning at about six weeks of age. One large prospective cohort study showed that 95% of 140 infected infants in whom 1-5 serial culture were performed had a first positive culture obtained by the 6-month visit. No infant demonstrated consistently negative serial cultures beyond 6 months, and all 3 infants with negative or missing cultures through the 6-month visit were positive when next sampled beyond 6 months (121).

Administration of antiretroviral treatment does not appear to delay or reduce ability to detect HIV infection by viral cultures in infants with perinatal HIV exposure. In AIDS Clinical Trials Group protocol 076, virtually all infected infants were identified by 6 months of age, and the estimated intervals before the first positive culture were virtually identical for infants who received zidovudine and infants who received placebo (122).

Based on these data, it is now accepted in clinical practice that infection status for nearly all infants can be determined by age 4-6 months. In 1995, existing guidelines for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) in HIV-exposed or infected infants and children were revised to indicate that HIV infection can be reasonably excluded at 4 months of age for purposes of clinical management. The CDC guidelines now state that HIV infection can be reasonably excluded among children who have had two or more negative HIV diagnostic tests (i.e., HIV culture or PCR), both of which are performed at 1 month of age or older and one of which is performed at 4 months of age or older (123).

However, although viral culture represents the reference standard, its practical utility is limited by the complex, time-consuming, and resource intensive nature of currently available techniques (124). Sample volume limitations in small infants impose an additional restriction on the use of standard techniques for viral culture.

As developments in therapeutic research provide possibilities for early prophylaxis against secondary infectious complications of HIV (125) and begin to provide prospects for early treatment with specific antiretroviral agents (126-128), the need becomes more pressing to develop capabilities to distinguish infected from uninfected but perinatally exposed, seropositive infants in **prompt, rapid, and reliable fashion, even earlier than current advances now permit.** Early ability to detect vertically transmitted HIV infection would facilitate the evaluation of agents designed to interrupt transmission. Through earlier diagnosis, benefits could accrue also in the complex and difficult decision-making process faced by state and local child welfare/protective services agencies with regard to foster care placement or adoptive services for infants in need, as well as in easing the psychological burden of waiting, anxiety, and uncertainty that presently available diagnostic methods impose in parents and other caregivers.

Detection of viral nucleic acid sequences using gene amplification techniques such as polymerase chain reaction has the advantage of being able to detect very small amounts of virus. The sensitivity and specificity of PCR as an early diagnostic tool for detection of proviral HIV-1 DNA has been evaluated by several investigators. One meta-analysis showed HIV-1 DNA detected by PCR in an estimated 38% (90% confidence interval, 29-46%) of infants tested on the day of or day after birth. Sensitivity rose rapidly during the second week to 93% by 14 days of age (129). However, false positive tests have been reported, most commonly secondary to laboratory error due to carryover of amplified product DNA from a previously analyzed sample. In addition, the optimal time of sampling remains to be established. Recently, techniques for detection of viral RNA have become available, permitting detection and quantitation of free viral particles. In theory, RNA detection may be presumed to be even more sensitive than DNA detection for early diagnosis of HIV infection, but evaluation of these methods for this indication remains to be accomplished.

The present study therefore proposed to include as a nested study, the evaluation of newer methods for early diagnosis of HIV infection, compared with viral culture. Because the purpose of the early diagnosis substudy will be to evaluate the use of these research diagnostic methods for HIV detection, assays will be performed retrospectively in batched fashion, and will not be available routinely for clinical management purposes. Evaluations may include DNA and RNA detection methods, as well as other methods to identify, quantify, and characterize virus, to be specified by the protocol team. Additionally, placental samples when available will be evaluated for the presence of HIV RNA, to evaluate the utility of this technique for early diagnosis and to address questions regarding the timing of transmission.

Protocol List of Changes

10. Section 3.7.1. Study Population and Rationale

7th Bullet

READ:

- The CD4+ lymphocyte counts and prior ZDV use patterns of the women enrolled in the study will be evaluated as part of each of the scheduled interim monitoring analyses provided to the DSMB. When the proporation of women with pre-entry CD4+ count $>200/mm^3$ AND less than six months ZDV use reaches 50 percent of the total study population, enrollment into this group will be terminated. No such enrollment restriction will be applied to women with pre-entry CD4+ counts $<200/mm^3$ or women with greater than six months of prior ZDV use.

CHANGED TO READ:

- The CD4+ lymphocyte counts and prior ZDV use patterns of the women enrolled in the study will be evaluated as part of each of the scheduled interim monitoring analyses provided to the DSMB. When the proportion of women with pre-entry CD4+ count $\geq$**200**/mm^3 AND less than six 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 pre-entry CD4+ counts $<200/mm^3$ or women with **six months or more** of prior ZDV use.

5th Paragraph

READ:

To ensure enrollment of women at highest risk of HIV transmission despite ZDV therapy and with a baseline control group transmission rate of at least 15 percent, at least 50 percent of women enrolling in ACTG 185 will have entry CD4+ lymphocyte counts $<200/mm^3$ or will have received ZDV for 6 months or more prior to their pregnancy. The rationale is the following: if 50 percent of the patients enrolled had CD4+ counts between 200-500/mm^3 and received <6 months of ZDV therapy (similar to the ACTG 076 population), a transmission rate of 10 percent is anticipated. Based on the above discussion, the anticipated transmission rate in patients with CD4+ $<200/mm^3$ and/or ZDV greater than or equal to 6 months would be approximately 20 percent or more. Thus, if at least 50 percent of women were at highest risk for transmission (low CD4+ count and/or longer duration ZDV), we anticipate a total control group transmission rate for at least 15 percent. With a sample size of 800 (400 per arm), there would be power adequate to detect a 50 percent treatment effect if the control group transmission rate was 15 percent.

DELETED:

1st sentence - "or more prior to the pregnancy."

CHANGED TO READ:

To ensure enrollment of women at highest risk of HIV transmission despite ZDV therapy and with a baseline control group transmission rate of at least 15 percent, **approximately** 50 percent of women enrolling in ACTG 185 **should** have entry CD4+ lymphocyte counts $<200/mm^3$ or will have received ZDV for **6 months or more**. The rationale is the following: if 50 percent of the patients enrolled had CD4+ counts between 200-500/mm^3 and received <6 months of ZDV therapy (similar to the ACTG 076 population), a transmission rate of 10 percent is anticipated. Based on the above discussion, the anticipated transmission rate in patients with CD4+ $<200/mm^3$ and/or ZDV greater than or equal to 6 months would be approximately 20 percent or more. Thus, if at least 50 percent of women were at highest risk for transmission (low CD4+ count and/or longer duration ZDV), we anticipate a total control group transmission rate for at least 15 percent. With a sample size of 800 (400 per arm), there would be power adequate to detect a 50 percent treatment effect if the control group transmission rate was 15 percent.

11. **Section 3.7.2. Rationale for Further Stratification**

2nd Paragraph

READ:

There is preliminary evidence that the length of ZDV therapy influences the effect of ZDV on the level of HIV virus and HIV susceptibility to ZDV, with individuals receiving ZDV for > six months having higher levels of HIV and less susceptible virus than those receiving ZDV for < six months (132-135). Accordingly, a further stratification will be done based on whether a woman received ZDV before pregnancy or was started on ZDV during this pregnancy.

CHANGED TO READ:

There is preliminary evidence that the length of ZDV therapy influences the effect of ZDV on the level of HIV virus and HIV susceptibility to ZDV, with individuals receiving ZDV for≥ **six months** having higher levels of HIV and less susceptible virus than those receiving ZDV for < six months (132-135). Accordingly, a further stratification will be done based on whether a woman received ZDV before pregnancy or was started on ZDV during this pregnancy.

12. **Section 4.2. Secondary Objectives**

1st Bullet

READ:

- Compare HIV plasma viremia and cell culture (qualitative and quantitative), p24 antigenemia, and CD4 cell counts between transmitting and non-transmitting mothers.

CHANGED TO READ:

- Compare HIV plasma viremia and **quantitative** cell culture, p24 antigenemia, and CD4 cell counts between transmitting and non-transmitting mothers.

3rd Paragraph

READ:

To compare polymerase chain reaction (PCR) detection of HIV DNA, HIV-IgA assay and placental HIV RNA PCR to HIV culture as methods of early diagnosis of HIV infection in infants born to HIV-infected women in this protocol.

CHANGED TO READ:

To 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 in this protocol.

13. **Section 5.0. Study Outline**

7th Paragraph

READ:

A subset of mother-infant pairs enrolled early in the study (up to 50 enrollees) will have pharmacokinetic studies performed to measure quantitative HIV-specific antibody levels achieved with HIVIG (as compared to IVIG control) in the mother and her infant. Additional studies nested in this protocol will evaluate maternal virologic and immunologic factors involved in HIV transmission from mother-to-infant, and compare the sensitivity and specificity of PCR and HIV-IgA tests to HIV culture for the early diagnosis of HIV infection in this population of infants who have all had both prenatal exposure to and neonatal treatment with ZDV. Placental samples, when available, will be evaluated for HIV RNA. In addition, HIV-related manifestations of disease progression in women receiving HIVIG and IVIG will be evaluated, as defined by measurement of certain laboratory parameters (HIV plasma viremia and cell culture, p24 antigen and CD4 count) and HIV-related clinical symptoms in women during pregnancy and postpartum.

CHANGED TO READ:

A subset of mother-infant pairs enrolled early in the study (up to 50 enrollees) will have pharmacokinetic studies performed to measure quantitative HIV-specific antibody levels achieved with HIVIG (as compared to IVIG control) in the mother and her infant. Additional studies nested in this protocol will evaluate maternal virologic and immunologic factors involved in HIV transmission from mother-to-infant, and compare the sensitivity and specificity of **newer** tests **for detection of HIV-1 genomic material to** HIV culture for the early diagnosis of HIV infection in this population of infants who have all had both prenatal exposure to and neonatal treatment with ZDV. Placental samples, when available, will be evaluated for HIV RNA. In addition,

HIV-related manifestations of disease progression in women receiving HIVIG and IVIG will be evaluated, as defined by measurement of certain laboratory parameters (HIV plasma viremia and cell culture, p24 antigen and CD4 count) and HIV-related clinical symptoms in women during pregnancy and postpartum.

14. **Section 6.2. Exclusion Criteria For Women**

6th Bullet

READ:

- Receipt of investigational antiretroviral agents during this pregnancy prior to study entry (e.g. rCD4, CD4-IgG, d4T); receipt of ddI or ddC during the pregnancy prior to entry requires protocol chair approval for entry.

CHANGED TO READ:

- 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.

8th Bullet

READ:

- 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 twenty-four hour urine collection, and one or more of the following:

CHANGED TO READ:

- Severe preeclampsia (HELLP syndrome: **hypertension, elevated liver enzymes, and low platelets**) 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 twenty-four hour urine collection, and one or more of the following:

Protocol List of Changes

9th Bullet

READ:

- When the proportion of women with pre-entry CD4+ count >200/mm^3 AND less than six months ZDV use reaches 50 percent of the total study population, enrollment into this group will be terminated. No such enrollment restriction will be applied to women with CD4+ pre-entry counts <200/mm^3 or women with greater than six months of prior ZDV use.

CHANGED TO READ:

- When the proportion of women with pre-entry CD4+ count **≥200**/mm^3 AND less than six 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 six months **or more** of prior ZDV use.

ADDED:

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

- **Prior enrollment to ACTG 185.**

15. **7.2. Source of Patients**

Last Paragraph

READ:

The essential points of the HIVIG implementation plan are similar in nature to those addressed in ACTG 076 implementation plans submitted to the Division of AIDS (DAIDS), NIAID. The review committee for the HIVIG protocol implementation plans will have overlapping personnel with the 076 plan review committee. A completed (updated if necessary) 076 site implementation plan must be attached to the 185 site implementation plan. The ACTG 185 site implementation plan is included with the site registration form attached to this protocol. The ACTG 076 site implementation plan can be obtained from the ACTG operations office via e-mail logon: ACTG.OPS, or telephone# (301) 230-3150 (Attn: Elizabeth Hawkins, ACTG 076 protocol specialist).

CHANGED TO READ:

The essential points of the HIVIG implementation plan are similar in nature to those addressed in ACTG 076 implementation plans submitted to the Division of AIDS (DAIDS), NIAID. The review committee for the HIVIG protocol implementation plans will have overlapping personnel with the 076 plan review committee. **The completed ACTG 076 Checklist adapted for ACTG**

185 must be attached to the 185 site implementation plan. The ACTG 185 site implementation plan **and the ACTG 076 Checklist adapted for ACTG 185 are** included with the site registration form attached to this protocol.

16. **Section 7.3.1. Management of Women**

2nd Paragraph

ADDED:

Following delivery, maternal treatment may include approved and/or investigational antiretroviral agents other than ZDV.

4th Paragraph

READ:

Women will be followed by their primary obstetrician at the study site. After completion of routine postpartum follow-up care and the final protocol-specified visit 6 months postpartum, if the study obstetrician is not the woman's primary care provider, referral to a primary care provider with expertise in HIV-related illness should be made, with an emphasis on referral to a caregiver with access or referral to HIV-related clinical trials.

CHANGED TO READ:

Women will be followed by their primary obstetrician at the study site. After completion of routine postpartum follow-up care and the final protocol-specified visit **18** months postpartum, if the study obstetrician is not the woman's primary care provider, referral to a primary care provider with expertise in HIV-related illness should be made, with an emphasis on referral to a caregiver with access or referral to HIV-related clinical trials.

17. **Section 7.5. Patient Compliance**

3rd Paragraph

READ:

Infants may be seen $\pm$ 1 day from the scheduled visit for the 1 week visit, $\pm$ 2 days for the 2 week visit, $\pm$ 1 week for visits at week 6 through 24, and $\pm$ 2 weeks for visits at week 36 through 78.

CHANGED TO READ:

Infants may be seen $\pm$ 1 day from the scheduled visit for the 1 week visit, $\pm$ 2 days for the 2 week visit, $\pm$ 1 week for visits at week 6 through 24, and $\pm$ **4** weeks for visits at week 36 through 78.

Protocol List of Changes

18. **Section 8.1.1. HIVIG and IVIG**

1st Paragraph

READ:

HIVIG (purchased from North American Biologicals, Inc.) and IVIG (purchased from Cutter Biologicals, Miles, Inc.) will be distributed through the National Heart, Lung, and Blood Institute (NHLBI) drug repository contractor (Ogden Bioservices Corporation, through the Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850, phone: **(301) 294-0741**, FAX #: (301) 294-2905), pharmacist John Ferinde. The study site pharmacist can obtain the study drug (HIVIG and IVIG) for this protocol by faxing orders to the above number after the site has received site registration approval. Guidelines for study drug administration (HIVIG/IVIG) may be found in **Appendix IV**.

CHANGED TO READ:

HIVIG (purchased from **NABI**) and IVIG (purchased from **Bayer**) will be distributed through the National Heart, Lung, and Blood Institute (NHLBI) drug repository contractor (**McKesson Bioservices Inc.**, through the Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850, phone: (301) 294-0741, FAX #: (301) 294-2905), pharmacist John Ferinde. The study site pharmacist can obtain the study drug (HIVIG and IVIG) for this protocol by faxing orders to the above number after the site has received site registration approval. Guidelines for study drug administration (HIVIG/IVIG) may be found in Appendix IV.

19. **Section 8.1.2. Zidovudine (ZDV)**

READ:

The intravenous ZDV for intrapartum infusion and ZDV syrup for administration to newborns is supplied by Burroughs Wellcome, and will be distributed through the National Heart, Lung and Blood Institute (NHLBI) drug repository contractor (Ogden Bioservices Corporation) through the NHLBI Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850, phone: **(301) 294-0741**, FAX: (301) 294-2905, pharmacist John Ferinde. The study site pharmacist can obtain ZDV after the site has completed site registration.

CHANGED TO READ:

The intravenous ZDV for intrapartum infusion and ZDV syrup for administration to newborns is supplied by **Glaxo** Wellcome, and will be distributed through the National Heart, Lung and Blood Institute (NHLBI) drug repository contractor (**McKesson Bioservices Inc.**) through the NHLBI Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850, phone: (301) 294-0741, FAX: (301) 294-2905, pharmacist John Ferinde. The study site pharmacist can obtain ZDV after the site has completed site registration.

Protocol List of Changes

20. Section 8.2. Randomization

Last Paragraph

READ:

When the proportion of women with pre-entry CD4+ lymphocyte counts >200/mm^3 AND less than six months ZDV use reaches 50 percent of the total study population, enrollment into this group will be terminated. No such enrollment restriction will be applied to women with pre-entry CD4+ count <200/mm^3 or women with greater than six months of prior ZDV use.

CHANGED TO READ:

When the proportion of women with pre-entry CD4+ lymphocyte counts **≥200**/mm^3 AND less than six 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 pre-entry CD4+ count <200/mm^3 or women with six months **or more** of prior ZDV use.

21. Section 8.3.2. Women: Intrapartum Treatment (IV ZDV)

2nd Bullet

READ:

- Treatment: When labor begins (labor being defined as regular uterine contractions associated with progressive effacement and dilation of the cervix) the woman should receive a loading dose of 2.0 mg/kg ZDV administered over one hour, followed by a continuous infusion at 1.0 mg/kg/hr. All women receive this dose, regardless of the time of the last dose of oral ZDV, or mode of delivery. If women are admitted for elective caesarean section at least 4 hours of ZDV infusion (the loading dose plus an additional 3 hours) is desirable. The length of treatment during labor will be recorded for all patients. Intravenous ZDV is terminated after the umbilical cord is clamped. Women who initiated ZDV during premature or false labor who are subsequently discharged and still pregnant should resume their pre-existing oral ZDV regimen; resume oral ZDV no sooner than 4 hours after infusion has stopped.

CHANGED TO READ:

- Treatment: When labor begins (labor being defined as regular uterine contractions associated with progressive effacement and dilation of the cervix) the woman should receive a loading dose of 2.0 mg/kg ZDV administered over one hour, followed by a continuous infusion at 1.0 mg/kg/hr. **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.** All women receive this dose, regardless of the time of the last dose of oral ZDV, or mode of delivery. If women are admitted for elective caesarean section at least 4 hours of ZDV infusion (the loading dose plus an additional 3 hours) is desirable. **Women admitted for induction of labor will have the ZDV**

infusion started at the time induction begins. The length of treatment during labor will be recorded for all patients. Intravenous ZDV is terminated after the umbilical cord is clamped. Women who initiated ZDV during premature or false labor who are subsequently discharged and still pregnant should resume their pre-existing oral ZDV regimen; resume oral ZDV no sooner than 4 hours after infusion has stopped.

3rd Bullet

READ:

- Dispensing: Intravenous ZDV must be diluted prior to administration. The calculated dose will be removed from the 20 ml vial (10 mg/ml) and added to 5 percent dextrose injection solution to achieve a concentration no greater than 4 mg/ml. After dilution, the solution is physically and chemically stable for 24 hours at room temperature, and 48 hours if refrigerated at 2-8 degrees Celsius. As an additional precaution, the diluted solution must be administered within 8 hours if stored at room temperature (25 degrees Celsius), or 24 hours if refrigerated at 2-8 degrees Celsius, to minimize potential administration of a microbially contaminated solution. The diluted drug does not need to be protected from light. Intravenous ZDV may be prepared by the site pharmacist or prepared on the labor & delivery unit.

CHANGED TO READ:

- Dispensing: Intravenous ZDV must be diluted prior to administration. **The dose of ZDV will be calculated based on the women's weight on the day of infusion.** The calculated dose will be removed from the 20 ml vial (10 mg/ml) and added to 5 percent dextrose injection solution to achieve a concentration no greater than 4 mg/ml. After dilution, the solution is physically and chemically stable for 24 hours at room temperature, and 48 hours if refrigerated at 2-8 degrees Celsius. As an additional precaution, the diluted solution must be administered within 8 hours if stored at room temperature (25 degrees Celsius), or 24 hours if refrigerated at 2-8 degrees Celsius, to minimize potential administration of a microbially contaminated solution. The diluted drug does not need to be protected from light. Intravenous ZDV may be prepared by the site pharmacist or prepared on the labor & delivery unit.

22. **Section 9.1. Concurrent Medications for Women**

READ:

Women may receive all medications/treatments as required for the obstetrical management of the HIV-infected woman (e.g., acyclovir for chronic suppressive therapy, ketoconazole, INH, antibiotics, or a change to other experimental antiretroviral therapy in pregnancy due to intolerance or disease progression on ZDV) except for anti-HIV vaccines or passive immunotherapy with HIVIG or IVIG (outside of the study drugs in this protocol).

Caution should be used with concomitant administration of drugs that are metabolized by hepatic glucuronidation, and may alter the metabolism of ZDV.

CHANGED TO READ:

Women may receive all medications/treatments as required for the obstetrical management of the HIV-infected woman (e.g., acyclovir for chronic suppressive therapy, ketoconazole, INH, antibiotics, or a change to other antiretroviral therapy in pregnancy due to intolerance or disease progression on ZDV) except for anti-HIV vaccines or passive immunotherapy with HIVIG or IVIG (outside of the study drugs in this protocol).

Caution should be used with concomitant administration of drugs that are metabolized by hepatic glucuronidation, and may alter the metabolism of ZDV.

Following delivery, maternal treatment may include approved and/or investigational antiretroviral agents other than ZDV.

23. **Section 10.0. Woman. Fetus and Infant Evaluations: General Issues**

5th Paragraph, 2nd Sentence

DELETED:

(e.g., PCR and HIV-IgA)

24. **Section 10.2. Evaluation of Infants: Outline and Rationale**

1st Paragraph

READ:

Infants will be evaluated at birth and at weeks 1, 2, 6, 12, 16, 20, 24, 36, 48, 60, and 78, or until reaching a study endpoint, whichever comes first. For infants who reach endpoint prior to the final study visit, a brief summary followup assessment, including vital status will be done by telephone every 3 months. This will be recorded on a study form and will replace the protocol required visits until the final study visit. All infant subjects, regardless of HIV infection status, will complete study visits through week 6 and will return for the final study visit, week 78.

CHANGED TO READ:

Infants will be evaluated at birth and at weeks 1, 2, 6, 12, 16, 20, 24, 36, 48, 60, and 78, or until reaching a study endpoint, whichever comes first. For infants who reach endpoint prior to the final study visit, a brief summary followup assessment, including vital status will be done by telephone every 3 months. This will be recorded on **the Pediatric Followup Form** and will replace the protocol required visits until the final study visit. All infant subjects, regardless of HIV infection status, will complete study visits through week 6 and will return for the final study visit, week 78.

Protocol List of Changes

4th Paragraph, 1st Sentence

DELETED:

(e.g., PCR and HIV-IgA)

5th Paragraph

READ:

HIV culture will be performed on newborn blood samples to evaluate study drug effects; HIV culture for diagnosis and for comparison to other early diagnostic tests will be performed at the newborn visit, weeks 6, 12, and 48. If HIV culture is positive (the child therefore meeting a study endpoint), prior to the final visit, an additional culture is drawn. In addition, all children, regardless of HIV infection status, will return at 18 months for a final evaluation, including HIV culture, due to concerns outlined below. At this visit, an HIV culture is repeated, unless 2 or more positive HIV cultures have been documented previously.

CHANGED TO READ:

HIV culture will be performed on newborn blood samples to evaluate study drug effects; HIV culture for diagnosis and for comparison to other early diagnostic tests will be performed at the newborn visit, weeks 6, **24**, and 48. If HIV culture is positive prior to the final visit, an additional culture **for confirmation** is drawn. In addition, all children, regardless of HIV infection status, will return at 18 months for a final evaluation, **which will include serology testing.**

DELETED:

5th and 6th Paragraph

A final visit (week 78) is scheduled for all children, regardless of HIV infection status, because of concerns that: a) administration of HIVIG to an infected child could delay the child's development of antibody (an infected child could become seronegative and then seropositive at a later date); and b) the less likely possibility that HIVIG could prolong the seropositive state in a child who is uninfected and truly seroreverting; and c) concerns that ZDV/HIVIG treatment could modify the sensitivity of HIV culture for the diagnosis of HIV infection.

Once a single HIV culture is positive, the child will meet HIVIG study endpoint for HIV infection; the child must be recalled and a second HIV culture must be drawn at this time. A child with negative HIV culture, but persistent HIV antibody positivity at 18 months of age also meets study endpoint for HIV infection. Children with ambiguous infection status (children with negative HIV cultures, but persistent antibody positivity less than 18 months of age) remain on study; if an investigator has concerns regarding the initiation of antiretroviral therapy in a specific child, consultation is available with the Case Classification Committee.

Protocol List of Changes

25. Section 10.2.2. Infant: Laboratory Evaluation

READ:

Pre-entry is defined as any time prior to the start of HIVIG therapy. Prior to initiation of ZDV, the infant must be screened to ensure the child meets criteria to begin drug (see Section 11.3). See Appendix XVI, Specimen Collection, Processing, and Storage Procedures.

CHANGED TO READ:

Pre-entry is defined as any time prior to the start of HIVIG/**IVIG** therapy. Prior to initiation of ZDV, the infant must be screened to ensure the child meets criteria to begin drug (see Section 11.3). See Appendix XVI, Specimen Collection, Processing, and Storage Procedures.

26. Section 11.2. HIV/IVIG Permanent Discontinuation - Women and Infants

5th Bullet

READ:

- Fetal death or development 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 Potter's syndrome.

CHANGED TO READ:

- 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 Potter's syndrome.

27. Section 11.4. Infant ZDV Toxicity: Permanent Discontinuation

DELETED:

6th Bullet. Evidence of HIV infection as defined in Section 12.1.

Protocol List of Changes

28. Section 12.1. Evaluation of HIV Infection in Infants

1st Paragraph

READ:

The efficacy of HIVIG to prevent the transmission of HIV in infants born to HIV-infected mothers receiving ZDV during pregnancy will be evaluated by comparing the rates of HIV infection among infants in the two treatment groups, HIVIG and IVIG. The laboratory evidence defined below are acceptable endpoint criteria. All infants satisfying endpoint criteria will be discontinued from further required interim study visits, and referred to other available pediatric trials or appropriate primary care upon completing the 6 week ZDV treatment period. For those infants not meeting definitive infection criteria, in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee.

CHANGED TO READ:

The efficacy of HIVIG to prevent the transmission of HIV in infants born to HIV-infected mothers receiving ZDV during pregnancy will be evaluated by comparing the rates of HIV infection among infants in the two treatment groups, HIVIG and IVIG. The laboratory evidence defined below are acceptable endpoint criteria. **All infants satisfying endpoint criteria will be discontinued from further required interim study visits except for study week 78 evaluation and referred to other available pediatric trials or appropriate primary care upon completing SV4 (week 6).** For those infants not meeting definitive infection criteria, in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee.

4th Paragraph

READ:

Definitively Infected: laboratory evidence of HIV infection demonstrated by:

- Children of any age: One (1) or more 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 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.

CHANGED TO READ:

For protocol purposes, an infant will be considered definitively infected on the basis of laboratory evidence of HIV infection **as** 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.

All endpoints will be reviewed and verified by a subcommittee of the protocol team. A verified endpoint will be defined as:

- **A positive culture confirmed by a second positive test for direct detection of HIV or components from a specimen obtained at the same or subsequent visits, or**

- **Repeated detection of HIV antibody as defined above.**

29. **Section 12.2. Safety and Tolerance of HIVIG**

READ:

The safety and tolerance of HIVIG therapy will be evaluated by examining adverse experiences and laboratory and clinical safety data between the two treatment groups (HIVIG and IVIG) both in women and infants. The development of HIV-related symptoms in women receiving HIVIG and IVIG will be compared, including development of HIV-related symptoms through 26 weeks postpartum following completion of HIVIG or IVIG therapy.

CHANGED TO READ:

The safety and tolerance of HIVIG therapy will be evaluated by examining adverse experiences and laboratory and clinical safety data between the two treatment groups (HIVIG and IVIG) both in women and infants. The development of HIV-related symptoms in women receiving HIVIG

and IVIG will be compared, including development of HIV-related symptoms through **78** weeks postpartum following completion of HIVIG or IVIG therapy.

30. **Section 13.1. Studies on Pharmocokinetic Samples**

2nd Bullet

DELETED:

(IgG, IgA, IgM)

31. **Section 14.1. Assessment of Major Endpoint**

1st Paragraph

READ:

The major endpoint of this trial is the proportion of HIV-infected infants born to women enrolled in the trial (the "HIV transmission rate"). Sample size for this trial is set assuming 10 percent noncompliance and 10 percent loss to follow-up. HIV infection status will be determined definitively for all children at 18 months of age. Data analysis will be undertaken on an intent-to-treat basis, provided that the HIV infection status of the infant or child is known.

CHANGED TO READ:

The major endpoint of this trial is the proportion of HIV-infected infants born to women enrolled in the trial (the "HIV transmission rate"). Sample size for this trial is set assuming 10 percent noncompliance and 10 percent loss to follow-up. **HIV infection status for the purposes of the primary efficacy analyses will be assessed on the basis of HIV culture data for all children by 6 months of age. Additional analyses will incorporate an assessment of infant HIV**

infection status on the basis of serologic testing at 18 months of age. Data analysis will be undertaken on an intent-to-treat basis, provided that the HIV infection status of the infant or child is known.

Last Paragraph

ADDED from Section 14.6

To address the theoretical possibility that the study drug could delay ability to detect HIV infection in infants by delaying infant seroconversion (false-negative endpoint) and to evaluate the possible occurrence of the phenomenon of spurious (nonrepeatable) detection of HIV in infants observed in other multicenter studies (130) of vertical HIV transmission (false-positive endpoint), subjects will be followed to 18 months until 100 culture-negative, antibody-negative infants have been followed to 18 months. This will assure that approximately 50 infants in the HIVIG treatment arm are followed for 18 months. If no delayed seroconversion occurs, there will be over 95 percent confidence that the delayed seroconversion rate for each arm separately is no more than 6 percent.

32. **Section 14.3. Monitoring the HIV Transmission Rate**

2nd Paragraph

READ:

The goal of this monitoring is to assure, as much as possible, that the completed study will have a minimum of 80 percent power to detect a 50 percent reduction in transmission. When monitoring of the overall transmission rate indicates that the transmission rate has dropped below 7.5 percent, the sample size will be increased. (**See Appendix XXI** for a statistical description of the methods used for monitoring the overall transmission rate and its independence from the efficacy analyses.)

CHANGED TO READ:

The goal of this monitoring is to assure, as much as possible, that the completed study will have a minimum of 80 percent power to detect a 50 percent reduction in transmission. When monitoring of the overall transmission rate indicates that the transmission rate has dropped below 7.5 percent, **alternative strategies to maintain adequate power to detect differences between the treatment groups will be considered including increases in sample size.** (See Appendix XXI for a statistical description of the methods used for monitoring the overall transmission rate and its independence from the efficacy analyses.)

33. **14.4. Planned Interim Analysis**

READ:

Interim analyses are planned using a Fleming, Harrington and O'Brien stopping rule (143, 144). It is planned that there will be four analyses occurring after approximately each quarter of the sample size is evaluated. The successive hypothesis tests will be conducted at the .005, .0061, .0075 and .0434 significance levels. At any analysis, if the difference in proportions of HIV transmission in the two arms attains the nominal significance level, the trial should stop. If not, the trial would continue and the next analysis (up to four) would occur. If the Chi-square test of the difference in proportions attains the nominal significance level for any analysis, the conclusion that one arm is better than the other can be drawn. Interim analyses will be stratified by CD4+ count, ZDV use, and enrollment region, within the limits of the data available. The DSMB will also monitor the toxicity of HIVIG plus ZDV and IVIG plus ZDV in women and infants.

Protocol List of Changes

CHANGED TO READ:

14.4 Efficacy Analysis

14.4.1 Endpoint Determination

As described earlier in Section 12.1, the endpoint for the efficacy analysis will be based on virology culture results up to six months of age. Infants with one or more confirmed culture results will be designated as HIV positive for the efficacy analysis; infants without such culture results will be designated as negative. As indicated above (end of Section 14.1), the analytical endpoint is defined as HIV transmission from the mother to one or more infants; thus the occurrence of transmission for multiple births is defined in terms of whether any of the offspring are HIV positive (see Section 14.1).

Some infants may have negative viral culture results throughout the first six months of life, but have positive viral culture results after six months. Based on data from ACTG 076 (142) and from WITS (121), we expect that approximately 2% of infants who will eventually test positive may *not* have positive cultures by six months. In the worst case, all new positive results after six months would be on the HIVIG arm, so that the actual treatment effect would be smaller that the one used in the efficacy analysis. However, even in this worst case, the effect on both power and Type I error are minimal, with a decrease in power of about 1% and an increase in Type I error of about 1%.

14.4.2 Timing of Analyses

There will be four efficacy analyses, occurring after approximately each quarter of the sample size has achieved six months of followup. The analyses will use stopping rules based on the method described by Fleming, Harrington, and O'Brien (143). The successive hypothesis tests will be conducted at the 0.005, 0.0061, 0.0075, and 0.0434 significance levels. At any analysis, if the difference in the estimated HIV transmission rate between the two arms attains the nominal level of significance, the trial should stop and the treatment

with the lower transmission rate would be concluded to be the better treatment. However, if the difference is not significant, the trial would continue and the next analysis would occur after the next quarter of patients has achieved the required followup.

14.4.3 Analysis Methods

The primary efficacy analysis will be based on transmission rates estimated using the Kaplan-Meier method (142, 144). The estimated transmission rate at six months will be used in these analyses. A simple, unstratified confirmatory analysis will be done based on the comparison of the proportion of transmissions among infants with six months or more followup between the two treatment arms.

The Kaplan-Meier estimates will be stratified by mother's CD4+ count at entry, mother's CD8+ count at entry, mother's quantitative viral culture (IUPM) at entry, mother's quantitative viral culture (IUPM) at labor and delivery, prior history of ZDV use, mode of delivery, infant birthweight, infant gestational age, other risk factors for HIV transmission (145), and enrollment region.

34. Section 14.6. Assessment of Primary Endpoint

DELETED:

Section was deleted and the information was moved to Section 14.1 as the last paragraph.

35. Sections 14.7 and 14.8

RENUMBERED:

Section 14.7 is now 14.6. Other Analysis

Section 14.8 is now 14.7. Late Outcomes

READS:

Section 14.6 Other Analyses

Additional analyses will be conducted on both mothers and infants. These analyses will include, but are not limited to, regression methods to identify factors that influence the occurrence or magnitude of the primary or secondary endpoints. Factors of interest will be of three main types: features of treatment, characteristics of the mother, and characteristics of the newborn. Examples include measures of compliance (e.g., the amount or number of infusions, whether or not the newborn received the planned infusion), CD4 counts and birth weight. For binary endpoints, such as infant HIV positivity, logistic regression will be used (146). For censored endpoints, such as time to HIV positivity, Cox regression will be used (147). For continuous endpoints, such as the **viral burden,** ordinary regression will be used (148).

Section 14.7 Late Outcomes

A pediatric late outcomes protocol (ACTG 219) has been developed to maintain surveillance for late sequelae in children enrolled in perinatal protocols. Assessment of growth and development, neurocognitive function and organ system abnormalities are performed on a regular basis, and children are followed through age 20 years. All children enrolled in ACTG 185, infected and uninfected, are eligible and encouraged to enroll in ACTG 219.

36. Section 15.2. Study Monitoring

5th Paragraph

READ:

An independent Data and Safety Monitoring Committee will meet, at regular intervals, to review all accumulated data on forms which it will approve. Furthermore, additional meetings will be convened if needed. This committee will determine whether a significant adverse effect or a clear treatment effect of HIVIG exists which could result in termination of the trial.

CHANGED TO READ:

An independent Data and Safety Monitoring Committee will meet at regular intervals, to review **accumulated data.** Furthermore, additional meetings will be convened if needed. This committee will determine whether a significant adverse effect or a clear treatment effect of HIVIG exists which could result in termination of the trial.

37. **Section 19.0 Site Registration**

READ:

* Site Registration Form;
* IRB approval letter;
* Copy of approved informed consent form;
* FDA form 1572 from each institution requiring an IRB approval;
* Curriculum vitae for pediatric and obstetric investigators involved with the study;

CHANGED TO READ:

* **Westat's** Site Registration Form;
* IRB approval letter **(to include OPRR assurance number for the site)**;
* Copy of approved informed consent form;
* FDA form 1572 from each institution requiring an IRB approval;
* Curriculum vitae for pediatric and obstetric investigators and **subinvestigators** involved with the study;

38. **Appendix IV. Study Drug (HIVIG/IVIG) Preparation and Administration**

READ:

Source: HIVIG - North American Biologic, Inc; IVIG - Mile, Inc.

Preparation: Aseptically place the correct volume of HIVIG/IVIG into a sterile bag or bottle. Study drug must be filtered with a 5.0 micron or smaller pore size filter prior to

dispensing. Follow individual institutional requirements regarding in-line filtration during patient administration of immune-globulin products.

CHANGED TO READ:

Source: HIVIG - **NABI**; IVIG - **Bayer**

Preparation: Aseptically place the correct volume of HIVIG/IVIG into a sterile bag or bottle. Study drug must be filtered **in the pharmacy** with a 5.0 micron or smaller pore size filter prior to dispensing. Follow individual institutional requirements regarding in-line filtration during patient administration of immune-globulin products.

39. **Appendix VII. HIVIG Pharmacokinetics**

Page 2

References of Ogden Bioservices was changed to McKesson Bioservices, Inc.

40. **Appendix X. Guidelines for Toxicity Management of HIVIG/IVIG: Women**

DELETED:

Asymptomatic - Level I, Symptomatic Level II, and Symptomatic Level III under Hypertension (Systolic) Category.

41. **Appendix XI. Guidelines for Toxicity Management of HIVIG/IVIG: Infants**

DELETED:

Asymptomatic - Level I and Level II and Symptomatic Level III under Hypertension Category.

Protocol List of Changes

READ:

Hypertension	Level I
	MAP 10 - 20 mmHg
	over baseline

CHANGED TO READ:

Hypertension	Level I
—	MAP **5 - 10** mmHg
	over baseline

42. Appendix XIV. Reporting of Adverse Experiences

READ:

3. For patients off drug:

   a. Report deaths which occur within three months;
   b. Report other adverse experiences/toxicities which occur within **8 weeks** and meet the reporting requirements as noted on the next page.

CHANGED TO READ:

3. For patients off drug:

   a. Report deaths **that** occur within three months **after coming off study**;
   b. Report other adverse experiences/toxicities **that** occur within 8 weeks and meet the reporting requirements as noted on the next page.

Protocol List of Changes

Page 3

READ:

AERs - Report initial abnormality when it reaches a reportable level. Chronic adverse events may be reported as continuing. When an adverse event improves to a non-reportable level, the event is resolved. If the event recurs, it should be reported as a new event. If the event increases in severity to another grade, the event at the lower grade is resolved, and the event at the increased grade is reported as a new event. If the nature/etiology of an adverse event changes, it should be reported as a new event.

CHANGED TO READ:

AERs - Report initial abnormality when it reaches a reportable level. When an adverse event improves to a non-reportable level, the event is resolved. If the event recurs, it should be reported as a new event. If the event increases in severity to another grade, the event at the lower grade is resolved, and the event at the increased grade is reported as a new event. If the nature/etiology of an adverse event changes, it should be reported as a new event.

READ:

Hospitalization - Unless the hospitalization is the result of an AE, the reason for the hospitalization should not be recorded on an AER form.

Oral ZDV taken by a woman during the antepartum period is not considered to be an investigational therapy for this protocol. Toxicities related to oral ZDV for the woman are not reported on an AER. However, intravenous ZDV administered intrapartum and ZDV administered to the infant are investigational therapies. An AER form must be completed for toxicities related to these therapies which satisfy the reporting criteria described above.

Protocol List of Changes

CHANGED TO READ:

Hospitalization - Unless the hospitalization is the result of an AE, the reason for the hospitalization should not be recorded on an AER form.

Oral ZDV taken by a woman during the antepartum period is not considered to be an investigational therapy for this protocol. Toxicities related to oral ZDV for the woman are not reported on an AER. However, **because** intravenous ZDV administered intrapartum and ZDV administered to the infant are **study drugs,** an AER form must be completed for toxicities related to these therapies which satisfy the reporting criteria described above.

READ:

MAIL all AER Forms to: Adverse Experience Report: WB 414
Westat, Inc.
1650 Research Boulevard
Rockville, MD 20852

CHANGED TO READ:

MAIL all AER Forms to: Adverse Experience Report: WB **427**
Westat, Inc.
1650 Research Boulevard
Rockville, MD 20852

43. **Appendix XVI. Specimen Collection, Processing, and Storage Procedures**

Page 1

References to Ogden Bioservices was changed to McKesson Bioservices. Shipping instructions are contained in **Appendix XVIII.**

Protocol List of Changes

Page 4

References to Ogden Bioservices was changed to McKesson Bioservices.

Page 8

References to Ogden Bioservices was changed to McKesson Bioservices. References to Maryland Medical Laboratory was changed to Corning Clinical Laboratories, Inc.

Page 13 and 14

SV #14 and SV #15, Processing for cells/plasma storage, information was added:

< 24 hr.: F-H, aliquot
cells and plasma, -70° C
freeze; ship q mo.

44. Appendix XVIII - Regulations for Shipping Etiological Agents

Information was updated to include ISS-2 packaging instructions and changes on the labelling of the boxes.

45. Appendix XX. Classification of Children Who Die or ar Lost to Follow-up While Still of Indeterminate HIV Infection Status, or Have Ambiguous HIV Infection Status

DELETED:

1. (e.g., children under 18 months old who are viral culture negative)

Protocol List of Changes

46. Appendix XXIIa. and XXIIb. Sample Informed Consent (English and Spanish)

READ:

ACTG 185 Version 4.0

CHANGED TO READ:

ACTG 185 Version 5.0

TABLE OF CONTENTS

APPENDICES

APPENDICES (continued)

1.0 PROTOCOL DESIGN

1.1 Title

Phase III Randomized, Double-Blind, Controlled Study of Hyperimmune Anti-HIV Intravenous Immunoglobulin (HIVIG) for the Prevention of Maternal-Fetal HIV Transmission in HIV-Infected Pregnant Women and Newborns Receiving Zidovudine (ZDV).

1.2 Study Design

A multicenter, randomized, controlled trial to evaluate the efficacy, safety, and tolerance of the combination of HIV hyperimmune globulin (HIVIG) (administered during pregnancy and to the newborn within 12 hours of birth) and ZDV (administered intrapartum and to the newborn for 6 weeks following birth), compared to IVIG and ZDV administered similarly, for the reduction of vertical HIV transmission in HIV-infected pregnant women who are receiving ZDV during pregnancy for medical indications.

1.3 Study Population

HIV-infected pregnant women who are receiving ZDV during their pregnancy for medical indications (i.e., have pre-entry CD4 count $\leq$ 500/mm^3). **An estimated** one-half will have pre-entry CD4 < **200**/mm^3 and/or ZDV treatment duration of 6 months or more.

1.4 Estimated Sample Size

800 women (720 evaluable mother-infant pairs).

1.5 Stratification

- Pre-entry CD4 count < or $\geq$200/mm^3
- ZDV therapy begun prior to or after conception
- Geographic region of study center

1.6 Randomization

HIV-infected pregnant women receiving ZDV, entry between 20-30 weeks gestation:

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

1.7 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 hrs of birth
	ZDV syrup:	2.0 mg/kg PO q6h birth to week 6

1.8 Endpoint

Definitive HIV infection status in the infant.

2.0 PROTOCOL TEAM MEMBERS

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3.0 BACKGROUND AND STUDY RATIONALE

3.1 Epidemiology

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.

As of **December 1995, 71,818** cumulative cases of acquired immunodeficiency syndrome (AIDS) in women have been reported to the Centers for Disease Control (CDC). **In 47** percent of women, **injection** drug use is reported as the route of HIV exposure, and in an additional 37 percent heterosexual contact is reported as the route of HIV exposure (2). The majority of these women are of childbearing age. Cumulatively, **6,948** cases of pediatric AIDS cases have been reported. The extent of AIDS and HIV infection in the pediatric population, where HIV is predominately acquired by vertical transmission from mother to infant, is clearly linked to the prevalence of HIV infection in women of childbearing age.

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 (3). Vertical transmission accounts for almost 90 percent of AIDS in U.S. children (2). 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).

Worldwide, the World Health Organization (WHO) estimates that during the first decade of the AIDS pandemic approximately 500,000 AIDS cases have occurred in women and children, with an additional three million deaths in women and children projected during the

1990s. The WHO estimates 30 percent excess infant and child mortality in major American, Western European, and sub-Saharan African cities where AIDS has become the leading cause of death for women aged 20-40, and expects not only hundreds of thousands of pediatric AIDS cases during the 1990s but also more than a million uninfected children orphaned because their HIV-infected mothers and fathers died from AIDS (6).

3.2 Maternal-Fetal Transmission

3.2.1 Timing of Vertical Transmission

Vertical transmission of HIV may occur before, during, or after parturition (via breast feeding) (7-11). Information regarding the timing of transmission and the relative proportion of transmission events occurring in relation to gestation and parturition is limited. Evidence for both intrauterine and peripartum timing of transmission exists.

HIV genome has been identified using polymerase chain reaction (PCR) as early as the 12th week of pregnancy by Courgnaud et al. (12). Soeiro et al. (13) studied human abortus tissue and suggested that up to 30 percent of HIV transmissions may occur by the second trimester of pregnancy. However, the possibility of contamination from maternal sources is difficult to exclude definitively in any study of aborted fetal tissues. The presence of p24 antigen in newborn serum or a positive HIV culture shortly after birth also suggests that the infant was infected during pregnancy (7-9), although it is possible that the presence of detectable virus in infected neonates may be due to intensive exposure to virus present in maternal blood and genital tract secretions at the time of birth.

Alternatively, the inability to detect by currently available laboratory methods direct or indirect evidence of HIV infection until up to four months of age in 50 percent to 70 percent of exposed infants ultimately proven to be infected suggests that the timing of transmission may be peripartum in the majority of cases (14). Ehrnst et al. (15) in a prospective evaluation of 47 pregnancies in 44 HIV-infected women found no consistent transplacental spread of HIV during maternal viremia. Maternal viremia, in either peripheral blood mononuclear cells or plasma, was

detected during pregnancy in 83 percent of women; however, HIV was isolated in 0 of 27 newborns, of whom 26 percent (5 of 19) were subsequently proven infected by six months. Viral genome was detected in only 2 of 12 abortuses. They concluded most cases of transmission occurred close to or at delivery.

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 (16).

To maximize the potential for therapeutic intervention(s) to prevent vertical transmission, it will probably be necessary to provide therapy both during pregnancy as well as intrapartum. Additionally, to provide adjunctive short-term antiretroviral activity following the intensive viral exposure presumed to occur at birth, therapy administered to the newborn may be necessary.

3.2.2 Maternal Factors and Vertical Transmission

Over the past few years, numerous attempts have been made to quantify the risk of HIV transmission from mother to infant. Prospective studies from the United States and Europe place the overall rate of vertical transmission between 15-32 percent, averaging approximately 25 percent (17, 18). Rates reported from Africa are somewhat higher, approaching 40 percent (19, 20). Geographic variation in vertical transmission rates may reflect differences in the severity of HIV infection within the cohorts of women of childbearing age in these locations.

Factors influencing HIV transmission from mother to child are incompletely defined, but appear to include those maternal clinical, virologic, or immunologic characteristics that are also likely to be regarded (independent of pregnancy) as indications for antiretroviral therapy. Advanced disease stage, high viral load and depressed immunologic status have all been associated with increased rates of vertical transmission:

- Disease stage: D'Arminio et al. (21) observed among a cohort of 66 patients in Italy increased rates of vertical transmission associated with more advanced disease stage (100% among the 10 patients with CDC class IV disease compared with 7 of 56 (13%) patients with CDC class II or III disease). Hague et al. also observed in a cohort of 58 HIV-infected women in Edinburgh increased rates of HIV vertical transmission in women who had AIDS during pregnancy or diagnosed after the birth of the child (22).

- Viral load: It is likely that pregnant women with a high virus load, evidenced by high titers of HIV virus or p24 antigenemia, represent a group at particularly high risk for HIV maternal-fetal transmission. Acute viremia associated with maternal seroconversion in the year prior to pregnancy or during breast feeding appears to be associated with increased rates of vertical transmission (22, 23). Kreiss et al. (24) observed among a Kenyan cohort of 22 patients a vertical transmission rate of 72 percent associated with proviral load of >10/100,000 lymphocytes within six months of delivery, compared with vertical transmission of 27 percent in patients with proviral load of <10/100,000 lymphocytes. Boue et al. (25) observed in a cohort of 88 patients in France vertical transmission rates of 78 percent associated with high levels of viral replication and 50 percent with p24 antigenemia, respectively, compared with rates of 16 percent in patients with low viral replication levels and 26 percent in patients without p24 antigenemia. In their cohort of 66 HIV positive pregnant women, D'Arminio et al. (21) observed transmission of 100 percent among seven p24 antigen positive women compared with 10 of 59 (17%) p24 antigen negative women.

- CD4+ lymphocyte count: Advanced immunologic deterioration associated with decreased maternal numbers of circulating CD4+ lymphocytes appears to be associated with increased risk of vertical transmission. St. Louis et al. (26) observed among 146 patients in Zaire an inverse relation between the CD4+ percentage of total lymphocytes and rates of vertical transmission (for percent CD4+ >30%, 20-29%, 10-19%, and <10%, transmission rates were 23%, 49%, 63%, and 77%, respectively). Similarly, Burns et al. (27) in a cohort of 74 pregnant women in New York City observed that women whose lowest prepartum CD4+ level was $\leq$ 20 percent were at greater risk of transmitting HIV to their child (42% versus 18%), particularly when analysis was limited to values obtained in the third trimester. Tibaldi et al. (28) observed in a 25-patient cohort in Italy vertical transmission rates of 71 percent in those with CD4+ lymphocyte counts <400/mm^3 and/or p24 antigenemia compared with rates of 6 percent in those without antigenemia and with CD4+ counts >400/mm^3. Boue et al. (25) observed among 88 patients in France a vertical transmission rate of 66 percent in those with CD4+ lymphocyte counts <150/mm^3 compared with vertical transmission of 26 percent in those with CD4+ counts >150/mm^3.

3.2.3 Maternal Antibodies to Specific HIV Epitopes

The level and specificity of maternal antibodies may play a crucial role in determining transmission. Several studies have suggested that HIV-infected pregnant women with high titers of antibodies to certain epitopes of the gp120 envelope protein, the third hypervariable loop (V3), may have a lower rate of HIV transmission to their infants.

Rossi et al. reported that the absence of antibody to two epitopes (C51 and C57 peptides) of the gp120 envelope of HTLV-IIIB located near the base of the V3 loop was correlated with HIV-1 transmission from infected mothers to their offspring (29). In a retrospective study of 33 newborns born to HIV infected women in Italy, 5 of 19 (26%) uninfected infants had C57 peptide antibody compared with 0 of 14 infected newborns. In the prospective portion of their report, C57 peptide antibody was detected in 9 of 13 (69%) non-transmitting women compared with 1 of 8 (12%) transmitting women; C51 peptide antibody was found in 8 of 13 (62%) non-transmitting and 1 of 8 (12%) transmitting women. A subsequent prospective study from the same group reported similar findings (30).

Goedert et al. (31), in a prospective study of 51 HIV-infected pregnant women in New York City, reported a higher transmission rate from women who lacked antibodies to native gp120 when evaluated during the third trimester; 28 of 35 (80%) nontransmitting women had antibody compared to 6 of 16 (38%) transmitting women. In infants born prematurely ($\leq$37 weeks) the amount of maternal antibody was not correlated with transmission, but in full term infants ($\geq$38 weeks) high reactivity against gp120 was associated with protection from transmission.

Devash et al. (32) reported that women with "high affinity/avidity" antibodies directed toward a peptide they termed the principal neutralizing domain (PND) of gp120 (derived from the top of the V3 loop) were less likely to vertically transmit HIV. In a prospective study of 15 HIV-infected women and their infants, they reported that sera from all 11 transmitting women had reactivity below cutoff, demonstrating presence of only low affinity/avidity antibody, whereas sera from 3 of 4 non-transmitting women had high affinity/avidity antibody.

Two studies have reported a potential increase in perinatal transmission from women with higher titers of antibody to gp160. Markham and colleagues reported in a selected group of women from a prospective cohort in Haiti that women who transmitted infection to their infants had somewhat higher mean concentrations of IgG1 antibody to a synthesized 35 amino acid concensus peptide sequence of the V3 loop of gp120 than did non-transmitters (33). Lallemant and colleagues reported from a study of a selected group of 70 HIV-infected pregnant women derived from a prospective cohort in Brazzaville, Congo that an increased risk of perinatal transmission was observed from women with higher antibody titers to synthesized peptides to V3 (V3Cons) and gp41 (TMSP18) of gp160 (34).

Other researchers have not found any association between maternal antibodies to various synthetic peptides and perinatal transmission (35, 36). It is unclear whether differences in results are due to minor differences in technique, variations in the HIV strains studied by the various groups and those in the population under evaluation, or other factors. Subtle but important methodologic differences exist between the various reported assays, including the methods for preparing peptides (37).

Important viral neutralizing activity may also be associated with antibody to regions outside the V3 loop or to a conformational epitope rather than a linear peptide. Ugen reported that women who have high titer antibody to gp41 were less likely to transmit to their infants (38). More recently, Ugen reported that transmitting mothers had lower levels of binding to epitopes that encompassed the entire envelope region than mothers who did not transmit (39).

Maternal neutralizing antibody activity may need to be evaluated in the context of her own and her infant's viral isolates. Several investigators have reported that nontransmitting mothers more frequently have antibody to their own virus than do transmitting mothers, and that transmitting mothers only rarely have neutralizing activity against their child's isolate (40, 41). It has also been reported that mothers with autologous neutralizing antibody frequently have antibodies that also neutralize heterologous primary isolates (40).

HIV shows variation over time in a given infected individual, particularly within the V3 loop region, and evolution of HIV variants in vivo may occur more rapidly in patients with high viral load and high rates of viral replication. This variation may result from immune-driven selection of neutralization-resistant viral variants. The specificity of circulating antibody may lag behind that of the existing viral variants within an individual by several months.

Several investigators have observed that the viral population found in infected infants is highly homogeneous in comparison to the maternal viral population (42 - 46). Such data suggest that there may be transmission of a single or very few maternal viral variants to the infant, perhaps involving selective transmission of neutralization-resistant maternal viral variants. The data from the above studies evaluating antibody against autologous primary isolates is consistent with this hypothesis.

Therefore, evaluation of an association of perinatal transmission with maternally-derived antibody to synthetic peptide sequences might be expected to yield conflicting results. Additionally, in the presence of high viral load and intensive viral replication, maternally-derived antibodies may not protect the fetus from concurrently transmitted virus, due to the lag between existing viral variants and the development of neutralizing antibody.

At present, no conclusion can be drawn regarding the potential for neutralizing antibody to attenuate, prevent or increase HIV perinatal transmission. Administration of pooled antibody from multiple donors could provide a broad range of antibodies that could neutralize maternal virus not capable of being neutralized by the existing maternal antibodies. Antibodies present in such a polyclonal preparation would have activities in addition to neutralization, such as binding to natural killer cells (antibody-dependent cellular cytotoxicity), which while not neutralizing, could prevent cell-cell transmission of virus. Administration of antibody could attenuate transmission by decreasing the amount of infectious virus in the maternal circulation, prevention of HIV infection of placental cells, providing protective antibody to the fetus during the last trimester of pregnancy and at delivery, or all of these. Therefore, evaluation of a polyclonal HIV immune globulin preparation for the prevention of perinatal HIV transmission is warranted.

3.3 Antiretroviral Therapy in Pregnancy and the Newborn

On 2/21/94, announcement of the preliminary results of a Phase III, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy, safety, and tolerance of zidovudine for the prevention of HIV transmission from infected pregnant women to their infants (ACTG protocol 076) provided for the first time proof of the concept that a preventive intervention can reduce vertical HIV transmission (47). Based on analysis of data for 364 evaluable births through December, 1993, zidovudine treatment according to the regimen employed in ACTG 076 appeared to reduce the risk of HIV transmission by two thirds, from 25.5 percent to 8.3 percent. Eligible subjects were HIV-infected pregnant women who had received no antiretroviral therapy during their current pregnancy, who had no maternal clinical indications for antiretroviral therapy, and who had CD4+ T-lymphocyte counts above 200 per microliter at study entry. The study treatment that was compared with placebo consisted of antepartum maternal oral zidovudine, 100 mg five times daily begun between 14 and 34 weeks of gestation, intrapartum maternal intravenous zidovudine, 2 mg/kg then 1 mg/kg/hr until delivery, and 6 weeks of oral newborn zidovudine, 2 mg/kg every 6 hours, begun 8 to 12 hours after birth. Zidovudine treatment in ACTG 076 was not associated with increases in reported maternal side effects, adverse fetal or neonatal outcomes, or infant toxicity except for mild, self-limited anemia.

Efficacy of ZDV for reduction of vertical HIV transmission in women with advanced HIV disease who are already receiving antiretroviral treatment according to current clinical indications for their own health, or with CD4+ T-lymphocyte counts of 200 per microliter or below, or both was not evaluated in ACTG 076. However, based on the results of ACTG Protocol 076 and the theoretical potential for prophylactic ZDV to reduce transmission in other groups of patients, the U.S. Public Health Service currently recommends that the components of the ACTG Protocol 076 regimen be recommended or considered (depending upon the particular clinical situation) for virtually all HIV-infected pregnant women. (47)

It is known that ZDV treatment reduces plasma viremia, temporarily increases CD4+ cell numbers, and mitigates disease progression for adults with CD4+ counts $\leq 500/mm^3$. Didanosine (ddI) and Zalcitabine (ddC), nucleoside reverse transcriptase inhibitors with antiretroviral action similar to ZDV, have been licensed as alternative therapies for ZDV in patients

failing or intolerant to ZDV. A State-of-the-Art Conference convened by NIH in 1992 made the following recommendations (48): For patients with symptomatic HIV infection or asymptomatic persons with CD4+ counts below 200/mm^3, ZDV is recommended as first line therapy; for asymptomatic patients with CD4+ counts between 200 and 500/mm^3, ZDV therapy should be considered. Accordingly, evolving obstetrical standards of care for HIV-infected pregnant women now include consideration of the use of orally administered ZDV for the medical benefit of those pregnant women with CD4+ counts $\leq$ 500 /mm^3, and the administration of ZDV to those pregnant women with CD4+ counts $\leq$ 200/mm^3.

The State-of-the-Art Conference also recommended consideration of switching from ZDV to ddI monotherapy in patients who are clinically stable but have received prolonged ZDV therapy. For those patients failing or intolerant to ZDV, change in therapy to either ddI or ddC is recommended (48). There is very little data regarding the use of ddI or ddC during pregnancy, and use of the drugs would, therefore, be considered experimental; for pregnant women with symptomatic HIV disease who can't tolerate ZDV or are experiencing disease progression, however, consideration of alternative drugs may be necessary.

Administration of an antiretroviral agent to a pregnant woman in theory could reduce the risk of neonatal infection by reducing the exposure of the fetus to maternal virus, or by prophylaxis of the fetus prior to exposure. Because it is postulated that intense exposure of a potentially uninfected fetus to HIV present in maternal blood and genital tract secretions occurs during parturition, the design of this study includes intrapartum administration of ZDV followed by six weeks of oral ZDV to the infant. An identical regimen for ZDV administration was employed in ACTG Protocol 076.

The proposed 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.

Resistance to ZDV has been observed to develop in some patients receiving prolonged ZDV therapy (49). It is unclear how often resistant virus could be vertically transmitted; only a few cases of vertical transmission of resistant virus have been reported (50, 51). Stored viral isolates from selected mother-infant isolate pairs in this study may be evaluated for the presence of genotypic/phenotypic ZDV resistance.

3.3.1 Safety and Pharmacokinetics of ZDV in Pregnancy

Comprehensive data regarding the use of ZDV is contained in the **Glaxo** Wellcome Investigator's Brochure **and package insert**. Additional information on ZDV pharmacokinetics in HIV-infected pregnant women and their infants and on clinical experience with ZDV in HIV-infected pregnant women is contained in ACTG Protocol 076 (52).

The following summarizes maternal ZDV dosing in the proposed study: HIV-infected pregnant women (20-30 weeks' gestation) receiving oral ZDV according to current FDA-approved label indications for HIV-infected adults are eligible for study participation. Women enrolled in the study will receive oral ZDV as prescribed by their physician until the intrapartum period, at which time intravenous ZDV in a loading dose of 2 mg/kg will be administered over one hour followed by continuous infusion of ZDV at 1.0 mg/kg/hour until the umbilical cord is clamped.

3.3.2 Safety and Pharmacokinetics of ZDV in Infants

A Phase I study to evaluate safety and pharmacokinetics of intravenous and oral ZDV in 32 asymptomatic infants from birth to three months of age with perinatal exposure has been completed (53). The pharmacokinetics of ZDV were evaluated in each infant after single intravenous and oral doses of ZDV on consecutive days, and during chronic oral administration of the drug for four to six weeks. Doses of ZDV were progressively increased during the study from two to four mg/kg. Therapy was continued for up to 12 months in four of the infants proven HIV-infected.

ZDV kinetics were linear within the dose range of two to four mg/kg. Total body clearance of ZDV increased significantly with age, from 15.0 ml/kg/min in infants less than one month to 23.4 ml/kg/min in older infants. Concurrently, ZDV half-life decreased after 14 days of age, from 2.5 to 1.6 hours. Oral absorption was satisfactory, and bioavailability varied significantly with age, from 64 percent in infants less than one month to 86 percent in older infants.

ZDV was well tolerated by all infants, with only nine infants developing anemia that was presumed to be drug-related during therapy. The onset of anemia occurred between study weeks two and three at dose levels $\geq$ three mg/kg. Nine other instances of one or more hemoglobin values < 10 g/dl were reported that were not felt to be related to drug therapy. Six infants had declines in hemoglobin detected between study days 29-46. These appeared to be dose related; five of six were receiving ZDV at four mg/kg/dose. Within one month off therapy, all six children had an increase in hemoglobin to > 10 g/dl. Three children had presumed drug related neutropenia which occurred between study days 7-29.

These data suggest that ZDV is safe and well tolerated by newborns and infants.

The infant ZDV dosing in the proposed study is as follows: ZDV dosing for infants enrolled in the present study will be identical to that for infants enrolled in ACTG Protocol 076. Infants without contraindication to ZDV will begin receiving oral ZDV within 24 hours after birth in a dose of 2 mg/kg every six hours for six weeks. Infants unable initially to receive oral medication will begin receiving ZDV intravenously in a dose of 1.5 mg/kg every six hours.

3.4 HIV Hyperimmune Globulin (HIVIG)

3.4.1 Preparation and Antibody Content

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 (54). This intravenous IgG solution

(HIVIG) is prepared from plasma of multiple HIV seropositive donors from geographically diverse regions of the United States who are selected according to strict clinical and biological criteria. Donors are clinically asymptomatic, with a CD4+ lymphocyte count equal to or above 400 cells/mm^3. The donor plasma contains high titers of anti-p24 antibody (used as an index of strong immune response to HIV), high virus neutralizing activity and high reactivity with MN strain V3 loop peptide, is negative for HIV antigen, and is unable to infect PHA stimulated normal lymphocytes in the presence of IL-2.

The preparation of HIVIG includes multiple steps to inactivate **and/or partition** HIV including treatment of the plasma with solvent/detergent, and fractionating the IgG by Cohn-Oncley alcohol precipitation and ion exchange chromatography. The final 5 percent solution of HIVIG contains 98 percent monomeric IgG.

As shown in Appendix VIII, Subclass Distribution and Specific Markers in HIVIG and IVIG, all prepared HIVIG lots have contained an anti-p24 antibody titer $\geq$ 100,000, anti-gp41 titer > 4000, and anti-gp120 titer > 1000. All preparations contained all four subclasses of IgG; however, HIVIG has a lower percentage of IgG2 and a higher content of IgG1 than does polyvalent IVIG. Lots all test negative by tissue culture and PCR for HIV. Data shown in Appendix IX demonstrate that all lots have elevated titers of neutralizing activity against the indicated HIV strains tested. HIVIG is active in antibody dependent cellular cytotoxicity (ADCC) and also contains antibodies to the V3 loop peptides present in four strains tested (IIIB, MN, WMJ and SC) (see Appendix IX, Blocking of HIV-Cell Interaction). HIVIG at concentrations of 500 mcg/ml provided inhibition of *in vitro* infectivity of HIV in T cells, and this inhibitory activity was enhanced when studied in combination with ZDV, suggesting that combination therapy with HIVIG and ZDV may provide additive or synergistic antiviral activity.

In cultures of HIV-infected monocytes/macrophages, HIVIG concentrations lower than 10^{-3} mcg/ml induced moderate enhancement of HIV infection. This effect was not present with higher concentrations of antibody or at concentrations present in an infected individual. In addition, a recent study evaluating HIVIG effects using primary human blood monocytes and peritoneal macrophages did not demonstrate any enhancing effect of HIVIG at high or low dilutions in non-cell line-derived, freshly isolated cells (55). Antibody levels achieved with HIVIG

at doses of 200 mg/kg in human safety studies would be 10,000 fold higher than those reported to be associated with *in vitro* enhancing activity (54).

3.4.2 Safety and Pharmacokinetics

The toxicity of HIVIG has been tested successively in two chimpanzees and 13 HIV-infected patients. In all cases, no clinical or biological sign of toxicity has been observed. Two chimpanzees received a total dose of one g/kg. No evidence of HIV infection was found, as evidenced by the absence of development of IgM immune response, negative plasma and lymphocyte culture and negative result with HIV PCR. In these animals, anti-HIV antibody to p24, gp41 and gp120 were noted with a biological half-life of these activities from 11 to 17 days. Antibody to hepatitis A virus used as control had similar half-life. Similar results were obtained with New York Blood Center HIVIG preparations (56).

The human safety study involved 13 HIV-infected patients: 12 HIV-infected persons who had a prior history of *Pneumocystis carinii* pneumonia, all of whom were receiving ZDV, and one patient who was asymptomatic and not receiving ZDV (57). The first episode of *Pneumocystis* pneumonia had occurred from 5 to 32 (mean 13.4) months prior to enrollment. CD4+ lymphocyte count at enrollment ranged from 5 to 435 (mean 54)/mm^3. Patients received four doses of HIVIG intravenously at 28 day intervals: the first two doses received were 50 mg/kg, and the last two were 200 mg/kg. Scheduled laboratory and clinical follow-up thus far has extended to 56 days after the fourth dose.

All 13 patients completed all four doses and were followed until death or continued under follow-up. Only one patient experienced a side effect attributed to infusion of HIVIG: a period of light-headedness shortly after receiving the third dose. During the study, three patients developed Kaposi's sarcoma, one subject lost weight to below 90 percent of baseline body weight, and two subjects developed hemoglobin below 8.5 gm/dl.

After completing the two low dose infusions, the total IgG rose 0.64 g/L; after completing the additional two high dose infusions, total IgG rose 2.63 g/L. Anti-p24 titers, as

measured by competitive EIA, increased to 5,436 after the two low dose infusions, and increased to 19,199 following the two high dose infusions. Half-life of IgG and of anti-p24 antibody were 17 and 15.9 days, respectively, following the fourth dose.

In the six patients who were p24 antigen positive at entry, p24 antigen became undetectable; in these patients the anti-p24 antibody half-life was shorter than in the p24 antigen negative patients. CD4+ lymphocyte count and beta-2-microglobulin levels remained level in all patients over the five month observation period. Plasma HIV cultures obtained before and 24 hours after the first dose (cultured in a paired fashion) showed a time-to-positivity in the post-infusion culture that was equal or longer to that observed prior to infusion in all patients (mean 8.9 days to positivity at study entry to mean 17.9 days to positivity after the first infusion). Thus, at the 50 mg/kg dose in HIV-infected humans, no enhancement of HIV infection was observed; in contrast, a delay in time to plasma culture positivity was seen. Differences in the titer of virus in paired frozen plasma specimens (prior to and 24 days following the first 50 mg/kg infusion) were equivocal. In the five patients evaluated, peripheral blood mononuclear cell proliferative response to pokeweed mitogen (1:200) rose during HIVIG administration.

Thus, HIVIG was safe and well tolerated when used at doses of 50 mg/kg and 200 mg/kg in HIV-infected symptomatic persons. No evidence of enhancement of HIV infection was observed. Anti-p24 antibody, anti-hepatitis A, and total IgG pharmacokinetics were within the expected range for immune globulin in these patients; however, the half-life of anti-p24 antibody was somewhat shorter in p24 antigen positive patients.

3.4.3 Preliminary Efficacy Studies

Initial studies in chimpanzees did not show HIVIG protected against a large experimental challenge with HIV (400 $TCID_{50}$) (56). However, HIVIG was found to be protective at a lower HIV challenge (120 $TCID_{50}$) and at a higher dose of HIVIG (1000 mg/kg) in one chimpanzee (Prince, personal communication). This preparation was assayed for its neutralization activity and compared to two clinical preparations of HIVIG; all lots had similar neutralization activity.

A cynomolgus monkey model, in which hyperimmune serum to HIV-2 and SIVsm obtained from vaccine-immunized monkeys was administered six hours preceding an intravenous challenge with live homologous cell-free virus, demonstrated that passive immunization was able to successfully prevent infection (58, 59). In the HIV-2 system, a low dose (3 cc/kg) of HIV-2 hyperimmune globulin protected one of four animals and a higher dose (9 cc/kg) protected two of three animals, as demonstrated by negative viral culture, PCR and antibody production. In the SIVsm system, a higher dose (9 cc/kg) protected three of four animals. All control animals were infected.

Eichberg et al. (60) reported on the success of passive immunization in chimpanzees. Similar to the report of Prince et al., HIVIG did not protect against a high dose viral challenge (up to 1200 $TCID_{50}$), but did provide protection against a lower viral challenge dose (120 $TCID_{50}$). When HIVIG was given in a dose of one ml/kg, with an antibody titer in the animal of 1:40 at the time of viral challenge, protection was not seen; however, when given in a dose of 10 ml/kg, with an antibody titer in the animal of 1:640 at the time of viral challenge, protection was seen, as evidenced by negative viral isolation and PCR. Thus, a dose response relationship was observed.

Emini and colleagues (61) used a passive immunization preparation that contained a mouse-human chimeric IgG1 antibody specific for the principal neutralizing domain (PND) of the V3 loop portion of gp120 of HIV-1 IIIb in a chimpanzee model. Twenty-four hours after passive immunization (achieving a titer of 1:320 at the time of challenge), the chimp was challenged with a 75 chimpanzee infectious dose of an HIV-1 IIIb isolate. The control animal became infected within three weeks post-challenge; the immunized chimp had no evidence of infection over 18 weeks post-challenge. These data provide evidence for an *in vivo* protective effect of anti-PND antibody, consistent with the preliminary and still indeterminate findings described in humans in Section 3.2.3.

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 (57). 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 HIV hyperimmune globulin preparations (62 - 66) and in one child with AIDS who received passive immunotherapy with HIV immune plasma (67).

In summary, HIVIG appears safe and well-tolerated in HIV-infected persons, persists in the circulation for substantial periods of time, similar to IVIG, and has demonstrable neutralizing capacity *in vitro*.

3.4.4 Establishment of HIVIG Study Dose

HIVIG will be studied at a 200 mg/kg intravenous dose based on the IgG levels achieved in clinical safety studies and anti-HIV activity observed in *in vitro* functional assays.

In all functional assays examining the antiviral activity of HIVIG, inhibitory activity was noted at antibody concentrations that can be achieved and sustained in recipients with monthly dosing at 200 mg/kg. Inhibition of syncytia formation occurred at concentrations of 375-1800 mcg/ml IgG, ADCC activity occurred at 2.5-250 mcg/ml, and inhibition of HIV replication in monocyte/macrophages occurred at 50-500 mcg/ml.

Based on previous human studies at the 200 mg/kg dose, HIVIG will produce plasma levels in excess of 2600 mcg/ml (57). Assuming a minimum of a 15 day half-life and monthly dosage, levels of > 650 mcg/ml could be maintained at all times. Even in pregnancy, where a three compartmental model of distribution could be considered, the antibody levels should be sufficient to provide adequate antiviral and/or neutralizing activity. It is anticipated that the provision of these levels of antiviral antibody in the HIV-infected pregnant woman and the newborn within 12 hours of delivery may neutralize circulating infectious HIV, and thereby presumably reduce or prevent transplacental and/or peripartum HIV infection of the fetus/infant.

3.5 Intravenous Immune Globulin (IVIG)

3.5.1 IVIG in Pregnancy

Both intramuscular (68-70) and intravenous immune globulin (71-73) have been used extensively in immunodeficient pregnant women, since such therapy is the treatment of choice for primary antibody deficiency syndromes. Several studies detail the successful use of repeated infusions of IVIG in pregnant women with passage of IgG to their fetus (71-73). Doses employed were 100-200 mg/kg every three to five weeks.

IVIG has also been used extensively in the treatment of immune thrombocytopenic purpura (ITP) of pregnancy, using considerably higher doses, i.e. one to two gm/kg over two to five days (74-80). IVIG therapy may also prevent thrombocytopenia of the infant, but not reliably.

IVIG has also been used in autoimmune hemolytic anemia of pregnancy (81), severe Rh sensitization (82-84), alloimmune thrombocytopenia (85), lupus anticoagulant syndrome with recurrent abortion (86), and recurrent abortions (87).

Very large doses of IVIG have been given to women at 27 to 36 weeks gestation who had signs of chorioamnionitis and were at risk for preterm delivery (88, 89). Doses ranged from 12 to 120 grams. If IVIG was given prior to 32 weeks gestation, minimal IgG crossed into the fetus. However, one study found increases of fetal IgG as early as 25 weeks gestation (90). After 32 weeks, all IgG subclasses traversed the placenta, as did specific antibodies present in the infused IgG. There is evidence that antibodies and IgG that cross to the fetus are conserved in the fetus, with the result that IgG levels in term newborns are higher than in maternal serum (91). This is probably because transfer of antibody from fetus to mother does not occur (92), so that antibodies accumulate in the fetus.

In all of these studies and the recent review of the use of IVIG in pregnancy by Sacher and King (93), IVIG was well tolerated in pregnant women, without adverse effects for the fetus. Limited pharmacokinetic studies indicate that the plasma volume is increased in

pregnancy so that IgG levels may be less than anticipated; thus replacement therapy for antibody deficiency may need to be increased to maintain a targeted IgG level (93). Studies of IVIG pharmacokinetics in pregnant women with ITP and their newborns indicate that the ability of exogenous IVIG administered to the mother to cross the placenta in amounts therapeutic to the fetus may be achieved only after multiple infusions (94, 95). Maintenance of high maternal IgG levels throughout pregnancy, or in the third trimester, may be most important for transplacental transport of IgG to the fetus.

3.5.2 IVIG in the Neonate

Human intramuscular immune serum globulin (HISG) has been used extensively in newborns with safety and efficacy. Several trials of repeated injections of HISG in premature infants to prevent infections have been completed with excellent safety records but variable efficacy (96-101). Furthermore, hepatitis B immune globulin, a high-titered preparation pharmacologically identical to regular HISG, is recommended to be given immediately after birth to all infants whose mothers are identified as hepatitis B antigen carriers. This therapy has been used for a decade in thousands of infants without reported adverse effects; it is 75-90 percent efficacious in preventing vertical transmission of hepatitis B and is even more efficacious when combined with hepatitis B vaccine.

More recently, IVIG (a further modified or purified derivative of HISG) has been used in the prevention and treatment of bacterial sepsis in newborns, particularly premature infants (< 1500 grams). IVIG doses have ranged from 200 mg/kg up to 1000 mg/kg with a mean dose of approximately 500 mg/kg; repeat doses are given at weekly intervals. Most of these studies are small (< 50 patients) from single institutions (102-109). However, several large multicenter studies are ongoing (110, 111). Only rare side effects of IVIG have been noted. Baker et al. (110) infused 250 premature infants with 500 mg/kg IVIG and noted only "rare transient tachycardia". Clapp et al. (111) infused 206 premature infants within 48 hours of birth with 500 to 700 mg/kg of IVIG; only one developed transient hypotension and tachycardia that disappeared with discontinuing the infusion. These studies suggest, but do not prove, that IVIG decreases morbidity and mortality, particularly in infants < 1500 grams. Such infants have

decreased transplacental IgG and profound physiologic hypogammaglobulinemia in proportion to their degree of immaturity.

The potential side effects of IVIG in newborns include: 1) adverse immediate reactions such as occasionally seen with IVIG in adults (allergic, cardiovascular); 2) the rare possibility of transmission of viral diseases such as non-A, non-B hepatitis, CMV or HIV; and 3) inhibition of antibody response to vaccines. In general, the risk of immediate reactions seems to be minimal and less than observed in adults receiving IVIG. With the exception of a single recalled product (Gammagard®) associated with hepatitis C transmission in a small number of patients, there are no reported cases of transmission of hepatitis, HIV or other viral diseases as a result of administration of FDA approved IVIG or HISG products. Both immunoglobulin preparations used in this trial have multiple inactivation steps and neither has been associated with transmission of bloodborne pathogens. (The Gammagard® product employed a single inactivation step.) In limited studies, antibody response to vaccines in infants who have received IVIG has not been affected (101, 112). In addition, a recent study evaluating the effect of high dose IVIG in preterm infants did not demonstrate any suppressive effect on the infant's own immunoglobulin production during the first year of life (113).

Since the dose of IVIG or HIVIG (200 mg/kg) to be used in this protocol is considerably below that used in many of the studies above, it is felt that the single infusion given in this study should be a safe and well-tolerated dose in any size or gestational age infant.

3.6 Diagnosis of HIV in Newborns

The diagnosis of vertically transmitted HIV infection in infants is complicated by difficulties unique to this age group. In newborns and young infants, transplacentally acquired maternal IgG antibody renders unreliable the standard HIV-specific antibody detection enzyme immunoassay or immunoblot assays used to establish the laboratory diagnosis of HIV infection in older children and adults. In the absence of clinical evidence of HIV infection in infants and children under 18 months of age, diagnosis of HIV infection requires **direct detection of virus**

or viral components in blood or tissues by HIV culture, viral nucleic acid detection methods such as polymerase chain reaction, or HIV p24 antigen assays (114).

Advances in viral detection assay development and performances have made it possible to diagnose HIV infection in nearly all HIV-infected infants by 4-6 months of age (115).

Definitive laboratory diagnosis of HIV infection by viral culture is the accepted reference standard (116). Although sensitivity of HIV culture is 50% or lower during the first week after birth, it increases to >90% by age 3 months and to nearly 100% by 6 months of age (117-119).

The performance of serial viral culture for diagnosis of HIV infection has been evaluated in prospective cohort studies. Sensitivity of a single culture is approximately 90% at ages from 1-6 months, with positive and negative predictive values 97-98%. When cultures are obtained at two separate ages from 1-6 months, at least one of any two cultures is positive in 95-100% of infected infants. The specificity of negative cultures obtained at two separate ages after one month is 99-100% for establishing the absence of HIV infection (117, 120).

With repeated sampling, the cumulative probability of first detecting a positive culture in an infected infant exceeds 95% beginning at about six weeks of age. One large prospective cohort study showed that 95% of 140 infected infants in whom 1-5 serial cultures were performed had a first positive culture obtained by the 6-month visit. No infant demonstrated consistently negative serial cultures beyond 6 months, and all 3 infants with negative or missing cultures through the 6-month visit were positive when next sampled beyond 6 months (121).

Administration of antiretroviral treatment does not appear to delay or reduce ability to detect HIV infection by viral cultures in infants with perinatal HIV exposure. In AIDS Clinical Trials Group protocol 076, virtually all infected infants were identified by 6

months of age, and the estimated intervals before the first positive culture were virtually identical for infants who received zidovudine and infants who received placebo (122).

Based on these data, it is now accepted in clinical practice that infection status for nearly all infants can be determined by age 4-6 months. In 1995, existing guidelines for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) in HIV-exposed or infected infants and children were revised to indicate that HIV infection can be reasonably excluded at 4 months of age for purposes of clinical management. The CDC guidelines now state that HIV infection can be reasonably excluded among children who have had two or more negative HIV diagnostic tests (i.e., HIV culture or PCR), both of which are performed at 1 month of age or older and one of which is performed at 4 months of age or older (123).

However, although viral culture represents the reference standard, its practical utility is limited by the complex, time-consuming, and resource intensive nature of currently available techniques (124). Sample volume limitations in small infants impose an additional restriction on the use of standard techniques for viral culture.

As developments in therapeutic research provide possibilities for early prophylaxis against secondary infectious complications of HIV (125) and begin to provide prospects for early treatment with specific antiretroviral agents (126-128), the need becomes more pressing to develop capabilities to distinguish infected from uninfected but perinatally exposed, seropositive infants in prompt, rapid, and reliable fashion, even earlier than current advances now permit. Early ability to detect vertically transmitted HIV infection would facilitate the evaluation of agents designed to interrupt transmission. Through earlier diagnosis, benefits could accrue also in the complex and difficult decision-making process faced by state and local child welfare/protective services agencies with regard to foster care placement or adoptive services for infants in need, as well as in easing the psychological burden of waiting, anxiety, and uncertainty that presently available diagnostic methods impose in parents and other caregivers.

Detection of viral nucleic acid sequences using gene amplification techniques such as polymerase chain reaction has the advantage of being able to detect very small amounts of virus. The sensitivity and specificity of PCR as an early diagnostic tool for

detection of proviral HIV-1 DNA has been evaluated by several investigators. One meta-analysis showed HIV-1 DNA detected by PCR in an estimated 38% (90% confidence interval, 29-46%) of infants tested on the day of or day after birth. Sensitivity rose rapidly during the second week to 93% by 14 days of age (129). However, false positive tests have been reported, most commonly secondary to laboratory error due to carryover of amplified product DNA from a previously analyzed sample. In addition, the optimal time of sampling remains to be established. Recently, techniques for detection of viral RNA have become available, permitting detection and quantitation of free viral particles. In theory, RNA detection may be presumed to be even more sensitive than DNA detection for early diagnosis of HIV infection, but evaluation of these methods for this indication remains to be accomplished.

The present study therefore proposes to include as a nested study, the evaluation of newer methods for early diagnosis of HIV infection, compared with viral culture. Because the purpose of the early diagnosis substudy will be to evaluate the use of these research diagnostic methods for HIV detection, assays will be performed retrospectively in batched fashion, and will not be available routinely for clinical management purposes. Evaluations may include DNA and RNA detection methods, as well as other methods to identify, quantify, and characterize virus, to be specified by the protocol team. Additionally, placental samples when available will be evaluated for the presence of HIV RNA, to evaluate the utility of this technique for early diagnosis and to address questions regarding the timing of transmission.

3.7 Study Rationale

3.7.1 Study Population and Rationale

The proposed 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.

The selection of the proposed study population and intervention is based on the following considerations:

- HIV-infected pregnant women who are receiving ZDV for medical indications are a different, and presumably noncomparable, patient population than HIV-infected women who do not have medical indications for ZDV therapy. The principal reasons for this difference are that certain of the clinical, virologic, and immunologic characteristics associated with ZDV use are presumed also to be associated with a higher rate of vertical HIV transmission, as discussed in Section 3.2.2.

- The selection of a patient population with higher risk of vertical transmission increases the likelihood that an effect of any intervention designed to interrupt transmission will be detected in a sample of limited size. While ZDV therapy may decrease the rate of vertical transmission in the population of women in this study, these women are also likely to have significantly higher rates of vertical transmission to begin with, and thus even with a ZDV treatment effect equivalent to that observed in ACTG 076 (67%), these women are likely, with ZDV treatment, to have transmission rates above that observed in the ACTG 076 participants.

- The selection of a combination regimen (HIVIG plus ZDV) over single agent therapy may enhance the likelihood that a reduction in vertical transmission will be observed.

- Single-agent therapy with ZDV has been demonstrated to reduce vertical transmission in a large multicenter randomized controlled clinical trial (ACTG Protocol 076) of patients with relatively early stage HIV disease and little or no prior antiretroviral use. Little or no data exists currently on the safety or efficacy of this or similar interventions in HIV-infected women with more advanced disease and/or prior antiretroviral use.

- The selection of a study population in whom presumed greater fetal risk of HIV infection exists better balances any (expected low) risk of fetal exposure to ZDV or HIVIG that may be incurred. Because of clinical and/or immunologic status, the women in this study and their physicians have already decided that ZDV therapy during pregnancy is necessary.

- The selection of the proposed control agent (IVIG) against which the proposed study agent (HIVIG) will be compared is designed to control for potential nonspecific beneficial immunoglobulin effect of the study agent

(HIVIG) on study outcome. Additionally, the use of IVIG as a control agent offers the theoretical potential advantage of beneficial immunoglobulin effects demonstrated in other populations (infection prophylaxis, treatment of autoimmune hematologic complications of HIV) to study participants randomized to the control arm of the study.

- The CD4+ lymphocyte counts and prior ZDV use patterns of the women enrolled in the study will be evaluated as part of each of the scheduled interim monitoring analyses provided to the DSMB. When the proportion of women with pre-entry CD4+ count $\geq$**200**/mm^3 AND less than six 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 pre-entry CD4+ counts <200/mm^3 or women with **six months or more** of prior ZDV use.

Based on results from ACTG 076, an HIV transmission rate of approximately 10 percent is anticipated in women with CD4+ T-lymphocyte count between 200-500/mm^3 who receive ZDV for the first time during pregnancy. Many studies have documented that HIV-infected pregnant women with CD4+ T-lymphocyte count below 200/mm^3 have an increased baseline risk of transmission to their infants compared to those with higher CD4+ count, with rates varying from as low as 31 percent to as high as 60 percent (20, 26 - 28, 130, 131). Even assuming ZDV is given for the first time during pregnancy to the women enrolling in ACTG 185 and that the ACTG 076 ZDV regimen would reduce perinatal transmission by the 67 percent observed in ACTG 076, perinatal transmission rates in women with CD4+ counts below 200/mm^3 could still be as high as 20 percent.

Additionally, the antiviral effect of ZDV is known to be time limited; increase in viral load as measured by PBMC culture, p24 antigen and RNA PCR can be observed after 4 to 6 months of chronic ZDV administration (132). Therefore, ZDV effectiveness in reducing perinatal transmission might be reduced in HIV-infected pregnant women with more prolonged ZDV therapy than was given in ACTG 076, and transmission rates would be anticipated to be above the 10 percent observed in ACTG 076 patients with CD4+ between 200-500/mm^3.

To ensure enrollment of women at highest risk of HIV transmission despite ZDV therapy and with a baseline control group transmission rate of at least 15 percent, **approximately** 50 percent of women enrolling in ACTG 185 **should** have entry CD4+

lymphocyte counts <200/mm^3 or will have received ZDV for **6 months or more**. The rationale is the following: if 50 percent of the patients enrolled had CD4+ counts between 200-500/mm^3 and received <6 months of ZDV therapy (similar to the ACTG 076 population), a transmission rate of 10 percent is anticipated. Based on the above discussion, the anticipated transmission rate in patients with CD4+ <200/mm^3 and/or ZDV greater than or equal to 6 months would be approximately 20 percent or more. Thus, if at least 50 percent of women were at highest risk for transmission (low CD4+ count and/or longer duration ZDV), we anticipate a total control group transmission rate for at least 15 percent. With a sample size of 800 (400 per arm), there would be power adequate to detect a 50 percent treatment effect if the control group transmission rate was 15 percent.

3.7.2 Rationale for Further Stratification

To account for higher potential for vertical transmission in those women with CD4+ <200 cells/mm^3 at entry, further stratification will be done to insure an equivalent number of women with CD4+ < 200/mm^3 in control (IVIG) or treatment (HIVIG) groups.

There is preliminary evidence that the length of ZDV therapy influences the effect of ZDV on the level of HIV virus and HIV susceptibility to ZDV, with individuals receiving ZDV for $\geq$ **six months** having higher levels of HIV and less susceptible virus than those receiving ZDV for < six months (132-135). Accordingly, a further stratification will be done based on whether a woman received ZDV before pregnancy or was started on ZDV during this pregnancy.

Centers will be grouped according to geographic region, and these two stratifications will be done for each region so that all regions have comparable treatment and control groups.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the effect of combination therapy with HIVIG (administered beginning between 20-30 weeks of pregnancy and to the newborn within 12 hours of birth), and ZDV (administered intrapartum and to the newborn for 6 weeks), compared to IVIG and ZDV, administered similarly, on the incidence of HIV infection in infants born to HIV-infected women who are receiving ZDV for medical indications.

4.2 Secondary Objectives

Establish the pharmacokinetics of the HIVIG preparation by measuring HIV-specific antibody (quantitative p24 antibody) pre- and post-infusion in a small subset of pregnant women and in their newborns (see Section 13.0 and Appendix VII, HIVIG Pharmacokinetics).

To evaluate maternal virologic and immunologic factors involved in HIV transmission from mother to infant, and the influence of HIVIG on these parameters, as delineated below:

- 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 HIV antibody, V3 loop antibody (type-specific MN and cross-reactive IIIB), and neutralizing antibody in transmitting and nontransmitting women and in their infants.
- Evaluation of ZDV genotypic/phenotypic resistance in selected mother-infant viral isolates.

To 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 in this protocol.

To evaluate the response of selected laboratory markers of HIV infection (plasma viremia and cell culture, p24 antigen, and CD4 count) and HIV-associated symptoms during pregnancy and through 78 weeks postpartum in women receiving HIVIG compared to those receiving standard IVIG.

To evaluate the safety and tolerance of HIVIG when administered in combination with ZDV to pregnant HIV-infected women.

To evaluate the safety and tolerance of HIVIG when administered in combination with ZDV (given for 6 weeks after delivery) to infants with perinatal HIV exposure.

5.0 STUDY OUTLINE

This Phase III randomized, double-blind, controlled, multicenter study is designed to evaluate the efficacy, safety and tolerance of the combination of HIVIG (administered during pregnancy and to the newborn within 12 hours of birth), and ZDV (administered intrapartum and to the newborn for 6 weeks following delivery), compared to IVIG and ZDV, administered similarly, for the reduction of HIV infection in infants born to HIV-infected women who are receiving ZDV during pregnancy for medical indications.

The estimated sample size is a total of 800 mother-infant pairs (720 evaluable pairs). Pregnant women with documented HIV infection who are receiving ZDV during their pregnancy for medical indications will be identified at participating NIAID or NICHD Clinical Trials Units or from the surrounding community. The women will be eligible for randomization to HIVIG or IVIG between 20 and 30 weeks of pregnancy (inclusive), and will be stratified by CD4 count at the time of entry ($<200/mm^3$ or $\geq 200/mm^3$), ZDV therapy begun prior to or after conception (as an initial surrogate for duration of ZDV therapy), and geographic region of study center. Treatment will consist of HIVIG, 200 mg/kg by intravenous infusion every 4 weeks up to delivery, or standard polyvalent, HIV-antibody negative IVIG, in the same dose and regimen. The newborn infant will receive within 12 hours of birth an intravenous infusion of HIVIG or IVIG, 200 mg/kg, with infant study drug matched to maternal study drug.

All pregnant women enrolled will receive intrapartum ZDV, given during labor in an intravenous loading dose of 2.0 mg/kg followed by a continuous infusion of 1.0 mg/kg/hr until the umbilical cord is clamped. All infants will receive ZDV syrup (2 mg/kg PO q 6 hr) as soon as he/she can tolerate p.o. fluids and within 8-12 hours of birth. If the child remains NPO, intravenous ZDV may be initiated at 1.5 mg/kg q 6 hr. Treatment of the infant with ZDV will continue for a total of six weeks.

Data relevant to the woman's pregnancy and HIV disease status will be collected, to evaluate the safety and tolerance of HIVIG when administered in combination with ZDV, and to evaluate the influence of HIVIG compared with IVIG on maternal disease progression.

Followup of the women will be extended through 18 months postpartum to evaluate longer-term safety and whether any influence of HIVIG on disease progression is sustained. Co-enrollment by women, who have completed the treatment portion of the protocol (through Labor and Delivery) is permitted in other investigational treatment studies.

Infants will be seen for toxicity monitoring and/or evaluation for evidence of HIV infection at weeks 1, 2, 6, and 12, then every 4 weeks through week 24, every 12 weeks through week 60, and a final evaluation at week 78 (18 months). Infants with documented HIV infection may co-enroll in other pediatric investigational treatment protocols. Long-term followup of infected and uninfected infants will occur through co-enrollment in ACTG 219.

The trial will be conducted on both an inpatient and outpatient basis. Women's visits will be conducted on an outpatient basis during pregnancy and postpartum, and on an inpatient basis during labor, delivery and the immediate postpartum period until discharge. Infants will be followed initially in the newborn nursery and later on an outpatient basis at the participating study site.

A subset of mother-infant pairs enrolled early in the study (up to 50 enrollees) will have pharmacokinetic studies performed to measure quantitative HIV-specific antibody levels achieved with HIVIG (as compared to IVIG control) in the mother and her infant. Additional studies nested in this protocol will evaluate maternal virologic and immunologic factors involved in HIV transmission from mother-to-infant, and compare the sensitivity and specificity of **newer** tests **for detection of HIV-1 genomic material to** HIV culture for the early diagnosis of HIV infection in this population of infants who have all had both prenatal exposure to and neonatal treatment with ZDV. Placental samples, when available, will be evaluated for HIV RNA. In addition, HIV-related manifestations of disease progression in women receiving HIVIG and IVIG will be evaluated, as defined by measurement of certain laboratory parameters (HIV plasma viremia and cell culture, p24 antigen and CD4 count) and HIV-related clinical symptoms in women during pregnancy and postpartum.

To conserve the amount of blood needed for the required substudy evaluations, special processing of blood samples has been devised to maximize the use of cells and plasma

obtained at women and infant visits. It is recognized that for some clinical centers who have currently ongoing federally-funded natural history studies there may be a conflict with duplicate sampling requirements for children or pregnant women participating in both a natural history study and the HIVIG maternal transmission factor or early diagnosis substudy. Such duplicate blood drawing is undesirable. Those sites with such conflict may be exempted from the maternal transmission factor or early diagnosis substudy blood sampling but still participate in the HIVIG protocol if they document in their implementation plan a detailed justification for such an exemption, including documentation of competing duplicate blood sampling requirements in another current federally-funded study. The decision for site exemption will be made by the Implementation Plan Review Committee; it is anticipated that such exemptions will be unusual.

The Data and Safety Monitoring Board (DSMB) will evaluate the safety and efficacy parameters and data from the nested protocols at regular intervals throughout the course of the study. A decision will be made by the DSMB at each of these reviews whether the study will continue as originally designed.

6.0 PATIENT SELECTION

6.1 Inclusion Criteria for Women

- Evidence of HIV infection documented by an EIA with an appropriate confirmatory test, positive p24 antigen, or positive viral culture (blood or CSF).
- On ZDV therapy during current pregnancy:
- Pre-entry CD4 count $\leq 500/mm^3$;
- An estimated gestational age on the day of randomization between 20 weeks, 0 days and 30 weeks, 6 days (inclusive) 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 $\geq$ 8.0 gm/dl;
  - * Serum creatinine $\leq$ 1.5 mg/dl; or eight-hour urine creatinine clearance > 70 ml/min.;
  - * Urine protein < 2+ by dipstick or < 4 gm protein in a 24-hour urine collection.
- Availability of venous access (placement of a central venous line or Hickman catheter for study purposes alone, is not indicated).
- At least $\geq$ 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 (see Appendix XXIII a & b: Sample Informed Consent).

6.2 Exclusion Criteria for Women

- 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.

- Illness 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 $\geq$ 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 of 140/90 on two or more occasions more than six hours apart, proteinuria at least 5 gm in a twenty-four 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 $\geq$ 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 $\geq$200/mm^3 AND less than six 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 six 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.**

7.0 NUMBER/SOURCE/MANAGEMENT OF PATIENTS

7.1 Number of Patients

A total of 720 evaluable mother-infant pairs (360 per arm) are expected for final analysis. Allowing for 10 percent non-evaluability, a target accrual of 800 (400 per arm) pregnant HIV-infected women who are receiving ZDV for medical indications and their infants will be enrolled in this trial.

7.2 Source of Patients

This will be a multicenter clinical trial.

All participating sites will receive approval from their local Institutional Review Board (IRB). Women participating as study subjects must be followed at a participating study center. Infants participating as study subjects must also be followed at a participating study center.

If a prenatal care or delivery site does not have a local IRB, approval must be obtained from another IRB approved by the Office for Protection of Research Risks (OPRR). Documentation of IRB approval at associated delivery sites must be submitted prior to enrolling pregnant women and infants. All sites must have assurances approved by the OPRR.

In addition, prior to enrolling pregnant women and infants in this protocol, each site must submit site registration material and an implementation plan for this protocol. The implementation plan must be approved by the designated Protocol Implementation Plan Review Committee prior to drug shipment.

The essential points of the HIVIG implementation plan are similar in nature to those addressed in ACTG 076 implementation plans submitted to the Division of AIDS (DAIDS), NIAID. The review committee for the HIVIG protocol implementation plans will have overlapping

personnel with the 076 plan review committee. **The** completed **ACTG 076 Checklist adapted for ACTG 185** must be attached to the 185 site implementation plan. The ACTG 185 site implementation plan **and the ACTG 076 Checklist adapted for ACTG 185 are** included with the site registration form attached to this protocol.

7.3 Management of Patients

7.3.1 Management of Women

This study will be initiated during the woman's prenatal visits. Women will be eligible for randomization to HIVIG or IVIG between 20 weeks and 30 weeks of pregnancy. Randomization will be stratified by geographic region of study center, the woman's pre-entry CD4 count (< 200 or $\geq 200/mm^3$), and receipt of ZDV therapy beginning prior to or begun after conception (as an initial surrogate measure for duration of ZDV therapy). A small subset of pregnant women enrolled early in the study will participate in a nested pharmacokinetic study (see Section 13.0, Pharmacokinetics).

All pregnant women must be receiving oral ZDV for medical indications to enter this study. Medical management of ZDV therapy and dose adjustments for toxicity should be consistent with currently recommended guidelines (48). At labor, all women will receive continuous intravenous ZDV, which will be discontinued after the umbilical cord is clamped. Women may receive any other therapies considered necessary for sound clinical management by their physicians, including prophylaxis for *Pneumocystis carinii* pneumonia (123). Pregnant women who have ZDV discontinued for medical indications (toxicity or disease progression) after study entry may remain on study, and will receive the intrapartum ZDV infusion, unless the investigator determines the infusion is contraindicated; decisions to omit the intrapartum infusion must be discussed with the Protocol Chair. Pregnant women who discontinue ZDV for medical indications, and who, for medical management at the discretion of their physician, receive experimental therapy with a different antiretroviral agent may remain on study, but will receive the intrapartum ZDV infusion as above. **Following delivery, maternal treatment may include approved and/or investigational antiretroviral agents other than ZDV.**

While pregnant women who have had CVS or PUBS prior to study entry or anticipated to be medically indicated during this pregnancy are excluded from study entry, if after entry any such procedure is medically indicated, patients may continue on study. Information regarding the occurrence of such procedures will be collected as part of the study.

Women will be followed by their primary obstetrician at the study site. After completion of routine postpartum follow-up care and the final protocol-specified visit 18 months postpartum, if the study obstetrician is not the woman's primary care provider, referral to a primary care provider with expertise in HIV-related illness should be made, with an emphasis on referral to a caregiver with access or referral to HIV-related clinical trials.

7.3.2 Management of Infants

Treatment will be initiated in the infant in the newborn nursery and will continue on an out-patient basis. Placenta and cord blood samples will be obtained at the time of birth. It is the responsibility of the principal investigator to coordinate site-specific logistics between obstetric, neonatal, pediatric, and pharmaceutical professional staff.

Infants will receive the same study treatment (HIVIG or IVIG) as the mother's randomized treatment assignment. HIVIG or IVIG will be given to the infant as soon as possible after birth. For theoretical 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 afterward. A small subset of infants will participate, along with their mothers, in a nested pharmacokinetic study (see Section 13.0).

All infants will receive oral ZDV syrup as soon as he/she can tolerate p.o. fluids and within 8-12 hours of birth. If the child remains NPO, intravenous ZDV may be initiated. ZDV treatment of the infant will continue for a total of 6 weeks.

Infants will be monitored at day 1 (newborn), weeks 1, 2, 6, 12, and every 4 weeks through week 24 (6 months), every 12 weeks through week 60, and a final visit at week 78 (18

months). Infants may receive therapy considered necessary for sound clinical management by their physicians, including prophylaxis for *Pneumocystis carinii* pneumonia, (123) while on protocol.

All infants must complete study visits through study week six (study visit 4) regardless of HIV infection status. An infant who satisfies study endpoint criteria for the definitive determination of HIV infection status (see Section 12.1) prior to the final study visit will be discontinued from further interim-required study visits after completing study week six and after the confirmatory culture is drawn. These infants will be referred to therapeutic care or to an experimental treatment protocol. The infants will be placed on an every three month schedule to obtain vital status information (telephone contact is acceptable). Every infant regardless of HIV status must complete the final visit at study week 78 (18 months). Refer to Section 10.2.3 for information about requirements for this study visit. For those infants not meeting definitive infection criteria (Section 12.1) in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee. All infants, regardless of HIV status, return for the final 78 week study visit.

7.4 Investigator Compliance

- Study site participation may be discontinued for any significant deviations from the protocol or for lack of enrollment.
- The study site investigator is responsible for a) the accuracy and completeness of research records; b) ensuring appropriate clinical and laboratory evaluations are conducted as scheduled; and c) the control and distribution of study drugs at the study sites, including pre- and post-natal clinical site, labor and delivery site, newborn nursery and pediatric clinical site.

7.5 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.

Infants may be seen $\pm$ 1 day from the scheduled visit for the 1 week visit, $\pm$ 2 days for the 2 week visit, $\pm$ 1 week for visits at week 6 through 24, and $\pm$ 4 weeks for visits at week 36 through 78.

Patients who deviate from the visit schedule will be eligible to continue therapy as randomized at their next study visit.

8.0 STUDY PROCEDURES

An implementation plan must include specifics regarding drug storage and distribution, for the study drugs (HIVIG and IVIG) as well as the intrapartum ZDV (given intravenously) and infant ZDV. The essential points that need to be addressed in implementation plans will be sent to sites upon request. The plan must be approved by the HIVIG Protocol Implementation Plan Review Committee prior to drug shipment.

8.1 Drug Supply and Storage

The study site pharmacist is required to maintain the complete records of all study drugs received from the repository and subsequently dispensed to the protocol participants. These records will be reviewed by the study monitor. All study drug not administered to women/infants must be retained or returned to the pharmacist according to policies as outlined in the Pharmacy Guidelines and Instructions for the AIDS Clinical Trials Group. No drug transfers will be authorized between this protocol and other ACTG protocols (i.e., ACTG 273, etc.).

8.1.1 HIVIG and IVIG

HIVIG (purchased from **NABI**) and IVIG (purchased from **Bayer**) will be distributed through the National Heart, Lung, and Blood Institute (NHLBI) drug repository contractor (**McKesson Bioservices Inc.**, through the Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850, phone: (301) 294-0741, FAX #: (301) 294-2905), pharmacist John Ferinde. The study site pharmacist can obtain the study drug (HIVIG and IVIG) for this protocol by faxing orders to the above number after the site has received site registration approval. Guidelines for study drug administration (HIVIG/IVIG) may be found in Appendix IV.

HIV-IG™ , HIV Immune Globulin (Human) is a preparation of highly purified human immune globulin containing high titres of antibody to HIV structural proteins. It is a 5% protein solution for intravenous usage. IVIG, Gamimune® N, Immune Globulin Intravenous (Human), is supplied as a 5% protein solution for intravenous usage.

- The study drugs will be supplied in the following dosage forms: HIVIG 50 mg/ml, in 10 ml, 50 ml, and 250 ml vials; IVIG 50 mg/ml, in 10 ml, 50 ml, 100 ml and 250 ml vials.

- The preparation contains no preservatives and must be stored refrigerated at 2-8 degrees Celsius. Precautions should be taken to protect against freezing or heating. Solutions which have been frozen or heated must not be administered to patients. Vials should be visually inspected at room temperature for unusual cloudiness, color changes, or gross particulate matter, etc. Vials must be returned if the solution fails inspection.

- Before preparation of HIVIG/IVIG, the unopened vials should equilibrate to ambient (room) temperature. This will provide for easier filtration and transferring. In circumstances when subjects do not show up for their scheduled infusion, the unopened vials may be allowed to be at room temperature for up to 8 hours and then may be returned to the refrigerator for future use.

  - Aseptically place the correct volume of HIVIG/IVIG into a sterile bag or bottle. Filter with a 5 micron or smaller pore size filter prior to infusion. The infusion must start within one hour of pooling. Entered vials must be used immediately; do not retain for future use.

  - HIVIG/IVIG should not be infused with other drugs. The bag or bottle should be piggybacked to 5% dextrose solution (D5W) in case the infusion needs to be stopped.

8.1.2 Zidovudine (ZDV)

The intravenous ZDV for intrapartum infusion and ZDV syrup for administration to newborns is supplied by **Glaxo** Wellcome, and will be distributed through the National Heart, Lung and Blood Institute (NHLBI) drug repository contractor **(McKesson Bioservices Inc.)** through the NHLBI Blood Specimen Repository, 685 Lofstrand Lane, Rockville, MD 20850,

phone: (301) 294-0741, FAX: (301) 294-2905, pharmacist John Ferinde. The study site pharmacist can obtain ZDV after the site has completed site registration.

- ZDV will be supplied for the intrapartum infusion and the infant in the following dosage forms:
  - ZDV for IV infusion, 10 mg/ml, in 20 ml vials
  - ZDV syrup, 10 mg/ml, in 240 ml bottles

8.2 Randomization

Pregnant women will be randomized, via a computer generated randomization schedule, to one of two treatment groups (HIVIG or IVIG) after stratification by geographic region of study center, pre-entry CD4 count (<200 versus $\geq 200/mm^3$) and ZDV therapy begun prior to or after conception.

Group 1: Pregnant women will receive HIVIG 200 mg/kg every 28 days until labor; during labor an intravenous loading dose of ZDV, 2 mg/kg, is administered over one hour, followed by continuous infusion of ZDV at 1.0 mg/kg/hr during the intrapartum period. As soon as the newborn infant has stabilized, an IV will be started. The infant will receive 200 mg/kg total dose of HIVIG by infusion, within 12 hours of delivery. The infant will begin ZDV syrup 2 mg/kg q 6 hr as soon as he/she can tolerate p.o. fluids and within 8-12 hours. 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.

After eligibility is established by the clinical center, a patient identification number (PID) is assigned. At this time the eligibility information will be sent by FAX to Westat at (301) 517-4188 for review of eligibility. After verification of eligibility, the subject's data will be

entered into the computer at Westat and then classified into strata formed using the following variables:

1. Geographic region of study center;
2. Pre-entry CD4 count < 200 versus $\geq$ 200/mm^3; and
3. ZDV therapy begun prior to versus after conception.

After stratification, women will be assigned a sequential study identification number (SID) by the randomization computer program. The assignment will be made using the method of random permuted blocks (136). The study coordinator at the clinical center will be informed by Westat via telephone of the SID number, and will receive by FAX from Westat a hard copy report of the PID and SID. The study coordinator will report the SID number to the clinical center pharmacist. The pharmacist will prepare the appropriate infusion after referring to a SID list, a computer generated listing provided by Westat at the outset of the study associating SID with treatment (i.e., the pharmacist will not be blinded for this trial). The site Principal Investigator, Study Coordinator and other associated personnel will be blinded to assigned therapy.

The infant will not be re-randomized and will receive the same study drug as the original randomization for the mother. Each infant of a multiple birth will receive the study drug according to the mother's randomized study drug assignment.

When the proportion of women with pre-entry CD4+ lymphocyte counts $\geq$**200/mm^3** AND less than six 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 pre-entry CD4+ count <200/mm^3 or women with six months **or more** of prior ZDV use.

8.3 Administration and Dispensing

8.3.1 Pregnant Women: Antepartum Treatment (HIVIG/IVIG Infusions)

HIVIG 200 mg/kg (4 ml/kg body weight) or IVIG will be administered by intravenous infusion every 28 days (± 7 days) until labor. The dose of HIVIG or IVIG will be calculated based on the woman's weight on the day of the infusion. If the study drug cannot be administered to the woman within the planned time period, it should be administered as soon as possible. The initial 28-day schedule should still be followed so that the woman may receive the maximum number of infusions for which she would be eligible.

- The study drug will not be mixed with any other fluids or medications (dilution with 5% dextrose solution (D5W) is the only allowed alteration of the HIVIG/IVIG study drug). To ensure that waste of HIVIG or IVIG is kept to a minimum, the pharmacist may alter the dose of HIVIG or IVIG to be given by ± 10 percent, or, if more than one patient has been scheduled for the same day, the contents of a vial(s) may be used to prepare both solutions.

- Premedication: Benadryl® and/or acetaminophen, and/or aspirin may be administered before and during the infusion for patients previously demonstrating mild reactions, or during infusion if a mild reaction occurs.

- Rate of infusion: 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. Auscultation for fetal heart sounds should be done at the beginning, middle and completion of infusion, and recorded on the infusion record.

- Labelling Instructions: In addition to the usual labelling requirements for investigational agents, the label must also include the following:

  Woman's name:
  Woman's #
  ACTG Protocol 185 HIVIG/IVIG Study Drug - 50 mg/ml

  Administer by infusion starting at 0.02 ml/kg/minute, for a total dose of 200 mg/kg (total 4cc/kg).

  ecm/RPh (site pharmacist) 08/08/91 (date)

- See Appendix IV (Study Drug (HIVIG/IVIG) Administration) for further instructions.

8.3.2 Women: Intrapartum Treatment (IV ZDV)

All women will receive an intrapartum infusion of ZDV, regardless of the time of the last dose, or whether ZDV dose during pregnancy has been modified or ZDV discontinued, unless the investigator determines the infusion is contraindicated. Decisions to omit the intrapartum infusion must be discussed with the Protocol Chair.

- Supply: IV ZDV will be supplied as a 20 ml single-use vial at a concentration of 10 mg/ml. The vials should be stored at 15-25 degrees Celsius and protected from light.

- Treatment: When labor begins (labor being defined as regular uterine contractions associated with progressive effacement and dilation of the cervix) the woman should receive a loading dose of 2.0 mg/kg ZDV administered over one hour, followed by a continuous infusion at 1.0 mg/kg/hr. **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.** All women receive this dose, regardless of the time of the last dose of oral ZDV, or mode of delivery. If women are admitted for elective caesarean section at least 4 hours of ZDV infusion (the loading dose plus an additional 3 hours) is desirable. **Women admitted for induction of labor will have the ZDV infusion started at the time induction begins.** The length of treatment during labor will be recorded for all patients. Intravenous ZDV is terminated after the umbilical cord is clamped. Women who initiated ZDV during premature or false labor who are subsequently discharged and still pregnant should resume their pre-existing oral ZDV regimen; resume oral ZDV no sooner than 4 hours after infusion has stopped.

- Dispensing: Intravenous ZDV must be diluted prior to administration. **The dose of ZDV will be calculated based on the women's weight on the day of infusion.** The calculated dose will be removed from the 20 ml vial (10 mg/ml) and added to 5 percent dextrose injection solution to achieve a concentration no greater than 4 mg/ml. After dilution, the solution is physically and chemically stable for 24 hours at room temperature, and 48 hours if refrigerated at 2-8 degrees Celsius. As an additional precaution, the diluted solution must be administered within 8 hours if stored at room temperature (25 degrees Celsius), or 24 hours if refrigerated at 2-8 degrees Celsius, to minimize potential administration of a microbially contaminated solution. The diluted drug does not need to be protected from light. Intravenous ZDV may be prepared by the site pharmacist or prepared on the labor & delivery unit.

- Admixture with other drugs, biologic or colloidal fluids is prohibited. A separate intravenous line should be used for the administration of ZDV.

Other medications, such as pitocin or magnesium sulfate, must be administered through a different intravenous line.

- Labelling Instructions: In addition to the usual labelling requirements for investigational agents, the label must also include the following:

  Woman's name:
  Woman's #

  ACTG Protocol 185 Intravenous ZDV concentration ____ mg/ml
  (study delivery site) _____

  Administer loading dose at 2.0 mg/kg over one hour followed by continuous IV infusion at dose of 1.0 mg/kg/hr

  ecm/RPh (site pharmacist) 08/08/91 (date)

8.3.3 Infant Treatment (HIVIG/IVIG Infusion)

As soon as the newborn infant (or infants, if a multiple birth) has stabilized, an IV will be started. A total dose of 200 mg/kg of study drug (HIVIG or IVIG) will be given, starting 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.

See Appendix IV (Study Drug (HIVIG/IVIG) Preparation and Administration) for further instructions.

Caution should be taken with administration of study drug in the presence of cardiopulmonary disease, due to concerns regarding 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. Intramuscular administration of HIVIG/IVIG is not permissible.

Labelling: In addition to the usual labelling requirements for investigational agents, the labels must also include the following:

Infant's name:

Infant's #

ACTG Protocol 185 HIVIG/IVIG Study Drug - 50 mg/ml

(study delivery site) _____

Administer by infusion starting at 0.01 ml/kg/minute, for total dose of 200 mg/kg (total 4 cc/kg).

Selected by: _____ (R.N. or M.D. name)

ecm/RPh (site pharmacist) 08/08/91 (date)

8.3.4 Infant Treatment (ZDV)

Oral ZDV

- Supply: ZDV syrup is a strawberry flavored clear formulation in a glycerin/sucrose base at a concentration of 10 mg/ml supplied in 240 ml (8 oz.) opaque plastic bottles with childproof caps. The syrup should be stored at room temperature and protected from light.

  Oral syringes with calibration to 0.01 ml will be needed to administer the ZDV; syringes WILL NOT be supplied by the repository.

- Dispensing: A pre-packaged, pre-labelled initial ZDV drug supply will be prepared by the site pharmacist. This supply may be kept in the newborn nursery at the study delivery site.

  It is recommended that 30 ml amber plastic bottles be used to dispense the initial therapy supply.

- Treatment: Infants will begin treatment with ZDV syrup at 2 mg/kg (0.2 ml/kg) every six hours as soon as they are able to tolerate liquids by mouth and within 8-12 hours. 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.

The infant will be weighed at study visits and the dose will be recalculated. If there is greater than a 10 percent difference in the infant's calculated dose, the dose will be adjusted accordingly (See Appendix V, ZDV Dosing, Infants.)

Duration of infant therapy is 6 weeks. An initial supply of ZDV syrup will be supplied at the time of the infant's discharge from the hospital. During outpatient therapy, the site pharmacist will dispense the appropriate amount of ZDV to the parent/guardian at each clinic visit (week 1 and 2). Empty or unused medication bottles must be returned by the parent/guardian at each clinic visit (week 1, 2, and 6).

- Labelling For Oral ZDV: In addition to the usual labelling requirements for investigational agents, the labels must also include the following:

  Infant's name:
  Infant's #

  ACTG Protocol 185 ZDV Syrup - 10 mg/ml
  (study delivery site)_____

  Administer _____ ml by mouth every six hours.

  ecm/RPh (site pharmacist) 08/08/91 (date)

- Parent/Guardian Instructions: It is anticipated that parents/guardians may have questions about administering ZDV to the infants. Parents/guardians must demonstrate the ability to dispense ZDV prior to receiving the infant's ZDV drug supply. All primary caregivers should receive written discharge instructions. The information provided in Appendix VI, ZDV Administration Instructions for Parents/Guardians should be included on the instruction sheet each site develops for their own use. Empty or unused medication bottles must be returned by the parent/guardian at each clinic visit (week 1, 2 and 6).

IV ZDV

- Supplied: For infants who remain NPO, IV ZDV will be supplied as a 20 ml, single-use vial at a concentration of 10 mg/ml. The vials should be stored at 15-25 degrees Celsius and protected from light.

- Preparation: Intravenous ZDV must be diluted prior to administration. The calculated dose will be removed from the 20 ml vial (10 mg/ml) and added to 5 percent dextrose in water injection solution to achieve a concentration no greater than 4 mg/ml. After dilution, the solution is physically and chemically stable for 24 hours at room temperature, and 48 hours if refrigerated at 2-8 degrees Celsius. As an additional precaution, the diluted

solution must be administered within 8 hours if stored at room temperature (25 degrees Celsius), or 24 hours if refrigerated at 2-8 degrees Celsius, to minimize potential administration of a microbially contaminated solution. The diluted drug does not need to be protected from light.

- Treatment: IV ZDV will be administered at 1.5 mg/kg infused over a 30-minute period, every six hours. Admixture of ZDV with other drugs, biologic or colloidal is prohibited. A separate intravenous line should be used for the administration of ZDV.

- Labelling for IV ZDV: In addition to the usual labelling requirements for investigational agents, the label must also include the following:

  Infant's name:
  Infant's #

  ACTG Protocol 185 Intravenous ZDV concentration _____ mg/ml
  (study delivery site)_____

  Infuse 1.5 mg/kg over 30 minutes.
  ecm/RPh (site pharmacist) 08/08/91 (date)

9.0 CONCURRENT MEDICATIONS/TREATMENTS

All prescription and non-prescription medications, received by the woman and the infant will be recorded.

9.1 Concurrent Medications for Women

Women may receive all medications/treatments as required for the obstetrical management of the HIV-infected woman (e.g., acyclovir for chronic suppressive therapy, ketoconazole, INH, antibiotics, or a change to other antiretroviral therapy in pregnancy due to intolerance or disease progression on ZDV) except for anti-HIV vaccines or passive immunotherapy with HIVIG or IVIG (outside of the study drugs in this protocol).

Caution should be used with concomitant administration of drugs that are metabolized by hepatic glucuronidation, and may alter the metabolism of ZDV.

Following delivery, maternal treatment may include approved and/or investigational antiretroviral agents other than ZDV.

9.2 Concurrent Medications for the Infant

Infants who require drug treatment for signs of drug withdrawal (e.g. phenobarbital, chlorpromazine, tincture of opium, paregoric or Valium) are NOT excluded or discontinued from therapy in this study.

Infants may receive all medications/treatments as medically indicated for medical management of an HIV-exposed infant (e.g., hepatitis B vaccine, syphilis treatment, *Pneumocystis carinii* pneumonia prophylaxis).

Antiretroviral therapy other than ZDV is not permitted during the initial six weeks of life while the infant is receiving ZDV. Antiretroviral therapy is not permitted after the initial six weeks of ZDV unless infants satisfy study endpoint criteria for definitive HIV infection. These infants will be discontinued from further interim-required study visits, and will be referred to therapeutic care or an experimental treatment protocol. For those infants not meeting definitive infection criteria in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee.

While the infant is receiving ZDV therapy, caution should be used with concomitant administration of drugs that are metabolized by hepatic glucuronidation, which may alter the metabolism of ZDV. Acetaminophen is allowed.

All infants will receive standard well-child care throughout the study period by their primary physician. Children should be immunized according to current recommendations of the Immunization Practices Advisory Committee.

10.0 WOMAN, FETUS AND INFANT EVALUATIONS: GENERAL ISSUES

Prior to initiation of study therapy, the pregnant woman will be screened to ensure that she meets required study criteria. The course of her pregnancy will be reviewed for possible exclusion criteria. The estimated gestational age at the time of enrollment must be between 20 and 30 weeks.

Prior to initiation of ZDV in the infant, the infant will be screened to ensure the child meets criteria to begin ZDV (see Section 11.3 Infant ZDV Toxicity).

Appropriate clinical laboratory evaluations of women and infants will be performed at the intervals designated in this section (refer to Appendices I and II). Included in this section are evaluations thought necessary to ensure the safety of the woman while being treated with HIVIG and IVIG and of the infant while being treated with HIVIG and IVIG after delivery and with 6 weeks of ZDV. If additional evaluations are necessary for the care of the patient, these should be performed based on the medical opinion of the obstetrician or pediatrician and the standard care at that institution.

For this protocol, women will be seen to receive and monitor study drug infusions every 4 weeks until delivery, and for evaluation at 6, 12, 26, 48 and 78 weeks postpartum; infants will be evaluated at birth and at weeks 1, 2, 6, 12, 16, 20, 24, 36, 48, 60, and 78, for clinical and laboratory assessment to a) monitor the safety of the initial 6 week course of ZDV and b) to ascertain HIV infection status.

Special virological and immunological studies will also be done on both mother and infant to further investigate the factors involved in enhancing or protecting the fetus/infant from HIV infection, and the effect of HIVIG on these parameters. Special studies will also be done on the infant to compare other methods to HIV culture for the early diagnosis of HIV infection in infants. Special studies to detect HIV RNA will be done on placental samples, if available.

It is recognized that for some clinical centers who have currently ongoing federally-funded natural history studies there may be a conflict with duplicate sampling requirements for children or pregnant women participating in both a natural history study and the ACTG 185 special studies. Such duplicate blood drawing is undesirable. Those sites with such conflict may be exempted from the maternal transmission factor or early diagnosis substudy blood sampling requirements but still participate in the HIVIG protocol if they document in their implementation plan a detailed justification for such an exemption, including documentation of competing duplicate blood sampling requirements in another current federally-funded study. The decision for site exemption will be made by the Implementation Plan Review Committee; it is anticipated that such exemptions will be unusual.

To conserve the amount of blood needed for the required evaluations, special processing of blood samples has been devised to maximize the use of cells and plasma obtained at each visit for women and infants. Specific blood sampling and processing instructions for each visit are outlined in Appendix XVI, Specimen Collection, Processing, and Storage Procedures.

Each site will maintain standardized records during the study which capture reasons for subject ineligibility or for non-participation. For patients who meet entry criteria but decline participation, the reason(s) for refusal to participate in the study will be recorded.

10.1 Evaluation of Women: Outline and Rationale

Women will be seen every 4 weeks until delivery, intrapartum, and then at 6, 12, 26, 48 and 78 weeks postpartum. Followup of women beyond the immediate postpartum period allows for additional data on safety and influence of HIVIG on disease progression to be collected.

Pre-entry history, clinical and laboratory evaluations will ensure the woman meets required study criteria, including verification of gestational age by sonogram, and provide

information necessary for stratification and evaluation of potential confounding variables, such as STD's.

Baseline history, clinical and laboratory evaluations relevant to the woman's HIV clinical status and to potential factors associated with maternal-fetal HIV transmission will be obtained at the first study infusion visit. Clinical and/or historical assessments of HIV-disease status are obtained at each study visit.

Additional blood will be sampled to evaluate potential immunologic and virologic variables associated with maternal-fetal HIV transmission at the study infusion visit #3 (prior to study drug infusion), and intrapartum (prior to ZDV infusion). Blood will also be sampled prior to study drug infusion #3 to evaluate the effect of HIVIG on immunologic and virologic parameters in the pregnant woman, and at the 12, 26, 48 and 78 week postpartum visits.

10.1.1 Women: Clinical Evaluations

Pre-entry is defined as within twenty-eight (28) days prior to randomization. Entry is defined as the date of study drug initiation. Protocol treatment must begin within 72 hours of randomization.

- History
  Every visit.

  The pre-entry history will include documentation of previous pregnancy outcomes, and a maternal medical (including STD) and behavioral history. The history taken during pregnancy will include documentation of antepartum procedures and conditions which might be associated with maternal/fetal bleeding, antepartum complications which occur during this pregnancy, confounders of perinatal transmission at the time of delivery, medications received during pregnancy, and HIV-related illnesses. The postpartum history will include HIV-related illnesses and a record of current medications.

- Physical Examination
  Every visit through 26 weeks postpartum.

  The physical exam with vital signs will focus on HIV-related signs, including AIDS-defining conditions as well as other infections, including herpes zoster infection, genital and extra-genital herpes simplex virus, vaginal mucocutaneous candidiasis, otitis media, and respiratory tract infections such as pneumonia.

- HIV Symptom Review (Fever, diarrhea, cough, SOB, sweats, lymph nodes, skin lesions, oral candida, etc.)
  Every visit.

- Sonogram
  Pre-entry (within 28 days) only.

10.1.2 Women: Laboratory Evaluations

Pre-entry is defined as within twenty-eight (28) days of randomization. Entry is defined as the date of study drug initiation. Treatment must be initiated within 72 hours of randomization. (See Appendix XVI, Specimen Collection, Processing, and Storage Procedures.)

- Hematology (CBC with indices, differential, platelet count).
  Pre-entry, entry, antepartum study visit #3 and 26, 48 and 78 weeks postpartum.

- Chemistries
  BUN, creatinine, SGOT, SGPT, total and direct bilirubin, alkaline phosphatase, electrolytes).
  Pre-entry (within 28 days).

- Urinalysis
  Pre-entry (within 28 days), entry, and every antenatal infusion visit.

- STD Screen (Neisseria gonorrhoea, Chlamydia trachomatis, Treponema pallidum [STS])
  Pre-entry (within 28 days).

- HIV-1 Viral Culture (quantitative HIV PBMC micro-culture).
  Entry, antepartum study visit #3, intrapartum and 26 weeks postpartum.

Antepartum visit blood samples must be drawn prior to study drug infusion.

Quantitative cell culture must be processed by an ACTG certified virology laboratory. Specific directions for blood sampling, processing and shipping are outlined in Appendix XVI. CDC regulations for shipping of samples are provided in Appendix XVIII, Regulations for Shipping Etiologic Agents.

- Total Lymphocyte count and lymphocyte subsets (Total and percent CD3, CD4, CD8, CD19, and CD4/CD8 ratio)
  Pre-entry, entry, antepartum study visit #3, and 26, 48 and 78 weeks postpartum.

  Lymphocyte subsets must be performed by an ACTG-certified immunology laboratory. See Appendix XVI, Specimen Collection, Processing, and Storage Procedures. For selected sites, lymphocyte subset analysis will be performed by a designated central laboratory, and may include additional markers.

- EIA (Confirm Positive EIA by Western blot or other appropriate confirmatory test)
  Pre-entry (within 28 days).

- Plasma and Cell Storage for Special Studies.
  Pre-entry, entry, prior to infusion at antepartum study visit #3, intrapartum, and 12, 26, 48 and 78 weeks postpartum.

  As a part of this clinical trial, blood is being collected to evaluate what immunological parameters are involved in protection of the fetus/infant from HIV infection, and the effect of HIVIG on these parameters. Specific directions for blood sampling, processing, storage and shipping are outlined in Appendix XVI. CDC regulations for shipping of samples are provided in Appendix XVIII, Regulations for Shipping Etiologic Agents.

10.2 Evaluation of Infants: Outline and Rationale

Infants will be evaluated at birth and at weeks 1, 2, 6, 12, 16, 20, 24, 36, 48, 60, and 78, or until reaching a study endpoint, whichever comes first. For infants who reach endpoint prior to the final study visit, a brief summary followup assessment, including vital status will be done by telephone every 3 months. This will be recorded on **the Pediatric Followup Form** and will replace the protocol required visits until the final study visit. All infant subjects, regardless

of HIV infection status, will complete study visits through week 6 and will return for the final study visit, week 78.

ZDV toxicity will be assessed by evaluation of hematologic and liver parameters prior to ZDV administration at birth, and at measurements at weeks 1, 2, and 6.

HIV-specific antibody delivery to the infant by HIVIG/IVIG infusions in the mother will be evaluated by special antibody studies performed on cord blood. Additional evaluation of antibody levels in the infant will be performed by obtaining special antibody studies at week 16.

Intensive comparison of tests for early diagnosis to HIV culture will be performed in the course of the study. The sensitivity and specificity of early diagnostic tests, including HIV culture, may be modified by ZDV therapy in the mother and newborn as well as HIVIG therapy. Early diagnostic tests will be evaluated in samples obtained from cord blood (if available), the newborn, and weeks 2, 6, 12, and 16; an additional sampling time at week 48 will be obtained to ensure one evaluation is performed when both ZDV and study drug (HIVIG/IVIG) are no longer systemically present in the infant.

HIV culture will be performed on newborn blood samples to evaluate study drug effects; HIV culture for diagnosis and for comparison to other early diagnostic tests will be performed at the newborn visit, weeks 6, **24**, and 48. If HIV culture is positive prior to the final visit, an additional culture **for confirmation** is drawn. In addition, all children, regardless of HIV infection status, will return at 18 months for a final evaluation **which will include serology testing.**

10.2.1 Infant: Clinical Evaluations

- Gestational Age Assessment: Based on clinical findings and the first Ballard or Dubowitz score.
  Newborn (within 24 hours of birth)

- Physical Examination: Including assessment of objective signs - weight, height, head circumference and vital signs, growth chart documentation, and HIV-targeted organ examination.
  Every visit.

- HIV-Associated Symptoms Assessment
  Every visit.

10.2.2 Infant: Laboratory Evaluations

Pre-entry is defined as any time prior to the start of HIVIG/**IVIG** therapy. Prior to initiation of ZDV, the infant must be screened to ensure the child meets criteria to begin the drug (see Section 11.3). See Appendix XVI, Specimen Collection, Processing, and Storage Procedures.

- Hematology Studies (CBC with 5-part differential and platelet count)
  Pre-entry (newborn blood), weeks 1, 2, 6, 12, 24.
  Results must be reviewed prior to administration of ZDV to newborn; however HIVIG/IVIG may be administered prior to reviewing results.

- SGOT/SGPT
  Pre-entry (cord blood OR newborn blood), weeks 2, 6.
  If cord blood is obtained for this test, newborn specimen does not need to be done. Results must be reviewed prior to administration of ZDV to newborn; however HIVIG/IVIG may be administered prior to reviewing results.

- Quantitative IgG, IgA and IgM
  Cord blood (if obtained), weeks 6, 12.
  If cord blood is not obtained for this test, specimen from newborn is not necessary.

- Lymphocyte subsets (Total and percent CD3, CD4, CD8, CD19, and CD4/CD8 ratio)
  Weeks 6, 12, 24.

Lymphocyte subsets must be performed by an ACTG-certified Immunology laboratory. See Appendix XVI, Specimen Collection, Processing, and Storage Procedures. For selected sites, lymphocyte subset analysis will be performed by a designated central laboratory, and may include additional markers.

- Retrovirologic Evaluation

Cord blood specimens do not substitute for newborn blood sample; newborn sample is required regardless of obtaining cord blood. See Appendix XV, Instructions For Obtaining Cord Blood, for further instructions on the required technique for obtaining cord blood. The newborn blood sample should be obtained prior to HIVIG/IVIG infusion and ZDV initiation.

* EIA (Confirm positive EIA by Western blot or appropriate confirmatory test)
  Weeks 60 and 78.

* Cells/Plasma for Storage
  Cord blood (if obtained), newborn,
  Weeks 2, 6, 12, 16, 24, 48, 60, and with confirmatory culture.

* Quantitative HIV PBMC microculture
  Newborn blood (prior to HIVIG/IVIG infusion and ZDV administration), weeks 6, 24, 48. An additional HIV (confirmatory) culture is obtained when the child has a positive culture.

  Cultures must be performed at a certified ACTG virology laboratory.

  Specific directions for blood specimen sampling, processing, storage and shipping are outlined in Appendix XVI. CDC regulations for shipping of samples are provided in Appendix XVIII.
  Newborn blood should be obtained prior to HIVIG/IVIG infusion and ZDV administration.

- Placental HIV RNA
  Placental biopsy (for selected sites). Refer to Appendix XVII, Placental Biopsy Preparation and Shipment, for instructions about tissue fixation and shipping.

10.2.3 Infants or Children Meeting HIV Infection Endpoint Prior to 18 Months: 78 Weeks (18 months) Study Visit

Once a single HIV culture is positive, the child has met HIVIG study endpoint for HIV infection; a second HIV culture should be drawn to confirm the first culture. Infants reaching an endpoint for HIV infection, after completing study week six and obtaining the confirmatory culture, will be followed at least every three months to obtain vital status information (telephone contact is acceptable). All infants regardless of HIV infection status must complete the final visit at 78 weeks (18 months). At study week 78 (18 months), the following are required:

- Physical Examination: Including assessment of objective signs - weight, height, head circumference, and vital signs, growth chart documentation, and HIV-targeted organ examination.
- HIV-Associated Symptoms Assessment.
- EIA-WB.

11.0 TOXICITY & TREATMENT DISCONTINUATION

11.1 HIVIG/IVIG Toxicity Management/Dose Modification - Women and Infants

Generally, adverse reactions to the study drug are directly related to the rate at which the drug is infused. Adverse experiences with HIVIG infusion are similar to those associated with other immune globulin preparations, such as IVIG. Adverse reactions are usually mild but rarely, serious symptoms may develop. Refer to Appendix X, HIVIG/IVIG Toxicity in Women, and Appendix XI, HIVIG/IVIG Toxicity in Infants, when signs or symptoms occur which may indicate an untoward reaction.

If mild signs or symptoms of adverse effects (level I) are seen, the rate of study drug infusion should be halved to see if the signs and symptoms disappear. If the lowered infusion rate is tolerated without problems for 30 minutes, the infusion rate may be increased to the previous rate. If adverse effects are, in the physicians judgement, more than mild (level II), the infusion should be interrupted until the adverse effects have disappeared for approximately 30 minutes, after which time the infusion can cautiously be restarted at 0.01 ml/kg/minute. Pregnant women who experience a level II reaction, should have an external fetal monitor in place when the infusion is restarted, and fetal monitoring should be performed with subsequent infusions. In the event of level III reaction, the infusion should be discontinued immediately. Treatment necessary to manage the reaction should be administered, and fetal well-being monitored. No subsequent infusions should be administered without prior approval of the study chair.

11.2 HIVIG/IVIG Permanent Discontinuation - Women and Infants

If the study drug requires discontinuation in a pregnant woman, her infant <u>should</u> receive the study drug unless the investigator determines the infant infusion is contraindicated; decisions to omit the infant infusion in this situation must be discussed with, and approved by the Protocol Chair. Women who discontinue therapy for any reason will continue to be followed,

as will their infants, to determine study endpoints. Women or infants will be permanently discontinued from study drug (HIVIG or IVIG) for any of the reasons listed below.

- Severe allergic reaction to 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, parent or guardian (for infants), 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 twenty-four 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 $\geq$ 3 times baseline;
  * Cerebral or visual disturbances such as altered consciousness, headache, scotomata, or blurred vision;
  * Pulmonary edema or cyanosis;
  * 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 Potter's syndrome.

11.3 Infant ZDV Toxicity: Newborn ZDV Drug Ineligibility

Infants will NOT begin ZDV therapy for any of the following reasons (all such infants will continue to be monitored according to the schedule of evaluations):

- A clinical condition which the on-site pediatrician believes is incompatible with life.

- 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 is not tolerated by the infant unless there is 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).
  - SGPT > 5X upper limit of age-adjusted normal
- Parent/guardian not available to give informed consent, if necessary.

11.4 Infant ZDV Toxicity: Permanent Discontinuation

Infants will be discontinued from ZDV during the first six weeks after initiation for the reasons listed below; all infants will continue to be monitored according to the schedule of evaluations.

- 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 > 5X upper limit of age-adjusted normal
- Grade III toxicity (as detailed in Appendix XIII) other than the defined laboratory values in this section. 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.

12.0 EVALUATION OF RESPONSE

12.1 Evaluation of HIV Infection in Infants

The efficacy of HIVIG to prevent the transmission of HIV in infants born to HIV-infected mothers receiving ZDV during pregnancy will be evaluated by comparing the rates of HIV infection among infants in the two treatment groups, HIVIG and IVIG. The laboratory evidence defined below are acceptable endpoint criteria. **All infants satisfying endpoint criteria will be discontinued from further required interim study visits except for study week 78 evaluations and referred to other available pediatric trials or appropriate primary care upon completing SV4 (week 6).** For those infants not meeting definitive infection criteria, in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee.

While this study contains a nested protocol to compare methods of early diagnosis of HIV infection, only the laboratory definition below will constitute definitive infection status. If, during the course of this study, one of the nested studies becomes an accepted and standardized test for infection, then the protocol may permit definition of infection by this test.

In addition, it is anticipated that a small number of children may die prior to laboratory confirmation of infection, or have ambiguous infection status. Fetal deaths in utero or stillbirths will be excluded from the efficacy analysis but included for the analysis of safety issues. Deaths following a live birth or those children with ambiguous infection status will have the available clinical and laboratory information independently reviewed by the Case Classification Committee and the child's probable infection status classified as described in Appendix XX, Classification of Children Who Die or Are Lost to Follow-up While Still of Indeterminate HIV Infection Status, or Have Ambiguous HIV Infection Status.

For protocol purposes, an infant will be considered definitively infected on the basis of laboratory evidence of HIV infection **as** 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.

All endpoints will be reviewed and verified by a subcommittee of the protocol team. A verified endpoint will be defined as:

- **A positive culture confirmed by a second positive test for direct detection of HIV or components from a specimen obtained at the same or subsequent visits, or**

- **Repeated detection of HIV antibody as defined above.**

Because of concerns regarding the potential modification of HIV antibody production by HIVIG, all children will be seen for clinical and laboratory evaluation at 18 months of age. For those infants < 18 months old with negative HIV culture but positive HIV antibody in whom the investigator has concerns regarding initiation of antiretroviral therapy, consultation is available with the Protocol Chair and the Case Classification Committee.

12.2 Safety and Tolerance of HIVIG

The safety and tolerance of HIVIG therapy will be evaluated by examining adverse experiences and laboratory and clinical safety data between the two treatment groups (HIVIG and IVIG) both in women and infants. The development of HIV-related symptoms in women receiving HIVIG and IVIG will be compared, including development of HIV-related symptoms through **78** weeks postpartum following completion of HIVIG or IVIG therapy.

13.0 PHARMACOKINETIC STUDY (SELECTED SITES ONLY)

Pharmacokinetic (PK) sampling will be performed in up to 50 mother-infant pairs selected from the first enrolled patients from selected sites.

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. A sample informed consent for Pharmacokinetic Sampling is contained in Appendix XXII.

The study drug code will not be broken to reveal whether the mother-infant pair received IVIG or HIVIG.

13.1 Studies on Pharmacokinetic Samples

- Quantitative HIV antibody: Evaluation of quantitative HIV p24 antibody will be performed. Other assays of specific HIV antibodies and/or functional activity may also be performed.
- Quantitative immunoglobulin levels.
- Antibody to a non-HIV antigen (i.e., rubella; if negative, CMV). Will be measured on maternal samples to evaluate the kinetics of this antibody for comparison to the measured HIV antibody.
- HIV p24 antigen and acid-hydrolyzed p24 antigen: Will be measured on the maternal samples, and on the cord blood specimen.

13.2 Pharmacokinetic Sampling Times

- Women
  Prior to first infusion of study drug, 1 hour, 24 hours, 3 days, 7 days, 14 days and 28 days post first infusion, and at the same time points (except day 3) after the 2nd, 3rd and 4th infusion; and 28 days post-delivery (see Appendix VII.)

  The one hour post-infusion sample must be drawn by peripheral venipuncture and not through the IV tubing line.

- Cord
  A PK sample will be obtained on the cord blood.

- Infants
  One hour post-infusion of study drug, 24 hours, 7 days, 14 days and 28 days post infusion, (see Appendix VII).

  Infant will receive the study drug infusion within 12 hours of birth. The one hour post-infusion sample must be collected by peripheral venipuncture or heel stick, and not through the IV tubing line. Infant specimens from day 7, 14, and 28 will have to be coordinated with early diagnosis draws.

13.3 Pharmacokinetic Sample Collection

- Women: obtain 4.0 ml of whole blood in a serum separator tube at each PK sampling time. Obtain an additional 2.6 ml of anticoagulated whole blood in a yellow top (ACD) tube at pre-infusion, 24 hour, 14 day and 28 day post-infusion sampling times.

- Infant: obtain 2.0 ml of whole blood in a serum separator tube at each PK sampling time, collected by peripheral venipuncture or heel stick. Obtain an additional 1.0 ml whole blood in a yellow top (ACD) tube at the 24 hour post-infusion sampling time.

- Specimen preparation: storage and shipping: Refer to Appendix VII, (HIVIG Pharmacokinetics).

13.4 Analysis of Pharmacokinetic Data

- Statistical methods: The pharmacokinetic (PK) data will be analyzed using one and two compartment models, as well as noncompartmental methods. One and two compartment models will be estimated and analyzed using ADAPT II (137). Non compartmental analyses, based on the statistical moment theory (138) will be used for estimation of pharmacokinetic parameters where appropriate. Other exploratory approaches for modeling the data may be employed, such as nonlinear random effects models for repeated measures (139, 140) or population pharmacokinetics using NONMEM (nonlinear mixed effects modeling) (141).

14.0 BIOSTATISTICAL CONSIDERATIONS

14.1 Assessment of Major Endpoint

The major endpoint of this trial is the proportion of HIV-infected infants born to women enrolled in the trial (the "HIV transmission rate"). Sample size for this trial is set assuming 10 percent noncompliance and 10 percent loss to follow-up. **HIV infection status for the purpose of the primary efficacy analyses will be assessed on the basis of HIV culture data for all children by 6 months of age. Additional analyses will incorporate an assessment of infant HIV infection status on the basis of serologic testing at 18 months of age.** Data analysis will be undertaken on an intent-to-treat basis, provided that the HIV infection status of the infant or child is known.

Fetal deaths or stillbirths will be censored in the primary analysis but included in the safety studies. For infant or child subjects who go off study prior to definitive determination of HIV infection status, the following approach will be taken. Deaths following a live birth, subjects lost to follow-up, or subjects with ambiguous infection status will undergo independent, blinded review of available clinical and laboratory data by the Case Classification Committee for classification of infection status (Appendix XX). For purposes of the primary analysis, those classified by this procedure as meeting definitive laboratory or clinical criteria for HIV infection will be considered HIV-infected, and the remaining categories will be considered uninfected. However, the DSMB will also review data using alternative definitions of HIV infection for those subjects requiring Case Classification Committee review, such as including within the definition of HIV infection additional categories (definitive plus probable, or definitive plus probable plus possible).

For those lost to follow-up, all practical means will be used to assess whether there was HIV transmission. Cases in which infection status cannot be assessed adequately despite Case Classification Committee review will be considered unclassifiable, and will not be considered in the data analysis. It is anticipated that no more than 10 percent of cases will be lost for any reason, and these will not be counted in the analysis of the primary endpoint.

Pregnancies which yield multiple births will be assessed as a single HIV transmission event if any of the infants are HIV infected and as a single nonoccurrence of transmission if none are HIV-infected.

To address the theoretical possibility that the study drug could delay ability to detect HIV infection in infants by delaying infant seroconversion (false-negative endpoint) and to evaluate the possible occurrence of the phenomenon of spurious (nonrepeatable) detection of HIV in infants observed in other multicenter studies (130) of vertical HIV transmission (false-positive endpoint), subjects will be followed to 18 months until 100 culture-negative, antibody-negative infants have been followed to 18 months. This will assure that approximately 50 infants in the HIVIG treatment arm are followed for 18 months. If no delayed seroconversion occurs, there will be over 95 percent confidence that the delayed seroconversion rate for each arm separately is no more than 6 percent.

14.2 Sample Size and Statistical Power

Four hundred women per arm will be randomized. With this sample size, the power to detect different treatment effects under several assumptions of HIV transmission rates in the IVIG arm is given in Appendix XIX, Sample Size and Statistical Power. With 400 patients per arm, there will be power of at least 80 percent to detect a 50 percent treatment effect if the IVIG perinatal transmission rate is 15 percent or more, and there will be the power of almost 80 percent to detect a 40 percent treatment effect, if the IVIG treatment arm perinatal transmission rate is 20 percent (two-sided test, overall α = 0.05). To monitor study feasibility and assess whether underlying assumptions regarding sample size and transmission rate are satisfied, monitoring of patient accrual and monitoring of overall transmission rate will be performed (Section 14.3).

14.3 Monitoring the HIV Transmission Rate

The results of ACTG 076 showed that treatment with ZDV lowers the HIV transmission rate from mothers to infants. Since the pregnant women enrolled in ACTG 185 will be receiving ZDV, it is possible that the transmission rate in ACTG 185 might be lower than the 15 percent assumed for sample size calculations. The overall HIV transmission rate for ACTG 185 will be evaluated by the DSMB after 200 infant subjects have been followed for at least six months and have received HIV culture test results. The results of cultures in the first six months will be used to estimate the overall HIV transmission rate while maintaining blinding of the treatment groups. This monitoring will be done prior to any efficacy review of the study data in order to avoid any effect on the significance levels used in the interim efficacy analyses.

The goal of this monitoring is to assure, as much as possible, that the completed study will have a minimum of 80 percent power to detect a 50 percent reduction in transmission. When monitoring of the overall transmission rate indicates that the transmission rate has dropped below 7.5 percent, **alternative strategies to maintain adequate power to detect differences between the treatment groups will be considered including increases in sample size.** (See Appendix XXI for a statistical description of the methods used for monitoring the overall transmission rate and its independence from the efficacy analyses.)

In the event that the sample size is increased, the schedule for interim analyses will be adapted to a longer time frame.

14.4 Efficacy Analysis

14.4.1 Endpoint Determination

As described earlier in Section 12.1, the endpoint for the efficacy analysis will be based on virology culture results up to six months of age. Infants with one or more confirmed culture results will be designated as HIV positive for the efficacy analysis; infants without such culture results will be designated as negative. As indicated above (end of

Section 14.1), the analytical endpoint is defined as HIV transmission from the mother to one or more infants; thus the occurrence of transmission for multiple births is defined in terms of whether any of the offspring are HIV positive (see Section 14.1).

Some infants may have negative viral culture results throughout the first six months of life, but have positive viral culture results after six months. Based on data from ACTG 076 (142) and from WITS (121), we expect that approximately 2% of infants who will eventually test positive may *not* have positive cultures by six months. In the worst case, all new positive results after six months would be on the HIVIG arm, so that the actual treatment effect would be smaller that the one used in the efficacy analysis. However, even in this worst case, the effect on both power and Type I error are minimal, with a decrease in power of about 1% and an increase in Type I error of about 1%.

14.4.2 Timing of Analyses

There will be four efficacy analyses, occurring after approximately each quarter of the sample size has achieved six months of followup. The analyses will use stopping rules based on the method described by Fleming, Harrington, and O'Brien (143). The successive hypothesis tests will be conducted at the 0.005, 0.0061, 0.0075, and 0.0434 significance levels. At any analysis, if the difference in the estimated HIV transmission rate between the two arms attains the nominal level of significance, the trial should stop and the treatment with the lower transmission rate would be concluded to be the better treatment. However, if the difference is not significant, the trial would continue and the next analysis would occur after the next quarter of patients has achieved the required followup.

14.4.3 Analysis Methods

The primary efficacy analysis will be based on transmission rates estimated using the Kaplan-Meier method (142, 144). The estimated transmission rate at six months will be used in these analyses. A simple, unstratified confirmatory analysis will be done

based on the comparison of the proportion of transmissions among infants with six months or more followup between the two treatment arms.

The Kaplan-Meier estimates will be stratified by mother's CD4+ count at entry, mother's CD8+ count at entry, mother's quantitative viral culture (IUPM) at entry, mother's quantitative viral culture (IUPM) at labor and delivery, prior history of ZDV use, mode of delivery, infant birthweight, infant gestational age, other risk factors for HIV transmission (145), and enrollment region.

14.5 Monitoring Noncompliance and Loss to Follow Up

Noncompliance and loss to follow-up will be monitored by the DSMB. Group differences in noncompliance and loss to follow-up will be calculated and compared. If either the cumulative proportion of noncompliance or loss to follow-up in either arm exceeds .15, the DSMB will evaluate the ability of the study to assess the efficacy of HIVIG. If required, proposals to reduce noncompliance or loss to follow-up will be considered.

14.6 Other Analyses

Additional analyses will be conducted on both mothers and infants. These analyses will include, but are not limited to, regression methods to identify factors that influence the occurrence or magnitude of the primary or secondary endpoints. Factors of interest will be of three main types: features of treatment, characteristics of the mother, and characteristics of the newborn. Examples include measures of compliance (e.g., the amount or number of infusions, whether or not the newborn received the planned infusion), CD4 counts and birth weight. For binary endpoints, such as infant HIV positivity, logistic regression will be used (146). For censored endpoints, such as time to HIV positivity, Cox regression will be used (147). For continuous endpoints, such as the **viral burden,** ordinary regression will be used (148).

14.7 Late Outcomes

A pediatric late outcomes protocol (ACTG 219) has been developed to maintain surveillance for late sequelae in children enrolled in perinatal protocols. Assessment of growth and development, neurocognitive function and organ system abnormalities are performed on a regular basis, and children are followed through age 20 years. All children enrolled in ACTG 185, infected and uninfected, are eligible and encouraged to enroll in ACTG 219.

15.0 DATA COLLECTION AND MONITORING

15.1 Data Collection

Case Report Forms (CRF) will be provided for each patient. Study participants will be identified by identification number provided by Westat at randomization. Names must not be permitted on any study forms or source documents.

Instructions concerning the recording of study data will be provided to the sites by Westat.

15.2 Study Monitoring

Federal regulations (21 CFR 312.50, Subpart D) require that the sponsor, or its designee, monitor its clinical trials. The purpose of site monitoring is to assure that:

- Accurate and complete case histories are developed and maintained;
- All studies are performed ethically according to federal requirements; and
- The protocol is correctly understood, and appropriately followed.

Westat will cooperate with the NIAID DAIDS Clinical Site Monitoring Group in the monitoring process. This contractor will provide site monitoring for NIAID ACTU sites. Westat will provide site monitoring for NICHD-sponsored sites. The investigator will allow their assigned site monitors and the FDA to inspect study documents such as consent forms, drug distribution forms, and case report forms, and pertinent hospital or clinic records for confirmation of the study data.

Site visits will be performed not less than twice a year by the monitoring agency to ensure that all regulatory requirements for the use of investigational agents have been met. Records of IRB approvals will be examined.

A Westat study manager will train and monitor study coordinators in documentation of adverse events, study drug compliance, toxicity managements, and clinical and laboratory problems through telephone contact, training meetings, data review, and site visits. The Clinical Site Monitoring Group monitors will receive protocol training and site specific information from Westat.

An independent Data and Safety Monitoring Committee will meet at regular intervals, to review **accumulated data.** Furthermore, additional meetings will be convened if needed. This committee will determine whether a significant adverse effect or a clear treatment effect of HIVIG exists which could result in termination of the trial.

This committee will be composed of experts representing the following disciplines: obstetrics, pediatrics, immunology, virology, biostatistics, and clinical trials. The committee will include one or more members of the ACTG Protocol 076 Data Safety Monitoring Board (DSMB).

Individual case data, clinical and laboratory, will be recorded on standardized forms and entered into a computer at Westat.

16.0 HUMAN SUBJECTS

The woman must sign an informed consent which will describe the objectives of the study and potential risks.

Potentially eligible subjects will be selected from participating study centers. Consecutive potential subjects will be randomized to reduce internal selection bias.

All laboratory specimens, evaluation forms and reports will be identified by a coded number to maintain patient confidentiality. All records will be kept in a locked file cabinet in the clinical research unit. All computer entry and networking programs will be recorded as coded numbers only. Clinical information will not be released without the written permission of the patient, except as required by the FDA.

16.1 Informed Consent

All patients will be given information about the general intent and rationale of the study, as well as the known toxicity and efficacy of ZDV, IVIG and HIVIG in adults and children.

All women must give written informed consent. The consent will specify the patient's freedom to withdraw the participant from the trial at any time without compromise of regular medical care. The father's written informed consent for the participation of the infant will also be obtained if he is reasonably available.

In addition to the study informed consent, when a patient participates in the pharmacokinetic sampling substudy, a specific consent must be obtained and documented. This consent form explains the purpose of the pharmacokinetic study, and the blood sampling procedures involved.

16.2 Investigator Responsibilities

The study center may be removed from participation in the study for any significant deviations from the protocol. The primary investigator is responsible for obtaining all appropriate clinical and laboratory evaluations and/or records from the infant's local physician when indicated.

16.3 Adverse Experience Reporting

Adverse experiences will be reported as either associated with use of the drug or not associated with use of drug, based on the investigator's judgement.

Any death or immediately life-threatening event which occurs during this study, must be reported to Westat within 24 hours, whether or not this reaction is considered to be related to the investigational drug.

Mothers or infants who experience an adverse event resulting in study drug discontinuation will be evaluated within 24 hours. This initial 24-hour evaluation may be completed by the patient's own physician or a facility other than the primary study center. However, all pertinent medical records must be retrieved by the study center.

Collection of adverse experience reports for this protocol will be complicated by the possible participation of non-ACTG delivery sites. For the non-ACTG delivery sites participating in this protocol, the AER forms must be available and nursery staff must be instructed on appropriate procedures for filing the forms.

All abnormalities observed in the infant at the time of birth and during the follow-up period, will be reported to Westat. Reporting will include abnormal laboratory evaluations, developmental abnormalities and congenital anomalies noted at the time of birth. Procedures for Adverse Experience Reporting are outlined in Appendix XIV. Adverse reaction tables are

included in Appendix XII (Adults) and Appendix XIII (Children) to provide guidelines for reporting specific events.

NOTE: Mean Corpuscular Volume (MCV) will not be reported as an adverse experience.

Reports of adverse events which are collected by Westat, will be provided to NHLBI, the institute which will be responsible for reporting adverse experiences to the FDA.

17.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this multicenter trial will be governed by predetermined policies as delineated below.

This study involves a unique collaborative effort of a large number of people, including investigators and statistical consultants from the three co-sponsoring Institutes (NHLBI, NICHD, and NIAID), clinical centers funded by NICHD and NIAID, and the study data center. Because of this, the primary analysis and any other major analyses which involve the entire group may be published under a study group name (e.g., HIVIG Perinatal Clinical Trial Study Group), with the two or three principal authors listed by name. Other publications which involve fewer authors may list the names of all authors separately.

To coordinate analysis and publication plans, a Steering Committee will be formed, composed of the Protocol team investigators, representatives of the three cosponsoring Institutes, the pharmaceutical sponsors, and the data center. Unless specified otherwise by the protocol, all study analyses will be performed at the study data center. Specific and detailed analytic plans will be developed by representatives from the three co-sponsoring institutes and the study data center. In order to assure that proposed publications are consistent with the stated analysis plan, use statistical techniques which are considered appropriate by the Committee, and do not overlap with other analyses which are underway, the Steering Committee will review each presentation, abstract or manuscript before it is submitted to a journal or conference. In addition, the ACTG Executive Committee will have an opportunity to comment on draft manuscripts (a five day time-to-comment period). The Steering Committee will be responsible for prioritizing analyses relating to secondary hypotheses and other substudies, and coordinating substudy analytic groups composed of investigators with similar interests to facilitate rapid analysis and publication of study results.

18.0 BIOHAZARD CONTAINMENT

As the transmission of HIV can occur rarely through contact with contaminated needles, blood and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling of all specimens for this study in a clinical or laboratory setting, as currently recommended by the Centers for Disease Control.

19.0 SITE REGISTRATION

This will be a multicenter clinical trial, jointly sponsored by NHLBI, NICHD and NIAID. All participating sites will receive approval from their local Institutional Review Board (IRB). Mothers and infants participating as study subjects must be followed at the registered site. All sites must also have assurances approved by the OPRR.

Prior to enrolling mothers and infants in this protocol, each site must submit the requisite site registration material. Registration requirements include:

* **Westat's** Site Registration Form;
* IRB approval letter **(to include OPRR assurance number for the site)**;
* Copy of approved informed consent form;
* FDA form 1572 from each institution requiring an IRB approval;
* Curriculum vitae for pediatric and obstetric investigators and **subinvestigators** involved with the study;
* Normal reference ranges for protocol-required assays to be performed by local site laboratories;
* Laboratory certification; and
* Site implementation plan.

For all sites, registration materials should be mailed to Westat, and a separate file should be maintained at the site. Westat will be responsible for ensuring that sites have appropriately documented materials for registration. When site registration (including site implementation plan) has been approved, a letter will be sent by Westat to the principal investigator and the pharmacist at the site. Instructions for ordering drugs from the repository will be sent to the pharmacist, and the repository will be notified that site registration was completed.

A Patient Identification Number (PID) which is assigned to each study patient, will be obtained from the ACTG PID Log. This PID log will contain identification numbers for assignment to the patient at pre-entry so that confidentiality may be maintained throughout the screening process.

After site registration approval and materials have been received by the site, the enrollment of study patients may commence.

20.0 CENTRALIZED STUDY SAMPLE REPOSITORY

During the course of this study, as part of the nested substudies, plasma and cells from mothers and infants enrolled in the study will be stored at the NHLBI Central Repository prior to batched evaluation at selected central laboratories. Because of the unique nature of these maternal-infant specimens, every effort has been made to develop blood specimen processing procedures to minimize the blood specimen requirements and maximize the use of cells and plasma obtained during the study. Due to concerns regarding the limited storage capability at many clinical sites, the Central Repository was developed to assist in the logistics of short-term storage (i.e., blood for special antibody evaluations or early diagnosis substudy testing, which will be shipped periodically from the Central Repository to the central laboratories selected to perform the tests) as well as longer-term storage (i.e., residual plasma/cells).

It is anticipated that there will be some amount of residual cells and plasma following the completion of the pre-determined substudy tests. Because this protocol is unique in the collaboration between multiple Institutes, pharmaceutical companies and clinical site investigators, there will be a special review process for any additional proposed studies that would use these stored specimens. The Repository Committee will be composed of staff from the three co-sponsoring Institutes (NHLBI, NICHD, and NIAID), the Chair and Vice-Chair of the Pediatric Executive Committee of the ACTG, and investigator members of the ACTG 185 Protocol Team, to ensure adequate representation of all interests. This Committee will review all proposed concept sheets that involve use of stored specimens for scientific content and importance, and prioritize and facilitate the conduct of studies the Committee deems should be accomplished.

21.0 REFERENCES

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

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

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

4. Institute of Medicine, Hardy LM (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. Chin J. Current and future dimensions of the HIV/AIDS pandemic in women and children. Lancet 1990; 336:221-24.

7. Bryson YJ, Luzuriaga K, Sullivan JL, Wara D. Proposed definition for in utero vs intrapartum transmission of HIV-I. (letter) N Engl J Med 1992; 327:1246-1247.

8. Mofenson LM. Preventing mother to infant HIV transmission: what we know so far. The AIDS Reader, March/April 1992; 42-51.

9. Borkowski W, Krazinski K, Pollack H, et al. Early diagnosis of human immunodeficiency virus in children < 6 months of age: comparison of polymerase chain reaction, culture and plasma antigen capture techniques. J Infect Disease 1992; 166: 616-619.

10. Jovaisas E, Koch MA, Schafer A, et al. LAV/HILV-III in 20 week fetus. Lancet 1986;2:1129.

11. Sprecher S, Soumenkoff G, Puissant F, Oegueidre M. Vertical transmission of HIV in 15-week fetus. Lancet 1986;2:288.

12. Courgnaud V, Laure F, Brossard A, et al. Frequent and early in utero HIV-1 transmission. AIDS Res Hum Retroviruses 1991; 7:337-341.

13. Soeiro R, Rashbaun WF, Rubenstein A, and Lyman WD. The incidence of human fetal HIV-1 infection as determined by the presence of HIV-1 DNA in abortus tissues. VII Intl. Congress on AIDS, Abstract WC3250, 1991 Florence, Italy.

14. Hanson CG and Shearer WT. Chapter: Pediatric AIDS: diagnosis of HIV infection in infants and children. In Feigin RD and Cherry JD (eds.). Textbook of Pediatric Infectious Diseases, 3rd edition, WB Saunders Co., Philadelphia, in press.

15. Ehrnst A, Lindgren S, Dictor M, et al. HIV in pregnant women and their offspring: evidence for late transmission. Lancet 1991; 338:203-7.

16. Van de Perre P, Lepage P, Homsy J, 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.

17. Mofenson L and Blattner W. Chapter: Human Retroviruses. In: Feigin RD, Cherry JD (eds). Textbook of Pediatric Infectious Diseases, 3rd Edition, WB Saunders Co, Philadelphia, 1992:1752-88.

18. Oxtoby MJ. Perinatally acquired human immunodeficiency virus infection. Pediatr Inf Dis J 1990; 9: 609-619.

19. Hira SK, Kamanga J, Bhat GJ, et al. Perinatal transmission of HIV-1 in Zambia. Br Med J 1989; 299:1250-1252.

20. Ryder RW, Nsa W, Hassig SE, et al. Perinatal transmission of HIV-1 in Zambia. Br Med J 1989;299: 1250-1252.

21. D'Arminio MA, Ravizza M, Muggiasca ML, et al. HIV-infected pregnant women: possible predictors of vertical transmission. VII International Conference on AIDS, Florence, Italy, June 1991, Abstract W.C. 49.

22. Hague RA, Mok JYQ, MacCallum L, et al. Do maternal factors influence the risk of HIV? VII International Conference on AIDS. Florence, Italy, June 1991, Abstract W.C, 3237.

23. Van de Perre P, Simonon A, Msellati P, et al. Post-natal transmission of human immunodeficiency virus type 1 from mother to infant: a prospective cohort study in Kigali, Rwanda. N Engl J Med 1992; 325: 593-598.

24. Kreiss J, Datta P, Willerford D, et al. Vertical transmission of HIV in Nairobi: correlation with maternal viral burden. VII International Conference on AIDS, Florence, Italy, June 1991, Abstract M.C. 3062.

25. Boue F, Pons JC, Keros L, et al. Risk for HIV-1 perinatal transmission vary with the mother's stage of HIV infection. VI International Conference on AIDS, June 1990, Abstract Th.C.44.

26. St. Louis ME, Kamenga M, Brown C, et al. Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic and placental factors. JAMA 1993; 269: 2853-2859.

27. Burns DN, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes and vertical transmission of HIV-1 among women with low CD4+ levels. J Acquir Immune Defic Syndr 1994 (in press).

28. Tibaldi C, Tova PA, Ziarati N, et al. Asymptomatic women at high risk of vertical HIV-1 transmission to their fetuses. Br J Obstet Gynecol 1994;100:334-337.

29. Rossi P, Moschese V, Broliden PA, et al. Presence of maternal antibodies to human immunodeficiency virus 1 envelope glycoprotein gp120 epitopes correlates with the noninfective status of children born to seropositive mothers. Proc Natl Acad Sci USA 1989;86:8055-58.

30. Broliden PA, Moschese V, Ljungren K. et al. Diagnostic implications of specific immunoglobulin G patterns born to HIV infected women. AIDS 1989; 3:577-582.

31. Goedert JJ, Mendez H, Drummond JE, et al. Mother-to-infant transmission of human immunodeficiency virus type 1: association with prematurity or low anti gp120. Lancet 1989;2:1351-4.

32. Devash Y, Calvelli T, Wood DG, et al. Vertical transmission of HIV is correlated with absence of high affinity/avidity maternal antibodies to the gp120 principal neutralizing domain. Proc Natl Acad Sci USA 1990;87:3445-49.

33. Markham RB, Coberly J, Ruff A, et al. Maternal IgG1 and IgA antibody to V3 loop consensus sequence and maternal-infant HIV-1 transmission. Lancet 1994;343:390-391.

34. Lallemant M, Baillou A, Lallemant-LeCoeur S, et al. Maternal antibody response at delivery and perinatal transmission of human immunodeficiency virus type 1 in African women. Lancet 1994;343:1001-1005.

35. Parekh BS, Shaffer N, Pau CP, et al. Lack of correlation between maternal antibodies to V3 loop peptides of gp120 and perinatal HIV-1 transmission. AIDS 1991;5: 1179-1184.

36. Halsey NA, Markham R, Wahren B. et al. Lack of association between maternal antibodies to V3 loop peptides and maternal-infant HIV-1 transmission. JAIDS 1992; 5:153-157.

37. Mofenson LM and Burns DN. Passive immunization to prevent mother-infant transmission of human immunodeficiency virus: current issues and future directions. Ped Inf Dis J 1991; 10:456-462.

38. Ugen KE, Goedert JJ, Boyer J, et al. Vertical transmission of HIV infection: correlation with reactivity of maternal sera with glycoprotein 120 and gp41 peptides from HIV type 1. J Clin. Invest. 1992; 89:1923-1930.

39. Ugen KE, Goedert JJ, Weiner DB. Maternal antibodies against HIV-1 envelope glycoprotein: model to evaluate vertical transmission/potential vaccine efficacy. Arch STD/HIV Res 1993;7:223-228.

40. Scarlatti G, Albert J, Rossi P, et al. Mother-to-child transmission of human immunodeficiency virus type 1: correlation with neutralizing antibodies against primary isolates. J Infect Dis 1993;168:207-210.

41. Bryson Y, Lehman D, Barratty et al. The role of maternal autologous neutralizing antibody in prevention of maternal fetal HIV-1 transmission. J Cell Biochem 1993;Suppl 17E:95 (abst. QZ005).

42. Wolinsky SM, Wike CM, Korber, BTM, et al. Selective transmission of human immunodeficiency virus type 1 variants from mothers to infants. Science 1992;255:1134-1137.

43. Scarlatti G, Leitner T, Halapi E, et al. Comparison of variable region 3 sequences of human immunodeficiency virus type 1 from infected children with the RNA and DNA sequences of the virus populations of their mothers. Proc Natl Aca Sci USA 1993;90:1721-1725.

44. Mulder-Kampinga GA, Kuiken C, Dekker J, et al. Genomic human immunodeficiency virus type 1 RNA variation in mother and child following intrauterine transmission. J Gen Virol 1993;74:1747-1756.

45. Mo H, Zhu T, Cao Y et al. Genotype and phenotype characteristics of HIV-1 transmitted from mother to infant. J Cell Biochem 1993;Suppl 17E:98 (abst. QZ111).

46. Jansson M, Wahren B, Scarlatti G, et al. PND antibody reactivity to vertically transmitted quasispecies in HIV-1 infected mothers. J Cell Biochem 1993;Suppl 17E:49 (abst. Q329).

47. Centers for Disease Control. Zidovudine for the prevention of HIV transmission from mother to infant. Morbidity and Mortality Weekly Report 1994; 43(16):285-7.

48. Sande MA, Carpenter CJ, Cobbs CG, et al. Antiretroviral therapy for adult HIV-infected patients. Recommendations from a state-of-the-art conference. National Institute of Allergy and Infectious Diseases State-of-the-Art Panel on Antiretroviral Therapy for Adult HIV-Infected Patients. JAMA 1993; 270(21): 2583-9.

49. Kozal MJ, Merigan TC. HIV resistance to dideoxynucleoside inhibitors. Infect Dis Clin Prac 1993;2:247-253.

50. Masquelier B, Lemoigne E, Pellegrin I, et al. Primary infection with zidovudine resistant HIV. (letter) N Engl J Med 1993;329:1123-1124.

51. Frenkel LM, Demeter LM, Wagner L, et al. Perinatal transmission of an AZT resistant mutation from a mother to her infant. (Abstract QZ102) J Cell Biochem 1993;17E (Suppl):96.

52. NIAID: ACTG 076, version 2.0, 9/1/92, pp.13-21

53. Boucher FD, Modlin JF, Weller S, et al. Phase one evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus (ACTG 049). J Pediatr 21993; 122: 137-144.

54. Cummins LM, Weinholt KJ, Matthews TJ, et al. Preparation and characterization of an intravenous solution of IgG from human immunodeficiency virus-seropositive donors. Blood 1991;77:1111-1117.

55. Shadduck PP, Weinburg JB, Haney AF, et al. Lack of enhancing effect of human anti-human immunodeficiency virus type 1 antibody on HIV-1 infection of human blood monocytes and peritoneal macrophages. J Virol 1991; 65:4309-4316.

56. Prince AM, Horowitz B, Baker L, et al. Failure of human immunodeficiency virus (HIV) immunoglobulin to protect chimpanzees against experimental challenge with HIV. Proc Natl Acad Sci USA 1988;85:6944-48.

57. Rhame FS, Goodroad RN, Cummins LM, et al. Safety and pharmacokinetics of human immunodeficiency virus immune globulin in persons with acquired immunodeficiency syndrome. (unpublished).

58. Putkonen P, Thorstensson R, Ghayamizadeh L, et al. Prevention of HIV-2 and SIV(m) infection by passive immunization in cynomolgus monkeys. Nature 1991;436-438.

59. Putkonen P, Thorstensson R, Albert J, et al. Prevention of HIV-2 and SIVsm infection by passive immunization in cynomolgus monkeys. VII International Conference on AIDS. Florence, Italy, June 1991, Abstract M.A. 21.

60. Eichberg JW. Experience with seventeen HIV vaccine efficacy trials in chimpanzees. VII International Conference on AIDS. Florence, Italy, June 1991, Abstract F.A. 2.

61. Emini EA, Scheif WA, Nunberg JH, et al. Prevention of HIV-1 infection in chimpanzees by gp120 V3-domain-specific monoclonal antibody. Nature 1992; 355:728-730.

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

63. 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.

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

65. 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-B28-2149.

66. Lefreve JJ, 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.

67. Wong VK, Gillette SG, Roth MJ, Miles S, Stiehm ER. Passive immunotherapy in a child with acquired immunodeficiency syndrome. Pediatr Infect Dis J 1993; 12:947-951.

68. Kobayashi RH, Hyman CJ, Steihm ER. Immunologic maturation in an infant born to a mother with agammaglobulinemia. Am J Dis Child 1980; 134: 942-944.

69. Hausser C, Muriot D. Gamma globulin therapy during pregnancy in a mother with hypogammaglobulinemia. Am J Obstet Gynecol 1982; 112.

70. Amarin ZO, Grant KA. Hypogammaglobulinemia during pregnancy in identical twin sisters. Int J Gynacol Obstet; 1982; 20: 471-473.

71. Williams PE, Leen CLS, Heppleston AD, et al. IgG replacement therapy for primary hypogammaglobulinemia during pregnancy: report of 9 pregnancies in 4 patients. Blut 1990; 60: 198-201.

72. Sorensen RU, Tomford JW, Gyves MT, et al. Use of intravenous immune globulin in pregnant women with common variable hypogammaglobulinemia. Am J Med 1984; Supplement: IVIG and the Compromised Host Symposium; 73-77.

73. Smith CIE, Hammarstrom L. Intravenous immunoglobulin in pregnancy. Obstet Gynecol 1985; 66: S395-396.

74. Besa E, MacNab M, Solan A, et al. High-dose intravenous IgG in the management of pregnancy in women with ITP. Am J Hematol 1985; 18: 373.

75. Gounder MP, Baker D, Saletan S, et al. Intravenous gammaglobulin therapy in the management of a patient with ITP and a warm autoimmune erythrocyte penagglutinin during pregnancy. Obstet Gynecol 1986; 67: 741.

76. Mizunuma H, Takahashi Y, Taguchi H, et al. A new approach to ITP during pregnancy by high-dose immunoglobulin G infusion. Am J Obstet Gynecol 1984; 148: 218.

77. Morgenstern GR, Measday B, Hedge M. Autoimmune thrombocytopenia in pregnancy: new approach to management. Br J Med 1983; 287: 584.

78. Sacks DA, Platt LD, Johnson CS. Autoimmune hemolytic disease during pregnancy. Am J Obstet Gynecol 1981; 140: 942.

79. Tchernia G, Dreyfus M, Laurian Y, et al. Management of immune thrombocytopenia in pregnancy: response to infusions of immunoglobulins. Am J Obstet Gynecol 1984; 148: 225.

80. Wenske G, Gaedicke G, Hayes H. Idiopathic thrombocytopenic purpura in pregnancy and neonatal period. Blut 1984; 48: 377.

81. Sacks DA, Platt LD, Johnson CS. Autoimmune hemolytic disease during pregnancy. Am J Obstet Gynecol 1981; 140: 942.

82. Berlin G, Selbing A. Rhesus hemolytic disease treated with plasma exchange and high-dose IV immunoglobulin. XXI Congress of the International Society of Hematology, Sydney, Australia, 1986, Abstract P-F-132A-17.

83. de la Camara C, Arrieta R, Gonzalez A, et al. High-dose intravenous immunoglobulin as the sole prenatal treatment for severe Rh immunization. N Engl J Med 1988; 318: 519.

84. Sacher RA, Zuckerman M, Queenan JT, et al. Severe Rh disease: successful management with intensive plasmapheresis and intravenous gamma globulin. XXI Congress of the International Society of Hematology, Sydney, Australia, 1986, Abstract P-F-132A-21.

85. Morales WJ, Stroup M. Intracranial hemorrhage due to isoimmune neonatal thrombocytopenia. Obstet Gynecol 1985; 65: 205.

86. Ballow M, Parke A. The uses of intravenous immune globulin in collagen vascular disorders. J Allerg Clin Immunology 1988; 84 (part II): 608-612.

87. Mueller-Eckhardt G, Heine O, Neppert J, et al. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin. Vox Sang 1989; 56: 151-154.

88. Sidiropoulos D, Herrmann U, Morell A, et al. Transplacental passage of intravenous immunoglobulin in the last trimester of pregnancy. J Pediatr 1986; 109: 505-508.

89. von Muralt G, Sidiropoulos D. Experience with intravenous immunoglobulin treatment in neonates and pregnant women. Vox Sang 1986; 51: (Supplement) 22-29.

90. Bussel JB, Berkowitz RL, McFarland JG, et al. Antenatal treatment of neonatal alloimmune thrombocytopenia. N Engl J Med 1988; 319: 1374-1378.

91. Kohler PF, Farr RS. Elevation of cord over maternal IgG levels - evidence for active placental IgG transport. Nature 1966; 210: 1070-1071.

92. Pollack JM, Bowman JM. Placental transfer of Rh antibody (anti-D IgG) during pregnancy. Vox Sang 1982; 43: 327-334.

93. Sacher RA, King JC. Intravenous gamma-globulin in pregnancy: a review. Obstet and Gynecol Survey 1988; 44: 25-34.

94. Hammarstrom L, Smith CIE. Placental transfer of intravenous immunoglobulin. Lancet 1986; i: 681

95. Newland AC, Boots MA, Patterson KG. Intravenous IgG for autoimmune thrombocytopenia in pregnancy. Lancet 1984; i: 261-262.

96. Steen JA. Gammaglobulin in preventing infections in premature infants. Arch Pediatr 1960; 77: 291-294.

97. Amer J, Ott E, Ibbott FA, et al. The effect of monthly gammaglobulin administration on morbidity and mortality from infection in premature infants during the first year of life. Pediatr 1983; 32: 4-9.

98. Diamond EF, Purugganan HB, Choi HJ. Effect of prophylactic gamma globulin administration on infection mortality in premature infants. Ill Med J 1966; 130: 668-670.

99. Conway SP, Gillies DRN, Docherty A. Neonatal infection in premature infants and use of human immunoglobulin. Arch Dis Child 1987; 62: 1252-1256.

100. Santoshan M, Reid R, Ambrosino DN, et al. Prevention of Hemophilus influenza type B infections in high-risk infants treated with bacterial polysaccharide immune globulin. N Engl J Med 1987; 317: 923-929.

101. Stiehm ER. Role of immunoglobulin therapy in neonatal infections: where we stand today. Rev Infect Dis 1990; 12: (Supplement 4) S439-442.

102. Sidiropoulos D, Boehme U, von Muralt G, et al. Immunoglobulin supplementation in prevention or treatment of neonatal sepsis. Pediatr Infect Dis J 1986; 5: (Supplement) S193-194.

103. Hague KN, Zaidi MH, Haque SK, et al. Intravenous immunoglobulin for prevention of sepsis in preterm and low birthweight infants. Pediatr Infect Dis J 1986; 5: 622-625.

104. Chirico G, Rondini G, Plebani A, et al. Intravenous gammaglobulin therapy for prophylaxis of infection in high-risk neonates. J Pediatr 1987; 110: 437-442.

105. Hague KN, Zaidi MH, Hasan B. IgM-enriched intravenous immunoglobulin therapy in neonatal sepsis. Am J Dis Child 1988; 142: 1293-1296.

106. Ruderman JW, Peter JB, Gall RC, et al. Prevention of hypogammaglobulinemia of prematurity with intravenous immune globulin. J Perinatol 1988; 10: 150-155.

107. Stabile A, Sopo SM, Roanelli V, et al. Intravenous immunoglobulin for prophylaxis of neonatal sepsis in premature infants. Arch Dis Chil 1988; 63: 441-443.

108. Christensen RD, Hardman T, Thornton J, et al. A randomized, double-blind, placebo-controlled investigation on the safety of intravenous immune globulin administration to preterm neonates. J Perinatol 1989; 9: 126-130.

109. Russel J. Intravenous gammaglobulin in the prophylaxis of late sepsis in very-low-birth-weight infants: preliminary results of a randomized, double-blind, placebo-controlled trial. Rev Infect Dis 1990; 12: (Supplement) S457-462.

110. Baker C, Rench M, Noya F, et al. Role of intravenous immunoglobulin in prevention of late-onset infection in low birth weight neonates. Rev Infect Dis 1990; 12: S463-469.

111. Clapp DW, Kleigman RM, Baley JE, et al. Use of intravenously administered immune globulin to prevent nosocomial sepsis in low-birth-weight infants: report of a pilot study. J Pediatr 1989; 115: 973-978.

112. Ruderman JW, Barka N, Peter JB, et al. Antibody response to MMR vaccination in children who received IVIG as neonates. Am J Dis Child 1991; 145: 425-426.

113. Kanakoudi-Tsakalidou F, Drossou-Agakidou V, Pratsidou P, et al. Prophylactic intravenous administration of immune globulin in preterm infants: effect on serum immunoglobulin concentrations during the first year of life. J Pediatr 1991; 119:624-629.

114. Centers for Disease Control. **1994 revised** classification system for HIV infection in children under 13 years of age. **MMWR** Morbidity and Mortality Weekly Report **1994; 43(RR-12)1-19.**

115. Report of a consensus workshop, Siena, Italy, January 17-18, 1992. Early diagnosis of HIV infection in infants. J Acquir Immun Defic Syndr 1992; 5:1169-78.

116. Rakusan T. Limitations in the laboratory diagnosis of vertically acquired HIV infection. JAIDS 1991; 4:116-121.

117. McIntosh K, Pitt J, Brambilla D, Carroll S, Diaz C, Handelsman E, Moye J, Rich K for the Women and Infants Transmission Study Group. Blood culture in the first 6 months of life for the diagnosis of vertically transmitted human immunodeficiency virus infection. J Infect Dis 1994; 170:996-1000.

118. Burgard M, Mayaux MJ, Blanche S, et al. The use of viral culture and p24 antigen testing to diagnose human immunodeficiency virus infection in neonates. N Engl J Med 1992; 327:1192-7.

119. **Borkowsky W, Krasinski K, Pollack H, Hoover W, Kaul A, Ilmet-Moore T. Early diagnosis of human immunodeficiency virus infection in children < 6 months of age: comparison of polymerase chain reaction, culture, and plasma antigen capture techniques. J Infect Dis 1992; 166:616-9.**

120. **Kline MW, Lewis DE, Hollinger B, et al. A comparitive study of human immunodeficiency virus culture, polymerase chain reaction and anti-human immunodeficiency virus immunoglobulin IgA antibody detection in the diagnosis during early infancy of vertically acquired human immunodeficiency virus infection. Pediatr Infect Dis J 1994; 13:90-4.**

121. **Kalish L, Pitt J, Lew J, Landesman S, Diaz C, Hershow R, Hollinger B, Pagano M, Smeriglio V, Moye J. Defining the time of fetal or perinatal acquisition of HIV-1 infection based on age at first positive culture. J Infect Dis; in press, 1996, and personal communication with Dr. Kalish, New Engl Institutes, Inc., Sept 1996.**

122. **Connor EM, Sperling RS, Gelber R, Kiseleve P, Scott G, O'Sullivan MJ, VanDyke R, Bey M, Shearer W, Jacobson RL, Jimenez E, O'Neill E, Bazin B, Delfraissy JF, Culnane M, Coombs R, Elkins M, Moye J, Stratton P, Balsley J for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994; 331:1173-80.**

123. **Centers for Disease Control. 1995 revised guidelines for prophylaxis against PCP for children infected with or perinatally exposed to HIV. MMWR Morbity and Mortality Weekly Report 1995; 44(RR-4):1-11.**

124. Rogers MF, Ou, C-Y, Kilbourn B. and Schochetman G. Advances and problems in the diagnosis of human immunodeficiency virus infection in infants. Ped Inf Dis J 1991; 523-531.

125. NICHD IVIG Study Group. IVIG for prevention of bacterial infections in children with symptomatic HIV infection. N Engl J Med 1991; 325:73-80.

126. Pizzo PA, et al. Effect of continuous intravenous infusion of zidovudine in children with symptomatic HIV infection. N Engl J Med 1988; 319:889-96.

127. McKinney R, et al. A multicenter trial of oral zidovudine in children with advanced HIV disease. N Engl J Med 1991; 324:1018-25.

128. Butler KM, et al. Dideoxyinosine in children with symptomatic HIV infection. N Engl J Med 1991; 324:137-44.

129. **Dunn DT, Brandt CD, Kirvine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intrauterine and intrapartum transmission. AIDS Res Human Retroviruses 1995; 9:F7-F11.**

130. European Collaborative Study: Children born to women with HIV-1 infection: natural history and risk of transmission. Lancet 1991; 337:253-260.

131. Pitt J, Landay A, McIntosh K, et al. Prenatal maternal circulating leukocyte HIV predisposes to HIV culture positivity in their infants: progress report from a North American cohort. Proceedings from the 32nd Interscience Conference on Antimicrobial Agents & Chemotherapy. Anaheim, CA; 1992 (Abstract 599).

132. Coombs R. July 1991 ACTG Plenary Session presentation, and personal communication with Dr. Mofenson (August 1991).

133. Willams IG, Gabriel F, Kelly G, et al. Response of serum p24 antigen and antibody to p24 antigen in patients with AIDS and AIDS-related complex treated with ZDV. AIDS 1990; 4: 909-912.

134. Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to ZDV isolated during prolonged therapy. Science 1989; 243: 1731-1734.

135. Land S, Treloar G, McPhee D, et al. Decreased in vitro susceptibility to ZDV of HIV isolates obtained from patients with AIDS. J Infect Dis 1990; 161: 326-329.

136. Simon R. (1979). Restricted randomization designs in clinical trials. Biometrics 35, 503-512.

137. D'Argenio, DZ and Schumitzky, A. ADAPT II User's Guide. University of Southern California, Los Angeles 1992.

138. Gibaldi M, Perrier D. Pharmacokinetics, 2nd edition. Marcel Dekkor, Inc., New York, 1982; pp 409-417.

139. Lindstrom MJ and Bates DM. Nonlinear mixed effects models for repeated measures data. Biometrics 46:673-687.

140. Hirst K, Zerbe G, Boyle DW, and Wilkening RB. On nonlinear random effects models for repeated measures. Communications in Statistics - Simulation 20:463-478, 1991.

141. Beal, SL and Sheiner, LB. NONMEM User's Guide. University of California at San Francisco, San Francisco.

142. Gelber RV, Lindsey JC, MaWhinney S. (1995). Clinical trials to reduce the risk of maternal-infant transmission of HIV infection. AIDS Clinical Trials, Eds. Finkelstein DM and Shoenfeld DA. John Wiley and Sons, New York.

143. Fleming TR, Harrington DP, and O'Brien PC. (1984). Designs for group sequential tests. Controlled Clinical Trials, 5, 348-361.

144. **Marubini E and Valsechhi MG. (1995). Analyzing Survival Data from Clinical Trials and Observational Studies. John Wiley and Sons, Chicester.**

145. **Landesman SH, Kalish LA, Burns DA, et al. Obstetrical factors and the transmission of human immunodeficiency virus Type 1 from mother to child. N Engl J Med 1995; 334:1617-1623.**

146. Anderson S, Auquier A, Hauck W, et al. (1980). Statistical methods for comparative studies. John Wiley & Sons, New York.

147. Kalbfleisch JD and Prentice RL. (1980). The statistical analysis of failure time data. John Wiley & Sons, New York.

148. Draper NR and Smith H. (1981). Applied regression analysis, 2nd edition. John Wiley & Sons, New York.

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 batched ICD p24 antigen determinations at NICHD central laboratory.
*Quantitative HIV PBMC Micro-culture.

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.

APPENDIX III

DEFINITION OF AIDS
WHEN THERE IS LABORATORY EVIDENCE OF HIV INFECTION

For persons 13 years of age and older, refer to 1993 Revised Classification System for HIV infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults (CDC: MMWR, December 18, 1992; 41 (RR-17): 1-19.)

For persons less than 13 years of age, refer to the following list of AIDS indicator conditions:
(Abstracted from: Centers for Disease Control. Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome. MMWR Supplement 1S, 1987); 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less than 13 Years of Age (CDC: MMWR, September 30, 1994: 43 (RR-12): 1-19).

Regardless of the presence of other causes of immunodeficiency, in the presence of laboratory evidence of HIV infection, any definitively diagnosed disease listed below indicates a diagnosis of AIDS.

1. Bacterial infections, multiple or recurrent (any combination of at least two culture-confirmed infections within a 2-year period), of the following affecting a child < 13 years of age:

   septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media or superficial skin or mucosal abscesses and indwelling catheter-related infections).

2. Candidiasis of the esophagus, trachea, bronchi, or lungs.

3. Coccidioidomycosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes).

4. Cryptococcosis, extrapulmonary.

5. Cryptosporidiosis with diarrhea persisting > one month.

6. Cytomegalovirus disease with onset of symptoms at age > one month (at a site other than liver, spleen, or lymph nodes).

7. Herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than one month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient > one month of age.

8. HIV encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance.

9. Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes).

10. Isosporiasis with diarrhea persisting > one month.

APPENDIX III (continued)

11. Kaposi's sarcoma at any age.

12. Lymphoma of the brain (primary) at any age.

13. Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype.

14. Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia (LIP/PLH complex) affecting a child < 13 years of age.

15. *Mycobacterium tuberculosis* disseminated or extrapulmonary.

16. *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes).

17. *Mycobacterium avium* complex or *mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes).

18. *Pneumocystis carinii* pneumonia.

19. Progressive multifocal leukoencephalopathy.

20. Salmonella (nontyphoid) septicemia, recurrent.

21. Toxoplasmosis of the brain affecting a patient > one month of age.

22. HIV wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: 1) persistent weight loss > 10% of baseline OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age OR c) < 5th percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for ≥ 30 days) OR b) documented fever (for ≥ 30 days, intermittent or constant).

APPENDIX IV

STUDY DRUG (HIVIG/IVIG) PREPARATION AND ADMINISTRATION

Source:	HIVIG - **NABI**; IVIG - **Bayer**.
Route of administration:	Intravenous
Storage:	Products contain no preservatives. Must be stored at 2-8°C. When subjects do not show up for their scheduled infusions, unopened vials may be at room temperature up to 8 hours and then returned to the refrigerator for future use.
Preparation:	Aseptically place the correct volume of HIVIG/IVIG into a sterile bag or bottle. Study drug must be filtered **in the pharmacy** with a 5.0 micron or smaller pore size filter prior to dispensing. Follow individual institutional requirements regarding in-line filtration during patient administration of immune-globulin products. Infusion must start within one hour of pooling. Product is to be at room termperature for the infusion. The pharmacist will record the product lot number (HIVIG or IVIG) on the pharmacy record form and send completed form directly to Westat.
Restrictions:	Frozen or heated products may not be used. Opened vials must be used within the indicated time frame or discarded; do not retain for future use.
Use with other IV fluids?	Use undiluted but piggyback to 5% dextrose solution (D5W) in case infusion needs to be stopped; flush with 5% dextrose solution only.
Use with other IV medications?	No
Dose:	200 mg/kg (4 ml/kg)
Medications:	Not required, antihistamines and/or antipyretics may be administered prior to infusion in patients previously demonstrating mild reactions or during infusion if reaction occurs.
Recommended Dosing Interval:	Women: Every 28 d ± 7 d until delivery. Infants: Single infusion within 12 h after birth.
Infusion rate:	Women: 0.02 cc/kg/min initially for 30 min, increase as tolerated to maximum 0.08 cc/kg/min. Infants: 0.01 cc/kg/min initially, double at 15 min intervals as tolerated to maximum 0.08 cc/kg/min.

Monitoring (minimum requirements):	Vital signs (P, BP, R, T, fetal heart sounds) before beginning, at the midpoint of infusion, and at end of infusion. If adverse reaction, vital signs at the time of reaction and until the reaction subsides. In interruption, vital signs at time of interruption and thirty minutes later.
Record:	Dosage; Study number; Vital signs; Duration of infusion; Adjustment of infusion rate, if necessary; Other medication administered, if any, Indication for medications; and Adverse reactions, if any.

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)

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

DOSE CALCULATION:

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

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

Example:

Infant weighs 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

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 appointments 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 supposed 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:_____

APPENDIX VII

HIVIG Pharmacokinetics

The pharmacokinetics and activity of the HIVIG preparation will be evaluated in the first approximately 50 women and their infants enrolled. All of the samples will be coded, and investigators will be blinded as to the treatment that the patients are receiving.

Collection, Processing, and Shipment of Specimens for Pharmacokinetic Substudy Assays

Two types of specimens are to be collected. The first is serum for real-time pharmacokinetic assays. The second is plasma for future assays of antiviral activity. Refer to the schedule contained in this appendix for times at which different specimen types are to be collected.

All specimens must be drawn by peripheral venipuncture (not through the infusion tubing) in the indicated type of blood collection tube.

Recommended types of blood collection tubes

a. For serum: 4.0 ml draw volume red-gray ("tiger") top "serum separator" tube with polymer gel and silica activator (B-D Vacutainer order no. 6514 or B-D Hemogard Vacutainer order no. 367783, or equivalent; telephone 1-800-631-0174 for Becton Dickinson order information).

b. For plasma: 2.6 ml draw volume yellow top tube with acid-citrate-dextrose (ACD) anticoagulant (B-D order #: 364012; contact Becton Dickinson 1-800-631-0174, for order information).

Specimen collection and processing

a. For specimens collected in red-gray ("tiger") top serum separator tubes (SST):

These specimens are to be collected, spun, and shipped the same or next business day for real-time pharmacokinetic assays.

Collect the indicated amount of whole blood (4.0 ml for women and cord blood specimens, 2.0 cc for infant specimens) at each pharmacokinetic sampling point in a 4.0 ml draw volume SST. Centrifuge until clot is separated from serum by gel in tube. Transfer serum from SST tube to two sterile polypropylene, leak-proof 1.5 ml vials. Discard clot tube. Label serum vial including patient identification number and date and time of draw. Refrigerate serum vial at 4°C (do not freeze) until ready to ship. Ship on the day of collection or the next business day with cold packs (do not use dry ice) by overnight commercial courier service, using shipping materials provided by Westat, to the protocol central repository for further processing.

b. For specimens collected in yellow top (ACD) tubes:

These specimens are to be processed within 6 hours of collection for separation of plasma and -70°C freezer storage on site, then batch shipped monthly to the protocol central repository for future assays of antiviral activity.

Collect the indicated amount of whole blood (2.6 cc for women, 1.0 cc for infants) at the specified sampling points in a 2.6 ml draw volume yellow-top ACD tube. Refrigerate (4°C) and separate plasma within 6 hours of collection. Centrifuge at 800xg for 20 minutes at 23°C (room temperature). Separate plasma, discard cells, and recentrifuge plasma as before. Aliquot twice-centrifuged plasma into 1.5 ml freezer vials (Sarsted catalog no. 72-694/006 or equivalent; telephone 1-800-321-4680 for Starsted order information), each containing 500 µL (3 to 4 500-µL plasma aliquots per specimen are anticipated). Label freezer vials, including patient identification number, date and time of draw, contents of vial (**plasma**) and anticoagulant type (ACD). Freeze at -70°C. Ship monthly on dry ice to the protocol central repository.

Specimen shipment

All specimens collected as part of the pharmacokinetic substudy will be shipped to the protocol central repository (shipping address: **McKesson Bioservices Inc.**, 685 Lofstrand Lane, Rockville, MD, 20850; telephone **301-340-1620**, FAX **301-340-9245**). For additional instructions or questions about shipping procedures, contact **McKesson** directly.

Schedule of Pharmacokinetic Evaluations

The pharmacokinetics of the HIVIG preparation will be evaluated for peak and trough values in a subset of women enrolled. All of the samples will be coded, and investigators will be blinded as to the treatment that the women are receiving. The evaluation will focus on identification of antibodies that are documented to be present in the HIVIG preparation.

All specimens must be drawn by peripheral venipuncture.

Timing of Sample (wk gestation)		Quantity of Blood to be Drawn	
	Women	4cc Serum Separator Tube (SST)	2.6cc (ACD) Yellow Top
Pre-entry/Baseline Pre-infusion (20-24 wk)		X	X
1 hr	post infusion #1 (peak)	X	
24 hr	post infusion #1	X	X
3 d	post infusion #1	X	
7 d	post infusion #1	X	
14 d	post infusion #1	X	X
	(wk 24-28)		
28 d	post infusion #1 (trough)	X	X
	(Just prior to infusion #2)		
1 h	post infusion #2 (peak)	X	
24 h	post infusion #2	X	X
7 d	post infusion #2	X	
14 d	post infusion #2	X	X
	(wk 28-32)		
28 d	post infusion #2 (trough)	X	X
	(Just prior to infusion #3)		
1 h	post infusion #3 (peak)	X	
24 h	post infusion #3	X	X
7 d	post infusion #3	X	
14 d	post infusion #3	X	X
	(wk 32-36)		
28 d	post infusion #3 (trough)	X	X
	(Just prior to infusion #4)		
1 h	post infusion #4 (peak)	X	
24 h	post infusion #4	X	X
7 d	post infusion #4	X	
14 d	post infusion #4	X	X
28 d	post infusion #4 (trough)	X	X
Postpartum (women)			
28d	post-delivery	X	
	Infant		
Cord blood (infant)		X	
1 h	post infusion (infant)	X (2 ml)	
24 h	post infusion (infant)	X (2 ml)	X (1 cc)
7 d	post infusion (infant)	X (2 ml)	
14 d	post infusion (infant)	X (2 ml)	
28d	post infusion	X (2 ml)	

APPENDIX VIII

SUBCLASS DISTRIBUTION AND SPECIFIC HIV MARKERS IN HIVIG AND IVIG[1]

		LOTS			
		1	2	3	IVIG
% IgG1	% of Total	82.1	81.9	84.5	65.2
% IgG2		13.0	12.3	10.2	25.7
% IgG3		4.1	4.4	9.2	8.2
% IgG4		.8	1.4	1.0	1.2
p24 Antigen		NEG	NEG	NEG	NEG
p24 Antibody	Titer	272500	243500	238500	<5
gp41 Antibody	Titer	8800	8700	7800	<5
pg120 Antibody	Titer	3400	2910	3100	<5
Culture		NEG	NEG	NEG	NEG
PCR[2] For Gag of HIV-1		NEG	NEG	NEG	NEG

[1]IVIG corresponds to intravenous polyvalent human IgG preparation.

[2]Polymerase chain reaction used to detect HIV genome.

APPENDIX IX

BLOCKING OF HIV-CELL INTERACTION

ASSAYS	TARGET	HIV STRAIN	HIVIG LOTS 1	2	3	IVIG
Neutralization[1]	AA5	IIIB	160	1280	320	0
of HIV Infection		MN	160	>2560	1280	0
V3 Loop[2]	Peptides	IIIB	.056	.112	.067	.045
Binding		MN	.447	1.082	.942	.023
		WMJ	.068	.405	.233	.036
		SC	.183	.891	.546	.026
Syncytia[3]	Molt cells	IIIB	900	950	375	NE[4]
Formation	CEM cells	RF	1060	1460	1800	NE

[1]Expressed as titer of neutralization (see Materials and Methods).

[2]Optical density recorded with specific peptide ELISA, Concentration of peptide in the coating solution was 2 ug/ml (see methods).

[3]Concentration (ug/ml) of IgG at which viral cytopathic effect is reduced by 50%.

[4]No effect was seen with IVIG at 5000 ug/ml of IgG.

1994 HIVIG Neutralization Data

Lots	Abbott 1	Abbott 2	NABI 1	NABI 2
Neutralization IIIB	2381	2658	1921	3089
SF2	3284	9647	3415	2196
MN	624	624	624	624

- Titers giving one log reduction of virus infectivity.
- All lots were tested in the same laboratory at the same time.

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 x 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	BP 21 - 40 mm Hg over baseline	BP >40 mm Hg over baseline
Allergic	Chest tightness, transient or local rash, mild itching	Tachypnea 1.3-2x baseline, wheeze, cough, diffuse rash or urticaria, mod. itching	Bronchospasm, tachypnea >2x 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 benadryl.	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.

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 x 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-spasm, severe rash or urticaria, anaphylaxis*
Systemic Temperature	37.2 - 38.0°C	38.1 - 39.9°C	Temp >39.9 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

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

APPENDIX XII

TABLE FOR GRADING SEVERITY OF ADVERSE EXPERIENCES (WOMEN)

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
HEMATOLOGY				
HEMOGLOBIN	9.5 gm/dL - 10.5	8.0 - 9.4 gm/dL	6.5 - 7.9 gm/dL	< 6.5 gm/dL
ABSOLUTE NEUTROPHIL COUNT	1000 x 1500/mm^3	750 - 999/mm^3	500 - 749/mm^3	< 500/mm^3
PLATELETS	75,000 - 99,000/mm^3	50,000 - 74,999/mm^3	20,000 - 49,999/mm^3	< 20,000/mm^3 or diffuse petechiae
PROTHROMBIN TIME (PT)	1.01 - 1.25 x upper normal limit	1.26 - 1.5 x upper normal limit	1.51 - 3.0 x upper normal limit	> 3 x upper normal limit
PARTIAL PROTHROMBIN TIME (PTT)	1.01 - 1.66 x upper normal limit	1.67 - 2.33 x upper normal limit	2.34 - 3 x upper normal limit	> 3 x upper normal limit
FIBRINOGEN	0.99 - 0.75 x lower normal limit	0.74 - 0.50 x lower normal limit	0.49 x 0.25 x lower normal limit	< 0.25 x lower normal limit
FIBRIN SPLIT PRODUCT	20 - 40 ug/ml	41 - 50 ug/ml	51 - 60 ug/ml	> 60 ug/ml
METHEMOGLOBIN	5 - 9.9%	10.0 - 14.9%	15.0 - 19.9%	> 20%
CHEMISTRIES				
HYPONATREMIA	130 - 135 meq/L	123 - 129 meq/L	116 - 122 meq/L	< 116 meq/L or mental status changes or seizures
HYPERNATREMIA	146-150 meq/L	151 - 157 meq/L	158 - 165 meq/L	> 165 meq/L or mental status changes or seizures
HYPOKALEMIA	3.0 - 3.4 meq/L	2.5 - 2.9 meq/L or replacement Rx req	2.0 - 2.4 meq/L or intensive replacement Rx. req. or hospitalization req.	< 2. meq/L or paresis or ileus or life-threatening arrhythmia
HYPERKALEMIA	5.6 - 6.0 meq/L	6.1 - 6.5 meq/L	6.6 - 7.0 meq/L	> 7.0 or paresis or ileus or life-threatening arrhythmias
HYPOGLYCEMIA	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL	< 30 mg/dL or mental status changes or coma, seizures
HYPERGLYCEMIA: (note if fasting)	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
HYPOCALCEMIA (correct for albumin)	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL	<6.1 mg/dL or life threat-ening arrhythmia or tetany
HYPERCALCEMIA (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or tetany or life-threatening arrhythmia
HYPOMAGNESEMIA	1.2 - 1.4 meq/L	0.9 - 1.1 meq/L or replacement Rx req.	0.6 - 0.8 meq/L or intensive Rx req. or hospitalization	< 0.6 meq/L or life threatening arrhythmias
HYPOPHOSPHATEMIA	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL or replacement Rx req.	1.0 - 1.4 mg/dL intensive Rx or hospitalization req.	< 1.0 mg/dL or life threatening arrhythmias or CHF
HYPERBILIRUBINEMIA	1 - 1.5 x upper normal limit	1.6 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	> 5 x upper normal limit
BLOOD UREA NITROGEN (BUN)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
CREATININE	1.1 - 1.5 x upper normal limit	1.5 - 3.0 x upper normal limit	3.1 - 6 x upper normal limit	> 6 x upper normal or requires dialysis

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
ENZYMES				
AST (SGOT)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
ALT (SGPT)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
GGT	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
ALKALINE PHOSPHATASE	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit	> 10 x upper normal limit
AMYLASE	1.1 - 1.5 x upper normal limit	1.6 - 2.0 x upper normal limit	2.1 - 5.0 x upper normal	> 5.1 x upper normal or clinical pancreatitis
URINALYSIS				
PROTEINURIA	1+ or < 0.3% or < 3 g/L or 200 mg - 1 gm loss/day	2 - 3+ or 0.3 - 1.0% or 3 - 10 g/L or 1 - 2 gm loss/day	4+ or > 1.0% or > 10 g/L, or 2 - 3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
HEMATURIA	microscopic only	gross, no clots	gross + clots	obstructive or req. transfusion
CARDIAC				
CARDIAC RHYTHM		asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires treatment
HYPERTENSION	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx req.	requires acute tx, no hosp. required	requires hospitalization
HYPOTENSION	transient orthostatic hypotension; no Rx	sympthoms correctable with oral fluid Rx;	requires IV fluids no hosp. required	requires hospitalization
PERICARDITIS	minimal effusion	mild/mod asymp. effusion, no Rx	symptomatic effusion, pain, EKG changes	tamponade; pericardio-centesis or surgery req.
HEMORRHAGE, BLOOD LOSS	microscopic/occult	mild, no transfusion	gross blood loss; 1 - 2 units transfused	massive blood loss, > 3 units transfused
CARDIOVASCULAR - INFUSION - ASSOCIATED				
TACHYCARDIA	HR 1.1-1.3x baseline	HR 1.4-1.6x baseline	HR >1.6x baseline	Tachycardia compromising cardiac output
ARRHYTHMIA	Occasional, asymptomatic	Continuous, <1 per min., and asymptomatic	Continuous, >1 per min., or symptomatic	V. Fib or Cardiac arrest
HYPOTENSION (SYSTOLIC)	BP 10-20 mm Hg below baseline	BP 21-40 mm Hg below baseline	BP >40 mm Hg below baseline	Shock
HYPERTENSION (SYSTOLIC)	BP 10-20mm Hg over baseline asymptomatic	BP 21-40mm Hg over baseline, symptomatic	BP >40mm Hg over baseline, symptomatic	Hypertensive crisis

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
RESPIRATORY				
COUGH - for aerosol studies	transient - no Rx	treatment associated cough; local Rx	uncontrolled	
BRONCHOSPASM ACUTE	transient; no Rx; <80% to >70% FEV, (or peak flow)	tachypnea 1.3-2x baseline, req. Rx; normalizes with bronchodilator; or FEV, 60%-70% (or peak flow)	tachypnea >2x baseline, no normalization w/bronchodilator; or FEV, (or peak flow) 25 - 60%; retractions	cyanosis; or FEV, (or peak flow) < 25% or intubated
GASTROINTESTINAL				
STOMATITIS	mild discomfort, no limits on activity	some limits on eating/drinking	eating/talking very limited	unable to drink fluids; req. IV fluids
NAUSEA	mild discomfort; maintains reasonable intake	mod. discomfort; intake dec. significantly; some activity limited	severe discomfort; no significant intake activities limited	minimal fluid intake
VOMITING	transient emesis	occ/moderate vomiting	orthostatic hypotension or IV fluid Rx req.	hypotensive shock or hospitalization for IV fluid therapy req.
CONSTIPATION	mild	moderate	severe	distension with vomiting
DIARRHEA	transient or 3 - 4 loose stools/day	5 - 7 loose stools/day or nocturnal loose stools	orthostatic hypotension or > 7 loose stools/day or req. IV fluid Rx	hypotensive shock or hospitalization for IV fluid therapy req.
NEURO/ NEUROMUSCULAR				
NEURO-CEREBELLAR	slight incoordination Dysdiadochokinesis	intension tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
MOOD	mild anxiety or depression	mod. anxiety or depression and therapy required	severe anxiety or depression or manic; (needs assistance)	acute psychosis; incapacitated, requires hospitalization
NEURO CONTROL (ADL = Activities of Daily Living)	mild diff. concen; no Rx; mild agitation; ADL unaffected	mod. confusion/ agitation; some sev. limitation of ADL; min. Rx	sev. confusion/agitation; some sev. limitation of ADL; min. Rx	toxic psychosis; hospitalization
MUSCLE STRENGTH	subjective weakness; no objective symptoms/signs	mild objective signs, symptoms, no dec. in function	objective weakness; function limited	paralysis

ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
OTHER PARAMETERS				
FEVER: oral, W/O infection, > 12 hours	37.7 - 38.4C or	38.5 - 39.4C or	39.5 - 40.5C or	> 40.5C or
HEADACHE	mild, no Rx therapy	transient, mod.; Rx req.	severe, responds to initial narcotic therapy	intractable, req. repeated narcotic therapy
FATIGUE	no dec. in daily activities	normal activity dec. 25 - 50%	normal activity dec. > 50%; can't work	unable to care for self
ALLERGIC REACTION	pruritus w/o rash	localized urticaria	generalized urticaria angioedema	anaphylaxis
LOCAL REACTION	tenderness or erythema	induration < 10 mm or phlebitis or inflammation	induration > 10 mm or ulceration	necrosis
MUCOCUTANEOUS	erythema, pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, ulceration	exfoliative dermatitis, mucous membrane involvement, suspected Stevens-Johnson or erythema multiforme; or necrosis requiring surgery

APPENDIX XIII

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS: CHILDREN

Parameter	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
Hematologic					
1. Hemoglobin (g/dl) < 2 yr.	> 10.0	9.0 - 9.9	7.0 - 8.9	< 7.0	Failure 2° anemia
> 2 yr.	> 11.0	10.0 - 10.9	8.0 - 9.9	6.5 - 7.9	< 6.5
2. Leukocytes ($\times 10^3/mm^3$)	> 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
3. Neutrophils + bands (total count/mm^3)				< 1,000	< 500
4. Platelets/mm^3	≥ 100,000	75,000 - 99,999	50,000 - 74,999	25,000 - 49,999	< 25,000
Gastrointestinal					
1. Bilirubin (total)	< 1.0 x N[1]	1.0 - 1.4 x N	1.5 - 1.9 x N	2.0 - 4.9 x N	≥ 5.0 x N
2. SGOT/SGPT	< 1.0 x N	1.0 - 1.9 x N	2.0 - 4.9 x N	5.0 - 9.9 x N	≥ 10.0 x N
3. Alkaline Phosphatase	< 1.0 x N	1.0 - 1.4 x N	1.5 - 1.9 x N	2.0 - 4.9 x N	≥ 5.0 x N
4. Hyperamylasemia	None amylase (or amylase and lipase) 1 - 1.4 x N	Mild - fractionated amylase (or amylase and lipase) 1.5 - 2 x N	Moderate - fractionated amylase (or amylase and lipase) 2.1 - 4.9 x N	Severe - fractionated (or amylase and lipase) ≥ 5 x N	Fractionated amylase
5. Abdominal Pain	None	Mild - no treatment	Moderate - no treatment	Moderate - requires Rx	Severe - Hosp. + Rx
6. Diarrhea	None	Soft stools	Increased no. of liquid stools	Liquid stools - dehydration	IV therapy required
7. Nausea and Vomiting	None	Nausea only	Transient vomiting	Vomiting > 3x day/ dehydrated	Intractable vomiting: IV rehydration
Allergic	None	Transient rash; fever ≤ 38.5°C	Diffuse rash or urticaria temp > 38.5°C	Bronchospasm - parenteral therapy required fever > 40°C	Anaphylaxis respiratory arrest
Cutaneous	None	Transient erythema; Local maculo-pap rash	Dry desquamation vesiculation, pruritus, persistent erythema	Moist desquamation, ulceration	Exfoliative dermatitis, necrosis requiring surgery, intervention
Renal					
1. BUN	< 20	20 - 39	40 - 59	60 - 79	≥ 80
2. Creatinine	≤ 1.2	1.3 - 1.9	2.0 - 3.9	4.0 - 5.9	≥ 6.0

[1]N = upper limit of age-appropriate normal.

APPENDIX XIII (Continued)

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS: CHILDREN

Parameter	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
Cardiovascular; Infusion-related					
Tachycardia		HR1.1-1.3x baseline	HR 1.4-1.6x baseline	HR>1.6x baseline	Tachycardia compromising cardiac output
Arrhythmia		Occasional, asymtomatic min., and asymptomatic	Continuous, <1 per min., or symptomatic	Continuous, >1 per min., or symptomatic	V. Fib or Cardiac arrest
Hypotension (systolic)		BP 10-20 mm Hg below baseline	BP 21-40 mm Hg below baseline	BP >40mm Hg below baseline	Shock
Hypertension (systolic)		BP 10-20mm Hg over baseline asymptomatic	BP 21-40 mm Hg, over baseline asymptomatic	BP >40 mm Hg over baseline, symptomatic	Hypertensive crisis
Serum Electrolytes					
1. Sodium (meq/L)					
Increased or	135 - 144	145 - 149	150 - 154	155 - 164	≥ 165
decreased		130 - 134	125 - 129	115 - 124	< 115
2. Potassium (meq/L)					
Increased or	3.5 - 5.4	5.5 - 5.9	6.0 - 6.4	6.5 - 6.9	≥ 7.0
decreased		3.0 - 3.4	2.5 - 2.9	2.0 - 2.4	< 2.0
3. Calcium (mg/dl)					
Increased or	8.5 - 10.4	10.5 - 11.2	11.3 - 11.9	12.0 - 12.9	≥13.0
decreased		7.8 - 8.4	7.0 - 7.7	6.0 - 6.9	< 6.0
Neurologic					
1. Peripheral -					
Muscular	Normal	DTR	Absent DTR	Severe weakness	Paralysis
Sensory	Normal	Mild paresthesia	Severe paresthesia	Sensory loss	
Autonomic	Normal	Normal	Normal	Obstipation and bladder dysfunction	
2. Central	Normal	Mild lethargy, headache - no therapy required, irritability	Obtunded, confusion, ataxia, slurred speech, HA requiring analgesic	Seizures, delirium, somnolent > 50% of waking hours, HA requiring narcotic	Comatose

APPENDIX XIII (Continued)

RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS: CHILDREN

Parameter	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life-threatening)
Peripheral Neuropathy	None	Mild discomfort - no therapy required	Moderate discomfort - requires non-narcotic analgesic	Severe discomfort - i.e., marked antalgic gait or unwilling to stand - requires narcotic analgesic	Incapacitating discomfort - not improved with narcotics

APPENDIX XIV

REPORTING OF ADVERSE EXPERIENCES

Timely and accurate reporting of adverse experiences is required, not only for regulatory compliance, but to determine if unexpected toxicities have occurred or if the incidence or severity is greater than expected, and if necessary, to quickly disseminate information to investigators working with the drug. Each Adverse Experience Report submitted to Westat is reviewed and evaluated to determine the adverse experience's likely relation to the drug. Based on the medical assessment, a decision is made concerning the need for further action and NHLBI is consulted. The prime consideration is whether the new findings affect the safety of patients enrolled in ongoing studies. If so, NHLBI takes immediate steps to notify the investigator community and the FDA.

The identification and definition of an adverse experience, as it relates to the drug treatment, presents special problems for the investigator and sponsor because many patients develop symptoms related to HIV virus infection and its associated complications. The centralization of information on suspected adverse experiences makes possible a much more accurate determination of the degree to which a suspected reaction is in fact drug-related. Monitoring toxicities from a multicenter perspective provides the opportunity to identify toxicities which may occur in a smaller percent of the population and which may range widely in severity.

1. The prompt reporting of adverse experiences to Westat is the responsibility of each investigator. Investigators are encouraged to submit reports if there is a possibility of a drug effect.

2. All deaths (including fetal deaths) must be reported to Westat.

3. For patients off drug:

   a. Report deaths **that** occur within three months **after coming off study**;
   b. Report other adverse experiences/toxicities **that** occur within 8 weeks and meet the reporting requirements as noted on the next page.

4. The need for a change in dosage is NOT an appropriate criterion for making the decision whether or not to report an adverse experience. Please report all adverse experiences, whether or not a dose change is required, that may possibly be related to the study drug.

5. Progression of disease that is DEFINITELY NOT related to drug treatment is not an adverse experience and should not be reported on AER forms.

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

7. Adverse experiences should also be reported to your local Institutional Review Board.

8. 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 a particular adverse experience may result in suspension of the investigator's clinical research privileges in this study.

9. Information about adverse experiences will be collected by Westat, reported to NHLBI and shared with NICHD and NIAID. NHLBI will be responsible for reporting adverse experiences to the FDA.

REPORTING REQUIREMENTS: MOTHER

Note: The reporting requirement for adults and infants differ.

Maternal: Adverse Experience Reporting Requirements

Expected	Grade 2	Send AER form with CRFs specific to study week.
	Grade 3	Send AER form with CRFs specific to week.
	Grade 4: not immediately life threatening	Send AER form within five days.
	Grade 4: immediately life threatening	Deaths and immediately life-threatening events which could possibly be related to study drug use must be phoned in within 24 hours (phone 1-800-825-4844), and send an AER form within three days.
Unexpected	Grade 2	Send AER form with CRFs specific to study week.
	Grade 3	Send AER form within five days.
	Grade 4 & 5	Deaths (including fetal deaths), and immediately life-threatening events which could possibly be related to study drug use, must be phoned within 24 hours (1-800-825-4844) and send an AER form within three days.

REPORTING REQUIREMENTS: NEONATE/INFANT

Neonate/Infant: Adverse Experience Reporting Requirements*

Expected	Grade 1 & 2	Send AER form with CRFs specific to study week.
	Grade 3	Send AER form within five days.
	Grade 4: not immediately life threatening	Send AER form within five days.
	Grade 4: immediately life threatening	Deaths and immediately life-threatening events which could possibly be related to study drug, must be phoned within 24 hours (1-800-825-4844) and send an AER form within three days.
Unexpected	Grade 1 & 2	Send AER form with CRFs specific to study week.
	Grade 3	Send AER within five days.
	Grade 4 & 5	Deaths and immediately life threatening events which could possibly be related to study drug, must be phoned within 24 hours (1-800-825-4844) and send an AER form within three days.
	Congenital Anomaly:	Send AER within five days.

*Elevated MCV in an infant will not be considered a reportable adverse event.

Overdoses must be reported irrespective of outcome, even if toxic effects were not observed.

AERs - Report initial abnormality when it reaches a reportable level. When an adverse event improves to a non-reportable level, the event is resolved. If the event recurs, it should be reported as a new event. If the event increases in severity to another grade, the event at the lower grade is resolved, and the event at the increased grade is reported as a new event. If the nature/etiology of an adverse event changes, it should be reported as a new event.

Intercurrent Illness - Illnesses (except deaths) definitely not related to study drug and otherwise documented in the CRF and the patient's record, are not reported on an AER form.

Deaths - All deaths (including fetal deaths), regardless of association with study drug(s), must be reported on an AER form and Cause of Death Form up to 3 months after coming off study.

Hospitalization - Unless the hospitalization is the result of an AE, the reason for the hospitalization should not be recorded on an AER form.

Oral ZDV taken by a woman during the antepartum period is not considered to be an investigational therapy for this protocol. Toxicities related to oral ZDV for the woman are not reported on an AER. However, **because** intravenous ZDV administered intrapartum and ZDV administered to the infant are **study drugs**, an AER form must be completed for toxicities related to these therapies which satisfy the reporting criteria described above.

Adverse Experiences in Health Care Workers: 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.

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

MAIL all AER Forms to:

Adverse Experience Report: WB 427
Westat, Inc.
1650 Research Boulevard
Rockville, MD 20852

APPENDIX XV

INSTRUCTIONS FOR OBTAINING CORD BLOOD

Drawing of Cord Blood

After the baby is delivered and the placenta has not yet been delivered, the cord is clamped and severed. There remains 3-6 inches of cord external to the birth canal. There are 2 umbilical arteries which are easy to distinguish from the much larger single umbilical vein. The cord is cleansed and the umbilical vein is cannulated by needle and blood is removed by suction into a syringe.

red top tube	2 cc for SGOT/SGPT
yellow (ACD) top tube	8.5 cc for special studies and storage
red top tube	2 cc for Ig's

Specimen processing is outlined in Appendix XVI.

Appendix XVI
SPECIMEN COLLECTION, PROCESSING AND STORAGE PROCEDURES
ACTG 185 (01 Nov 96)

Laboratory procedures for obtaining, processing, storing, and analyzing blood specimens required by the protocol are contained in this appendix. Principles that have been followed in developing these procedures are (a) to minimize blood volumes; (b) to simplify specimen handling and processing; and (c) to assure that laboratory endpoints essential to the study objectives are obtained.

Procedures for phlebotomy and specimen processing will vary at each site, depending on laboratory arrangements. Real-time assays are <u>not</u> required for the following virology specimens:

Women	Infants
Rapid Processed Plasma (PV) (≤ 6 hr) for Viral Quantitation	
Cells (PBL) for storage	Cells (PBL) for storage
Plasma (PL) for storage	Plasma (PL) for storage

The specimens listed above will be frozen and batch shipped monthly to the protocol central repository for storage (shipping address: **McKesson BioServices Inc.**, 685 Lofstrand Lane, Rockville, MD 20850; telephone (301) 340-1620; FAX (301) 340-9245). Shipping instructions are contained in **Appendix XVIII**. For additional instructions or questions about shipping procedures for these specimens, contact **McKesson** directly.

All other protocol-required assays are to be performed in <u>real-time</u> by the appropriate laboratories (indicated below).

The following abbreviations are used throughout the text and tables of Appendix XVI:

B-D	Becton Dickinson
CBC/diff	Complete blood count and differential
CC	Confirmatory Culture
Chem panel	BUN, Creatinine, SGOT, SGPT, bilirubin (total/direct), alkaline phosphatase, electrolytes
CR	Cord blood
Dx	Diagnosis
EIA/WB	HIV antibody enzyme immunoassay/Western blot
Ficoll-Hyp	Ficoll-Hypaque gradient centrifugation
Ig's	Quantitative immunoglobulins G, A, & M
ISO	Isolate from positive HIV quantitative microculture
Lymph	Lymphocyte
PBL	Peripheral Blood Lymphcytes (Peripheral Blood Mononuclear Cells)
PCR	Polymerase Chain Reaction Assay (PCR)
PK	Pharmacokinetics
PL	Plasma
PV	Rapid Processed plasma for Viral Quantitation
q mo	Every month
STS	Serologic test for syphilis

Part 1. Blood Collection (phlebotomy)

Table 1 (women) and Table 2 (infants) indicate the recommended type and size (draw volume) blood collection tube and the laboratory destination for each protocol-required test.

Table 3 (women) and Table 4 (infants) list for each visit the specimens to be drawn (in order of priority), and for each specimen the type and size (draw volume) blood collection tube to be used, the type of processing required, and the laboratory destination.

Note that all specimens are to be drawn PRIOR TO infusion of drug (for visits at which infusions of HIVIG/IVIG or ZDV occur).

Part 2. Specimen Processing

A. Local Assays (red top tubes)

These specimens are to be processed according to local laboratory procedures and requirements for the indicated tests.

B. Flow Cytometry Assays (purple top tubes)

These specimens should be processed for CBC, 5-part differential, and enumeration of specified lymphocyte subset percentages and absolute counts within 24 hours.

Transport both specimens (one for CBC and one for subsets) at room temperature to the ACTG certified flow laboratory for your site.

[Exception: Infant specimens for CBC and differential at newborn, 1-week and 2-week study visits are stat local hematology laboratory assays.]

C. Virology Assays (yellow top tubes)

The following sections contain detailed specimen processing instructions according to the patient source (woman, infant, cord), size of blood collection tubes, and purpose for which the specimen is intended. Process these specimens for real-time HIV quantitative microculture and to obtain cells, plasma, and positive isolates for storage.

Specimen Tracking (Form 18534): A specimen tracking form, Form 18534, must be initiated for each virology blood specimen (yellow top tube) collected. A tracking form barcode label must be placed on the tracking form to provide the link between the patient and the processed barcode labeled specimens. The tracking form collects information on time elapsed from phlebotomy to processing, and on disposition of the specimen into cell or plasma aliquots. The time of blood draw must be recorded on the tracking form.

Specimen Barcode Labels: Preprinted barcode labels will be supplied by Westat for each protocol-required virology specimen aliquots. Each label contains two six-character barcodes separated by two six-character human readable codes. Each human readable code represents each barcode and can be substituted for a barode in the event a barcode becomes damaged or lost and cannot be electronically scanned. These labels will be adhered to specimen tracking forms and to aliquotted samples prepared by local or ACTG laboratories. The preprinted barcode labels must accompany each virology yellow top blood specimen tube (together with test requisition and specimen tracking form) to the virology laboratory. The laboratory will affix the labels to freezer vials into which cells or plasma from the specimen have been aliquotted. For specimens requiring storage in liquid nitrogen, a piece of scotch tape must be placed over the barcode label and around the cryovial eventually overlapping itself. This procedure insures the barcode label remains on the cryovial while stored in the liquid nitrogen.

Specimen Storage (freezer vials): All virology cell (PBL) or plasma aliquots should be stored in 1.5 ml skirted V-bottom sterile polypropylene freezer vials with screw cap lid and O-ring (Sarstedt catalog no. 72.694/006, or equivalent; telephone 1-800-321-4680 for Sarstedt order information).

1. WOMEN: VIROLOGY SPECIMEN PROCESSING

a. Rapid Processed Plasma (≤ 6 hr) for Viral Quantitation

2.6 ml Draw Volume Yellow Top Tube - These specimens should be processed to separate and freeze the plasma portion of the sample within 6 hours of collection.

Transport specimens at room temperature to your site's PV specimen processing laboratory. Centrifuge at 400-800 x g for 20 minutes at 20-24°C. Separate plasma, discard cells, and recentrifuge plasma at 800 x g for an additional 20 minutes to completely remove platelets and cell debris.

Aliquot twice-centrifuged plasma into 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent) each containing 500 µl (two to four 500-µl plasma aliquots per specimen are anticipated).

Label freezer vials with preprinted barcode labels marked "PV". Freeze at -70°C. Ship monthly on dry ice to central repository.

b. HIV Quantitative Microculture

8.5 ml Draw Volume Yellow Top Tube - These specimens should be processed for: (1) real-time HIV quantitative microculture assay according to the current ACTG Virology Manual, Section MIC; and (2) cells (PBL) and stored plasma according to the current ACTG Virology Manual, Section MIC and LAB.

Cell (PBL) Processing

Transport specimens at room temperature to the ACTG certified virology laboratory for your site. Isolate cells (PBL) as described in the current ACTG Virology Manual, Section MIC III.A. Assays for HIV quantitative microculture should be set up within 24 hours of specimen collection.

Excess cells (PBL) not used for real-time HIV quantitative microculture should be combined with those cells (PBL) obtained from the 8.5 ml draw volume yellow top blood collection tube designated for cell/plasma storage (see below).

Positive Isolate Processing and Storage

For known positive HIV quantitative microcultures, a viral isolate/cell suspension should be preserved as described in the current ACTG Virology Manual, Section LAB II.E. Aliquot 1 ml of suspension into each of four 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent). Apply preprinted barcode labels marked "ISO" to freezer vials and freeze at -70°C or lower. Ship monthly on dry ice to the repository (**McKesson**).

Plasma Processing

Reserve single-centrifuged plasma obtained from this yellow top tube for combination with plasma obtained from the blood collection tube designated for cell/plasma storage collected at defined study intervals.

c. Cell/plasma Storage

8.5 ml Draw Volume Yellow Top Tube - These specimens should be processed in parallel with the HIV quantitative microculture specimen drawn at the same time, to separate and freeze cells and plasma within 24 hours of specimen collection.

Transport specimens at room temperature to the ACTG certified virology laboratory for your site. Isolate cells (PBL) and single-centrifuged plasma for storage by processing this 8.5 ml draw volume yellow top tube according to the current ACTG Virology Manual, Section MIC III.A.

Cell (PBL) Processing and Storage

If the recovery of cells (PBL) from the HIV quantitative microculture tube is less than 3 million cells, then utilize the cells obtained from the cell/plasma specimen tube as a supplement to attain this number. After the HIV quantitative microculture has been set up,

freeze all residual cells (PBL) from both 8.5 ml draw volume yellow top blood tubes in 5 million cell portions (500,000 cell minimum) in 1 ml volumes in DMSO-containing freezer medium as described in the current ACTG Virology Manual, Section CRY.

Aliquot the cell (PBL) suspension into 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent). Approximately 1 to 2 aliquots of 5-million cells each are anticipated per blood collection event. (Cell recovery may vary by patient and according to processing times.) Label freezer vials with preprinted "PBL" barcode labels. Freeze according to current ACTG Virology Manual, Section CRY-II, or by utilizing a programmable freezer. Store in the vapor phase of liquid nitrogen (-135°C). Ship monthly on dry ice to central repository.

Note: For specimens requiring storage in liquid nitrogen, a piece of scotch tape must be placed over the barcode label and around the cryovial eventually overlapping itself. This procedure insures the barcode label remains on the cryovial while stored in the liquid nitrogen.

Plasma Processing and Storage

Aliquot single-centrifuged plasma from this tube from the HIV quantitative microculture tube processed in parallel into ten (10) 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent) each containing 500 µl. Discard excess plasma. Label freezer vials with preprinted "PL" barcode labels. Freeze at -70°C or lower. Ship monthly on dry ice to central repository.

2. INFANT: VIROLOGY SPECIMEN PROCESSING

a. HIV Quantitative Microculture

2.6 ml Draw Volume Yellow Top Tube - This specimen should be processed for real-time HIV quantitative microculture according to the current ACTG Virology Manual, Section MIC.

Cell (PBL) Processing and Storage

Transport specimens at room temperature to the ACTG certified virology laboratory for your site. Isolate cells (PBL) as described in the current ACTG Virology Manual, Section MIC III.A. Assays for HIV quantitative microculture should be set up within 24 hours of specimen collection.

Excess cells (PBL) not used for real-time HIV quantitative microculture should be combined with those cells (PBL) obtained from the blood collection tube designated for cell/plasma storage (see below).

Positive Isolate Processing and Storage

For known positive HIV quantitative microcultures, a viral isolate/cell suspension should be preserved as described in the current ACTG Virology Manual, Section LAB II.E. Aliquot 1 ml of suspension into each of 4 1.5-ml freezer tubes (Sarstedt catalog no. 72.694/006 or equivalent). Apply preprinted "ISO" barcode labels to freezer vials. Freeze at -70°C or lower. Ship monthly on dry ice to central repository.

Plasma Processing

Reserve single-centrifuged plasma obtained from this yellow top tube for combination with plasma obtained from the blood collection tube designated for cell/plasma storage collected at defined study intervals.

b. Cell/plasma Storage

2.6 ml Draw Volume Yellow Top Tube - These specimens should be processed to separate and freeze cells and plasma within 24 hours of specimen collection. When infant specimens for HIV quantitative microculture are drawn at the same time (Newborn, 6-week, 24-week, 48-week, and confirmatory culture visits), the cell/plasma storage specimen should be processed in parallel with the real-time HIV quantitative microculture specimen.

[Exception: The cord blood specimen (8.5 ml draw volume yellow top tube) should be processed separately from the newborn specimens and should remain identified as cord blood for aliquotting and storage.]

Transport specimens at room temperature to the ACTG certified virology laboratory for your site. Isolate cells (PBL) and single-centrifuged plasma for storage by processing this 2.6 ml draw volume yellow top tube within 24 hours of specimen collection according to the current ACTG Virology Manual, Section MIC III.A.

Cell (PBL) Processing and Storage

If the recovery of cells (PBL) from the HIV quantitative microculture tube is less than 3 million cells, then utilize the cells obtained from the cell/plasma storage blood tube as a supplement to attain this number for those visits when two tubes are collected (newborn, 6-week, 24-week, 48-week, and confirmatory culture visits).

[Exception: The 8.5 ml cord blood specimen for cell/plasma storage should be processed separately from the newborn specimens. Cells (PBL) obtained from cord blood should be separately aliquotted and stored in DMSO containing freezer medium in freezer vials with barcode labels marked "CR" in the Specimen Source ID and "PBL" in the Specimen Type ID.]

Aliquot infant cells (PBL) (from one or both yellow top tubes, as available) into dry and wet pellets as follows after any scheduled real-time HIV quantitative microculture has been set up.

First, prepare and aliquot cells (PBL) into two (2) 1-million cell dry pellets as described in the current ACTG Virology Manual, Section DNA III.B. for future HIV-DNA PCR. Place cells into 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent). Apply preprinted "PCR" barcode labels to the freezer vials with the dry pellets. Freeze at -70°C. Ship monthly to the central repository.

Second, aliquot cells (PBL) in 5-million cell portions (500,000 cell minimum) in 1 ml volumes in DMSO-containing freezer medium as described in the current ACTG Virology Manual, Section CRY. Aliquot the cell suspension into 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent). Approximately 3 aliquots of 5-million cells each are anticipated per blood collection event. (Cell recovery may vary by patient and according to processing times.) Apply to freezer vials the preprinted barcode labels marked "PBL". Freeze according to the current ACTG Virology Manual, Section CRY-II or by utilizing a programmable freezer. Store in the vapor phase of liquid nitrogen (-135°C). Ship monthly on dry ice to the central repository.

Note: For specimens requiring storage in liquid nitrogen, a piece of scotch tape must be placed over the barcode label and around the cryovial eventually overlapping itself. This procedure insures the barcode label remains on the cryovial while stored in the liquid nitrogen.

Plasma Processing and Storage

Aliquot single-centrifuged plasma from this tube and any excess plasma from the HIV quantitative microculture tube, (processed in parallel at the newborn, 6-week, 24-week, 48-week, and confirmatory culture visits), into 1.5 ml freezer vials (Sarstedt catalog no. 72.694/006 or equivalent) each containing 500 μl. It is anticipated that between 2 and 4 plasma aliquots per blood collection event will be obtained. Apply preprinted "PL" barcode labels to freezer vials. Freeze at -70°C or lower. Ship monthly on dry ice to central repository.

[Exception: The 8.5 ml cord blood specimen for cell/plasma storage should be processed separately from the newborn specimens. Plasma obtained from cord blood should be separately aliquotted and stored in freezer vials with barcode labels marked "CR" in the specimen source ID and "PL" in the specimen type ID.]

c. **Confirmatory Culture**

Two 2.6 ml Draw Volume Yellow Top Tubes - A Confirmatory HIV quantitative microculture specimen and a Cell/plasma Storage specimen. A Confirmatory HIV quantitative microculture must be performed at an ACTG-certified virology laboratory to confirm a previous study-related positive HIV quantitative microculture or, at $\geq$ 15 months, a positive EIA/WB in an infant with no previous positive culture. At all confirmatory culture collection events, a 2.6 ml yellow top tube should be collected for Cell/plasma Storage.

The barcode labels for the confirmatory culture specimen and the Cell/plasma Storage specimen obtained from this blood draw have the letters "CC" in the Specimen Source ID and can be found in the Confirmatory Culture section of the Infant Virology Specimen Tracking notebook. For a positive confirmatory culture, process and store viral isolates as described above. If the previously positive culture or other positive test for direct detection of HIV was from a non-study related specimen, contact the study team for instructions.

Part 3. Specimen Shipping

Real-time Specimen Shipping: Where transport of specimens for real-time virology or flow cytometry assays involves shipment to an ACTG certified laboratory, ship specimens by overnight commercial courier service. Assays should begin within 24 hours of specimen collection.

All specimens for real-time virology or flow cytometry assays should be maintained at room temperature (not to exceed 22°C or 72°F) if they are being transported for only a brief period (i.e., less than 6 hours). When real-time specimens are shipped by an overnight commercial service then -20°C frozen cold pack(s) should be included in the package if the external ambient temperature exceeds 65°F. If cold packs are utilized with the shipment, then provide insulation between the blood tubes and cold pack(s) to prevent blood from freezing.

Frozen Specimen Shipping: Ship the monthly batched frozen specimens with dry ice. Supply the shipping container with sufficient dry ice to last 48 hours (approximately 12 lbs.)

On the day of a shipment, call the destination laboratory or repository to notify them of the shipment.

For additional instructions or questions about shipping, contact your ACTG lab, **Corning Clinical Laboratories, Inc. or McKesson.**

Corning Clinical Laboratories, Inc.
1901 Sulphur Spring Road
Baltimore Maryland 21227
Dr. William Meyer
Virology Department
PHONE: (800) 368-2576

McKesson Bioservices, Inc.
685 Lofstrand Lane
Rockville, MD 20850
Attn: Mr. Steve Lindenfelser
PHONE: (301) 340-1620
FAX: (301) 340-9245

Table 1. Recommended Tube Sizes: WOMEN

TUBE TYPE (additive)	TUBE SIZE (draw volume)	EXAMPLE	USE	LABORATORY
Red top (no additive)	2.0 ml	B-D Vacutainer Nº 6380 or B-D Hemogard Vacutainer Nº 367611, or equivalent (Becton Dickinson 1-800-631-0174)	EIA/WB	Local
			Chem. panel	Local
			STS	Local
Purple top (K_3EDTA)	2.0 ml	B-D Vacutainer Nº 6384 or B-D Hemogard Vacutainer Nº 367651 or equivalent (Becton Dickinson 1-800-631-0174)	CBC/diff	ACTG Flow
			Lymph. subsets	
Yellow top (ACD)	2.6 ml	B-D Vacutainer Nº 364012 or equivalent (Becton Dickinson 1-800-631-0174)	Rapid Processed plasma for Viral Quantitation (PV)	ACTG VIrology
Yellow top (ACD)	8.5 ml	B-D Vacutainer Nº 4606 or equivalent (Becton Dickinson 1-800-631-0174)	HIV Quantitative Microculture	ACTG Virology
			Cells/plasma Storage	ACTG Virology
Freezer vials	1.5 ml	Sarstedt Nº 72.694/006 skirted V-bottom sterile polypropylene freezer vial w/screw cap lid and O-ring, or equivalent (Sarstedt 1-800-321-4680)	Stored specimens	Central Repository

Abbreviations: CBC/diff - complete blood count & differential; Chem. panel - BUN, creatinine, SGOT, SGPT, bilirubin (total/direct), alkaline phosphatase, electrolytes; EIA/WB - HIV antibody enzyme immunoassay/Western blot; Lymph - lymphocyte; PV - Rapid Processed plasma for Viral Quantitation; STS - serologic test for syphilis.

04/25/94

Table 2. Recommended Tube Sizes: INFANT

TUBE TYPE (additive)	TUBE SIZE (draw volume)	EXAMPLE	USE	LABORATORY
Red top (no additive)	2.0 ml	B-D Vacutainer Nº 6380 or B-D Hemogard Vacutainer Nº 367611, or equivalent (Becton Dickinson 1-800-631-0174)	SGOT/SGPT	Local
			Ig's	Local
			EIA/WB	Local
Purple top (K_3EDTA)	2.0 ml	B-D Vacutainer Nº 6384 or B-D Hemogard Vacutainer Nº 367651 or equivalent (Becton Dickinson 1-800-631-0174)	CBC/diff	Local
			CBC/diff	ACTG Flow
			Lymph. subsets	
Yellow top (ACD)	2.6 ml	B-D Vacutainer Nº 364012 or equivalent (Becton Dickinson 1-800-631-0174)	HIV Quantitative Microculture	ACTG Virology
			Cells/plasma Storage	ACTG Virology
Freezer vials	1.5 ml	Sarstedt Nº 72.694/006 skirted V-bottom sterile polypropylene freezer vial w/screw cap lid and O-ring, or equivalent (Sarstedt 1-800-321-4680)	Stored specimens	Central Repository

Abbreviations: CBC/diff - complete blood count & differential; SGOT/SGPT - serum glutamic-oxaloacetic transaminase/serum glutamic-pyruvic transaminase; EIA/WB - HIV antibody enzyme immunoassay/Western blot; Ig's - quantitative immunoglobulins A, G & M; Lymph - lymphocyte.

TABLE 3. LABORATORY EVALUATIONS: WOMEN

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #0 (Pre-entry)	1. Red	2.0	EIA/WB	Local	Routine	Eligibility
	2. Red	2.0	Chem. panel	Local	Routine	Eligibility
	3. Purple	2.0	CBC/diff for subsets	ACTG Flow	<24 hr	Eligibility; absolute counts
	4. Purple	2.0	Lymphocyte subsets			Transmission, progression
	5. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20", aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	6. Yellow	8.5	Cells/plasma Storage		<24 hr: F-H, aliquot cells and plasma, -70°C freeze, ship q mo	Cells/plasma
	7. Red	2.0	STS	Local	Routine	Transmission predictors, confounders
	TOTAL DRAW	21.1				
Visit #1 (Entry)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20", aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	HIV Quantitative Microculture		<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Transmission, progression
	3. Yellow	8.5	Cells/plasma Storage			Transmission, cells/plasma
	4. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Transmission, progression
	5. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	23.6				

TABLE 3. LABORATORY EVALUATIONS: WOMEN

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #3	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	HIV Quantitative Microculture		<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Transmission, progression
	3. Yellow	8.5	Cells/plasma Storage			Transmission, cells/plasma
	4. Purple	2.0	Lymphocyte subsets	ACTG Flow	< 24 h	Transmission, progression
	5. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	23.6				
Visit #10 (Intrapartum)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmissio, progression
	2. Yellow	8.5	HIV Quantitative Microculture		<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Transmission, progression
	3. Yellow	8.5	Cells/plasma Storage			Transission, cells/plasma
	TOTAL DRAW	19.6				

TABLE 3. LABORATORY EVALUATIONS: WOMEN

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #12 (12 wks pp)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	Cells/plasma Storage		<24 hr: F-H, aliquot cells & plasma, -70°C freeze; ship q mo	Transmission, cells/plasma
	TOTAL DRAW	11.1				
Visit #13 (24 wks pp)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	HIV Quantitative Microculture		<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Transmission, progression
	3. Yellow	8.5	Cells/plasma Storage			Transmission, progression
	4. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Transmission, progression
	5. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	23.6				
Visit #14 (48 wks pp)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	Cells/plasma Storage		<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	
	3. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Transmission, progression
	4. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	15.1				

TABLE 3. LABORATORY EVALUATIONS: WOMEN

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #15 (78 wks pp)	1. Yellow	2.6	Rapid Processed plasma (≤ 6 hr) for Viral Quantitation (PV)	ACTG Virology	<6 hr: spin x 2 @ 800 x g x 20', aliquot plasma only, -70°C freeze, ship q mo	Transmission, progression
	2. Yellow	8.5	Cells/plasma Storage		<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	
	3. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Transmission, progression
	4. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	15.1				
	OVERALL TOTAL DRAW	152.80				

Abbreviations: CBC/diff - complete blood count & differential; Chem. panel - BUN, creatinine, SGOT, SGPT, bilirubin (total/direct), alkaline phosphatase, electrolytes; Dx - diagnosis; F-H - Ficoll-Hypaque gradient centrifugation; EIA/WB - HIV antibody enzyme immunoassay/Western blot; Ig's - quantitative immunoglobulins A, G & M; PP - postpartum; q mo - every month; STS - serologic test for syphilis.

TABLE 4. LABORATORY EVALUATIONS: INFANT

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #1 (Cord blood)	1. Red	2.0	SGOT/SGPT	Local	Stat	Eligibility, toxicity
	2. Yellow	8.5	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells and plasma, -70°C freeze, ship q mo	Early Dx, cells/plasma
	3. Red	2.0	Ig's	Local	Routine	HIVIG/IVIG Transfer, Dx (secondary)
	TOTAL DRAW	12.5				
Visit #1 (Newborn)	1. Purple	*2.0	CBC/diff	Local	Stat	Eligibility, toxicity
	2. Yellow	2.6	HIV Quantitative Microculture	ACTG Virology	<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Dx (primary)
	3. Yellow	2.6	Cells/plasma Storage			Early Dx, cells/plasma
	TOTAL DRAW	7.2				
Visit #2 (1 week)	1. Purple	*2.0	CBC/diff	Local	Stat	Toxicity
	TOTAL DRAW	2.0				
Visit #3 (2 weeks)	1. Red	*2.0	SGOT/SGPT	Local	Stat	Toxicity
	2. Purple	*2.0	CBC/diff	Local	Stat	Toxicity
	3. Yellow	2.6	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	Early Dx, cells/plasma
	TOTAL DRAW	6.6				

TABLE 4. LABORATORY EVALUATIONS: INFANT

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #4 (6 weeks)	1. Red	*2.0	SGOT/SGPT	Local	Stat	Toxicity
	2. Purple	2.0	CBC/diff for subsets	ACTG Flow	<24 hr	Toxicity, absolute counts
	3. Yellow	2.6	HIV Quantitative Microculture	ACTG Virology	<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Dx (primary)
	4. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Safety, Dx (secondary)
	5. Yellow	2.6	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	Early Dx, cells/plasma
	6. Red	*2.0	Ig's	Local	Routine	HIVIG/IVIG elimination
	TOTAL DRAW	13.2				
Visit #5 (12 weeks)	1. Yellow	2.6	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	Early Dx, cells plasma
	2. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Safety, Dx (secondary)
	3. Purple	2.0	CBC/diff for subsets			Absolute counts
	4. Red	*2.0	Ig's	Local	Routine	HIVIG/IVIG elimination
	TOTAL DRAW	8.6				
Visit #6 (16 weeks)	1. Yellow	2.6	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	Early Dx, cells/plasma
	TOTAL DRAW	2.6				
Visit #8 (24 weeks)	1. Yellow	2.6	HIV Quantitative Microculture	ACTG Virology	<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Dx (primary)
	2. Yellow	2.6	Cells/plasma Storage			Cells/plasma
	3. Purple	2.0	Lymphocyte subsets	ACTG Flow	<24 hr	Safety, Dx (secondary)
	4. Purple	2.0	CBC/diff for subsets			Absolute counts
	TOTAL DRAW	9.2				

TABLE 4. LABORATORY EVALUATIONS: INFANT

VISIT	TUBE PRIORITY & TYPE	DRAW (ml)	TEST	LAB	PROCESSING	PURPOSE
Visit #10 (48 weeks)	1. Yellow	2.6	HIV Quantitative Microculture	ACTG Virology	<24 hr: F-H, set up culture, aliquot cells & plasma, -70°C freeze, ship q mo	Dx (primary)
	1. Yellow	2.6	Cells/plasma Storage			Early Dx, cells/plasma
	TOTAL DRAW	5.2				
Visit #11 (60 weeks)	1. Red	2.0	EIA/WB	Local	Routine	Dx (primary)
	2. Yellow	2.6	Cells/plasma Storage	ACTG Virology	<24 hr: F-H, aliquot cells & plasma, -70°C freeze, ship q mo	Cells/plasma
	TOTAL DRAW	4.6				
Visit #20 (78 weeks)	1. Red	*2.0	EIA/WB	Local	Routine	Dx (primary)
	TOTAL DRAW	2.0				
	OVERALL TOTAL DRAW	73.7				
Confirmatory Culture +	1. Yellow	2.6	HIV Quantitative Microculture	ACTG Virology	<24 hr: F-H, set up culture, aliquot cells and plasma, -70°C freeze, ship q mo	Dx (primary)
	2. Yellow	2.6	Cells/plasma Storage			Cells/plasma
	TOTAL DRAW	5.2				

* Maximum recommended volume for this assay. Lesser volume may be employed depending upon site capabilities.
+ To confirm positive HIV Quantitative Microculture or positive EIA/WB. Not included in OVERALL TOTAL DRAW.

Abbreviations: CBC/diff - complete blood count & differential; Chem. panel - BUN, creatinine, SGOT, SGPT, bilirubin (total/direct), alkaline phosphatase, electrolytes; Dx - diagnosis; F-H - Ficoll-Hypaque gradient centrifugation; EIA/WB - HIV antibody enzyme immunoassay/Western blot; Ig's - quantitative immunoglobulins A, G & M; PP - postpartum; q mo - every month; STS - serologic test for syphilis.

APPENDIX XVII

PLACENTAL BIOPSY PREPARATION AND SHIPMENT

Placental tissue for in situ hybridization should be obtained promptly following delivery and fixed according to the attached protocol prior to submission.

The placenta should be examined and the fixation process begun promptly following delivery (within one hour) in order to obtain optimal preservation of RNA. This means that a procedure to do this has to be developed and persons identified who will be available at all times to be responsible for examination and preliminary fixation. This is done in the Pathology Department, with the pathologist and resident or fellow on call being responsible for placental examination and initiation of the fixation procedures when placentas become available at night or on the weekend. Because the placentas to be examined may become available at any time with little advance notice, it is necessary to have the required reagents (See attached Procedure for Preservation of RNA in Human Tissues) always available. They will be kept aliquoted and refrigerated in the histology laboratory. All reagents but the RNase-free paraformaldehyde will keep indefinitely in the refrigerator; the RNase-free paraformaldehyde deteriorates after two weeks and must be made fresh at least that often. Aliquots of the RNase-free paraformaldehyde may be kept frozen and are stable indefinitely at 20°C and may be thawed as needed.

When the placenta is available for examination, it must be handled in a setting which can be easily cleaned and disinfected, and where tissue can be examined, processed and stored appropriately. The placenta should be transported promptly to that site in an appropriately labeled closed tissue container. If examination is slightly delayed, it should be refrigerated.

Placental tissue for HIV-RNA in situ hybridization should consist of a full-thickness section of the placental disc from a central location. The tissue section should extend from the fetal to the maternal surface of the central placenta, about 1.5 cm wide and no more than 0.4 cm thick.

This section should be placed in RNase free paraformaldehyde on ice for 5 to 6 hours. The procedure for Tissue Fixation should be followed (see attached); after paraformaldehyde fixation, the tissue section should be washed twice with RNase-free PBS, placed in two changes of RNase free 60% ethanol for 10 minutes each, placed in RNase-free 80% ethanol for 10 minutes, and then placed in an easily sealed specimen container in RNase free 80% ethanol and kept at 4°C prior to shipping. The tissue in RNase-free 80% ethanol should be shipped by overnight mail. It does not have to be kept cold during shipping. Shipment may be made in small batches.

Please call Dr. Edwina Popek (713) 770-2250, FAX (713) 770-1032 in advance so that they will be expecting the tissue.

Send to: Department of Pathology
Texas Children's Hospital
6621 Fannin
Houston, TX 77030

Attention: Dr. Edwina Popek

APPENDIX XVII (Continued)

Procedure for Preservation of RNA in Human Tissues

Reagents:

1. RNase-free paraformaldehyde
2. 10X RNase-free PBS
3. RNase-free ETOH
4. RNase-free 80% ETOH
5. RNase-free H_2O
6. RNase-free 1M NaOH

1. Paraformaldehyde (New Bottle): (This will make only 1-2 aliquots. If freezing aliquots, this may be multiplied.)

   a. Bring to a boil 20-25 ml RNase-free H_2O in sterile 50 ml tube. All the other reagents should be added to this boiling water.
   b. Add 1.3 g Fisher paraformaldehyde. (The paraformaldehyde does not go into solution readily, continue and it will dissolve during the remainder of the procedure.)
   c. Add 1 drop (20 µl) 1M NaOH - (mix solution).
   d. Add 3 ml 10X PBS (RNase-free).
   e. Bring volume to 30 ml with RNase-free H_2O.
   f. The RNase-free paraformaldehyde can be aliquoted into new small specimen bottles. Store at 4°C. **Good for 1-2 weeks ONLY.** Aliquots may be frozen at -20°C indefinitely and can be thawed as needed.

2. 10X PBS (RNase-free) pH 7.4:

   a. 164 g - NaCl (MW = 58.44) = 1.403 M.
   b. 25.6 g - Na_2HPO_4 (MW = 141.96) = 0.090 M.
   c. 3.12 g - Na_2HPO_4 (MW = 120) = 0.013 M.
   d. Prepare with DEPC-treated H_2O -> 2 liters.
   e. Filter sterilize.

3. 60% ETOH (RNase-free):

   a. Use a fresh bottle of 100% ETOH and dilute with RNase-free H_2O.

4. 80% ETOH (RNase-free):

   a. As above.

5. RNase-free H_2O:

   a. Treat H_2O with 0.1% diethypyrocarbonate.
   b. Shake vigorously to get the DEPC into solution.
   c. Autoclave the solution. (Use gloves to handle).

6. RNase-free 1 M NaOH:

   a. NaOH - New bottle.
   b. Use RNase-free H_2O to dilute.

APPENDIX XVII (Continued)

7. 1X PBS:

   a. Use 10X PBS RNase-free and dilute with DEPC H_2O.

Tissue Fixation:

1. Place one section of the full thickness of the placenta from fetal to maternal surface (may be several cm in this dimension, but should only be 3 to 4 mm thick) in a container of RNase-free paraformaldehyde. The tissue in the container should be placed on ice for 5 to 6 hours for adequate fixation, shorter times will result in poor fixation, longer in progressive nucleic acid degradation.

2. Pour off paraformaldehyde and wash twice with 1X RNase-free PBS.

3. Pour off PBS and pour RNase-free 60% ETOH into container and place back on ice for 10 minutes. Repeat.

4. Pour off 60% ETOH and pour 80% RNase-free ETOC into container and place on ice for 10 minutes. Repeat.

5. Store specimens in 80% RNase-free ETOH at 4°C prior to shipping. Specimens are stable indefinitely. They do not need to be shipped in ice, but should be shipped promptly by overnight mail. Shipments may be made in small batches.

Notes:

1. Only the RNase free paraformaldehyde need be made up fresh at regular intervals or kept frozen. All the other reagents using RNase free water in their preparation can be made up in quantity and stored for prolonged periods at refrigerator temperature.

2. Gloves should be worn throughout the preparation of reagents and the handling of specimen bottles and specimens, as RNase is ubiquitous and may be transferred from bare hands to the glassware.

APPENDIX XVIII

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS PACKAGING OF INFECTIOUS SUBSTANCES

ISS -1 PACKAGING INSTRUCTIONS

All patient specimens for ACTG study protocols that need to be mailed to another facility for additional studies or tests will be handled in compliance with appropriate regulations for the transportation of etiologic agents.

1. Purpose:

   The purpose of this section is to describe procedures used to package and ship infectious substances. This section follows the procedures mandated by the International Air Transport Association Dangerous Goods Regulations - Packing Instruction 602. All infectious specimens will be sent using the ISS-1 SAF-T-PAK or equivalent United Nations (UN) packaging certified for shipping. The ISS-1 is certified to contain a maximum of 50 ml of infectious substance. If several specimens are being shipped and the total volume exceeds 50 ml, additional ISS-1 containers and mailing boxes should be used.

2. Materials

   2.1 ISS-1 SAF-T-PAK contents:

   one absorbent disc;
   two plastic dividers;
   one plastic container;
   one "O" ring;
   one orange screw-on lid;
   one corrugated wrap;
   one outer carton;
   one hazard label.

   2.2 ziplock bags

   2.3 dry ice

   2.4 styrofoam shipping container with fibreboard box overpack

   2.5 Federal Express airbill

   2.6 airbill holder

   2.7 packing tape

   2.8 shipping labels

   2.9 wadding

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS

3.0 Procedure

3.1 Ship all infectious substances by Federal Express.

3.2 Vials containing the infectious substances must be placed in ziplock bags and sealed. Only one vial per ziplock bag **or two vials can be used by placing cotton balls between the vials to prevent vials from touching.**

3.3 Place the vials into the ISS-1 SAF-T-PAK. Remove the dividers if necessary.

3.4 Screw on the lid and tighten firmly.

3.5 Insert securely closed, packed container into corrugated cushioning material.

3.6 Close box flaps in numbered seequence.

3.7 Remove backing from double-sided adhesive tape on flap #3 and press #4 down firmly.

3.8 Mark the number of milliliters contained in the package on UN2814 label on outer carton. No package should contain more than 50 ml of infectious substance.

3.9 Place the ISS-1 into the shipping container.

3.10 Place 14 pounds of dry ice into the shipping container.

3.11 Fill the remainder of the box with wadding or newspaper.

3.12 Replace the styrofoam cover on the box and place the appropriate paperwork on top.

3.13 Seal the cardboard container on the top and corners with packing tape.

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS

3.14 Place the shipping labels on the box. Do not allow any labels to overlap. The placement of the shipping labels is as follows:

Return address label	placed on top in upper left corner
Consignee address label	placed on top in lower right corner
Infectious substance "HIV" label	placed on top above consignee address label
Infectious substance "6" label	placed on top in upper right corner
Dry ice "9" label	placed on top in lower left corner
Arrow labels	placed on sides
Responsible person label	placed on top under return address label
Inner package comply .... label	placed on top next to dry ice label
Keep frozen label (optional)	placed on any side

3.15 The name of the infectious substance (Human Immunodeficiency Virus) and its volume must be recorded on the infectious substance "HIV" label.

3.16 Enter the weight of dry ice (in kilograms) on the dry ice "9" label.

3.17 Place the Federal Express airbill holder on the front of the package.

3.18 Complete the Federal Express Dangerous Goods airbill and place in the airbill holder.

3.19 Call or fax the recipient of the package the following information:

date of shipment
expected arrival date
Federal Express airbill number
The nature and quantity of infectious substance

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS

ISS-2 PACKAGING INSTRUCTIONS

1. Place vials into the 81 cell white freezer box. Place the freezer box into the zip-lock bag along with the absorbent strip.

2. Place the bagged box into the ISS-2 shipping box.

3. Fill the shipping box with dry ice.

4. Insert the foam cover into the ISS-2 shipping box.

5. Place the forms which correspond to the vials in the box in an envelope. Place this envelope on top of the foam cover.

6. Close the outer fiberboard box and seal the top and corners with tape.

7. The following labels must be attached:

Label	Location in box
McKesson Address label	Side of box under "TO:"
Return Address Label	Side of box under McKesson address
Responsible Person Label	Side of box above McKesson address
Class 6 Label	Opposite side of box-diamond in upper right corner
Class 9 Label	Side of box in diamond below Class 6 label
Infectious Substance Label (UN2814)	Side of box to the upper left of Class 6 label - Fill in the amount of infectious substance
Keep Frozen Label	Side of box under the Infectious substance label

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING EITOLOGIC AGENTS

Label	Location in box
Dry Ice Label	Side of box below Keep Frozen label-fill in amount of dry ice in kilograms
Cargo Aircraft Only Label (Used when sending > 50 mls.)	Side of box, lower left corner under the dry ice label

None of the labels should touch each other.

Pounds	Kilograms
5	2.2
6	2.6
7	3.1
8	3.5
9	4.0
10	4.4
11	4.8
12	5.3
13	5.7
14	6.2
15	6.6

8. Complete the airbill by filling in the amount of infectious substance, the amount (in kilograms) of dry ice and sign the airbill.

9. Place airbill in the airbill holder and attach to top of the box.

10. Call Darrin Power or Stephen Lindenfelser at 301-340-1620 to inform of the shipment or FAX the information to 301-340-9245. Please provide the airbill number of the shipment.

* ISS-2 shipping containers can be purchased from First Packaging of New England, telephone number 1-800-200-0366.

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS COMPLETING THE DANGEROUS GOODS AIRBILL (FEDERAL EXPRESS) FOR ISS-1 and ISS-2 PACKAGES

1. Purpose:

The purpose of this section is to describe procedures used to complete a Federal Express Dangerous Goods airbill. This section follows the procedures mandated by the International Air Transport Association Dangerous Goods Regulations - Packing Instruction 602.

2. Materials:

Federal Express Dangerous Goods airbill

3. Procedure:

3.1 Airbills should be typed. They may be handwritten when time does not allow for typing.

3.2 Type the date of the shipment in the space provided.

3.3. Type the name of the person sending the shipment under "Sender's Name" in Section one.

3.4 Type the telephone number under "Your Phone Number" in Section one.

3.5 Type the name of your affiliation, and address in the appropriate areas of Section one.

3.6 Type the recipient's name, address, and telephone number in Section three. The telephone number is mandatory.

3.7 Determine if the shipment is to be paid for by the recipient. If so, type the recipient's Federal Express account number in Section seven and type an "X" in the "Bill Recipeint" box. If you are paying for the shipment, type and "X" in the "Bill Sender" box.

3.8 Type an "X" in the "Priority Overnight" box in Section four.

3.9 Type an "X" in the "Deliver Weekday" box unless otherwise specified.

3.10 If the package contains dry ice, type an "X" in the "Dry Ice" box and record the weight of the dry ice (in kilograms) and the number of boxes in Section six.

3.11 Complete the package and weight sections by typing or printing with a ballpoint pen. Total these sections at the bottom of the appropriate column in Section seven.

3.12 Type an "X" in "Dangerous Goods" per attached shipper's declaration box in the "Instructions" column in Section six.

3.13 Obliterate with several "X"s the "Cargo Aircraft Only" box for shipments containing infectious substances > 50 mls. Obliterate with several "X's" the "Passenger Cargo Aircraft" box for shipments containing infectious substances 50 mls or less. Obliterate with several "X"s the "Radioactive" box.

APPENDIX XVIII (continued)

REGULATIONS FOR SHIPPING ETIOLOGIC AGENTS

3.14 Type "Infectious Substance Affecting Humans (Human Immunodeficiency Virus)" under "Proper Shipping Name" column.

3.15 Type "6.2" in the "Class or Division" column.

3.16 Type "UN2814" in the "UN or ID" column.

3.17 Leave the "Subsidiary Risk" column blank.

3.18 Type "1 fibreboard box x ____ ml." in the "Quantity and Type of Packing" column. Fill in the volume of infectious substance (expressed in milliliters).

3.19 Type the number "602" in the "Packing Instruction" column.

3.20 Leave the "Authorization Column" blank.

3.21 For shipments containing Dry Ice, type "Carbon Dioxide, solid (Dry Ice)" in the "Proper Shipping Name" column.

3.22 Type "9" under "Class or Division" column.

3.23 Type "UN1845" under "UN or ID No." column.

3.24 Leave "Subsidiary Risk" column blank.

3.25 Type " ____ kg." in the "Quantity and Type of Packing" column. Then fill in the amount in kilograms. Then type "Overpack Used" under " ____ kg."

3.26 Under the "Additional Handling Information" section, type "Prior arrangements as required by IATA Dangerous Goods Regulation 1.3.3.1 have been made". Then enter the name and phone number of the Responsible Person.

3.27 Type your name and title in the "Name and Title of Shipper" box.

3.28 Type your city, state, and date of the shipment in the "Place and Date" box.

3.29 Sign the airbill.

3.30 Type the 24 hour phone number in the space provided at the bottom of the form.

APPENDIX XIX

SAMPLE SIZE AND STATISTICAL POWER

Power to detect a difference in HIV transmission rates based on 400 patients per arm

IVIG transmission rate	Net Treatment effect	Effective HIVIG transmission rate	Power for accrual of 400 per arm
0.05	0.25	0.039	0.108
0.05	0.30	0.037	0.140
0.05	0.40	0.032	0.224
0.05	0.50	0.028	0.339
0.10	0.25	0.078	0.181
0.10	0.30	0.073	0.246
0.10	0.40	0.064	0.413
0.10	0.50	0.055	0.609
0.15	0.25	0.116	0.260
0.15	0.30	0.110	0.359
0.15	0.40	0.096	0.589
0.15	0.50	0.083	0.801
0.20	0.25	0.155	0.345
0.20	0.30	0.146	0.474
0.20	0.40	0.128	0.735
0.20	0.50	0.110	0.913
0.25	0.25	0.194	0.435
0.25	0.30	0.183	0.586
0.25	0.40	0.160	0.844
0.25	0.50	0.138	0.968

APPENDIX XX

CLASSIFICATION OF CHILDREN WHO DIE OR ARE LOST TO FOLLOW-UP WHILE STILL OF INDETERMINATE HIV INFECTION STATUS, OR HAVE AMBIGUOUS HIV INFECTION STATUS

There are two groups of children in this category: 1) children who die in utero or 2) those who die following a live birth, are lost to follow-up, or are alive but of ambiguous infection status. The first group will be censored.

The latter group includes:

1. children who do not meet the definitive laboratory criteria for HIV infection (Section 12.1) at the time of death or loss to follow-up, and are not old enough to have "definitively" ruled out infection; and

2. children who do not meet the definitive infection criteria in Section 12.1, but in whom the investigator has concerns regarding initiation of antiretroviral therapy.

It is possible that there could be sufficient information to classify children as HIV infected if the child has had an AIDS-defining condition ("definitively/probably infected") or if the child has certain relatively predictive HIV-related symptoms/signs ("possibly infected").

All children who die after a live birth will have a Cause of Death form completed, in addition to the clinical data forms collected during their study visits prior to death. The Cause of Death form will contain information regarding the presumed cause of death and collection of the source documentation on the causes of death (i.e., death certificate, autopsy, pre-mortem or post-mortem lab results).

Information regarding intercurrent AIDS-defining conditions (both lab-confirmed and presumptively diagnosed) and the specified HIV-related findings will be collected at each study visit on history/clinical/lab forms.

Clinical information from the study visits and from death form/source documents, if applicable, will be reviewed independently by a Case Classification Committee to classify the child's probable infection status in one of the following categories:

1. **Definitively HIV-infected (Laboratory-proven):** This definition meets the criteria in Section 12.1.

2. **Definitively HIV-infected (Clinically-proven):** This would be a child who had laboratory-confirmed evidence of an AIDS-defining condition pre- or post-mortem. For example, a 6 month old child who died of lab-confirmed *Pneumocystic carinii* pneumonia, or had histologic Kaposi's sarcoma diagnosed on autopsy, or had documentation of two or more episodes of invasive bacterial infection (these must be lab-documented: sepsis; meningitis; bone/joint; abscess internal organ; pneumonia).

3. **Probably HIV-infected:** This would be a child who had presumptive diagnosis of an AIDS-defining condition pre- or post-mortem, as defined in the Centers for Disease Control pediatric AIDS case definition. For example, a 6 month old child died secondary to presumptively-diagnosed *Pneumocystis carinii* pneumonia and did not have an autopsy or had a history of ophthalmologist-documented CMV retinitis or presumptively diagnosed candida esophagitis.

4. **Possibly HIV-infected:** This would be a child who did not have a definitively or presumptively diagnosed AIDS condition documented pre- or post-mortem, but had developed certain specified relatively predictive HIV-related findings, as documented on study visit forms (clinical, history, or lab forms).

Specified "predictive" conditions used to classify the child would be the presence of one or more of the following (see NOTE below):

- failure to thrive, defined as a child who downwardly crosses two percentile lines on the standard NCHS growth chart, or a child who is in less than the fifth percentile for height and weight and does not follow the growth curve
- loss of ability to sit, walk or talk
- oral candidiasis, persistent more than 2 months
- two or more episodes of recurrent herpes stomatitis in a year
- multidermatomal or disseminated herpes zoster infection
- CD4 absolute count 2 standard deviations below age-related normals (<1500 in child under 12 months; <750 in child 12-24 months old)
- CD4/CD8 ratio $\leq$ 0.9
- Hyper- or hypo-gammaglobulinemia (any of classes): IgG or M, defined as $\geq$ 1.5 x upper and $\leq$ 0.67 x lower age-adjusted normal limits
- Persistent hepatosplenomegaly (liver AND spleen enlargement, persisting for more than 2 months)

5. **Indeterminate infection status:** This would be an antibody positive child under 18 months of age with negative HIV cultures who did not have any clinical/laboratory findings as delineated in 2 and 3 above prior to going off study (i.e., death, lost to follow-up, etc). This group may be stratified by age at time of off study (i.e., antibody positive without symptoms under 15 months old; and antibody positive without symptoms over 15 months old).

6. **Probably uninfected:** This would be an antibody negative child with negative HIV culture, without clinical or laboratory findings as delineated in 2 and 3, but who was under 18 months of age when went off study.

7. **Definitively uninfected:** This is a child with negative HIV cultures and negative antibody status at 18 months of age.

NOTE: The above (in #4) were proposed based on clinical experience and data from:

1. Scott GB, Hutto C, Makuch RW, et al. Survival in children with perinatally acquired HIV type 1 infection. N Engl J Med 1989; 321: 1791-1796.

2. European Collaborative Study. Children born to women with HIV-1 infection: natural history and risk of transmission. Lancet 1991; 337: 253-260.

3. Denny TN, Niven P, Skuza C, et al. Age-related changes of lymphocyte phenotypes in healthy children [Abstract 916] Pediatr Res 1990; 27: 155A.

4. Centers for Disease Control. Guidelines for prophylaxis against PCP for children infected with HIV. MMWR 1991; RR-2.

5. Principi N, Marchisio P, Tornaghi R, et al. Occurrence of infections in children infected with HIV. Pediatr Infect Dis J 1991; 10: 190-193.

Appendix XXI:

INDEPENDENCE BETWEEN THE OVERALL TRANSMISSION RATE AND THE TEST OF HIVIG EFFICACY

Introduction

Let π_0 and π_1 represent the HIV transmission rates in the control and HIVIG groups, respectively. Based on r patients, the test of the hypothesis

$$H_0: \quad \pi_0 = \pi_1$$

would be based on the statistic

$$\hat{\tau}_r = \hat{\pi}_{0r} - \hat{\pi}_{1r},$$

where

$\hat{\pi}_{0r}$ = Estimated control group transmission rate after accruing r patients
$= \frac{h_{0r}}{b_{0r}}$

h_{0r} = HIV^+ births in control group after accruing r patients

b_{0r} = Total births in control group accruing r patients

$\hat{\pi}_{1r}$ = Estimated HIVIG group transmission rate after accruing r patients
$= \frac{h_{1r}}{b_{1r}}$

h_{1r} = HIV^+ births in HIVIG group after accruing r patients

b_{1r} = Total births in HIVIG group after accruing r patients.

Specifically, H_0 would be rejected when $|\hat{\tau}|$ exceeds a critical value c_r. Notice that the critical value depends on r the number of accrued patients.

Let θ represent the overall transmission rate and define the estimated overall transmission rate as

$$\hat{\theta}_r = \text{Estimated overall transmission rate after accruing } r \text{ patients}$$

$$= \frac{h_{0r}+h_{1r}}{b_{0r}+b_{1r}}$$

We assume that this estimate is to be monitored and that the sample size will be increased if $\hat{\theta}_r$ is below a given value, say d_r, at some predetermined point in study accrual. Thus, we define the event B_r as

$$B_r = \left\{\hat{\theta}_r < d_r\right\}.$$

Define the experiments E_1 and E_2 as

E_1 = Increase the planned 185 protocol sample size by v units

and

E_2 = Follow the planned 185 protocol.

Note that v may depend on the overall transmission rate; i.e.,

$$v = v(\hat{\theta}_r).$$

Let A_1 and A_2 represent the event that a Type 1 error occurs under experiments E_1 or E_2, respectively. If the choice is made between E_1 and E_2 based on the event B_r, then the chance of a Type 1 error is

$$P(\text{Type I error}) = P(A_1 \mid B_r)P(B_r) + P(A_2 \mid \bar{B}_r)P(\bar{B}_r).$$

I will argue that B_r is independent of A_1 and A_2, so that

$$\begin{aligned} P(A_1 \mid B_r)P(B_r) + P(A_2 \mid \bar{B}_r)P(\bar{B}_r) &= P(A_1)P(B_r) + P(A_2)P(\bar{B}_r) \\ &= (.05)\left(P(B_r) + P(\bar{B}_r)\right) \\ &= .05. \end{aligned}$$

This enables us to monitor the overall transmission rate without jeopardizing the significance level of the test for the primary outcome. In fact, because of the independence between B_r and the

Type I error, we can actually monitor the overall transmission rate as often as desired while maintaining an overall significance level of $\alpha = .05$.

Independence of the Overall Rate from the Treatment Effect

In this section, the estimated overall transmission rate is shown to be independent of the estimated treatment effect. First, if we assume that loss to follow-up and other factors affecting the final sample size will be the same both the HIVIG and the control group, then

$$b_{0r} = b_{1r} = \frac{b_{0r} + b_{1r}}{2}$$

and

$$\hat{\theta}_r = \frac{h_{0r}+h_{1r}}{b_{0r}+b_{1r}}$$

$$= \frac{1}{2}\frac{h_{0r}+h_{1r}}{(b_{0r}+b_{1r})/2}$$

$$= \frac{1}{2}\left(\frac{h_{0r}}{(b_{0r}+b_{1r})/2} + \frac{h_{1r}}{(b_{0r}+b_{1r})/2}\right)$$

$$= \frac{1}{2}\left(\frac{h_{0r}}{b_{0r}} + \frac{h_{1r}}{b_{1r}}\right)$$

$$= \frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2}.$$

That is, the overall transmission rate can be expressed as the average of the transmission rates of the HIVIG and control group transmission rates.

Since $\hat{\pi}_{0r}$ and $\hat{\pi}_{1r}$ are independent and have asymptotically normal distributions, one can apply an orthogonal transformation argument to show that under the null hypothesis that $\pi_0 = \pi_1$ the quantities

$$\frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2} \quad \text{and} \quad \hat{\pi}_{0r} - \hat{\pi}_{1r}$$

are statistically independent as $n \to \infty$. Specifically, the random vector

$$\mathbf{w} = \begin{pmatrix} \hat{\pi}_{0r} \\ \hat{\pi}_{1r} \end{pmatrix} \to \mathcal{N}(\pi, \Sigma)$$

where

$$\pi = \begin{pmatrix} \pi_0 \\ \pi_1 \end{pmatrix}$$

and

$$\Sigma = \begin{pmatrix} \pi_0(1-\pi_0) & 0 \\ 0 & \pi_1(1-\pi_1) \end{pmatrix}.$$

Under the null hypothesis, $\pi_0 = \pi_1$; thus,

$$\Sigma = \begin{pmatrix} \pi_0(1-\pi_0) & 0 \\ 0 & \pi_0(1-\pi_0) \end{pmatrix} = \pi_0(1-\pi_0)\ \mathbf{I}$$

where **I** is a 2x2 identity matrix. If we define the matrix **C** as

$$\mathbf{C} = \begin{pmatrix} \frac{1}{\sqrt{2}} & \frac{-1}{\sqrt{2}} \\ \frac{1}{\sqrt{2}} & \frac{1}{\sqrt{2}} \end{pmatrix}$$

then the random vector

$$\mathbf{Cw} = \begin{pmatrix} \frac{\hat{\pi}_{0r} - \hat{\pi}_{1r}}{\sqrt{2}} \\ \frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{\sqrt{2}} \end{pmatrix} \to \mathcal{N}(\mathbf{C}\pi, \mathbf{C}\Sigma\mathbf{C}').$$

Under the null hypothesis, $\mathbf{C}\Sigma\mathbf{C}' = \pi_0(1-\pi_0)\ \mathbf{I}$, showing that

$$\frac{\hat{\pi}_{0r} - \hat{\pi}_{1r}}{\sqrt{2}} \quad \text{and} \quad \frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{\sqrt{2}}$$

are asymptotically independent, from which it follows that

$$\frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2} \quad \text{and} \quad \hat{\pi}_{0r} - \hat{\pi}_{1r}$$

are asymptotically independent.

This shows that the overall transmission rate up to time r is independent of the difference between the transmission rates for the two arms at time r. However, the overall transmission rate at time r will be used to decide whether to extend the trial by accruing v additional patients. Thus, to establish the independence of B_r from A_1 and A_2, it is necessary to show that the overall transmission rate at time r is independent of the treatment effect at the end of the trial when either 800 patients (E_2) or 800 + v patients (E_1) will have accrued. Let

$$m = (800 - r) + v.$$

We need to show that

$$\frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2} \quad \text{and} \quad \hat{\pi}_{0,r+m} - \hat{\pi}_{1,r+m}$$

are independent. Clearly, the overall transmission rate would be independent of the control and HIVIG transmission rates *after* time r; that is,

$$\frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2}, \quad \frac{h_{0,r+m} - h_{0r}}{b_{0,r+m} - b_{0r}}, \text{and} \quad \frac{h_{1,r+m} - h_{1r}}{b_{1,r+m} - b_{1r}}$$

are independent.* But then it follows that

$$\frac{\hat{\pi}_{0r} + \hat{\pi}_{1r}}{2} \quad \text{and} \quad \hat{\pi}_{0,r+m} - \hat{\pi}_{1,r+m}$$

are independent (as $n \to \infty$), since the second term is a function of quantities which are independent of the overall transmission rate:

* This independence will hold even though the number of additional patients may depend on the estimated overall transmission rate, since the clinical outcomes of the patients would clearly be independent of the number of patients.

$$\hat{\pi}_{0.r+m} - \hat{\pi}_{1.r+m} = \frac{h_{0.r+m}}{b_{0.r+m}} - \frac{h_{1.r+m}}{b_{1.r+m}}$$

$$= \frac{h_{0.r+m} - h_{0r} + h_{0r}}{(b_{0.r+m}+b_{1.r+m})/2} - \frac{h_{1.r+m} - h_{1r} + h_{1r}}{(b_{0.r+m}+b_{1.r+m})/2}$$

$$= \frac{\left(h_{0.r+m} - h_{0r}\right) - \left(h_{1.r+m} - h_{1r}\right) + h_{0r} - h_{1r}}{(b_{0.r+m}+b_{1.r+m})/2}$$

$$= \frac{b_{0.r+m} - b_{0r}}{(b_{0.r+m}+b_{1.r+m})/2}\left(\frac{\left(h_{0.r+m} - h_{0r}\right)}{b_{0.r+m} - b_{0r}} - \frac{\left(h_{1.r+m} - h_{1r}\right)}{b_{0.r+m} - b_{0r}}\right)$$

$$+ \frac{(b_{0r}+b_{1r})/2}{(b_{0.r+m}+b_{1.r+m})/2}\left(\hat{\pi}_{0r} - \hat{\pi}_{1r}\right).$$

Since A_1 and A_2 are functions of the treatment effect (i.e., $\hat{\pi}_{0.r+m} - \hat{\pi}_{1.r+m}$), while B_r is a function of the overall transmission rate ($(\hat{\pi}_{0r} + \hat{\pi}_{1r})/2$), it follows that A_1 and A_2 are independent of B_r. The implications of this result for monitoring are discussed in the next section.

Implications for Monitoring

If A_1 and A_2 are independent of B_r then they are also independent of $\bar{B}_r$ (the complement of B_r). This leads to the result that

$$\begin{aligned} P(\text{Type I error}) &= P(A_1 \mid B_r)P(B_r) + P(A_2 \mid \bar{B}_r)P(\bar{B}_r) \\ &= P(A_1)P(B_r) + P(A_2)P(\bar{B}_r) \\ &= (0.05)(P(B_r) + P(\bar{B}_r)) \\ &= 0.05. \end{aligned}$$

This result shows that we can look at the overall transmission at time r to decide whether to extend the trial by m patients. The question arises next of how often we can monitor the overall transmission rate. To take an extreme example, consider continuous monitoring. In continuous monitoring, one of the following would occur:

Experiment E_1 is selected at Time 1: B_1

Experiment E_1 is not selected at Time 1 but is selected at Time 2: $\bar{B}_1 B_2$

Experiment E_1 is not selected at Times 1 or 2 but is selected at Time 3: $\bar{B}_1 \bar{B}_2 B_3$

$\vdots$

Experiment E_1 is not selected until Time n: $\bar{B}_1 \bar{B}_2 \ldots \bar{B}_{n-1} B_n$

Experiment E_1 is not selected at all: $\bar{B}_1 \bar{B}_2 \ldots \bar{B}_n$

Thus E_1 would occur if one of the n sequences of events shown above occurs (n is the total patient accrual, currently set at 800), while E_2 will occur only if the last sequence shown above occurs. However, these events are both exhaustive and mutually exclusive; by the latter and the arguments discussed earlier, A_1 and A_2 are independent of all of these outcomes. It follows that

$$P(\text{Type I error}) = P\left(A_1 \mid \bigcup_{i=1}^{n}\left(B_i \bigcap_{j=1}^{i-1} \bar{B}_j\right)\right) P\left(\bigcup_{i=1}^{n}\left(B_i \bigcap_{j=1}^{i-1} \bar{B}_j\right)\right) + P\left(A_2 \mid \bigcap_{i=1}^{n} \bar{B}_i\right) P\left(\bigcap_{i=1}^{n} \bar{B}_i\right)$$

$$= P(A_1) P\left(\bigcup_{i=1}^{n}\left(B_i \bigcap_{j=1}^{i-1} \bar{B}_j\right)\right) + P(A_2) P\left(\bigcap_{i=1}^{n} \bar{B}_i\right)$$

$$= (0.05)\left(P\left(\bigcup_{i=1}^{n}\left(B_i \bigcap_{j=1}^{i-1} \bar{B}_j\right)\right) + P\left(\bigcap_{i=1}^{n} \bar{B}_i\right)\right)$$

$$= 0.05.$$

Thus, we can monitor the overall transmission rate as often as desired without affecting the Type I error of the main endpoint. However, assessing the transmission rate more than once, without

using a formal sequential testing procedure*, would increase the chance of incorrectly concluding that the transmission rate is low and thus extending the trial unnecessarily.

* The Lan-DeMets (1983) procedure might be adapted for this application if frequent monitoring is to be used.

APPENDIX XXII

SAMPLE INFORMED CONSENT FOR SPECIAL PHARMACOKINETIC STUDIES (PATIENTS FROM SELECTED SITES ONLY)

In addition to your participation in the study ACTG 185: "The Use of HIVIG in Prevention of Maternal-Fetal Transmission in Mothers Receiving ZDV," you are being asked to take part in a "nested study", a smaller, added study which is part of the regular study in which a small group of women and babies will have pharmacokinetic (PK) testing during the study. Up to 50 women in the regular study who agree and up to 50 infants whose parent(s) agree(s) will be included in the nested study. Only patients from selected sites will be asked to participate in the nested study.

Pharmacokinetic testing measures how much of a drug or substance gets into the blood, and how long it lasts. In this study, blood samples from you will be tested for the amount of antibodies present before you receive any study drug (HIVIG or IVIG). Once you or your baby receives study drug, blood samples will be collected and tested for the amount of HIV antibody and other antibodies that are present. A blood sample will also be taken from the umbilical cord. These tests will determine the amount of study drug in your and your baby's system over time, and also determine the activity of the HIV virus, by measuring one of the HIV virus proteins that can be found in the blood, the p24 antigen.

MOTHER'S PARTICIPATION:

Testing will be done on the mothers before the first infusion of the study drug and at these times after each infusion: 1 hour, 24 hours, 7 days, 14 days, and 28 days. In addition, the mothers will have a blood test 3 days after the first infusion and 28 days after delivery. Each test will require the drawing of 4-7 ml, or about 1-1 1/2 of a teaspoon of blood. Some of the blood draws may be combined with other tests being done at regular study visits.

BABY'S PARTICIPATION:

Testing will be done on your baby at the following times after he/she receives an infusion of HIVIG/IVIG: 1 hour, 24 hours, 7 days, 14 days, and 28 days. The baby's blood tests will be done by heel stick or venipuncture (blood draw from a vein). The amount required for each test is 2-3 ml, or less than 1/2 of a teaspoon.

The risks of the testing are the same as for other blood tests done during the study - bleeding or bruising at the site of the test and a slight risk of infection. Participation in the PK study requires more frequent clinic visits for blood testing.

I understand that by signing this form I am agreeing to participate in an additional part of the ACTG 185 study. I have already consented for myself to take part in ACTG 185: "The Use of HIVIG in Prevention of Maternal-Fetal Transmission in Mothers Receiving ZDV." The purpose of the pharmacokinetic testing, the procedures, and risks have been fully explained to me. I understand that I may withdraw my participation at any time without affecting my rights to receive medical care.

Name* (print or type)	Signature*	Date
*Volunteer's name or that of legal representative or guardian, as appropriate.		
Witness' Name (print or type)	Witness' Signature	Date

Father (print or type)* *If reasonably available.	Father's Signature*	Date
Witness' Name (print or type)	Witness' Signature	Date

I have explained the purpose of this part of the study to the patient. To the best of my knowledge, she understands the purpose, procedures, and risks to her.

Investigator Name (print or type)	Investigator Signature	Date

I understand that by signing this form I am agreeing to have my baby participate in an additional part of the ACTG 185 study. I have already consented for myself to the part in ACTG 185: "The Use of HIVIG in Prevention of Maternal-Fetal Transmission in Mothers Receiving ZDV." The purpose of the pharmacokinetic testings, the procedures, and risks have been fully explained to me. I understand that I may withdraw my participation at any time without affecting my baby's rights to receive medical care.

Name* (print or type)	Signature*	Date
*Volunteer's name or that of legal representative or guardian, as appropriate.		
Witness' Name (print or type)	Witness' Signature	Date

Father (print or type)*	Father's Signature*	Date
*If reasonably available.		
Witness' Name (print or type)	Witness' Signature	Date

I have explained the purpose of this part of the study to the patient. To the best of my knowledge, she understands the purpose, procedures, and risks to the baby.

Investigator Name (print or type)	Investigator Signature	Date

APPENDIX XXIIIa

SAMPLE INFORMED CONSENT

ACTG 185 Version 5.0: "A Phase III Randomized, Double-blind, Controlled Study of Hyperimmune Anti-HIV Intravenous Immune Globulin (HIVIG) in Prevention of Maternal-Fetal Transmission in Women and Newborns Receiving Zidovudine (ZDV)"

You are being asked to take part in a research study entitled "Use of HIVIG in Prevention of Maternal/Fetal HIV Transmission in Seropositive Pregnant Women Receiving Zidovudine." To decide whether or not you wish to take part in this study, you need to understand enough about the risks and benefits to make an informed decision. This process is called informed consent.

This consent form gives you detailed information about the research study which your doctor will discuss with you. Once you understand the study and if you agree to take part, you will be asked to sign this consent form and you will be given a copy to keep. The father of your baby will also be asked to sign a consent form if, in your opinion, he is reasonably available.

It is really important that you understand the following:

1. Your participation in the study is entirely voluntary.

2. You may refuse to take part in the study or drop out of the study at any time without penalty or loss of benefits to which you are otherwise entitled.

3. A decision to withdraw from the study will not affect your future medical care or possible participation in future research studies.

4. The father of the baby may refuse to give consent and this would prevent the mother's participation in the study.

Nature of the Study:

Women in this study are all pregnant and all infected with the Human Immunodeficiency Virus (HIV or AIDS Virus). HIV can be passed to your baby during your pregnancy, during birth, or after birth through breast milk. It is estimated that for every 100 babies born to HIV-infected mothers, some 15 to 32 of them will become infected with the HIV virus. If infected, the babies are at risk of dying from AIDS during the first years of life. It is not known exactly when the virus can infect an unborn baby or why some babies are infected and others are not.

All of the women in the study are taking Zidovudine (ZDV or AZT) by mouth during pregnancy. The decision about your taking ZDV (AZT) during pregnancy has already been made by you and your doctor prior to this study. The dose of ZDV (AZT) you are taking is set by your doctor, and will be checked by your doctor and changed if needed. The ZDV (AZT) you are taking is not part of the study, and is not supplied as part of the study.

All women in the study will receive ZDV (AZT) intravenously during labor. The intravenous ZDV (AZT) is supplied as part of the study. After your delivery, the decision about continuation of your oral ZDV (AZT) regimen will be made by you and your doctor; your oral ZDV (AZT) is not supplied as part of this study.

In addition, about half of the women in the study will take hyperimmune intravenous immune globulin (HIVIG), a drug containing concentrated antibodies to HIV, and the other half will take intravenous immune globulin (IVIG), a drug without specific antibodies to HIV. The study drug assignment will be done randomly (like flipping a coin) and neither you nor your doctor will know which drug you are taking.

APPENDIX XXIIIa (continued)

After your baby is born, your baby will also receive a dose of HIVIG or IVIG (whichever you were receiving) and also will receive ZDV (AZT) for 6 weeks after birth. About half of the infants will take HIVIG and half will take IVIG (whichever you were receiving). All infants will receive ZDV (AZT) for 6 weeks, which is supplied as part of the study, and your infant will be closely monitored for any side effects of the ZDV (AZT).

The purpose of the study is to see if giving HIVIG to women who are taking ZDV (AZT) can lower the chance that a baby will get HIV from his/her mother. Therefore, the group taking HIVIG will be compared to the group taking regular IVIG control to see if there is any difference in the number of babies who become infected from their mothers in these two groups. This is not known at this time.

HIVIG (HIV hyperimmune intravenous immune globulin) is the experimental treatment that is being tested in this study. It is made from the blood of people who have HIV infection but are not sick. Their blood contains substances called antibodies that fight HIV by attaching to it and keeping it from infecting blood cells. The HIV antibodies from this blood are concentrated and treated so that HIVIG contains specific antibodies to HIV, but no live HIV virus and is non-infectious.

IVIG (intravenous immune globulin) is being used as a control drug. It is made from the blood of people who do not have HIV infection, so it has antibodies to some illnesses, but not the HIV virus. It is also concentrated and prepared so that it contains no live HIV virus and is non-infectious.

You are taking a drug called Zidovudine, or ZDV (previously called AZT) because your doctor has decided that it is medically necessary for your own health, based on laboratory tests and your general medical condition. ZDV (AZT) is an antiretroviral drug (a drug that slows or prevents the HIV virus from multiplying). It has been shown to prevent the growth of HIV in non-pregnant adults and children infected with the AIDS virus.

Study Procedures:

If you agree to take part in the study, you will first have some tests to see if you qualify to take part in the study. These tests include a history and physical examination, laboratory tests (including blood tests), and a sonogram (an ultrasound examination of your baby).

During the study, you will be seen by your doctor every 4 weeks for a physical examination and blood tests, through the time of delivery, and at 6, 12, 26, 48 and 78 weeks afterwards. The total amount of blood to be drawn for blood tests during the study will not be more than 153 cc (which is about 5 fluid ounces). Some of the blood will be saved and stored for further testing. A sample of the placenta may also be saved for testing.

You will receive the study medication (either HIVIG or IVIG) intravenously (into your vein) every 4 weeks until delivery. The amount of drug will vary with your weight; for example, a 130-pound woman would receive about 8 ounces (1 cup) of drug at each infusion. During your labor and delivery, you will receive ZDV (AZT) intravenously (into your vein) until your baby is born. After delivery of your baby, you and your doctor will decide about continuation of the ZDV (AZT) by mouth you were taking during your pregnancy. Your oral ZDV (AZT), during pregnancy or afterward, is not part of this study. You will not receive HIVIG or IVIG after delivery.

Your baby will be examined at birth, and if his/her medical condition indicates that he/she is eligible to continue the study, the baby will be given HIVIG or IVIG (whichever one you were given during pregnancy) by vein during the first twelve hours after birth. For example, a 7 pound baby would receive slightly less than 3 teaspoons of drug over a period of 1 1/2 hours. If the drug is given more slowly, the infusion will take longer. Your baby will also be given ZDV (AZT) every 6 hours, beginning 8 to 12 hours after birth, either by mouth (as a flavored syrup) or by vein (if your baby is not taking liquids by mouth yet). Your baby will take the ZDV (AZT) syrup every 6 hours for a total of 6 weeks. In addition to being examined at birth, blood samples will also be drawn. The blood sample will be taken from the umbilical cord and your baby's vein. After you and your baby go home from the hospital, your baby will be seen for physical examinations

APPENDIX XXIIIa (continued)

at: 1 week of age, 2 weeks, 6 weeks, and at months 3, 4, 5, 6, 9, 12 (1 year), 15, and 18. Blood tests will be taken at some of these visits to check for any side effects of the medicine or signs of HIV infection. The total amount of blood to be drawn from the baby for blood tests during the study will not be more than 80 cc's which is less than 3 fluid ounces. Some of the blood will be saved and stored for further testing.

Risks to You, the Mother:

HIVIG has not been used in HIV infected pregnant women. It has been tested in animals and a small number of adult males with HIV infection. The results suggest that HIVIG is non-toxic and as safe as IVIG, which has been used in pregnancy and in the newborn. Side effects that can occur in some people who receive HIVIG or IVIG include: fever, chills, backache, flushing, redness or swelling of hands or feet, vomiting, muscle aches, tiredness, changes in vital signs, rash and itching, and, rarely, shock. These side effects are usually related to the rate (speed) at which the medication is given. Very rare but reported side effects include hemolysis (breakdown of red blood cells), thrombosis (development of blood clots), lung or kidney abnormalities, or aseptic meningitis. Although the HIVIG or IVIG used in this study is made so as to be as sure as possible that it is safe, there is always a small but real risk that any product made from blood could transmit germs that cause infections (such as hepatitis).

The decision about you taking zidovudine (ZDV or AZT) by mouth during your pregnancy has been made by you and your doctor before this study, and is not part of this study. You and your doctor have discussed that ZDV (AZT) has not been approved for general use in pregnant women. The major side effect seen in adult patients taking ZDV (AZT) is anemia (a decrease in the number of red blood cells in your blood) that may in some instances cause premature labor. A decrease in hemoglobin (the part of the red blood cell that carries oxygen from the lungs to the tissues) and a decrease in the number of white blood cells could reduce your body's ability to fight infection. Minor side effects have included nausea, vomiting, and dizziness.

The ZDV (AZT) you receive by vein during labor is part of this study. The intravenous ZDV (AZT), like oral ZDV (AZT), is approved for use in adults who are infected with the HIV virus who are not pregnant. The side effects of intravenous ZDV (AZT) are the same as ZDV (AZT) by mouth. An IV infusion may cause some discomfort, bleeding, swelling, or bruising at the site of entry of the needle, as can drawing of blood samples. There is also a slight chance of infection.

Risks to the Fetus:

Information on the effects of HIVIG on the unborn baby is not yet known. HIVIG, in the laboratory, has been noted to increase HIV infection of cells. This effect was not present at higher concentrations of HIVIG, such as that used in humans. In tests of HIVIG in HIV-infected persons, no increase in virus multiplication has been observed, but rather a decrease in viral multiplication has been seen. The dose of HIVIG used in this study should provide antibody levels 10,000 times greater than the antibody level seen to increase infection in cell culture. However, HIVIG has not been used in pregnant women, and, while unlikely, it may be possible that HIVIG could increase the risk of HIV infection of the fetus.

However, there is significant experience with the use of IVIG in pregnant women; HIVIG and IVIG differ only in that HIVIG contains concentrated HIV antibodies. There have been no bad effects (miscarriages, fetal deaths or abnormalities) reported in pregnancies or children born to mothers who have received IVIG during pregnancy. Although the HIVIG or IVIG used in this study is made so as to be as sure as possible that it is safe, there is always a small but real risk that any product made from blood could transmit germs that cause infections (such as hepatitis).

The decision about your taking ZDV (AZT) during your pregnancy has already been made by you and your doctor. Although your unborn baby is at risk of developing anemia and a low white blood cell count from ZDV (AZT), data from earlier studies suggest that this occurs infrequently and does not harm the newborn. The long term effect ZDV (AZT) may have on your unborn baby is not known.

APPENDIX XXIIIa (continued)

Risks to Your Baby:

The major side effects of Zidovudine (ZDV or AZT) in children is anemia and low white cell count, but this usually occurs when the drug is taken for more than 6 weeks. The possible side effects of HIVIG or IVIG for a child are the same as those mentioned above for adults. In addition, protection against childhood illnesses (such as polio, diphtheria, whooping cough, tetanus, and other diseases) by vaccines (immunizations) your child receives as part of regular medical care may be reduced (that is, the risk of these illnesses may be increased by HIVIG or IVIG). HIVIG or IVIG may decrease the effect of vaccines (immunizations) your child receives. It is not known what long term effects of HIVIG in newborns there might be. Drawing of blood or an IV infusion may cause some discomfort, bleeding, swelling, or bruising at the site of entry of the needle. There is also a slight chance of infection. Although the HIVIG or IVIG used in this study is made so as to be as sure as possible that it is safe, there is always a small but real risk that any product made from blood could transmit germs that cause infections (such as hepatitis).

Benefits to You and Your Baby:

HIVIG and Zidovudine (ZDV or AZT) may help in fighting your HIV infection during pregnancy and possibly help prevent transmission of the HIV from you to your baby. At this time, it is not known if there is any benefit from the experimental treatment provided in the study. HIVIG and IVIG both contain antibodies to other infections and may help prevent or fight infections that you and your baby have or get.

Confidentiality of Records:

Research records of you and your baby's participation in the study will be kept confidential to the full extent of the law, and will not be released without your written permission. Your and your baby's research records will be identified only by a code number, and the code will be stored in a secure place with access only to clinic staff and designated staff from the Food and Drug Administration (FDA). Medical records which identify you or your baby by name may be inspected by monitoring personnel from the FDA, the National Heart, Lung, and Blood Institute (NHLBI),the National Institute of Child Health and Human Development (NICHD), the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), and the manufacturer of the study drugs, but confidentiality will be maintained to the extent permitted by law. You or your baby will not be identified by name in any publication or presentation resulting from this study.

Circumstances for Withdrawal from the Study:

You or your baby's participation in this study may end for the following reasons:

1. Voluntary withdrawal on your part.
2. Worsening health or other conditions that might make continued participation harmful to you or your baby.
3. Failure to keep appointments or take medications as instructed.
4. A serious reaction to the study drug.
5. Ending of the study by the study sponsor.
6. If the father of the baby withdraws consent for your participation in the study.

APPENDIX XXIIIa (continued)

Safeguards:

You and your baby (before and after birth) will be carefully evaluated during the study. Your doctor will carefully check all results of you and your baby's tests to ensure the safety of the study. In addition, any adverse (bad) side effects will be reported and reviewed by a panel at the National Institutes of Health (NIH).

Alternatives to Participation:

There is no known treatment available at this time that has been proven to prevent the transmission of the HIV virus from mother to infant during pregnancy and delivery in women who are receiving ZDV for their own health, who have CD4 counts 200 or below, or both. In pregnant HIV infected women who have not received antiretroviral treatment during their current pregnancy, who do not need antiretroviral treatment for their own health, and who have CD4 counts above 200, zidovudine treatment beginning after 13 weeks of pregnancy, during labor and delivery, and of the newborn for 6 weeks has been shown to reduce the risk of transmission of HIV by two-thirds (from 25.5% to 8.3%). HIVIG is an investigational new drug and is not available for general use.

Policy Regarding Research Related Injuries:

Immediate necessary care is available if you or your baby become injured due to participation in this study. However, no financial compensation will be given to you by (Name of Institution), the study drug manufacturers, NHLBI, NICHD, or NIAID. Treatment will be at your expense or the expense of your insurance carrier.

Significant New Findings:

You will be notified of any new findings or discoveries that occur during the study that could affect your willingness to take part in the study.

APPENDIX XXIIIa (continued)

Problems or Questions:

If you have any questions about this study or your rights as a participant, you should contact your doctor, who is the principal investigator responsible for safeguarding your welfare and the welfare of your baby, or the Institutional Review Board (IRB) of the hospital where the study is being conducted, at the following:

_____
(Name of Investigator)

OR

_____
(Name of Clinic Nurse or Coordinator)

Phone: _____

Address: _____

_____

_____

_____

OR

_____
(Name of IRB Contact Person)

Address: _____

_____

_____

_____

APPENDIX XXIIIa (continued)

Statement of Consent:

The purpose of the study, the procedures to followed, and risks and benefits have been fully explained to me. I understand that I may withdraw my participation or my baby's participation at any time without affecting my rights or those of my baby to receive medical care.

Name* (print or type)	Signature*	Date
*Volunteer's name or that of legal representative or guardian, as appropriate.		
Witness' Name (print or type)	Witness' Signature	Date

Father* (print or type)	Father's Signature*	Date
*If reasonably available.		
Witness' Name (print or type)	Witness' Signature	Date

I have explained the purpose of this study to the patient. To the best of my knowledge, she understands the purpose, procedures, risks, and benefits to her and her baby.

Investigator Name (print or type)	Investigator Signature	Date

APPENDIX XXIIIb

EJEMPLO DE AUTORIZACION INFORMADA

ACTG 185 Version 5.0: "Un Estudio Fase III al Azar, doblemente encubierto, en el cual la paciente no sabe cual medicina está recibiendo ni el investigador tampoco, Controlado de Inmuno Globulina Hiperinmune Anti-HIV Intravenosa en la Prevención de la Transmisión Materno-Fetal en Mujeres y Recién Nacidos que Reciben Zidovudina (ZDV)".

A usted se le está pidiendo que tome parte en un estudio de investigación llamado "Uso de IGHIV en la Prevención de la Transmisión Materno-Fetal de VIH en Mujeres Embarazadas Seropositivas que Reciben Zidovudina". Para decidir si usted desea participar en el estudio o no, usted necesita comprender completamente acerca de los riesgos y beneficios para tomar una decisión informada. Este proceso se llama autorización informada.

Este formulario de autorización informada le provee a usted información detallada acerca del estudio de investigación que su médico discutirá con usted. Una vez que entienda el estudio y si acepta tomar parte, se le pedirá que firme este formulario dando su autorización y se le dará copia. Al padre del bebé también se le pedirá que firme este formulario dando su autorización si, en su opinión, él está razonablemente disponible.

Es realmente importante que usted comprenda lo siguiente:

1. Su participación en el estudio es enteramente voluntaria.

2. Usted puede rehusar a tomar parte en el estudio o retirarse del estudio en cualquier momento sin penalidad o pérdida de sus beneficios a los cuales de otra forma tiene derecho.

3. Una decisión de retirarse del estudio no afectará su cuidado de salud futuro o posible participación en estudios de investigación futuros.

4. El padre del bebé puede rehusar a dar la autorización y esto impediría la participación de la madre en el estudio.

Naturaleza del Estudio:

En este estudio todas las mujeres están embarazadas y todas están infectadas con el Virus de Inmunodeficiencia Humana (VIH o SIDA). El VIH puede pasar a su bebé durante su embarazo, durante el nacimiento, o después del nacimiento a través de la leche materna. Se ha estimado que por cada 100 bebés nacidos de madres infectadas con VIH, entre 15 y 32 de ellos serán infectados con el virus de VIH. Si se infectan, los bebés tendrán el riesgo de morir de SIDA durante el primer año de vida. No se sabe exactamente cuando el virus puede infectar un bebé antes de nacer o por qué algunos bebés se infectan y otros no.

Todas las mujeres en el estudio están tomando Zidovudine (ZDV o AZT) por boca durante el embarazo. La decisión de que usted tome ZDV (AZT) durante el embarazo ya ha sido hecha por usted y su médico anterior a este estudio. La dosis de ZDV (AZT) que usted está tomando es establecida por su médico, y será revisada por su médico y cambiada si es necesario. La ZDV (AZT) que usted está tomando no es parte del estudio, y no se proporciona como parte del estudio.

Todas las mujeres en el estudio recibirán ZDV (AZT) intravenosamente (en la vena) durante el parto. La ZDV (AZT) intravenosa es proporcionada como parte del estudio. Después del parto, la decisión acerca de

APPENDIX XXIIIb (Continued)

la continuación de su régimen de ZDV (AZT) oral será hecha por usted y su médico; su ZDV (AZT) oral no es proporcionada como parte de este estudio.

En adición, más o menos la mitad de las mujeres en el estudio recibirán Inmuno Globulina Hiperinmune Intravenosa (IGHIV), una droga que contiene anticuerpos concentrados de VIH, y la otra mitad recibirá Inmuno Globulina Intravenosa (IGIV), una droga sin anticuerpos específicos para VIH. La asignación de droga del estudio se hará al azar (como tirando una moneda al cara o sello) y ni usted ni su médico sabrán cual droga está tomando usted.

Después que nazca su hijo, su bebé también recibirá una dosis de IGHIV o IGIV (cualquiera que usted esté recibiendo) y también recibirá ZDV (AZT) por 6 semanas después del nacimiento. Más o menos la mitad de los infantes recibirán IGHIV y la otra mitad recibirá IGIV (cualquiera que usted esté recibiendo). Todos los infantes recibirán ZDV (AZT) por 6 semanas, la cual es provista como parte del estudio, y su bebé será monitoreado estrechamente por si tiene algún efecto secundario de la ZDV (AZT).

El propósito del estudio es ver si dándole IGHIV a mujeres que están tomando ZDV (AZT) pueden reducir la posibilidad de que el bebé contraiga VIH de su madre. Por lo tanto, el grupo que esté recibiendo IGHIV será comparado con el grupo regular recibiendo IGIV como control para ver si hay alguna diferencia en el número de bebés que son infectados por sus madres en estos dos grupos. Esto no se sabe hasta este momento.

IGHIV (VIH Inmuno Globulina Hiperinmune Intravenosa) es el tratamiento experimental que está siendo examinado en el estudio. Este es hecho con la sangre de personas que tienen la infección del VIH pero que no están enfermas. La sangre de ellos contiene sustancias llamadas anticuerpos que luchan contra el VIH atacándolo e impidiéndole que infecte las células de la sangre. Los anticuerpos del VIH de esta sangre se concentran y se tratan de manera que el IGHIV contenga anticuerpos de VIH, pero no virus vivos de VIH y no son infecciosos.

La IGIV (Inmuno Globulina Intravenosa) está siendo usada como droga de control. Está hecha con sangre de personas que no tienen la infección de VIH, de manera que tiene anticuerpos para algunas enfermedades, pero no para el virus de VIH. Esta también es concentrada y preparada de manera que no contiene virus vivos de VIH y no es infecciosa.

Usted está tomando una droga llamada Zidovudina, o ZDV (previamente llamada AZT) porque su médico ha decidido que es medicamente necesaria para su salud, basado en pruebas de laboratorio y en su condición médica general. La ZDV (AZT) es una droga antiretroviral (una droga que detiene o previene que el virus de VIH se multiplique). Se ha demostrado que previene el crecimiento del VIH en adultos sin incluir mujeres embarazadas y niños infectados con el virus de SIDA.

Procedimientos del Estudio:

Si usted acepta tomar parte en el estudio, primero se le harán algunos exámenes para ver si cualifica para tomar parte en el estudio. Estos exámenes incluyen una revisión de su historial médico y un exámen físico, pruebas de laboratorio (incluyendo exámenes de sangre), y un sonograma (un exámen de ultrasonido para su bebé).

Durante el estudio, a usted la verá un médico cada 4 semanas para hacerle un exámen físico y exámen de sangre, hasta el momento del parto, y a las 6, 12, 26, 48, y 78 semanas después. La cantidad de sangre que se le tomará no será más de 153 cc (lo cual es más o menos 5 onzas líquidas). Parte de la sangre será reservada y almacenada para futuros análisis. Es posible que también se conserve una muestra de la placenta para análisis.

APPENDIX XXIIIb (Continued)

Usted recibirá la droga del estudio (ya sea IGHIV o IGIV) intravenosamente (en la vena) cada 4 semanas hasta el parto. La cantidad de droga variará de acuerdo a su peso; por ejemplo, una mujer de 130 libras podría recibir acerca de 8 onzas (1 taza) de droga en cada infusión. Durante el parto y alumbramiento, usted recibirá ZDV (AZT) intravenosamente (en la vena) hasta que su bebé nazca. Después del alumbramiento de su bebé, usted y su médico decidirán acerca de la continuación del uso del ZDV (AZT) oral que usted estaba tomando durante el embarazo. Su ZDV (AZT) oral, durante el embarazo o después, no es parte del estudio. Usted no recibirá IGHIV o IGIV después del parto.

Su bebé será examinado al nacer, y si sus condiciones médicas indican que él/ella es elegible para continuar en el estudio, al bebé se le dará IGHIV o IGIV (cualquiera que sea la que le dieron a usted durante el embarazo) intravenosamente (en la vena) durante las primeras doce horas después del nacimiento. Por ejemplo, un bebé de 7 libras podría recibir un poco menos de 3 cucharaditas de droga en un período de 1 1/2 hora. Si la droga se da más lentamente, la infusión tomará más tiempo. A su bebé también se le dará ZDV (AZT) cada 6 horas, empezando 8 a 12 horas después del nacimiento, ya sea por la boca (como un jarabe con sabor) o por la vena (si su bebé aún no toma líquidos). Su bebé tomará el jarabe de ZDV (AZT) cada 6 horas por un total de 6 semanas. Además de ser examinado al nacer se le sacarán muestras de sangre. La muestra de sangre se sacará del cordón umbilical y de la vena de su bebé. Después que usted y su bebé salgan del hospital y vayan a su casa, su bebé será visto para hacerle exámenes físicos a: 1 semana de edad, 2 semanas, 6 semanas, y en los meses 3, 4, 5, 6, 9, 12 (1 año), 15 y 18. Se le harán exámenes de sangre en algunas de estas visitas para verificar si hay efectos secundarios de la medicina o signos de infección de VIH. La cantidad total de sangre que se le sacará al bebé para los exámenes de sangre durante el estudio no será más de 80 cc lo cual es menos de 3 onzas fluidas. Parte de la sangre será reservada y almacenada para futuros análisis.

Riesgos para Usted, la Madre:

La IGHIV no ha sido usada en mujeres embarazadas infectadas con VIH. Ha sido ensayada en animales y en un pequeño número de hombres adultos infectados con VIH. Los resultados sugieren que la IGHIV no es tóxica y es tan segura como la IGIV, la cual ha sido utilizada en mujeres embarazadas y los recién nacidos. Los efectos secundarios que pueden ocurrir en algunas personas que reciben la IGHIV o IGIV incluye: fiebre, escalofríos, dolor de espalda, bochornos, enrojecimiento o inflamación de las manos o pies, vómitos, dolores musculares, cansancio, cambios en los signos vitales, salpullido, picazón, y raramente temblores. Aunque son raros, se han reportado efectos secundarios que incluyen hemólisis (rompimiento de células rojas de la sangre), trombosis (desarrollo de coágulos), anormalidades de los pulmones o de los riñones o meningitis acéptica. Aunque el HIVIG o el IVIG utilizado en este estudio se hace para asegurar lo más posible que no hay peligro, siempre hay un riego pequeño pero real que cualquier producto hecho de la sangre podría trasmitir gérmenes que causan infecciones (tales como la hepatitis).

La decisión de que usted tome zidovudina (ZDV o AZT) oral durante su embarazo ha sido hecha por usted y su médico antes de este estudio, y no es parte de este estudio. Usted y su médico han discutido que la ZDV (AZT) no ha sido aprobada para uso general en mujeres embarazadas. El mayor efecto secundario visto en pacientes adultos tomando ZDV (AZT) es anemia (una reducción de los glóbulos rojos en la sangre) que en algunos casos puede producir parto prematuro. Una reducción en la hemoglobina (la parte de las células rojas de la sangre que transporta el oxígeno de los pulmones a los tejidos) y una reducción en el número de glóbulos blancos que puede reducir la capacidad del cuerpo para atacar las infecciones. Los efectos secundarios menores incluyen náusea, vómito y mareo.

La ZDV (AZT) que usted recibe intravenosamente (por la vena) durante el parto es parte del estudio. La ZDV (AZT) intravenosa, igual que la ZDV (AZT) oral (por boca), está aprobada para el uso en adultos que están infectados con el virus VIH sin incluir mujeres embarazadas. Los efectos secundarios de la ZDV (AZT) intravenosa son los mismos de la ZDV (AZT) oral . Una infusión IV puede causar algún malestar,

APPENDIX XXIIIb (Continued)

sangramiento, hinchazón, o enrojecimiento en el lugar donde entra la aguja, como cuando se saca una muestra de sangre. Hay también una pequeña posibilidad de infección.

Riesgos para el Feto:

No se conoce aún información acerca de los efectos de la IGHIV en el feto. En el laboratorio, se ha notado que la IGHIV aumenta la infección de VIH de las células. Este efecto no se ha presentado en concentraciones más altas de IGHIV, tal como las que se usan en los seres humanos. En pruebas de IGHIV en personas infectadas con VIH, no se ha observado incremento en la multiplicación del virus, más bien se ha visto una disminución en la multiplicación viral. La dosis de IGHIV usada en este estudio debe producir anticuerpos a niveles 10.000 veces más grande que el nivel que se ha visto que incrementa la infección en el cultivo celular. Sin embargo, la IGHIV no ha sido usada en mujeres embarazadas, y a pesar de que no parece probable, es posible que IGHIV pueda aumentar el riesgo de infección de VIH en el feto.

Sin embargo, hay una experiencia significativa en el uso de IGIV en mujeres embarazadas; la IGHIV y IGIV se diferencian solamente en que la IGHIV contiene anticuerpos concentrados de VIH. No ha habido efectos negativos (pérdidas, muerte del feto o anormalidades) reportadas en embarazos o niños nacidos de madres que han recibido IGIV durante el embarazo. Aunque el HIVIG o el IVIG utilizado en este estudio se hace para asegurar lo más posible que no hay peligro, siempre hay un riego pequeño pero real que cualquier producto hecho de la sangre podría trasmitir gérmenes que causan infecciones (tales como la hepatitis).

La decisión acerca de que usted tome ZDV (AZT) durante su embarazo ya ha sido tomada por usted y su médico. Si bien su bebé antes de nacer corre el riesgo de contraer anemia y una baja en la cantidad de glóbulos blancos en la sangre debido a la ZDV (AZT), la información de estudios anteriores sugiere que esto no ocurre muy frecuentemente y no afecta al recién nacido. Los efectos a largo plazo que la ZDV (AZT) puede tener en el feto son desconocidos.

Riesgos para su Bebé:

El mayor efecto secundario que tiene la Zidovudina (ZDV o AZT) en los niños es la anemia y la disminución en la cantidad de glóbulos blancos en la sangre, pero esto ocurre usualmente cuando la droga es tomada por más de 6 semanas. Los posibles efectos secundarios de IGHIV o IGIV para un niño son los mismos mencionados anteriormente para los adultos. En adición la protección por vacunas (inmunizaciones) contra enfermedades infantiles (tales como polio, difteria, tos ferina, tétano y otras enfermedades) que su niño recibe como parte de su cuidado médico regular puede ser reducido (es decir, el riezgo de estas enfermedades puede aumentar por la IGHIV o IGIV). La IGHIV o IGIV puede reducir el efecto de las vacunas (inmunizaciones) que su niño recibe. No se sabe cuales puedan ser los efectos a largo plazo. El sacar sangre o recibir una infusión IV puede causar cierta molestia, sangramiento, hinchazón y enrojecimiento en el área donde entra la aguja. Existe también una pequeña posibilidad de infección. Aunque el HIVIG o el IVIG utilizado en este estudio se hace para asegurar lo más posible que no hay peligro, siempre hay un riego pequeño pero real que cualquier producto hecho de la sangre podría trasmitir gérmenes que causan infecciones (tales como la hepatitis).

Beneficios para Usted y su Bebé:

La IGHIV y Zidovudina (ZDV o AZT) pueden ayudar a combatir su infección de VIH durante el embarazo y posiblemente ayuden a prevenir la transmisión de VIH de usted a su bebé. En este momento, no se sabe si hay algún beneficio del tratamiento provisto en el estudio. La IGHIV y la IGIV ambas contienen anticuerpos contra otras infecciones y pueden ayudar a prevenir o combatir infecciones que usted y su bebé puedan tener o contraer.

APPENDIX XXIIIb (Continued)

Confidencialidad de los Expedientes:

Los expedientes de la participación suya y de su bebé en el estudio serán mantenidos confidencialmente en toda la extensión de la ley, y no serán divulgados sin su autorización escrita. Los expedientes suyos y de su bebé serán identificados sólo por un número de código, y el código será guardado en un lugar seguro al que sólo tendrán acceso el personal clínico y el personal designado por la Administración de Alimentos y Drogas (FDA). Los expedientes médicos que la identifican a usted y a su bebé por el nombre puede que sean inspeccionados para monitoreo por el personal de la FDA, el Instituto Nacional del Corazón, Pulmón y Sangre (NHLBI), el Instituto Nacional de Salud del Niño y Desarrollo Humano (NICHD), el Instituto Nacional de Alergia y Enfermedades Infecciosas (NIAID) División de SIDA (DAIDS), y la compañía manufacturadora de la droga. pero la confidencialidad será mantenida en toda la extensión de la ley. Usted o su bebé no serán identificados por el nombre en ninguna publicación o presentación resultante de este estudio.

Circunstancias para Retiro del Estudio:

Usted o su bebé pueden retirar su participación en este estudio por las siguientes razones:

1. Retiro voluntario de su parte.
2. Empeoramiento de la salud u otras condiciones que puedan hacer que la continuación de la participación sea peligrosa para usted o para su bebé.
3. Fracaso para mantener las citas o tomar las medicinas de acuerdo a lo instruido.
4. Una reacción seria a la droga del estudio.
5. Cancelación del estudio por parte del auspiciador.
6. Si el padre retira la autorización para su participación en el estudio.

Protecciones:

Usted y su bebé (antes y después del nacimiento) serán cuidadosamente evaluados durante el estudio. Su médico verificará cuidadosamente todos los resultados de las pruebas suyas y de su bebé para reenforzar la seguridad del estudio. En adición, todos los efectos secundarios adversos (malos) serán reportados y revisados por un panel del Instituto Nacional de Salud (NIH).

Alternativas de Participación:

En este momento no se conoce ningún tratamiento disponible que se haya probado que prevenga la transmisión del virus VIH de la madre al infante durante el embarazo y parto en mujeres que están recibiendo ZDV para su propia salud, que tienen cantidades de CD4 de 200 o menos, o ambos. En el caso de las mujeres embarazadas que tienen HIV, que no han recibido tratamiento antiretroviral durante el embarazo actual, que no necesitan tratamiento antiretroviral para su propia salud, y que tienen cantidades de CD4+ de más de 200, el tratamiento de zidovudina comenzando después de 13 semanas de embarazo, durante el parto, y durante 6 semanas después del recién nacido ha demostrado que reduce la trasmisión del HIV a la tercera parte (de 25.5% a 8.3%).

APPENDIX XXIIIb (Continued)

Política Referente a Lesiones Relacionadas con la Investigación:

Si su bebé o usted resultan lesionados debido a la participación en el estudio el cuidado necesario está disponible inmediatamente. Sin embargo, ni (Name of the Institution), la compañía manufacturera de la droga del estudio, el NHLBI, NICHD, o NIAID le darán compensación financiera. El tratamiento será a sus expensas o a las expensas de su compañía de seguro.

Resultados Nuevos Significativos:

Usted será notificada de los nuevos resultados o descubrimientos que ocurran durante el estudio que pudiesen afectar su disposición a tomar parte en el estudio.

Problemas o Preguntas:

Si usted tiene algunas preguntas acerca de este estudio o de sus derechos como participante, usted debe comunicarse con su médico, quien es el investigador principal responsable de la protección de su bienestar y el bienestar de su bebé, o el Comité de Revisión Institucional (IRB) del hospital donde se está realizando el estudio, como sigue.

_____
(Nombre del Investigador)

O

_____
(Nombre de la Enfermera Clínica o Coordinador)

Teléfono: _____

Dirección: _____

_____

_____

_____

O

_____
(Nombre de la Persona Contacto del IRB)

Dirección: _____

_____

_____

_____

APPENDIX XXIIIb (Continued)

Declaración de Autorización:

Se me han explicado ampliamente el propósito del estudio, los procedimientos a seguir, los riesgos y beneficios. Entiendo que puedo retirar mi participación o la participación de mi bebé en cualquier momento sin afectar mis derechos ni los derechos de mi bebé a recibir cuidado médico.

Nombre* (imprenta o maquinilla)	Firma*	Fecha
*Nombre del voluntario(a) representante legal o tutor(a), lo que sea apropiado.		
Nombre del Testigo	Firma del Testigo	Fecha

Padre* (Imprenta o maquinilla)	Firma del Padre*	Fecha
*Si está razonablemente disponible.		
Nombre del testigo	Firma del Testigo	Fecha

He explicado el propósito de este estudio a la paciente. A mi mejor entender, ella comprende el propósito, procedimientos, riesgos y beneficios para ella y su bebé.

Nombre del Investigador (Imprenta o maquinilla)	Firma del Investigador	Fecha