

PACTG P1031A

MOTHER INFANT RAPID INTERVENTION AT DELIVERY  
(MIRIAD)

International Version - Cape Town, South Africa

A Limited Trial of the Pediatric AIDS Clinical Trials Group

Sponsored by:

The National Institute of Allergy  
and Infectious Diseases

In Collaboration with:

The Centers for Disease Control and Prevention

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**Version 3.0**

**FINAL**

**January 18, 2006**

PACTG P1031A PROTOCOL TEAM ROSTER

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**SUMMARY OF CHANGES FOR PACTG P1031A, VERSION 3.0, dated 01/18/06:  
MOTHER INFANT RAPID INTERVENTION AT DELIVERY (MIRIAD)  
International Version – Cape Town, South Africa**

**Background and Rationale for Protocol Amendment**

PACTG P1031A was originally designed as a prospective, cluster-randomized study to be conducted in three phases:

- Phase I: address feasibility, acceptance, and performance objectives for rapid tests performed concurrently, and select a dual test sequential algorithm for Phases II and III
- Phase II: address feasibility, acceptance, and performance objectives for the dual test sequential algorithm, and determine if Phase III is likely to lead to interpretable comparison of peripartum transmission rates
- Phase III: compare HIV transmission rates in the two study arms

The three phase study was to enroll 12,000 eligible women for approach for testing in order to identify 3,300 HIV seropositive women. However, the completion of the three phase study model is no longer feasible because Dora Nginza Hospital in the Eastern Cape Province – anticipated to be the largest contributor to study accrual – will not be participating. Based on a comprehensive review by and discussion with the PACTG Leadership, the team has refocused and consolidated the study design to evaluate the dynamics of intrapartum versus postpartum HIV rapid test acceptance and feasibility in labor wards in primary and district hospital settings. Accordingly, this has resulted in significant revisions in the targets for subject accrual and the roster of primary and secondary objectives. Version 2.0 primary objectives concerning the comparison of MTCT rates in the intrapartum versus postpartum groups and rapid test performance have been changed to secondary objectives to describe the rate of MTCT and rapid test performance. Version 2.0 secondary objectives concerning evaluation of factors impacting MTCT and evaluation of risk of MTCT in relation to timing of ARV prophylaxis and feeding method have also been removed. However, the scientific rigor of the investigation of the remaining primary and secondary objectives has been preserved in this amended study design.

The following summary reflects both changes related to the revised study design as well as other changes designed to enhance the quality and efficiency of the core study design. Editorial changes, including corrections of typographical errors and other changes required to update information not affecting regulatory issues or the Sample Informed Consent may be included. Revisions outlined in Clarification Memo #1, dated 10/18/04 are also included. All changes in this version appear in boldface type.



**VERSION 3.0 SUMMARY OF CHANGES (CONT.)**

- 1. The team roster has been updated.**
- 2. The three study phases no longer exist. The study design is now limited to a prospective, cluster-randomized study to address feasibility and acceptance of voluntary HIV counseling and rapid testing. (Schema, Sections 3.0, 8.0)**
- 3. The sample size has been reduced to enrollment of approximately 400 eligible women in order to identify at least 60 HIV seropositive women. (Schema, Sections 3.0, 8.0)**
- 4. The testing algorithm will continue to be that originally outlined for Phase I in Version 2.0. (Schema, Section 5.1, Appendices IIA and IIB)**
- 5. As the study will only continue at sites in the Western Cape Province, ARV prophylaxis will only be in accordance with the Western Cape PMTCT protocol. (Schema, Section 5.2)**
- 6. Certain aspects of the qualitative assessment have been modified. At the two study sites combined, approximately 36 women with concordant positive rapid test results and 36 women with concordant negative rapid test results (matched only by age) will be asked to complete the qualitative assessment at Entry. The Week 12 qualitative assessment has been eliminated. (Schema, Section 3.0, Appendix IA)**
- 7. Version 2.0 primary objectives 2.14 and 2.15 have been changed to secondary objectives in Version 3.0 to describe the rate of MTCT (2.24) and rapid test performance (2.22). Version 2.0 secondary objectives 2.23 and 2.24 have been removed. (Schema, Section 2.0)**
- 8. Women with planned medical induction of delivery, planned Cesarean delivery, or obstetrical conditions which warrant the decision to plan delivery (all previously covered under Section 4.22 in Version 2.0) are now eligible for study participation. (Section 4.114)**
- 9. For women enrolled in the intrapartum group with at least one positive rapid test result, specimens for entry laboratory evaluations will be obtained as soon as the positive test result is known and prior to administration of ARV prophylaxis. (Sections 6.211 and 6.213, Appendix IA)**
- 10. In the event of concordant negative rapid test results, no further maternal or infant follow-up is required unless the ELISA and Western blot come back positive (Section 6.212 and 6.222).**

**VERSION 3.0 SUMMARY OF CHANGES (CONT.)**

- 11. In the event of initially discordant rapid test results with concordant negative repeat rapid test results, no further maternal or infant follow-up is required unless the ELISA and Western blot come back positive. (Section 6.213 and 6.223)**
- 12. Sections 8.1 and 8.6 have been updated to include discussion of the cluster randomization and its limitations and planned sensitivity analyses.**
- 13. Outcome measures in Section 8.2 have been revised to match the revised set of objectives.**
- 14. Sections 8.41 and 8.42 have been updated to include information on study accrual thus far, the rationale for the reduced sample size, and accrual projections for the remainder of the study.**
- 15. Study accrual will be monitored by the network oversight committee; the feasibility of study completion will be reassessed if accrual falls substantially below targets set in Section 8.42. (Section 8.51)**
- 16. There will be one formal interim review of the study by the SMC, approximately two to three months after enrollment to Version 3.0 begins. (Section 8.52)**
- 17. The Week 12 maternal study visit has been removed. (Appendix IA)**
- 18. Infant schedule of evaluations:**
  - a. Within 48 hours of birth, collect 1 ml of blood by heelstick or venipuncture. Specimen will be shared for dried blood spot preparation for DNA PCR and plasma and cell pellet storage.**
  - b. At Weeks 6-10 and 8-12 (as appropriate), collect 1 ml of blood by heelstick or venipuncture for dried blood spot preparation for DNA PCR.**
  - c. DNA PCR will be done at Pathcare Laboratories on whole blood; results will be reported directly to the sites.**
  - d. Dried blood spot preparations will be batched and shipped monthly to the PACTG Repository along with plasma and PBMC aliquots.****(Appendices IB and V)**
- 19. The template rapid test accountability log fields have been updated. (Appendix IV)**
- 20. The cord blood specimen should be collected in a 5 ml EDTA tube. The specimen should only be labeled with site name/number, month and year of collection, group (intrapartum or postpartum). (Appendix V)**
- 21. Appendix VI has been revised to only discuss measures to reduce the number of subjects lost to follow-up in the context of the Somerset West sites.**

VERSION 3.0 SUMMARY OF CHANGES (CONT.)

22. Version 2.0 Appendix VII (Summary of Approach to Assessing Interpretability of the Transmission Analysis) is no longer relevant and has been removed.
23. Appendix VIII (Intrapartum Group Sample Informed Consent):
- a. Under the section “*Why Is This Study Being Done?*” the third bullet point in the 3<sup>rd</sup> paragraph was removed.
  - b. Under the subsection “*If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV*”:
    - i. In item #1, the last sentence should read: “You will probably be offered a medicine called nevirapine (NVP). Your baby will probably be offered NVP and another medicine called zidovudine (AZT).”
    - ii. Item #2 should begin: “As soon as the positive test results are known, about 2 teaspoons of blood....”
    - iii. Item #5 should read: “A few drops of blood will be taken from either your baby’s heel or from a vein in your baby’s arm to test your baby for HIV.”
    - iv. In Item #6, the first sentence of the second paragraph should read: “A few drops of blood will again be taken from either your baby’s heel or arm to test your baby for HIV.”
    - v. In Item #7, the first sentence should read: “If your baby’s second result is positive for HIV, another few drops of blood will be taken from either your baby’s heel or arm .....”
    - vi. In Item #8, the first sentence should read: “You may be asked to be interviewed again at 6 months after you deliver your baby.”
  - c. Under the subsection “*If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are negative for HIV*”, the following language should be added to Item #3:

“There are no further requirements for you or your baby, unless both of the standard HIV tests are positive for HIV. If this happens, the study staff will contact you and ask you and your baby to come back to the clinic as soon as possible. If this is within 72 hours of birth, the study staff will arrange for your baby to start anti-HIV medicine. The kind of anti-HIV medicine that is offered to your baby will depend on the medicines available at the delivery facility. Your baby will probably be offered both NVP and AZT. You and your baby will then follow steps 3-8 listed under “If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV.”

VERSION 3.0 SUMMARY OF CHANGES (CONT.)

d. Under the subsection “*Storage of Blood Specimens*”:

- i. The first sentence was revised to read: “Your/your baby’s blood samples will be shipped to and stored at a special facility in the United States where only approved researchers will have access to them.”
- ii. The third sentence was revised to read: “As your/your baby’s samples are needed, they will be sent to CDC laboratories in the United States, where the studies will be done.”

e. The section “*How Many Women Will Take Part In This Study*” should read “About 400 women will take part in this study.”

f. Under the section “*Will I Receive Any Payment?*” the third sentence was revised to read “If the study staff asks to interview you at 24 weeks after you deliver your baby.....”

24. Appendix IX (Postpartum Group Sample Informed Consent):

a. Under the section “*Why Is This Study Being Done?*” the third bullet point in the 3<sup>rd</sup> paragraph was removed.

b. Under the subsection “*If your OraQuick® and Determine® rapid test results are positive for HIV*”:

- i. In Item #1, the last sentence was revised to read: “Your baby will probably be offered two medicines called nevirapine (NVP) and azidothymidine (AZT).”
- ii. Item #5 should read: “A few drops of blood will be taken from either your baby’s heel or from a vein in your baby’s arm to test your baby for HIV.”
- iii. In Item #6, the first sentence of the second paragraph should read: “A few drops of blood will again be taken from either your baby’s heel or arm to test your baby for HIV.”
- iv. In Item #7, the first sentence should read: “If your baby’s second result is positive for HIV, another few drops of blood will be taken from either your baby’s heel or arm .....”
- v. In Item #8, the first sentence should read: “You may be asked to be interviewed again at 6 months after you deliver your baby.”

c. Under the subsection “*If your OraQuick® and Determine® rapid test results are negative for HIV*”, the following language should be added to Item #3:

“There are no further requirements for you or your baby, unless both of the standard HIV tests are positive for HIV. If this happens, the study staff will contact you and ask you and your baby to come back to the clinic as soon as possible. If this

**VERSION 3.0 SUMMARY OF CHANGES (CONT.)**

is within 72 hours of birth, the study staff will arrange for your baby to start anti-HIV medicine. The kind of medicine that is offered to your baby will depend on the medicines available at the delivery facility. Your baby will probably be offered both NVP and AZT. You and your baby will then follow steps 3-8 listed under **“If your OraQuick® and Determine® rapid test results are positive for HIV.”**

- d. Under the subsection *“Storage of Blood Specimens”*:
- iii. The first sentence was revised to read: **“Your/your baby’s blood samples will be shipped to and stored at a special facility in the United States where only approved researchers will have access to them.”**
  - iv. The third sentence was revised to read: **“As your/your baby’s samples are needed, they will be sent to CDC laboratories in the United States, where the studies will be done.”**
- e. The section *“How Many Women Will Take Part In This Study”* should read: **“About 400 women will take part in this study.”**
- f. Under the section *“Will I Receive Any Payment?”* the third sentence was revised to read **“If the study staff asks to interview you at 24 weeks after you deliver your baby.....”**

## SCHEMA

MOTHER INFANT RAPID INTERVENTION AT DELIVERY  
(MIRIAD)

International Version - Cape Town, South Africa

- DESIGN:** Prospective, cluster-randomized study
- SAMPLE SIZE:** Enrollment will continue until 60 HIV seropositive women have been identified or until August 31, 2006, whichever comes first. Assuming that approximately 25% of women approached will decline to enroll, and that the seroprevalence among women tested will be approximately 16%, approximately 530 women will need to be approached for enrollment and approximately 400 women will need to be enrolled and tested in order to identify 60 HIV seropositive women.
- POPULATION:** Pregnant women with undocumented HIV serostatus who present for delivery at  $\geq 28$  weeks gestation and infants born to women with at least one positive rapid test result.
- RANDOMIZATION:** This is a cluster-randomized study in which the basic unit of randomization is the calendar week (Monday through Sunday) rather than the individual subject. Eligible women will be offered enrollment into one of two study arms: intrapartum HIV counseling and rapid testing or postpartum HIV counseling and rapid testing.
- STRATIFICATION:** The randomization will not be stratified and women will not be stratified at the time of study entry.
- TESTING ALGORITHM:** OraSure OraQuick<sup>®</sup> and the Abbott Determine<sup>®</sup> HIV rapid tests will be performed concurrently on a single blood specimen. ELISA will be performed on the same blood specimen. Western blot will be performed to resolve any discordance between the rapid test results or between the rapid test results and the ELISA result. OraQuick<sup>®</sup> will also be done on an oral fluid specimen for comparative purposes.

## SCHEMA (Cont.)

REGIMEN: ARV prophylaxis for women identified as HIV seropositive and their infants will be in accordance with the protocol for ARV prophylaxis generated by the provincial government of the Western Cape Province. Neither maternal nor neonatal antiretrovirals will be provided through this study.

STUDY DURATION: Women with at least one positive rapid test result will be followed until 6-10 weeks postpartum. A subset of women will be **interviewed at 6-10 and 24 weeks postpartum** as part of the qualitative assessment. HIV-exposed infants will be followed until at least 8-12 weeks of age.

OBJECTIVES:Primary

1. To evaluate the feasibility, rate of acceptance, and acceptability of voluntary HIV counseling and rapid testing among pregnant women with undocumented HIV serostatus who present for delivery, and to compare intrapartum versus postpartum rapid testing with respect to these measures.
2. To examine the rate of acceptance of and ability to administer antiretroviral prophylaxis prior to delivery to women who are identified as HIV seropositive through intrapartum rapid HIV testing and to their infants.
3. To examine the rate of acceptance of and ability to administer antiretroviral prophylaxis to infants born to women who are identified as HIV seropositive through postpartum rapid HIV testing.

Secondary

1. To estimate the HIV seroprevalence among women with undocumented HIV serostatus who are tested during the peripartum period.
2. **To describe the performance of rapid HIV serologic tests on blood and saliva in the perinatal setting.**
3. To assess adherence to infant follow-up and to the feeding method selected by the mother at discharge.
4. **To describe the rate of peripartum/early postpartum mother-to-child transmission among women identified as HIV seropositive through intrapartum or postpartum rapid HIV testing.**

## SCHEMA (Cont.)

5. To assess acceptance of HIV counseling and testing among clinical personnel at primary, secondary, and tertiary care facilities.
6. To contribute repository specimens for specified CDC MIRIAD biomedical studies, as outlined in Appendix **VII**.



## 1.0 INTRODUCTION

### 1.1 Background

Pediatric HIV infection is an important public health problem in South Africa. In 2000, sentinel surveillance revealed that the HIV seroprevalence among pregnant women was approximately 25%; a dramatic increase from 0.7% in 1990 [1]. Extrapolations from the surveillance data suggest that 5 million people in South Africa are living with HIV infection, inclusive of approximately 250,000 children and 2.5 million women. Almost all cases of pediatric HIV infection are the result of mother-to-child HIV transmission (MTCT).

The implementation and expansion of voluntary HIV counseling and testing (VCT) and antiretroviral (ARV) prophylaxis strategies in resource-rich countries have resulted in the reduction of MTCT rates to less than 5%. In resource-poor countries, similar VCT strategies and abbreviated courses of ARV prophylaxis have also been effective in reducing MTCT. The Centers for Disease Control (CDC) Bangkok trial demonstrated a 51% reduction in MTCT with a two-part zidovudine (ZDV) regimen administered solely to women during pregnancy and labour [2]. However, ZDV-based regimens are too complicated and expensive to be practical options for peripartum prophylaxis in South Africa. In Uganda, the HIVNET 012 study demonstrated that nevirapine (NVP) administered to ARV-naïve women during labour and to their infants within 72 hours of birth reduced MTCT to approximately 13% at 14-16 weeks after delivery; a nearly 50% reduction compared to those women treated exclusively with intrapartum ZDV [3]. Faced with a more affordable intervention that could be delivered within the context of South Africa's health care system, the two-part NVP regimen was adopted as the national standard for South Africa's Prevention of Mother-To-Child Transmission (PMTCT) program. The PMTCT program incorporates VCT in antenatal clinics and peripartum NVP prophylaxis in delivery facilities.

The South African national government initiated the development of two PMTCT pilot sites in each of its nine provinces. An interim evaluation of the pilot sites in February 2002 led to the recommendation that PMTCT programs be established across the country [4]. While efforts are underway to make PMTCT programs available to all pregnant women, 90% of women are currently not offered VCT during pregnancy due to limitations of the primary health care system. Thus most HIV-infected women fail to receive peripartum NVP prophylaxis, despite the widespread availability of the drug. But most pregnant women in South Africa deliver in health facilities, providing a crucial opportunity for systematic VCT and intervention prior to delivery. MTCT rates may be as high as 40% among women who do not receive peripartum prophylaxis, who are not provided with infant feeding

options, and for whom labour management is not modified. Infants born to unidentified (and therefore untreated) HIV-infected mothers receive neither the benefit of ARV prophylaxis nor the close monitoring and PCP prophylaxis that can be life-sustaining.

## 1.2 Rationale

### 1.21 Rationale for Randomized Study Design

PACTG P1031A is designed as a cluster-randomized trial to compare the feasibility, acceptance, and acceptability of intrapartum versus postpartum VCT in a resource-limited setting which serves a high HIV seroprevalence obstetric population. Perceptions and opinions of peripartum VCT will be assessed. It is anticipated that qualitative outcomes will assist health policy development and establishment of standard of care in South Africa with respect to the most appropriate timing of peripartum VCT.

For P1031A, a cluster-randomized design was chosen for both scientific and logistical reasons. The basic unit of randomization is the calendar week (Monday through Sunday) rather than the individual subject. An individual subject randomization was considered, but would have required a multi-step enrollment and testing process that would not permit a realistic evaluation of postpartum testing. Specifically, an individually-randomized design would require offering study participation to and obtaining informed consent from all women in labour, then randomizing each woman to either the intrapartum VCT arm or the postpartum VCT arm. Thus, women randomized to the postpartum VCT arm would actually receive information about the study (including the fact that HIV testing would be offered) during labour and might make a different decision in the postpartum period than if they had not received any information during labour. With the cluster-randomized design, women can be approached for study participation either intrapartum or postpartum, and offered VCT immediately after consenting to study participation, which is closer to what would happen in practice. Furthermore, an individually-randomized design would require providing VCT in both the labour and delivery suites and the postpartum wards every day. This would result in substantial intermingling of women randomized to the intrapartum and postpartum arms, with additional opportunity for women in the postpartum arm to receive information about HIV testing during labour, due to conversations between women.

In 2001, the CDC issued recommendations supporting the use of rapid HIV testing among women in labour with undocumented HIV serostatus [5]. Limited clinical experience in the U.S. has demonstrated the potential efficacy of intrapartum rapid HIV testing in reducing MTCT. However, in

resource poor countries in Sub-Saharan Africa, there are no examples of public health interventions which incorporate VCT and prophylaxis measures for women in labour who have failed to determine their serostatus antenatally. Although rapid HIV testing is employed in antenatal clinics in South Africa, it is not routinely used in labour and delivery settings given time constraints, limited staff resources, and most significantly, the overriding ethical concerns about testing women in labour for HIV infection. There is a perception in the South African medical community that offering HIV counseling and testing to women in labour is unethical. Women in labour are felt to be under duress and unable to appreciate the significance of undergoing HIV testing (similar to the prohibition of counseling women for sterilization procedures while in labour). As a result, women presenting to a delivery facility with unknown HIV status are not, as a matter of protocol, offered HIV counseling and testing. Formal structures for conducting VCT in the intrapartum setting have not been proposed or developed, and the nationally developed PMTCT guidance for health care providers describes "Counseling for special circumstances" which stipulates that "When a woman presents in advanced labour, without a previously determined HIV status, counseling should be deferred until after delivery. Then the woman must be counseled appropriately and her consent sought for the administration of nevirapine to her baby." When health care facilities are sufficiently resourced, women with unknown HIV serostatus may be offered postpartum VCT, with an option for treating the neonates of HIV seropositive women with one or two doses of NVP. As most VCT resources are directed to antenatal service, postpartum VCT is available in very few of South Africa's delivery facilities.

In this context, the efficacy of postexposure NVP prophylaxis for exposed infants remains unclear, and postpartum VCT does not allow for administration of a two-part NVP regimen to the woman in labour and to the infant. Inherent in an evaluation of VCT strategies is an assessment of the efficacy of ARV prophylaxis strategies in preventing MTCT. Two studies suggest that prophylactic antiretroviral therapy, administered to neonates alone, might have similar efficacy as abbreviated peripartum dual therapy administered to mother and infant. Wade, in an observational study, found that ZDV administered to neonates born to HIV-infected mothers who had not received the benefit of antepartum or intrapartum ZDV therapy, when started within 24 hours of birth and continued for six weeks, was associated with a vertical transmission rate of 9.3%, while initiation of ZDV intrapartum was associated with a vertical transmission rate of 10.0% [6]. Gray demonstrated in a randomized clinical trial that women with unknown HIV status could be effectively counseled for HIV testing in the early postpartum period, and if positive, started on a prophylactic antiretroviral regimen [7]. Gray's comparison groups, single dose NVP to the neonate versus six weeks

of ZDV to the baby, both started within 24 hours of delivery were found to be similarly effective, with 6-week transmission rates of 13.4% and 16.2%, respectively. Taha's randomized comparison of postexposure prophylaxis of HIV-exposed infants with NVP alone versus NVP plus one week of oral ZDV demonstrated transmission rates of 22.7% and 14.7%, respectively [8].

While historical comparisons are not necessarily valid; these rates observed in Gray's study population compare favorably with transmission rates in the HIVNET 012 trial. It is important to recognize that the majority of populations used in studying the application of peripartum ARV prophylaxis have consisted of women identified as seropositive through the conduct of antepartum VCT in resource poor settings where only abbreviated peripartum ARV prophylaxis was available. In contrast, there is a paucity of data in similar settings which describe the application of peripartum ART among women newly diagnosed at the time of delivery. The acceptance rates of VCT and ARV prevention measures is undefined in this population. Given significant limitations of both Gray's and Taha's reports, there remains an important need and challenge to evaluate effective interventions for HIV-exposed infants delivered without the benefit of intrapartum therapy in resource-poor settings.

These examples along with the recognition that the application and acceptance of intrapartum VCT in South Africa has been limited due to ethical concerns about offering VCT to women experiencing the physical and emotional stress of labour underscore the fact that the best practice strategy for peripartum HIV testing in South Africa, along with many similar nations, remains undetermined. If postpartum treatment of the infant demonstrates similar efficacy as intrapartum/postpartum treatment of mother and infant in reducing MTCT, then postpartum VCT might be considered an appropriate strategy, especially if intrapartum VCT is not considered feasible or acceptable.

There are additional considerations in determining best practice strategies for peripartum VCT and ART prophylaxis, which also have significant public health ramifications for maternal outcomes. While strategies incorporating the use of nevirapine have demonstrated efficacy in reducing MTCT (when administered as a dual regimen to mothers and infants), this success comes at a potential price. Nevirapine resistance has been identified in 19% of mothers after a single dose of NVP and in 66% of mothers after two doses of NVP [9]. Recent reports, with more sensitive measures of NVP resistance, suggest rates in mothers in excess of 80% (Personal communication, Dr. Mitchell Besser). Additionally, the risk of developing resistance with two-part NVP administration has been observed among as many as 15% of women

receiving standard ART, regardless of CD4 count, viral load at the time of delivery, or ARV regimen [10].

Concerns regarding NVP resistance after prophylactic use in pregnancy are two-fold: first, will NVP be an effective prophylactic agent in subsequent pregnancies? Follow-up studies of mothers in the HIVNET 012 trial demonstrated that among women with NVP resistance at 14-16 weeks, none demonstrated resistance at 12 months [11]. However, among NVP resistant women in the SAINT trial, 20% still demonstrated NVP resistant viral species at 12 months [9]. The clinical significance of these findings is unclear. More importantly, additional concerns stem from prospects to deliver therapeutic ARV regimens to women with AIDS in South Africa. Recent commitments from the South African government suggest that therapeutic treatment regimens will be offered to those with AIDS. In accordance with the World Health Organization's (WHO) recommendation, NVP is a cornerstone of the contemplated therapeutic regimens. Using prophylactic NVP in pregnancy may render ineffective the therapeutic use of NVP in future treatment programs; disabling national treatment campaigns for child-bearing women. In the absence of the ability to employ longitudinal or combination ARV prophylaxis, perinatal NVP prophylaxis strategies, administered to the neonate alone, would prevent inducing NVP resistance in mothers. In a comprehensive public health model, strategies which balance and prioritize both maternal and child well-being are essential.

#### 1.22 Rationale for Testing Algorithm

The sensitivity and specificity of blood-based rapid HIV tests are comparable to the sensitivity and specificity of ELISA [12].

Rapid testing technology has been an accepted part of the PMTCT program since its inception in December 2000. Requirements for effective implementation of peripartum VCT using rapid HIV tests include simple methodology, ease of performance and interpretation, reliable sensitivity and specificity, and low cost. A dual sequential rapid test algorithm has become the standard for antenatal PMTCT testing. The Abbott Determine<sup>®</sup> HIV 1/2 is the primary screening test, with a second rapid test (such as GuyFaar or WhiteStar) to confirm a positive Determine<sup>®</sup> result. ELISA is employed to resolve rapid test discordance. However, a standard testing algorithm has not been defined for peripartum use.

P1031A will incorporate a dual concurrent rapid test algorithm with the Abbott Determine<sup>®</sup> HIV 1/2 and the OraSure OraQuick Rapid HIV-1 Antibody Test<sup>®</sup>. Determine<sup>®</sup> is highly sensitive and specific, detecting antibodies to HIV-1 and HIV-2 in both whole blood and serum. Results are

available in as little as 20 minutes. OraQuick® was used in the MIRIAD and P1031 studies. This test is a qualitative, lateral-flow, immunochromatographic assay that detects antibodies to HIV-1 and HIV-2 in human oral fluid and whole blood. Results are available in 20 minutes. Both tests offer simple test design and easily interpretable, fast results, requisite for timely initiation of intrapartum ARV prophylaxis.

Oral fluid rapid tests would offer a simpler, non-invasive and clearly demonstrable approach to HIV testing if found to be equivalent to blood-based rapid tests in terms of sensitivity and specificity. In addition, oral fluid rapid tests are particularly well-suited for confidential testing in a labour or postpartum ward. A comparison of OraQuick® on whole blood versus oral fluid was made as part of the CDC MIRIAD study. To date, direct comparisons of Determine® against OraQuick® on oral fluid secretions and OraQuick® on whole blood have not been completed.

In an effort to identify the best practice option for peripartum testing, women will be tested concurrently with three rapid tests and real time ELISA. Only Determine® and OraQuick® on whole blood will be used to determine clinical management. Comparative OraQuick® on oral fluid will be analyzed in concert with whole blood specimens but will be blinded for the purposes of clinical management. Conventional ELISA/Western blot will serve as the standard reference for the evaluation of rapid test performance.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary

- 2.11 To evaluate the feasibility, rate of acceptance, and acceptability of voluntary HIV counseling and rapid testing among pregnant women with undocumented HIV serostatus who present for delivery, and to compare intrapartum versus postpartum rapid testing with respect to these measures.
- 2.12 To examine the rate of acceptance of and ability to administer antiretroviral prophylaxis prior to delivery to women who are identified as HIV seropositive through intrapartum rapid HIV testing and to their infants.
- 2.13 To examine the rate of acceptance of and ability to administer antiretroviral prophylaxis to infants born to women who are identified as HIV seropositive through postpartum rapid HIV testing.

### 2.2 Secondary

- 2.21 To estimate the HIV seroprevalence among women with undocumented HIV serostatus who are tested during the peripartum period.

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- 2.22 **To describe the performance of rapid HIV serologic tests on blood and saliva in the perinatal setting.**
- 2.23 To assess adherence to infant follow-up and to the feeding method selected by the mother at discharge.
- 2.24 **To describe the rate of peripartum/early postpartum mother-to-child transmission among women identified as HIV seropositive through intrapartum or postpartum rapid HIV testing.**
- 2.25 To assess acceptance of HIV counseling and testing among clinical personnel at primary, secondary, and tertiary care facilities.
- 2.26 To contribute repository specimens for specified CDC MIRIAD biomedical studies, as outlined in Appendix VII.

### 3.0 STUDY DESIGN

This is a prospective, cluster-randomized study designed to evaluate (1) the feasibility, acceptance, and acceptability of intrapartum versus postpartum HIV counseling and rapid testing and (2) the acceptance of and ability to administer maternal and/or neonatal antiretroviral prophylaxis to those women identified as HIV seropositive through peripartum rapid HIV testing and/or their infants. The feasibility and acceptance of HIV counseling and rapid testing will be evaluated among a sufficient number of women to identify at least 60 HIV seropositive women. **The study will be closed to enrollment when 60 HIV seropositive women have been identified or on August 31, 2006, whichever occurs first.**

The basic unit of randomization is the calendar week rather than the individual subject. Only one of the two strategies (intrapartum HIV counseling and rapid testing or postpartum HIV counseling and rapid testing) will be open to enrollment each week. Women meeting the eligibility criteria who present for delivery in a given week (defined as the beginning of the Monday day shift through the end of the Sunday night shift) will be offered the strategy designated for that week. Women who present for care during intrapartum counseling/testing weeks will be approached during the day or night shift. Women who present for care during postpartum counseling/testing weeks during night shifts will be approached on the next day shift after delivery.

Research counselors will provide pretest counseling as specified by the Department of Health, South Africa. Women may refuse testing at any time during counseling. The study staff will perform rapid testing procedures as outlined in Section 5.1 and Appendix II.

Women who receive intrapartum counseling/testing and have at least one positive rapid test result (performed on blood) will receive ARV prophylaxis immediately. Their infants will receive ARV prophylaxis within 72 hours of birth and prior to discharge, unless the mother

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has initially discordant rapid test results that are both negative on repeat testing. Infants born to women who receive postpartum counseling/testing and have at least one positive rapid test result will receive ARV prophylaxis as soon as possible after the positive result becomes available, unless the mother has initially discordant rapid test results that are both negative on repeat testing. (Refer to Sections 6.21 and 6.22.) All women will receive posttest counseling prior to discharge from the delivery facility.

Women with at least one positive rapid test result will be followed until 6-10 weeks postpartum. A subset of women will be **interviewed** at **6-10 and 24** weeks postpartum as part of the qualitative assessment (see **Qualitative Assessment section** below). HIV-exposed infants will be followed until at least 8-12 weeks of age.

Refer to Appendix IA and IB for specific maternal and neonatal requirements.

#### Cord Blood Serosurveillance

Fetal cord blood specimens will be collected in an anonymous, unlinked fashion from all women approached for study participation, regardless of whether or not women consent to study participation. This method of anonymous sampling will be similar to the national annual antenatal HIV seroprevalence survey, which is accomplished by obtaining an additional blood specimen, without consent, at the time blood is obtained for syphilis serology and blood grouping from women that book for antenatal care. For the purposes of this study, cord blood sampling will also allow an assessment of potential HIV seroprevalence differences in women who decline versus accept study participation. No method of patient identification will be included on the cord blood specimens; only the site name/number, date and time of collection, and the study arm will be indicated.

#### Qualitative Assessment

The qualitative assessment is designed to assess perceptions and opinions of peripartum HIV counseling/testing and treatment intervention. **At the two study sites combined, approximately 36** women with concordant positive rapid test results and **36** women with concordant negative rapid test results (matched by age) will be asked to complete the qualitative assessment at Entry. Eighteen women will be from the intrapartum counseling/testing group and 18 women will be from the postpartum counseling/testing group. Those women with concordant positive rapid test results who are interviewed at Entry will be interviewed again **at Week 6-10 and Week 24**. All women with initially discordant rapid test results will be asked to complete the qualitative assessment at Entry. Women whose repeat test results are both positive will be interviewed again at **Week 6-10 and Week 24**.



#### 4.0 SELECTION AND ENROLLMENT OF SUBJECTS

##### 4.1 Inclusion Criteria

###### 4.11 Women

- 4.111  $\geq 14$  years of age, or lowest age of consent (if  $>14$  years of age) allowed by site Ethics Committee.
- 4.112 Undocumented HIV serostatus, defined as no documentation of HIV serostatus in the woman's antenatal record for the current pregnancy, and no previous documentation of a positive HIV test result.
- 4.113  $\geq 28$  weeks gestation, based on best clinical estimate at presentation.
- 4.114 Anticipation or promotion of delivery, defined as active labour based on clinical estimate, premature rupture of membranes with anticipation of delivery, **planned medical induction of delivery, planned Cesarean delivery, or obstetrical conditions which warrant the decision to plan delivery.**

###### 4.12 Infants

- 4.121 Maternal study participation.
- 4.122 At least one positive maternal HIV rapid test result on a blood specimen.

##### 4.2 Maternal Exclusion Criteria

- 4.21 Documentation of previous or current maternal ART for treatment of HIV infection or prevention of perinatal HIV transmission.
- 4.22 Progression to the second stage of labour, or clinical indication for immediate delivery.
- 4.23 Obstetrical emergencies in which the woman is medically unstable or that require emergency delivery (i.e. placental abruption, eclamptic seizures, placenta previa with hemorrhage, etc.) as determined by the treating clinician.
- 4.24 Diagnosis of fetal death, or fetal condition incompatible with life during the current pregnancy.

##### 4.3 Allowed Medications

Any.

#### 4.4 Disallowed Medications

None.

#### 4.5 Enrollment Procedures

The research counselor will determine eligibility based on the woman's hospital folder/antenatal record. Eligible women will be offered enrollment into one of the two study arms (intrapartum HIV counseling/testing or postpartum HIV counseling/testing) depending on the randomization assignment for the given week. Women who present for care during a week designated for postpartum counseling/testing but who have not yet delivered when the transition to intrapartum counseling/testing occurs will still be offered postpartum counseling/testing. Women may be enrolled for subsequent pregnancies as long as they still meet eligibility criteria and re-consent to study participation. Sites should contact the Data Management Center at the time of re-enrollment.

Written informed consent must be obtained before any study-related procedures are performed (with the exception of anonymous cord blood collection). The pregnant women being considered for this study are considered to be a vulnerable population. Therefore, study staff should avoid recruitment approaches that could be perceived as coercive or misleading when discussing P1031A with these women and/or consenting them for P1031A enrollment.

Eligible women who elect to participate in P1031A will be enrolled according to standard procedures through the PACTG Data Management Center (DMC). Enrollment may occur 24 hours per day, 7 days per week. An enrollment log will be maintained on site. Eligibility form data and the counseling/testing strategy offered will be transferred to the DMC within three business days of obtaining informed consent. The number of women who are approached for study participation but decline will be submitted to the DMC regularly.

#### 4.6 Co-enrollment Guidelines

Women enrolled in P1031A and their infants may be co-enrolled in other clinical trials after the infant's HIV infection status has been confirmed. All co-enrollments require the consent of the PACTG P1031A Protocol Co-Chairs.

### 5.0 STUDY INTERVENTION

Refer to Appendix II for schematic diagrams of the testing algorithm for each study group.

## 5.1 Testing Algorithm

OraQuick<sup>®</sup> and Determine<sup>®</sup> will be performed concurrently as point-of-care tests on a single whole blood specimen. ELISA will be performed real time on the same blood specimen at the designated laboratory.

If both rapid test results are positive, the woman will be considered HIV seropositive. If both rapid test results are negative, the woman will be considered HIV seronegative. Discordant rapid test results will be resolved as outlined in Section 5.11.

OraQuick<sup>®</sup> will also be performed on an oral fluid specimen concurrently with whole blood rapid testing procedures. The oral OraQuick<sup>®</sup> result will only be used for comparative purposes, and will not influence clinical management. Clinical management will be based solely on the results of rapid testing performed on the whole blood specimen.

### 5.11 OraQuick<sup>®</sup> / Determine<sup>®</sup> Discordance

In the event of discordance between rapid test results, both tests will be repeated on a second blood specimen after delivery. If both repeat results are positive, the woman will be considered HIV seropositive. If both repeat results are negative, the woman will be considered HIV seronegative. If the discordance persists, a Western blot will be performed. A positive ELISA and Western blot will indicate seropositivity and a negative ELISA and Western blot will indicate seronegativity. An indeterminate Western blot will be evaluated with DNA and RNA PCR to determine ultimate infection status.

### 5.12 Rapid Test/ELISA Discordance

In the event of discordance between concordant rapid test results and the ELISA result, Western blot will be performed. A positive Western blot will indicate seropositivity and a negative Western blot will indicate seronegativity. An indeterminate Western blot will be evaluated with DNA and RNA PCR to determine ultimate infection status.

## 5.2 Drug Regimens, Administration, and Duration

ARV prophylaxis for women identified as HIV seropositive and their infants will not be provided through this study, but will be administered in accordance with the **Western Cape Province** PMTCT protocol. Although NVP is currently utilized, this may change over the course of the study. Any changes in treatment recommendations will be monitored and controlled for in data analyses.

Women who receive intrapartum counseling/testing and have at least one positive rapid test result (performed on whole blood) will receive ARV prophylaxis immediately. Their infants will receive ARV prophylaxis within 72 hours of birth and prior to discharge, unless the mother has initially discordant rapid test results that are both negative on repeat testing. (Refer to Section 6.21.) With regimens incorporating the use of NVP: if maternal prophylaxis is not administered or is administered less than two hours prior to delivery, the infant will receive one dose of NVP as soon as possible following delivery and a second dose prior to discharge (at least four hours after the first dose).

Infants born to women who receive postpartum counseling/testing and have at least one positive rapid test result (performed on whole blood) will receive ARV prophylaxis as soon as possible after the positive result becomes available, and again prior to discharge (unless the mother has initially discordant rapid test results that are both negative on repeat testing). (Refer to Section 6.22.).

### 5.3 Device Supply, Distribution and Accountability

An initial number of OraQuick<sup>®</sup> test kits and controls will be supplied by the CDC. The PACTG will supply all subsequent OraQuick<sup>®</sup> test kits and controls and all Determine<sup>®</sup> test kits and controls.

OraQuick<sup>®</sup> will be available through the UCB Pharma distribution center in Braamfontein, South Africa. Determine<sup>®</sup> will be available through the Abbott Diagnostic Division in Germany.

All OraQuick<sup>®</sup> and Determine<sup>®</sup> study supplies will be shipped to the University of Stellenbosch Tygerberg Hospital central pharmacy. The designated pharmacist at Tygerberg Hospital will be responsible for maintaining an accountability log to track receipt and distribution of both OraQuick<sup>®</sup> and Determine<sup>®</sup> study supplies. Study sites will contact the designated pharmacist to order study supplies. Study sites will also be required to track receipt and use of study supplies. Refer to Appendix IV.

## 6.0 SUBJECT MANAGEMENT

### 6.1 Toxicity Management

Treatment-related adverse experiences must be documented on the appropriate case report forms.

The Division of AIDS (DAIDS) standardized Toxicity Table for Grading Severity of Adult Adverse Experiences (August 1992) will be used in documenting adverse experiences for women. The Supplemental Toxicity Table for Grading Severity of

Cutaneous/Skin Rash/Dermatitis Adverse Experiences (Appendix III) will be used to report skin manifestations, and supercedes descriptions of skin toxicity in the DAIDS Toxicity Table for Grading Severity of Adult Adverse Experiences (August 1992). The Division of AIDS (DAIDS) standardized Toxicity Table for Grading Severity of Pediatric Adverse Experiences (<3 months [November 1993] and/or  $\geq$ 3 months [April 1994]) will be used for grading toxicities for infants.

## 6.2 Management of Maternal/Neonatal Clinical Care

Management of maternal and neonatal clinical care will be based on the results of initial rapid tests performed on whole blood.

Note: In the event of rapid test discordance, management of neonatal clinical care will depend on the resolution of the discordance.

### 6.21 Intrapartum Group

#### 6.211 Positive OraQuick<sup>®</sup>/Positive Determine<sup>®</sup>

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available and prior to delivery, and will receive abbreviated posttest counseling.
- **Entry laboratory evaluations will be obtained as soon as the positive rapid test result is known and prior to administration of ARV prophylaxis.**
- The woman will receive ARV prophylaxis immediately, according to the local standard of care.
- The infant will receive ARV prophylaxis within 72 hours of birth and prior to discharge.
- Comprehensive posttest counseling will be completed after delivery.
- A subset of women will be asked to complete the qualitative interview.
- Follow-up study visits will be scheduled for the mother and infant.
- Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

#### 6.212 Negative OraQuick<sup>®</sup>/Negative Determine<sup>®</sup>

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available and prior to delivery, and will receive abbreviated posttest counseling.

- Comprehensive posttest counseling will be completed after delivery.
- A subset of women will be asked to complete the qualitative interview.
- No further maternal or infant follow-up is required, unless the **ELISA and Western blot** come back positive.
- If the **ELISA and Western blot** come back positive, efforts will be made to notify the woman and to provide infant ARV prophylaxis within 72 hours. At this point, both the woman and infant will be managed as though the woman were HIV seropositive. Ultimate serostatus will be determined by Western blot. Subsequent management will be based on the result of the Western blot.

6.213 Discordant OraQuick<sup>®</sup>/Determine<sup>®</sup>

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available and prior to delivery, and will receive abbreviated posttest counseling.
- **Entry laboratory evaluations will be obtained as soon as the positive rapid test result is known and prior to administration of ARV prophylaxis.**
- The woman will receive ARV prophylaxis immediately, according to the local standard of care.
- Repeat rapid testing will be performed after delivery but prior to comprehensive posttest counseling and prior to initiation of infant ARV prophylaxis, if appropriate.
- All women with discordant rapid test results will be asked to complete the qualitative interview.

If repeat test results are both positive:

- The woman will be considered HIV seropositive.
- The infant will receive ARV prophylaxis within 72 hours of birth and prior to discharge.
- Comprehensive posttest counseling will be completed.
- Follow-up study visits will be scheduled for the mother and infant.
- Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

If repeat test results are both negative:

- The woman will be considered HIV seronegative.
- The infant will not receive ARV prophylaxis.
- Comprehensive posttest counseling will be completed.

- No further maternal or infant follow-up is required.
- If the ELISA **and Western blot** come back positive, efforts will be made to notify the woman and to provide infant ARV prophylaxis within 72 hours. At this point, both the woman and infant will be managed as though the woman were HIV seropositive. Ultimate serostatus will be determined by Western blot. Subsequent management will be based on the result of the Western blot.

If repeat test results confirm initial discordance:

- The discordance and discordance resolution procedures will be explained to the woman within the context of posttest counseling.
- The infant will receive ARV prophylaxis within 72 hours of birth and prior to discharge.
- The woman will return to the delivery facility in 1-2 weeks for the results of the ELISA and Western blot. If the woman is ultimately HIV seropositive, follow-up study visits will be scheduled for the mother and infant. Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

6.22 Postpartum Group

6.221 Positive OraQuick<sup>®</sup>/Positive Determine<sup>®</sup>

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available.
- The infant will receive ARV prophylaxis immediately.
- Comprehensive posttest counseling and laboratory evaluations will be completed.
- A subset of women will be asked to complete the qualitative interview.
- Follow-up study visits will be scheduled for the mother and infant.
- Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

6.222 Negative OraQuick<sup>®</sup>/Negative Determine<sup>®</sup>

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available.
- Comprehensive posttest counseling will be completed.
- A subset of women will be asked to complete the qualitative interview.

- No further maternal or infant follow-up will be required, unless the ELISA **and Western blot** come back positive.
- If the ELISA **and Western blot** come back positive, efforts will be made to notify the woman and to provide infant ARV prophylaxis within 72 hours. At this point, both the woman and infant will be managed as though the woman were HIV seropositive. Ultimate serostatus will be determined by Western blot. Subsequent management will be based on the result of the Western blot.

#### 6.223 Discordant OraQuick®/ Determine®

- Test results will be documented by the study staff. The woman will be informed of her test results as soon as they are available.
- Repeat rapid testing will be performed after delivery but prior to comprehensive posttest counseling and prior to initiation of infant ARV prophylaxis, if appropriate.
- All women with discordant rapid test results will be asked to complete the qualitative interview.

##### If repeat test results are both positive:

- The woman will be considered HIV seropositive.
- The infant will receive ARV prophylaxis immediately.
- Comprehensive posttest counseling and laboratory evaluations will be completed.
- Follow-up study visits will be scheduled for the mother and infant.
- Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

##### If repeat test results are both negative:

- The woman will be considered HIV seronegative.
- The infant will not receive ARV prophylaxis.
- Comprehensive posttest counseling will be completed.
- No further maternal or infant follow-up is required.
- If the ELISA **and Western blot** come back positive, efforts will be made to notify the woman and to provide infant ARV prophylaxis within 72 hours. At this point, both the woman and infant will be managed as though the woman were HIV seropositive. Ultimate serostatus will be determined by Western blot. Subsequent management will be based on the result of the Western blot.



If repeat test results confirm initial discordance:

- The discordance and discordance resolution procedures will be explained to the woman within the context of posttest counseling.
- The infant will receive ARV prophylaxis immediately.
- Laboratory evaluations will be completed.
- The woman will return to the delivery facility in 1-2 weeks for the results of the ELISA and Western blot. If the woman is ultimately HIV seropositive, follow-up study visits will be scheduled for the mother and infant. Referrals for clinical follow-up will be arranged in accordance with the local standard of care.

6.3 Criteria for Study Discontinuation

- The woman refuses further study participation for herself and/or her infant.
- The woman refuses further follow-up evaluations for herself and/or her infant.
- The investigator determines that further participation would be detrimental to the woman's health or well-being, or to her infant's health or well-being.

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

Although ARV prophylaxis is recommended for those women with a positive rapid test result prior to delivery and for all exposed infants, it is not specified by this protocol. Serious Adverse Experiences (SAE) are therefore not required to be submitted to the DAIDS Regulatory Compliance Center (RCC) SAE Office. However, any unanticipated SAE should be reported to the local IRB as appropriate.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

PACTG P1031A is a prospective, cluster-randomized study of peripartum voluntary HIV counseling and rapid testing of pregnant women with undocumented HIV serostatus who present for delivery. The primary objectives of the study are to evaluate **and compare** the feasibility, rate of acceptance, and acceptability of rapid HIV testing **using** intrapartum versus postpartum counseling/testing strategies, **and** to evaluate the acceptance of and ability to administer maternal ARV prophylaxis prior to delivery and post-exposure prophylaxis to the infant **among women identified as HIV seropositive**.

Although the design and objectives of P1031A differ in several important respects from those of the P1031 and CDC MIRIAD studies being conducted in the United States, data collected for the PACTG P1031A study will be kept as similar as possible to the data collected for the P1031 and CDC MIRIAD studies to facilitate future data pooling where appropriate.

**The cluster randomized design has a number of advantages in the setting of perinatal or early post-natal intervention, as discussed in Section 1.21. Like all cluster randomized trials, however, there are challenges that do not arise with trials randomizing individuals. For example, each study arm has its own Informed Consent (IC), introducing at least a theoretical bias caused by different refusal patterns for the two study arms. This does not affect the comparison of acceptance rates between arms, but it would confound any other comparisons between arms. Specifically, the randomization will protect the comparison of acceptance of intrapartum versus postpartum testing from confounding, because these comparisons can be conducted using an intent-to-treat analysis that includes all women randomized. However, comparisons of all other outcome measures between arms, such as feasibility of testing, and acceptance and ability to administer ART prophylaxis, will not be intent-to-treat comparisons, because the outcome measures will be unknown for women who decline testing.**

Several design and analysis measures will be taken to address this limitation:

- **The HIV seroprevalence among all women approached for study participation will be estimated through infant umbilical cord blood serosurveillance, in an anonymous, unlinked fashion but stratified by randomization arm. This will allow an evaluation of any HIV seroprevalence differences that may be operative in the two arms, specifically among decliners (by comparing the overall seroprevalence with the seroprevalence among women who accept testing in each arm).**
- **Historical information will be collected on all enrolled women (such as ethnicity, region of residence, prior sexually-transmitted disease diagnosis/treatment, sexual partner history, history of sex trade work, and medical history) to assist in characterizing differences between women who accept testing in each arm. This information will be used to control for potential confounding, which could lead to spurious associations between randomized arm and outcome measures other than acceptance of testing.**
- **The data analysis will include sensitivity analyses to assess the potential impact of missing data on the conclusions of the study, including the extent to which the unobserved difference in outcome measures among all women in each randomization arm (the intent-to-treat comparison) might differ from the observed difference in outcome measures among the acceptors in each arm (see Section 8.6).**

8.2 Outcome Measures

8.21 Primary Outcome Measures

– Feasibility, rate of acceptance and acceptability of intrapartum versus postpartum voluntary rapid HIV testing

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Feasibility:

- Time required to obtain informed consent
- Time from initiation of HIV pre-test counseling until test results are available
- Proportion of test evaluations completed prior to delivery
- Proportion of test evaluations completed prior to discharge
- Qualitative measures, including available space, study staff allocation and support for counseling and testing

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Rate of acceptance:

- Proportion of women offered testing who accept testing

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Acceptability:

- Qualitative measures, including women’s perceptions and opinions of counseling and testing

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– Acceptance of and ability to administer ARV prophylaxis to women identified as HIV seropositive in labour and their infants

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- Proportion of women identified as HIV seropositive in labour who accept antiretroviral prophylaxis
- Timing of initiation of peripartum ARV prophylaxis, as a proportion of women identified as HIV seropositive in labour (e.g., proportion of women initiated prior to delivery and/or infants initiated within 12 hours of birth) and as a continuous variable (e.g., number of hours drug is received before delivery and/or time to administration of drug to the infant)

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– Acceptance of and ability to administer ARV prophylaxis to infants born to women identified as HIV seropositive postpartum

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- Proportion of women identified as HIV seropositive postpartum who accept antiretrovirals for their infants
- Timing of initiation of postpartum ARV prophylaxis to the infant, as a proportion of infants born to women identified as HIV seropositive postpartum (e.g., proportion initiated within 12 hours of birth) and as a continuous variable (e.g., number of hours of drug received during the first 12 hours of life)

8.22 Secondary Outcome Measures

– HIV seroprevalence

The proportion of women with undocumented HIV serostatus who are tested during the peripartum period and determined to be HIV seropositive

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– Performance of rapid HIV serologic testing as measured by sensitivity and specificity.

Initially, the ELISA (and Western blot, if necessary to resolve discordance among the three blood tests) will be used as the reference standard (a.k.a. “gold standard”) for true HIV status. Other reference standards (e.g., composite gold standard based on other data) may be used as they are developed. Because either of the rapid tests may identify early seroconversion sooner than the ELISA, the RNA PCR may be used to confirm whether apparent false positive rapid test results actually represent early seroconversion.

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– In fant adherence to follow-up and feeding method

- The proportion of infants who complete the Week 6 study visit, and a description of the efforts needed to accomplish this visit
- The proportion of infants being fed according to the method chosen at discharge (exclusive breastfeeding, exclusive formula feeding, or mixed feeding), as reported by the mother at the Week 6 study visit

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– The proportion of HIV-exposed infants who acquire HIV infection during delivery and early postpartum

Deleted: The proportion of doses taken over the preceding 3 days (assessed using the PACTG adherence module) at 2, 4, 6, 14, and 24 weeks of age¶  
<#>Infant plasma ZDV concentrations measured at ages 2, 4, and 6 weeks¶  
The proportion of infant study visits completed.

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Infant HIV status will be classified as follows:

	Week 6-10 DNA PCR Result		
Birth DNA PCR Result	Positive	Negative	Missing
Positive	Infected (in utero)	Indeterminate <sup>2</sup>	Infected (in utero)
Negative	Infected <sup>1</sup> (peripartum)	Uninfected <sup>1</sup>	Unknown status
Missing <sup>3</sup>	Infected (unknown timing)	Uninfected <sup>1</sup>	Unknown status

<sup>1</sup> These infants will be included in the primary analysis (see Section 8.6 for details). Secondary analyses will be conducted to assess whether the results change if the analysis is restricted to infants who have a negative DNA-PCR at birth or if infants infected with unknown timing are included as peripartum infections.

<sup>2</sup> If an infant has a positive DNA PCR at birth and a negative at Week 6-10, then DNA PCR will be repeated on the same Week 6-10 blood specimen, if available. If the repeat result is positive, the infant will be considered infected (in utero). If the repeat result is negative, or if the repeat DNA PCR cannot be performed, the infant will be considered of indeterminate infection status and a repeat DNA PCR will be performed at Week 8-12. If the Week 8-12 result is negative, the infant will be considered uninfected (and included in the primary analysis); if positive, the infant will be considered infected (unknown timing). The stored cell pellet collected at birth can be used for repeat DNA PCR if subsequent tests are negative in order to confirm that the initial DNA PCR was in error.

<sup>3</sup> If the birth DNA PCR is not done or is indeterminate, an attempt will be made to obtain a DNA PCR result within the first week of life, or as soon as possible thereafter (prior to the Week 6-10 visit).

- Qualitative measures of acceptance of HIV counseling and testing among clinical personnel at primary, secondary, and tertiary care facilities
- Refer to individual biomedical studies outlined in Appendix VII

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### 8.3 Randomization and Stratification

A randomized schedule defining which of the two arms/strategies to offer each week will be determined before the study opens to accrual, using the method of permuted blocks. A block size of two will be used to ensure that no more than two consecutive weeks will be assigned to a single arm (to minimize the potential association between seroprevalence and week [the clustering variable], due to seasonal fluctuations [e.g., due to travel during annual holiday time]). The randomization will not be stratified, i.e., the same weekly schedule will be used at all the study sites. However, as described in Section 8.6, certain data analyses will be stratified by site.

## 8.4 Sample Size and Accrual

### 8.41 Sample Size and Power

#### 8.411 Phase I

**The sample size of approximately 400 women tested and 60 HIV seropositive women identified was chosen to provide good power to detect meaningful differences between intrapartum and postpartum groups with respect to the primary outcome measures, while completing the study within the shortest possible timeframe. We hypothesize that the overall rate of acceptance of testing will be approximately 77.5% (70% in the intrapartum group and 85% in the postpartum group) and the seroprevalence will be approximately 15%. The selected variance in acceptance rates for peripartum VCT among women approached during labour versus postpartum are estimates. At present, there are no data available describing the acceptance of intrapartum HIV testing in resource poor settings. There is a perception in the South African medical community that offering VCT to women in labour is unethical. Women in labour are felt to be under duress, and unable to appreciate the significance of undergoing HIV testing (similar to the prohibition of counseling women for sterilization procedures during labour). As a result, women presenting to a delivery facility with unknown HIV status are not, as a matter of protocol, offered VCT.**

Varying degrees of acceptance of postpartum VCT have been documented among women without a prior antenatal HIV test result in high seroprevalence settings. In a study of Kenyan women, Inwani demonstrated that 87% of women agreed to rapid HIV testing of infant cord blood when approached after delivery [13]. Only half of the women identified as HIV seropositive agreed to infant ARV prophylaxis. In contrast, 62.5% of women in a postexposure prophylaxis trial in Soweto accepted rapid HIV testing; 25.6% were identified as HIV seropositive [14]. Thus the variance in acceptance rates are accepted as best estimates which relate to the environmental differences in the intrapartum versus postpartum settings that may influence a woman's perception of autonomy and privacy.

**From August through November 2005, after accrual restrictions at both Macassar and Hottentots Holland had been lifted, 107 eligible women were offered enrollment in P1031A;**

74 (70%) women agreed to enroll, of whom 12 (16%) were identified as HIV seropositive. If these rates of acceptance of enrollment and identification of seropositive women continue, approximately 530 women will have to be offered enrollment and rapid testing, and approximately 400 women tested in order to achieve a sample size of 60 HIV seropositive women identified. Table 1 shows that with at least 400 women tested, the study will have 80% power to detect differences of 7-14% between the randomized groups with respect to acceptance of rapid testing. Table 2 indicates that with a total of 60 HIV seropositive women identified, the study will have 80% power to detect differences of 29-36% between the randomized groups with respect to acceptance of and ability to administer ARV prophylaxis.

**Table 1: Differences in acceptance of testing that could be detected with 80% power (two-sided alpha=0.05) according to the total number of women offered testing in both groups combined**

<b>Difference in acceptance of testing in the intrapartum vs. postpartum group detectable with 80% power</b>		
<b>Total N=200* women offered HIV testing</b>	<b>Total N=400* women offered HIV testing</b>	<b>Total N=600* women offered HIV testing</b>
<b>50% vs. 70%</b>	<b>50% vs. 64%</b>	<b>50% vs. 62%</b>
<b>60% vs. 79%</b>	<b>60% vs. 74%</b>	<b>60% vs. 71%</b>
<b>70% vs. 87%</b>	<b>70% vs. 82%</b>	<b>70% vs. 80%</b>
<b>80% vs. 94%</b>	<b>80% vs. 90%</b>	<b>80% vs. 89%</b>
<b>90% vs. 99%</b>	<b>90% vs. 97%</b>	<b>90% vs. 96%</b>

\*Assuming equal sample sizes in the two groups

**Table 2: Differences in acceptance of and ability to administer ARV prophylaxis that could be detected with 80% power (two-sided alpha=0.05) according to the total number of HIV positive women identified in both groups combined**

<b>Difference in acceptance of and ability to administer ARV prophylaxis in the intrapartum vs. postpartum group detectable with 80%* power</b>		
<b>Total N=30** HIV+ women identified</b>	<b>Total N=60** HIV+ women identified</b>	<b>Total N=90** HIV+ women identified</b>
50% vs. 98%	50% vs. 86%	50% vs. 80%
(67% power: 60% vs. 100%)	60% vs. 93%	60% vs. 87%
(46% power: 70% vs. 100%)	70% vs. 99%	70% vs. 94%
(23% power: 80% vs. 100%)	(58% power: 80% vs. 100%)	80% vs. 99.6%

\*Power=80% except as noted

\*\* These calculations are for equal sample sizes in the two groups, but the numbers are virtually identical if the sample size in the postpartum group is larger by 20% (as would be expected if test acceptance rates are higher in the postpartum group than in the intrapartum group).

#### 8.42 Accrual

From August through November 2005, after accrual restrictions at both Macassar and Hottentots Holland had been lifted, an average of 27 eligible women per month were approached for enrollment at both sites combined, of whom an average of 19 women per month (70%) agreed to enroll. During this time period, the observed seroprevalence among all women enrolled was 16% and an average of 3 HIV seropositive women were identified per month. As of the end of November 2005, a total of 24 HIV seropositive women had been identified in P1031A since the start of enrollment. It is anticipated that the broader inclusion criteria under Version 3.0 of the protocol, which allow enrollment of women scheduled for induction of labor and elective Cesarean section, will increase the numbers of eligible women approached for enrollment, enrolled, and identified as HIV seropositive to approximately 35, 25, and 4 per month, respectively. Under these assumptions, we project that the additional 36 HIV seropositive women needed to reach the target of 60 total can be identified by August 31, 2006.



Although PMTCT is already in place at Macassar Community Health Center and Hottentots Holland Hospital, a review of public health trends and facility demographics at these two sites confirms that (1) the overall HIV seroprevalence of the background population is not likely to decline significantly over the accrual period and (2) the proportion of women who do not receive antenatal care or HIV testing during pregnancy is anticipated to remain stable at approximately 15%.

## 8.5 Monitoring

### 8.51 Routine Monitoring

**A protocol monitoring plan will be developed to detail the contents and frequency of monitoring reports that will be distributed to the protocol team. Regular team teleconference calls will be held to review these reports. All monitoring reports sent to the protocol team** will present results that are pooled across the two randomized groups and not broken out according to group. Accrual will be reviewed monthly by the protocol team and by the network oversight committee. **If accrual falls substantially below the targets listed in Section 8.42 once enrollment to protocol Version 3.0 has begun, (e.g., if fewer than 15 women per month are enrolled in 3 consecutive months after enrollment to protocol Version 3.0 has begun), the feasibility of completing the study will be reconsidered.** The performance of the rapid testing algorithm, adverse experiences (including false positives and false negatives), and discrepancies between rapid test results will also be reviewed monthly by the protocol team. If any unexpected issues arise in individual site or overall performance of the rapid test, the protocol team will take appropriate action (e.g., modify procedures, conduct additional training). The number of women tested at each site will be monitored quarterly to ensure that continued participation and expenditure of resources is justified. However, lower than expected site seroprevalence will not be a reason for site discontinuation, since low seroprevalence sites will still provide important information for several of the primary and secondary objectives. A summary of maternal and infant toxicities will be produced quarterly. Data and specimen completeness will also be assessed regularly.

### 8.52 Interim Analysis

**The study will also be monitored by** an independent, study-specific Study Monitoring Committee (SMC). The members of the SMC must have no financial interest in the outcome of the study, and must be free of perceived conflict of interest (e.g., must not be enrolling or treating patients in P1031A, or directly supervising those enrolling or treating patients). They must agree

to adhere to a code of conduct that prohibits disclosure. Members of the SMC will include the study statisticians and medical officers, one representative **each** from the Perinatal Research Agenda Committee (RAC), the International Steering Committee, **and the network oversight committee**, and one or two South African investigators. Meetings of the SMC will be held by teleconference. All SMC reports will be forwarded to DAIDS.

**There will be one formal interim review of the study by the SMC, approximately two to three months after enrollment to protocol Version 3.0 begins (i.e., approximately in May 2006). This will be an administrative and safety review of all the parameters listed in Section 8.5.1, including accrual, data and specimen completeness, and adverse experiences. The SMC will assess whether any modifications to the study are needed, e.g. if assumptions used to design the study are no longer valid, and will make a recommendation for study continuation or modification to the Perinatal RAC, network oversight committee, and PACTG Executive Committee (PEC).**

## 8.6 Analysis

A detailed analysis plan will be prepared prior to each analysis. Unless otherwise noted, analyses will follow the intent-to-treat principle. In particular, women who present in labor during an intrapartum testing week but who are not tested until after delivery will be included in the intrapartum group. Although re-enrollment for a subsequent pregnancy is permitted for logistical reasons, only the data from the first study pregnancy will be included in the data analyses. The outcome measures during a subsequent pregnancy would likely be influenced by the previous study participation and therefore not be comparable to the outcome measures during an initial pregnancy. Also, since re-enrollment is expected to be a rare event, there will likely be insufficient data from subsequent pregnancies to warrant analyzing them separately.

As noted in Section 8.1, a limitation of the cluster-randomized design is the possibility of different refusal patterns in the two randomized arms, which could confound the comparisons of outcome measures between arms (other than test acceptance rates). Sensitivity analyses will be conducted to evaluate the potential impact of missing data on the conclusions of the study, including the extent to which the unobserved differences in outcome measures among all women in each randomization arm (the full intent-to-treat comparison) might differ from the observed difference in outcome measures among the acceptors in each arm. This will be done in two ways: (a) as an extreme, by imputing a missing outcome measure in a way that would minimize the difference between treatment groups, and (b) more plausibly, by imputing a missing outcome

**measure according to the probability distribution of that outcome measure among participants with data available who were randomized to the same arm. For outcome measures with sufficient numbers of events, logistic regression models will be used to control for potential confounding due to differences in characteristics of women who accepted testing in the two randomized arms.**

#### 8.61 Primary Analyses

Analyses of the feasibility and acceptance of rapid testing (primary objective 2.11) and the ability to administer ART (primary objectives 2.12 and 2.13) will be conducted based on combined data from **both** delivery facilities and separately for each delivery facility (**since Macassar Community Health Centre is a community-based primary care facility and Hottentots Holland Hospital is a district hospital**). It is estimated that approximately 25% of women who present in labour at Macassar may be transferred to Hottentots Holland prior to delivery. Analyses will be done two ways, using the delivery facility where the woman first presented and the delivery facility at which rapid testing was actually performed. Proportions (for dichotomous outcomes such as acceptance of testing or ARV prophylaxis) and means (for continuous outcomes such as time required for consent) will be estimated along with 95% confidence intervals, and compared using the chi-square test and t-test. Exact binomial methods will be used if event rates are too low or too high for the normal approximation to be valid.

#### 8.62 Secondary Analyses

For dichotomous outcomes including HIV seroprevalence and infant adherence, proportions will be estimated with 95% confidence intervals, and compared using the chi-square test or exact methods if appropriate.

Analyses of rapid test performance will be based on combined data from both delivery facilities and from both randomized groups. Sensitivity and specificity will be estimated for each rapid test with 95% confidence intervals, and compared between rapid tests using McNemar's test for paired proportions and interval estimation of the paired differences. Exact binomial methods will be used if event rates are too low or too high for the normal approximation to be valid. In cases where the rapid tests were repeated due to discordance, the primary analysis will use the initial rapid test result. Although the primary analysis of the performance of each rapid testing algorithm will estimate its sensitivity and specificity using the ELISA/Western blot combination as the gold standard for true HIV status, a secondary analysis will consider both the rapid testing algorithm and ELISA/Western Blot to be screening tests with no true gold standard. This secondary analysis will assess the equivalence of the rapid testing algorithm

and the ELISA/Western Blot by calculating a confidence interval for the ratio of the percentage positive by the rapid testing algorithm and the ELISA/Western blot [15].

## 9.0 HUMAN SUBJECTS

The Division of AIDS has concluded that this protocol does not meet Federal requirements governing prisoner participation in clinical trials and should not be considered by local IRBs for the recruitment of prisoners.

### 9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents (Appendices IX and X), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The mother must give written informed consent for her and her infant's participation in the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the mother.

### 9.2 Subject Confidentiality

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

### 9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID.

## 10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this study will be governed by PACTG policies.

## 11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and

handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) for specific instructions.

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APPENDIX IA  
MATERNAL SCHEDULE OF EVALUATIONS

EVENT	STUDY VISIT*			Lab
	Entry <sup>8</sup>	Week 6-10 <sup>9,10</sup>	Week 24 <sup>12</sup> (+/-2 weeks)	
<b>CLINICAL EVALUATIONS</b>				
Informed Consent <sup>1</sup>	X			
History <sup>2</sup>	X <sup>11</sup>	X		
Physical examination <sup>3</sup>	X <sup>11</sup>			
Qualitative assessment	X <sup>11,12</sup>	X <sup>14</sup>	X <sup>14</sup>	
<b>HIV TESTING</b>				
OraQuick <sup>®</sup> HIV 1/2 (blood)	X <sup>13</sup>			Site
OraQuick <sup>®</sup> HIV 1/2 (oral fluid)	X			Site
Determine <sup>®</sup>	X <sup>13</sup>			Site
ELISA/Western blot <sup>4</sup>	5 ml			Pathcare
<b>LABORATORY EVALUATIONS</b>				
Cord blood <sup>5</sup>	X			Pathcare
Hematology <sup>6</sup>	5 ml <sup>10,11</sup>			Pathcare
CD4/CD8 T cell counts <sup>6</sup>				Pathcare
HIV-1 RNA PCR <sup>7</sup>	5 ml <sup>10,11</sup>			Pathcare
Stored plasma/cell pellet <sup>7</sup>				Pathcare
<b>TOTAL BLOOD VOLUME</b>	15 ml			

\*If a woman who has discordant results (either rapid test or rapid test/ELISA) is determined to be HIV seronegative through repeat rapid testing/standard testing, no further maternal or infant follow-up is required.



## APPENDIX IA

1. Signed informed consent required for maternal study enrollment. Refer to Appendices IX and X.
2. History will include signs/symptoms and diagnoses.
3. Physical examination will include blood pressure, temperature, weight, and height.
4. Specimen will be shared for serum storage for CDC MIRIAD Study #2. Refer to Appendix VII.
5. Collect cord blood in a 10 ml EDTA tube. Specimen must be labeled with site name/number, date and time of collection, and group (intrapartum or postpartum). Do not include any subject identifiers. Specimen will be used for dried blood spot preparation at Pathcare. Refer to Appendix V.
6. Draw one 5 ml EDTA tube for hematology and CD4/CD8 T cell counts. Hematology will include CBC and platelet count.
7. Draw one 5 ml EDTA tube for RNA PCR and stored plasma/cell pellet. Plasma and cell pellet storage for CDC MIRIAD Study #5. Refer to Appendix VII.
8. May be intrapartum or postpartum, depending on randomization assignment.
9. Visit should coincide with infant visit at 6-10 weeks of age.
10. Only for women with at least one positive rapid test result.
11. **For women randomized to the intrapartum group, specimens for laboratory evaluations will be obtained as soon as the positive rapid test result is known and prior to administration of ARV prophylaxis. For women randomized to the postpartum group, these evaluations will be completed after delivery.**
12. For selected women only. Refer to Section 3.0.
13. Specimens obtained by fingerstick. Additional blood may be required for repeat testing in the event of discordant rapid test results. Refer to Section 6.2 and Appendix II.
14. Only for women who completed the qualitative assessment at Entry, and had either (a) concordant positive rapid test results or (b) discordant test results (either rapid test or rapid test/ELISA) that resolved to positive.

APPENDIX IB  
INFANT SCHEDULE OF EVALUATIONS

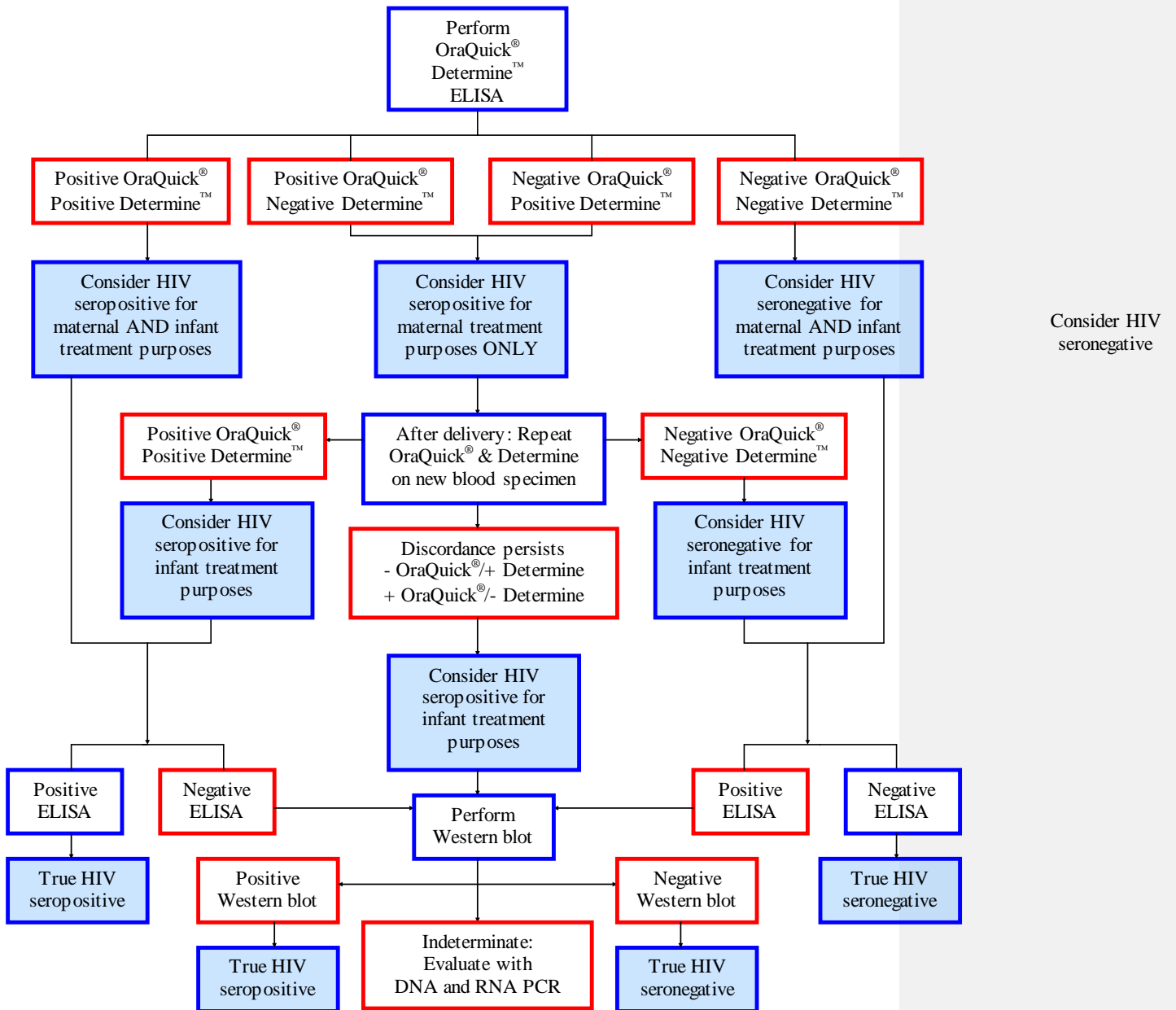
EVENT	STUDY VISIT				Lab
	ONLY INFANTS BORN TO WOMEN WITH AT LEAST ONE POSITIVE RAPID TEST RESULT*				
	Birth - 48 hours	Week 6-10 <sup>4</sup>	Week 8-12 <sup>5</sup>	Week 10-14 <sup>6</sup>	
<b>CLINICAL EVALUATIONS</b>					
Informed Consent <sup>1</sup>	X				
History <sup>2</sup>	X	X	X	X	
Physical examination <sup>3</sup>	X				
Gestational age & birth weight	X				
<b>LABORATORY EVALUATIONS</b>					
HIV DNA PCR	1 ml <sup>7,8</sup>	1 ml <sup>9</sup>	1 ml <sup>9,10</sup>		Pathcare
Stored plasma/cell pellet					Pathcare
<b>TOTAL BLOOD VOLUME</b>	<b>1 ml</b>	<b>1 ml</b>	<b>1 ml</b>		

\*If a woman with discordant results (either rapid test or rapid test/ELISA) is determined to be HIV seronegative through repeat rapid testing/standard testing, no further infant follow-up is required.

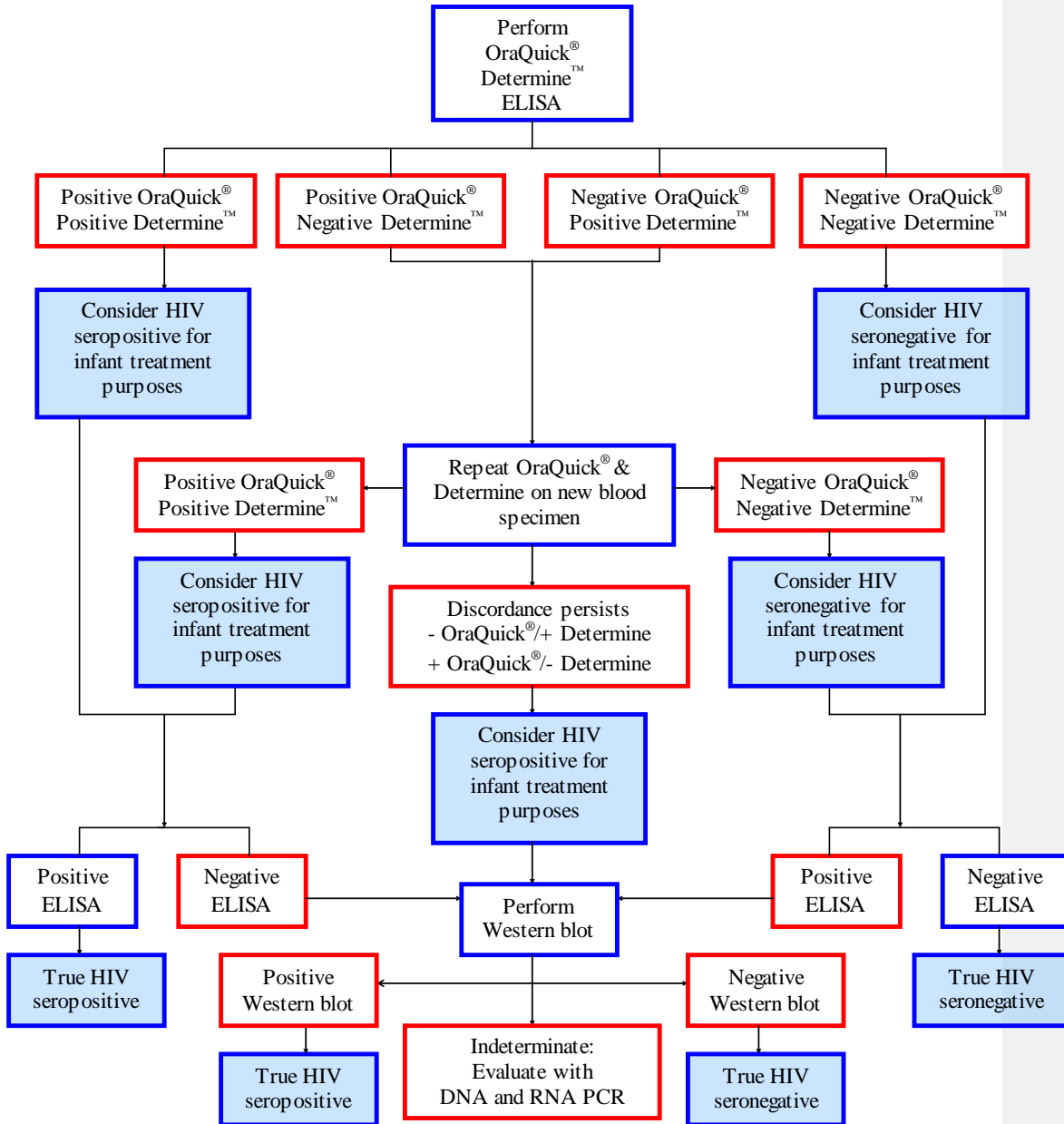
APPENDIX IB

1. Signed informed consent required for infant enrollment. Refer to Appendices IX and X.
2. History will include signs/symptoms and diagnoses.
3. Physical examination will include vital signs, weight, length, and head circumference.
4. Visit should coincide with maternal visit at 6-10 weeks postpartum.
5. Visit should occur approximately 2 weeks after the Week 6-10 visit.
6. Only for infants who had repeat DNA PCR at Week 8-12. Visit should occur approximately 2 weeks after the Week 8-12 visit.
7. Collect 1 ml **whole blood** by heelstick **or venipuncture**. Specimen will be **shared** for **(a)** dried blood spot preparation **for DNA PCR** at Pathcare (refer to Appendix V) **and (b)** plasma and cell pellet storage for CDC MIRIAD Study #5 (refer to Appendix VII).
8. If the DNA PCR is not done or is indeterminate, attempt to repeat DNA PCR within the first week of life or as soon as possible thereafter (prior to the Week 6-10 visit).
9. Collect 1 ml **whole blood** by heelstick **or venipuncture**. Specimen will be **used** for dried blood spot preparation **for DNA PCR** at Pathcare (refer to Appendix V).
10. Only if the Week 6-10 DNA PCR is positive or missed, OR the birth DNA PCR is positive and the Week 6-10 DNA PCR is negative.

APPENDIX IIA  
 HIV TESTING ALGORITHM  
 INTRAPARTUM GROUP



APPENDIX IIB  
 HIV TESTING ALGORITHM  
 POSTPARTUM GROUP



Consider HIV seronegative

APPENDIX III  
SUPPLEMENTAL TOXICITY TABLE FOR GRADING SEVERITY OF ADULT AND PEDIATRIC  
CUTANEOUS/SKIN RASH/DERMATITIS ADVERSE EXPERIENCES

GRADE 1	GRADE 2	GRADE 3	GRADE 4
CUTANEOUS/SKIN RASH/DERMATITIS			
Erythema, with or without pruritis	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritis (without the presence of any additional constitutional findings as described in Grade 3 of DAIDS Toxicity tables); OR typical target lesions without blistering, vesicles, or ulcerations in the lesions.</p> <p>B. Urticaria</p>	<p>A. Diffuse erythematous macular or maculopapular cutaneous eruption or moist desquamation with or without pruritis together with any of the following constitutional findings considered related to study drug:</p> <ol style="list-style-type: none"> <li>1. 5 x ULN AST, ALT or 2 x baseline if baseline &gt; ULN.</li> <li>2. fever, &gt;39°C</li> <li>3. blistering and/or vesiculation of cutaneous eruptions</li> <li>4. any site of mucosal lesions; OR</li> </ol> <p>B. angioedema; OR</p> <p>C. exfoliative dermatitis defined as severe widespread erythema and dry scaling of the skin, with generalized superficial lymphadenopathy, and with other constitutional findings such as fever, weight loss, hypoproteinemia possibly related to study drug; OR</p> <p>D. diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, edema, myalgia, and/or arthralgia; OR</p> <p>E. diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus one of the following:</p> <ol style="list-style-type: none"> <li>1. cutaneous bullae, sometimes confluent with widespread sheet-like detachment of skin (&lt;10% body surface area), (Nikolski's sign)(Stevens Johnson Syndrome, SJS)</li> <li>2. two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause.</li> </ol>	<p>Diffuse cutaneous eruptions, usually starting on the face, trunk or back, often with prodromal symptoms plus cutaneous bullae with widespread sheet-like detachment of skin (&gt;10% of body surface area), (Nikolski's sign), (SJS/Toxic Epidermal Necrolysis (TEN) overlap syndrome; TEN)</p>







APPENDIX V  
 VIROLOGY AND STORED SPECIMENS PROCESSING AND SHIPMENT INSTRUCTIONS

PLASMA FOR QUANTITATIVE HIV-1 RNA PCR; PLASMA FOR STORAGE; PBMC CELL PELLETS FOR HIV DNA PCR; DRIED BLOOD SPOT PREPARATION (MATERNAL AND INFANT)			
ASSAY REQUIREMENT	SPECIMEN COLLECTION	COLLECTION CONTAINER	IMMEDIATE SPECIMEN HANDLING
Plasma  PBMC (dry cell pellets)	<i>Blood collected by:</i>  Venipuncture: 5 ml (women) <b>1 ml</b> (infants)	Tripotassium EDTA Vacutainer® tube (purple-top tube) Tube sizes as indicated	<ul style="list-style-type: none"> <li>• Gently invert tubes several times to mix. Do not shake.</li> <li>• Specimens should be labeled with patient ID#, study ID#, site ID#, visit ID#, date of collection, specimen type, and anticoagulant.</li> </ul> <p><u>Exception for cord blood specimens:</u> Only label with site name/number, <b>month and year</b> of collection, and group (intrapartum or postpartum). Pathcare will assign specimen ID numbers <b>and prepare dried blood spots.</b></p> <ul style="list-style-type: none"> <li>• Specimen should be kept at room temperature (18°-24°C) and processed within 30 hours of collection (preferably within 4-6 hours).</li> </ul>
Cord Blood	<b>5 ml</b>		
Infant DNA PCR	Heelstick or <b>venipuncture:</b> <b>1 ml</b> <b>(at birth, shared from 1 ml for plasma/cell storage, above)</b>		

APPENDIX V

WHOLE BLOOD SPECIMEN PROCESSING:

1. Centrifuge blood at 800 x g for 10 minutes at 18°-24°C.
2. Transfer plasma to a centrifuge tube; recentrifuge at 800 x g for 10 minutes to completely remove platelets and cell debris.
3. If plasma is not to be tested within 30 minutes of separation, aliquot plasma into sterile, labeled cryovials (label with same information as blood tubes) and store at -70°C or below.
4. PBMC are separated from red blood cells and neutrophils by density centrifugation on Ficoll-Hypaque and frozen in standard aliquots.

ALIQUOTS:

1. Women: 0.6 ml of plasma (at least 4 aliquots); 1 million PBMC/vial in dry pellets (2 aliquots)
2. Infants: 0.25 ml of plasma (save all plasma available); 1 million PBMC/vial in dry cell pellets (2 aliquots)

DRIED BLOOD SPOT PROCESSING:

1. Dried blood spots (DBS) should be prepared first before shared samples are processed further.
2. All DBS preparations are to be made using S&S 903 cards.(Schleicher and Schuell, Keene NH, USA Cat.# 28170-016, grade 903 with 5 half inch circles).
3. Add 50 microliters of blood to each circle (prepare at least 3 circles).
4. Allow blood spots to dry at room temperature for at least 2 hours.
5. Label the filter paper card with an LDMS generated label.
6. Place dried, labeled card into LDMS labeled resealable bag (Zip-lock type) with Fisherbrand (Cat #07-580-1, Fisher Scientific) sponge dessicant. The blood spot containing filter paper card should be placed between 2 plain pieces of filterpaper to avoid artifactual contamination of the DBS preps.
7. Store DBS preparations at room temperature (climate controlled room) until shipping to the PACTG specimen repository at Biomedical Research Institute (BRI).

SPECIMEN SHIPPING:

Plasma and PBMC pellets **and DBS preparations** will be batched and shipped monthly to BRI. Refer to remainder of Appendix V for shipping instructions.

## APPENDIX V

### GENERAL INSTRUCTIONS FOR VIROLOGY SPECIMEN PROCESSING AND SHIPMENT

All specimens should be packaged according to the PACTG Virology Manual with strict attention to Federal and carrier specific regulation for the shipment of hazardous biological material. Include sufficient dry ice to keep the specimens frozen.

For shipments greater than 15 vials, the samples should be placed in the Nalgene cryovial box in the order of the shipping manifest (if an LDMS program is available). If less than 15 vials are to be sent they can be placed in plastic baggies inside the orange topped shipping canister. The orange topped container is placed in the cardboard box, which is placed inside the polystyrene insulated box and the box filled with sufficient solid carbon dioxide (dry ice) to last 48 hours. Likewise the Nalgene cryovial box should be wrapped in absorbent material and placed inside a heavy duty plastic bag, sealed and placed in the polystyrene insulated box filled as above with dry ice. The outer box is sealed with packing tape and marked with the appropriate stickers, which will be provided.

A PACTG Virology shipment notice, a shipping diskette and shipping manifest should accompany the shipment. Please fax the ACTG Shipping Notice prior to sending the shipment. The samples and appropriate paperwork should be sent to appropriate person as instructed.

Shipments may be made Monday through Thursday only by overnight courier service using the before 10:30 am option. **DO NOT SHIP SAMPLES WHEN THEY WOULD BE RECEIVED ON A HOLIDAY. HOLIDAYS INCLUDE:** New Year's Day, M.L. King's Birthday, Good Friday, Memorial Day, July 4, Labor Day, Thanksgiving and the day after Thanksgiving, and several days around Christmas. Prior to shipment, please fax the ACTG Virology Shipping Notice to appropriate person (a copy should also be included with all shipments in addition to the other paperwork). This is a Federal regulation. At the time of shipment, please contact the laboratory by phone to advise that a shipment has been sent and provide the airway bill number. Any questions relating to specimen handling shipment or identification should be directed to the appropriate person.

APPENDIX V

INSTRUCTIONS FOR SHIIPMENT OF REPOSITORY SPECIMENS

REPOSITORY FACILITY

Biomedical Research Institute (BRI)  
c/o John C. Ward, Jr.  
12264 Wilkins Avenue, Bay F  
Rockville, MD 20852  
Phone: 301-881-7636  
Fax: 301-770-9811  
E-mail: [BRIRepository@AOL.com](mailto:BRIRepository@AOL.com)  
LDMS code: 999

SPECIFICATIONS/INSTRUCTIONS

*Please refer to the Repository Guidelines on the PACTG Web Page for more detailed instructions and to determine which specimens are eligible to be stored at the Repository. Send only those protocol specimens approved by the PACTG Leadership to be stored at the Repository.*

1. Per the Repository Guidelines, Section 2.0, sites should send specimens to the PACTG Specimen Repository at BRI ("Specimen Repository") once a month following the schedule below. Shipments to the Specimen Repository should be limited to Monday through Wednesday of your designated week. Shipments should be sent via overnight courier. Do not ship the day before a holiday. The Specimen Repository is closed on weekends and holidays and will be unable to receive the specimens. Please call the Specimen Repository around a holiday to determine the available days for shipping.

	<i>Week 1*</i>	<i>Week 2</i>	<i>Week 3</i>	<i>Week 4</i>
<i>Site Numbers</i>	<i>2802-4401</i>	<i>4501-5043</i>	<i>5044-6505</i>	<i>6601-8101</i>
<i>* Week 1 = First week that includes a Monday</i>				

If a site is unable to ship specimens during their designated week, the site must wait until the following month to ship OR contact the Specimen Repository to determine if there is an alternate shipping date available. Non-compliance with the designated shipping week will be monitored.

2. All specimens must be clearly and completely labeled according to the ACTG specifications (PID, date of draw, study number, specimen type, etc) and entered into the LDMS.

APPENDIX V

3. Ship only full boxes of specimens to the Specimen Repository. For sites that have a low number of subjects and are unable to fill a storage box on a monthly basis, less frequent shipments to the Specimen Repository would be allowed (e.g., every 3 months). Boxes may be filled with specimens from multiple protocols to meet the full box requirement.
4. The 2-inch fiberboard storage boxes with 9x9 or 8x8 arrays are recommended for the 2.0 ml Nunc, Wheaton, and Corning brand cryovials; the 10x10 array should only be used for the 2.0 ml Sarsted cryovials.
5. Laboratories that process and store specimens for both the PACTG and AACTG should not mix Pediatric and Adult specimens in the same box, nor send Pediatric and Adult specimens in the same shipment.
6. Frozen viable cells should not be sent in the same storage box with plasma and serum.
7. Every shipment must be accompanied by a LDMS diskette, manifest, and boxmap (when preparing the LDMS diskette, the LDMS code for the Specimen Repository is 999). The specimens, manifest, and boxmap should be QC'd prior to shipping to ensure that they match. Boxes with >10% discordance will be returned to the sender for reconciliation. Specimens sent to the Specimen Repository not accompanied by an LDMS diskette or incorrectly labeled will be returned to the sender. Returned boxes and other shipment problems will be reported to the DMC for submission to the Pediatric Laboratory Steering Committee.
8. Subunits without the LDMS must send specimens to their Main Unit for logging into the LDMS and shipping to the Specimen Repository according to the schedule recommended for that site.
9. At least one week prior to your designated shipping week, the site should order shipping containers from the Specimen Repository using the Shipping Container Order Form on the Web (<http://pactg.s-3.com/labs.htm>).
10. The sites are encouraged to use the shipping containers provided by the Specimen Repository to reduce improper packaging problems. All the components of the shipping containers must be used in order to comply with the regulations. Do not substitute any components from other containers.
11. The shipping diskette and storage boxes must be labeled with the batch number and laboratory or clinic site number. Treat each box as a batch. The LDMS diskette should be inserted into a cardboard diskette mailer and placed on top of the polystyrene insulated package along with the paperwork.

Note: The diskette and paperwork should not be placed on the dry ice.

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12. All International Air Transportation (IATA) Dangerous Goods regulations must be followed when packing, labeling, and shipping specimens. Please refer to the ACTG Shipping Guidelines and Shipping Checklist on the Web: (<http://pactg.s-3.com/labs.htm>).
13. The site must FAX a notification to the Specimen Repository prior to shipping using the “ACTG Specimen Shipment Notice” document on the Web (<http://pactg.s-3.com/labs.htm>).

## APPENDIX VI

## MEASURES TO REDUCE THE NUMBER OF SUBJECTS LOST TO FOLLOW-UP

At each of the **two** delivery facilities, measures will be taken to reduce the number of women and infants lost to follow-up. This is particularly important with respect to the infants and the Week 6-10 DNA PCR testing **for** determination of infant infection status.

Aspects of the Somerset West community, served by Macassar Community Health Centre and Hottentots Holland Hospital will help facilitate good subject compliance with study visits. Somerset West is a semi-urban community. It is small, well-demarcated and has a relatively stable population (i.e little in-and-out migration). Distances from homes to Macassar and Hottentots Holland are short. Consequently, community health workers should have little difficulty locating subjects.

The measures listed below have been field-tested and found to be successful in other studies in Cape Town and South Africa. These measures are sensitive to the need for confidentiality in caring for subjects infected with HIV, and often can enhance the care provided to mothers participating in the study.

1. Community health workers will contact women after discharge from the delivery facility. Ideally, these contacts will take place on a weekly basis, either by telephone or home visit. In either case, service will be attributed to follow-up care initiatives, not to HIV-related service. Women will be screened for complications associated with delivery. Questions associated with self and infant care can be addressed during telephone conversations. Women will be reminded to attend the Week 6-10 study visit for their infant's DNA PCR test.
2. Community health workers will assist women with transportation to clinic appointments for the Week 6-10 study visit.
3. Women will be compensated R100 for attending the Week 6-10 study visit. This will defray the cost of transportation and will be an incentive for these women to remember to attend the visit. A recent study found that 4.4% of subjects quoted monetary issues as a reason for non-attendance at follow-up visits.
4. Before discharge from the delivery facility, we will ensure that women are verbally instructed in their primary language about when to return and that written instructions are also provided. A recent study found that 0.8% of subjects did not attend their follow-up visit because they did not understand their discharge instructions.
5. We will strive to make the baby's DNA PCR test coincide with an immunization visit. This will give the woman/family another reason to make sure the infant returns for follow-up.
6. We will collect as many contact numbers as possible for each woman/family. Using the contact numbers, we will remind the family 2-3 days before the study visit. For women without contact numbers, community health workers will be deployed to visit them and remind them about the upcoming study visit.

APPENDIX VII  
CDC MIRIAD BIOMEDICAL STUDIES

PACTG P1031A sites will participate in two CDC MIRIAD biomedical studies. The studies will utilize stored specimen aliquots and will be conducted at CDC laboratories. The background, rationale and objectives of the two studies are outlined below. Refer to Appendix V for specimen processing information.

STUDY 2	A Simple Assay for Detecting Recent HIV Infection and Estimating Incidence Among Women Enrolled Peripartum
STUDY 5	Role of HLA and Other Genetic Factors in Influencing Maternal Infant Transmission of HIV, Despite ART Intervention in the Peripartum Period

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STUDY 2: "A Simple Assay for Detecting Recent HIV Infection and Estimating Incidence Among Women Enrolled Peripartum"

Background and Rationale

For many infectious agents that can be congenitally transmitted, primary infections in the mother during pregnancy are often associated with increased risk of transmission to the offspring and/or more severe clinical manifestations. A simple and practical method of identifying recently HIV-1 infected persons has recently been validated in HIV-1 subtype B-infected individuals (1). The Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) is based on differential antibody titers in recent versus long-term infection (2). To identify a person in the period of early infection (when the antibody titer is increasing but before peak and persistently high antibody response), a serologic testing algorithm is employed in which a blood specimen from a person with early infection is reactive on a sensitive HIV-1 EIA but not reactive on a less sensitive EIA. This has also been referred to as the S/LS enzyme immunoassay (EIA) testing strategy (3,4). This strategy detects early HIV-1 infection a number of months after seroconversion is detectable by standard antibody assays. The ability to differentiate persons with early HIV infection from those with later infection is considered a breakthrough for HIV/AIDS epidemiologic research, in particular to estimate HIV-1 incidence without the necessity of serial blood sampling. Knowledge of the approximate timing of seroconversion, in combination with viral load levels, may also provide valuable information regarding risk of transmission and clinical prognosis.

The modified "less-sensitive" commercial HIV-1 antibody assay (3A11-LS) performs well and has been used for estimating seroincidence using cross-sectional specimens in various U.S. populations (1,3,4,5,6). However, it has not been widely applied because of problems



## APPENDIX VII

with availability (relies on an early-generation commercial assay) and less than optimal performance when applied to populations infected with non-B HIV-1 subtypes (2,7). CDC has evaluated a number of other approaches, based on different assay principles, for their ability to distinguish recent from established HIV-1 infection (7). The BED-CEIA (capture enzyme immuno assay) procedure, described in detail elsewhere (8), has had the most optimal performance characteristics in extensive testing. The test is performed in a single-well, EIA format and is suitable for high-throughput testing (96-well format). The branched synthetic peptide incorporates immunodominant gp41 sequences from multiple HIV-1 subtypes and performs well with well-characterized specimens, collected around the world (8, CDC, unpublished data). We note also that the BED-CEIA assay has been applied successfully by CDC to pregnant women in the USA, participating in the Perinatal AIDS Collaborative Transmission Study (PACTS) (9), and to pregnant women in a cohort study in Rwanda (personal communication: Marc Bulterys).

Employing the BED-CEIA testing strategy on maternal and/or cord blood sera collected in P1031A at the time of delivery could identify those mothers who were in the early HIV infection stage during the last few months of their pregnancy.

Specific Aims:

1. To estimate incidence of HIV-1 infection among women close to the time of delivery.
2. To determine whether detection of maternal incident HIV-1 infection is associated with infant DNA-PCR positivity at birth and at 6-8 weeks postpartum.

Laboratory Samples Required:

A 50ul aliquot of serum or plasma is sufficient for the BED-CEIA assay at CDC. Transfer of the technology from the CDC laboratory to a laboratory in Cape Town, South Africa, can be envisioned at a later stage.

References

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3. McFarland W, Busch MP, Kellogg TA, et al. Detection of early HIV infection and estimation of incidence using a sensitive/less sensitive enzyme immunoassay testing strategy at anonymous counseling and testing sites in San Francisco. *JAIDS* 1999; 22:484-489.

## APPENDIX VII

4. Machado DM, Delwart EL, Diaz RS, et al. Use of the sensitive/less-sensitive (detuned) EIA strategy for targeting genetic analysis of HIV-1 to recently infected blood donors. *AIDS* 2002; 16:113-119.
5. Schwarcz S, Kellogg T, McFarland W, et al. Differences in the temporal trends of HIV sero-incidence and seroprevalence among sexually transmitted disease clinic patients, 1989-1998: application of the serologic testing algorithm for recent HIV seroconversion. *Am J Epidemiol* 2001; 153:925-934.
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9. Nesheim S, Parekh B, Sullivan K, Bulterys M, Lindsay M, Cashat-Cruz M, et al. Temporal trends in HIV-1 incidence among inner-city childbearing women in Atlanta: application of a serologic testing algorithm for recent HIV seroconversion. Submitted for clearance review (*Am J Public Health*).

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### STUDY 5: "Role of HLA and Other Genetic Factors in Influencing Maternal Infant Transmission (MIT) of HIV, Despite ART Intervention in the Peripartum Period"

#### Background and Rationale

The transmission of HIV from infected to uninfected, exposed persons is influenced by several host genes (1). In the MIT setting, transmission could be influenced by the genes of either the mother or the child or both. One good example is the finding of MacDonald *et al* that the more similar baby and mother are at HLA, the more likely HIV is to be transmitted. Conversely, a complete HLA dissimilarity between mother and infant reduced HIV transmission in this Kenyan study almost as much as short course AZT. Preliminary data from a pilot HLA investigation in the Perinatal AIDS Collaborative Transmission Study (PACTS) also provides evidence in support of the hypothesis that concordance in HLA types is associated with MIT of HIV. Other genes in mother or child that could influence transmission include genes of the chemokine or chemokine receptor family, genes of the cytokine or cytokine receptor family, and genes of other immune response factors. With the rapid expansion of our knowledge of the host genes that influence transmission or progression of HIV, and with the sequencing of the >100,000 human genes almost complete, it is likely that many more candidate genes will be available to examine in the context of HIV transmission.

## APPENDIX VII

While antiretroviral therapy in MIRIAD will likely reduce MIT of HIV, we still believe that host factors will play a role in determining which infants become infected. Support for this is given by the finding that persons with one copy of the CCR5 del 32 gene have improved responses to antiretroviral therapy than those without (5). It is our hypothesis that children who become HIV infected despite peripartum antiretroviral prophylaxis in MIRIAD may be a unique group with a high prevalence of host genes associated with increased risk of HIV transmission.

### Objective:

To determine if host genes associated with resistance to HIV infection (or with delayed HIV disease progression) are more prevalent in children who become HIV infected despite adequate intrapartum and/or neonatal antiretroviral therapy compared with randomly chosen HIV-exposed but uninfected children.

Formatted: Bullets and Numbering

### Laboratory Samples Required:

One PBMC 'cell' sample is required from which DNA can be extracted from each transmitting mother and her infant (and a comparison non-transmitting mother-infant pair with complete data on potential confounders such as maternal viral load). Usually, 1 ml whole blood is more than adequate for this purpose (a minimum of 1 million cells is requested by the HLA lab).

In a nested case-control study (1:1 ratio) of HIV infected versus uninfected children born to seropositive mothers, 57 transmitter pairs and 57 non-transmitter pairs would be needed for a minimum detectable relative risk of 3.0, assuming 80% power. Given the large sample size of P1031A, we expect to have a sufficient number of transmitter pairs for this HLA substudy.

### References:

1. Kaslow RA and McNicholl JM. Genetic determinants of HIV-1 infection and its manifestations. *Proc Assoc Am Physicians*. 1999 Jul-Aug; 111(4): 299-307. Review.
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5. Valdez H, Purvis SF, Lederman M, et. al. Association of the CCR5delta32 mutation with improved response to antiretroviral therapy. *JAMA*. 1999 Aug 25; 282(8): 734.

APPENDIX VIII

DIVISION OF AIDS  
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)  
SAMPLE INFORMED CONSENT

FOR PROTOCOL:

PACTG P1031A, Version **3.0**: Mother Infant Rapid Intervention At Delivery  
(MIRIAD), **dated 01/18/06**

SHORT TITLE:

PACTG P1031A, Version **3.0**: MIRIAD

INTRAPARTUM GROUP

INTRODUCTION

You are being asked to take part in this research study because you are in labour and you do not know if you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. This study is sponsored by the National Institutes of Health (NIH) in the United States, in collaboration with the Centers for Disease Control (CDC). The doctor in charge of this study at (*insert name of delivery facility*) is (*insert name of Principal Investigator*). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

HIV can be passed from a pregnant woman to her baby during delivery. If a woman finds out she has HIV, then she and/or her baby can take an anti-HIV medicine around the time of delivery to decrease the risk of passing HIV to the baby. The current South African guideline for women who do not know their HIV status is to offer HIV counseling and testing during pregnancy, where available. For women who miss being offered HIV counseling and testing during pregnancy and are in labour, HIV counseling and testing is offered after the baby is born, where available. Another approach, offering HIV counseling and testing during labour, is recommended in the United States and other countries for women who miss being offered HIV counseling and testing before labour.

APPENDIX VIII  
*INTRAPARTUM GROUP*

In this study, there will be two groups of women:

- women who are offered HIV counseling and testing during labour, and
- women who are offered HIV counseling and testing after delivery.

You will be in one group or the other depending on when you came to the hospital to have your baby. Women who have a positive test during labour will be offered anti-HIV medicine before delivery. Their babies will also be offered anti-HIV medicine. Women who have a positive test after delivery will not be offered anti-HIV medicine, but their babies will be. How well anti-HIV medicine works when given only to babies is not known.

To help us decide which approach is better for South Africa, the study will:

- look at how women feel about HIV counseling and testing during labour compared to HIV counseling and testing after delivery
- see if women who have positive HIV test results accept anti-HIV medicine for themselves and/or their babies

This study will also compare two rapid HIV tests, called OraQuick<sup>®</sup> and Determine<sup>®</sup> on blood and on oral fluid. These tests will be compared to standard HIV tests, called ELISA and Western blot. All of these tests are approved for use in South Africa.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Once you agree to participate in this study:

- you will receive HIV counseling by a trained counselor.
- the OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid HIV tests will be done on a small amount of blood taken by pricking your finger.
- the OraQuick<sup>®</sup> rapid test will also be done on a small amount of your saliva, taken by rolling a swab on the inside of your cheek.
- the standard HIV tests will be done on a small amount of blood (about 1 teaspoon) taken from a vein in your arm. The purpose of these tests is to make sure the results of the rapid tests are right.

The rapid test results will be ready within 30 minutes.

After you deliver your baby:

- you will have a physical examination.
- you will be asked some questions about your medical history. Your medical records may be reviewed by the study staff, but all personal information will be kept as confidential as possible.
- A small amount of blood will be taken from the umbilical cord to test for HIV. This cord blood sample and the test result will not be linked to you in any way.

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*INTRAPARTUM GROUP*

If your OraQuick® and Determine® rapid test results are positive for HIV:

1. You will be offered anti-HIV medicine immediately. Your baby will be offered anti-HIV medicine very soon after birth. The kind of anti-HIV medicine that is offered to you and your baby will depend on the medicines available at the delivery facility. You will probably be offered a medicine called nevirapine (NVP). **Your baby will probably be offered NVP and another medicine called zidovudine (AZT).**
2. **As soon as the positive test results are known**, about 2 teaspoons of blood will be taken from a vein in your arm to do a routine blood check and to determine the amount of HIV and CD4/CD8 cells (cells that fight HIV) in your blood.
3. After delivery, you will receive counseling about what a positive test result means for you and for your baby. The midwife, nurse, or counselor will tell you where you can go for treatment and social services.
4. After delivery, you may be asked some questions about how you feel about receiving HIV counseling, testing, and treatment during labour. All of your answers will be kept as confidential as possible.
5. Your baby will have a physical examination. A few drops of blood will be taken from **either** your baby's heel **or from a vein in your baby's arm** to test your baby for HIV. If this test is not done or if the results are not clear, the study staff will ask you to bring your baby back to the clinic as soon as possible to repeat this test.
6. You and your baby will be asked to come back in about 6-10 weeks. At this time, you will be told the result of the ELISA and Western blot standard tests and the results of the special blood tests. You may be asked to be interviewed again about how you feel about receiving HIV counseling, testing, and treatment during labour. All of your answers will be kept as confidential as possible.

A few drops of blood will again be taken from **either** your baby's heel **or arm** to test your baby for HIV. The result of your baby's HIV test at birth and the result of your baby's HIV test at this visit are both needed to determine if your baby is really infected with HIV. You will be asked to bring your baby back in two weeks to get this test result. Sometimes the mother's antibodies to HIV (proteins that fight HIV infection) can still be in the baby's blood at birth, making it seem that the baby is infected with HIV. So it is very important to come back for the second test result.

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7. If your baby's second test result is positive for HIV, another few drops of blood will be taken from **either** your baby's heel **or arm** to repeat the tests and make sure this result is right. You will be asked to bring your baby back in another two weeks to get this test result.
8. You may be asked to be interviewed again at 6 months after you deliver your baby. If you agree to this, a nurse will visit you at your home to do the interviews. The purpose of the interviews is to see if your feelings about HIV counseling, testing, and treatment during labour have changed since you delivered your baby.

You can decide at any time that you don't want to be part of the study anymore, or that you don't want your baby to be part of the study anymore. If you decide this, there won't be any other tests or questions for you or your baby.

If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are negative for HIV:

1. After delivery, you will receive counseling about HIV, and told about some things you can do to keep from getting HIV.
2. You may be asked some questions about how you feel about HIV counseling and testing during labour. All of your answers will be kept as confidential as possible.
3. There are no further study requirements for you or for your baby, **unless both of the standard HIV tests are positive for HIV. If this happens, the study staff will contact you and ask you and your baby to come back to the clinic as soon as possible. If this is within 72 hours of birth, the study staff will arrange for your baby to start anti-HIV medicine. The kind of medicine that is offered to your baby will depend on the medicines available at the delivery facility. Your baby will probably be offered both NVP and AZT. You and your baby will then follow steps 3-8 listed under "If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV."**

If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are not the same:

There is a chance that one of your rapid test results will be positive and one will be negative.

1. Because of the positive test result, you will be offered anti-HIV medicine immediately.
2. After delivery, the rapid HIV tests will be repeated on a small amount of blood taken by pricking your finger to determine which rapid test result is the correct one.
3. If both of your repeat test results are positive, your baby will be offered anti-HIV medicine. You and your baby will follow steps 2-8 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV.*

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4. If both of your repeat test results are negative, then your baby does not need anti-HIV medicine. You will follow steps 1-3 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are negative for HIV.*
5. If one repeat test result is positive and one is negative, your baby will be offered anti-HIV medicine. The standard HIV tests will determine which result is the right one. You and your baby will follow steps 2-8 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV.*

Storage of Blood Specimens

If you have a positive test result, some of your blood (about 1 teaspoon) and your baby's blood (about ½ teaspoon) will be taken right after delivery and stored (with usual protectors of identity) for use in specified, PACTG-approved, HIV-related research studies. These studies have been approved by NIH, and the (*insert name of delivery facility*) Institutional Review Board (IRB). An IRB is a special committee that watches over the safety and rights of research subjects.

The research studies include genetic testing, which is a study of your/your baby's genes (DNA). Genetic testing will determine if you or your baby have genes which make it more likely that your baby will be infected with HIV. If you would like to know more about other studies that will be done with your/your baby's blood samples, ask the study staff.

Your/your baby's blood samples will be **shipped to and** stored at a special facility **in the United States** where only approved researchers will have access to them. People who work at the facility will also have access to your/your baby's samples to keep track of them, but these people won't have information that directly identifies you/your baby. As your/your baby's samples are needed, they will be sent to **CDC laboratories in the United States**, where the studies will be done. Your/your baby's samples will not be sold or directly used to produce commercial products. Once the CDC research is complete, your/your baby's samples will be discarded.

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

You may decide that you do not want your blood and/or your baby's blood stored for research studies. You and your baby can still participate in this study even if you make this decision. Please read the following statement, and mark your initials in the appropriate space provided.



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I agree to have my blood stored for use in specified, PACTG-approved, HIV-related research studies.

\_\_\_\_\_ Yes                      \_\_\_\_\_ No                      \_\_\_\_\_ Date

I agree to have my baby's blood stored for use in specified, PACTG-approved, HIV-related research studies.

\_\_\_\_\_ Yes                      \_\_\_\_\_ No                      \_\_\_\_\_ Date

Other Information

The information collected in this study may be used for other PACTG-approved, HIV-related research.

HOW MANY WOMEN WILL TAKE PART IN THIS STUDY?

About **400-500** women will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

If you have a positive rapid test result, you will be part of this study until 6-10 weeks after you deliver your baby. If you are asked to be interviewed, you will be in this study until 6 months after you deliver your baby. Your baby will be part of this study for up to 3½ months.

If you do not have a positive rapid test result, you will be part of this study for only a few hours and your baby will not be part of this study at all.

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

Your doctor may need to take you/your baby off the study early without your permission if the doctor decides that staying on the study would be harmful to you/your baby, or if the study is cancelled by the NIH or the South African Research Ethics Committee. This is a committee that watches over the safety and rights of people in research studies.

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WHAT ARE THE RISKS OF THIS STUDY?

Risks of HIV Testing

Rapid tests are not perfect. There is a very small chance that one or both of the rapid test results will not be correct. Decisions about your treatment will be based on these initial results. So you might receive treatment if you are not infected with HIV. Thinking you have HIV when you really do not could make you anxious or upset. Or, you might not receive treatment if you are infected with HIV, and your baby might not receive treatment either.

If you have a positive test result, there is a small chance that someone involved in your care (like a family member or friend), may accidentally become aware of your positive test result as you receive an anti-HIV drug. If this happens, you may become anxious or upset.

Risks When Drawing Blood

You/your baby may feel some discomfort when you/your baby are having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of fainting or of a minor infection forming where the needle goes into the skin.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Knowing whether or not you are infected with HIV is important to your health.

If you are infected with HIV, anti-HIV medicine can be given to you and/or your baby to lower the risk of passing HIV to your baby. You can choose not to breastfeed your baby, because HIV can be passed to your baby through breast milk. The nurse or counselor will give you some advice on feeding your baby if you are infected with HIV.

If you are not infected with HIV, you can still receive counseling about HIV, and told about some things you can do to keep from getting HIV.

If you/your baby take part in this study, there may be a direct benefit to you/your baby, but no guarantee can be made. It is also possible that you/your baby may receive no benefit from being in this study. Information learned from this study may help other people with HIV.

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WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being part of this study, you could decide that you want to be counseled and tested for HIV after delivery, or that you don't want to be counseled and tested for HIV at all. The nurse or counselor will talk to you about your choices and what they mean for you and your baby.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. The results of this study may be published, but your name would not be used. Your records may be reviewed by the (*insert name of delivery facility*) IRB, the South African Research Ethics Committee, NIH, CDC, the study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for any of the HIV tests, examinations, laboratory tests, or study-related visits. If you test positive for HIV, anti-HIV medicines will be provided at no cost for you and for your baby through the Prevention of Mother To Child Transmission (PMTCT) programs of the Western Cape Province and the Eastern Cape Province.

WILL I RECEIVE ANY PAYMENT?

If you are found to be infected with HIV, you will be asked to bring your baby back to the hospital at 6-10 weeks after delivery. If you do so, you will receive some money for your time. If the study staff asks to interview you at **6 months** after you deliver your baby, you will receive some money for your time. The study staff will tell you how much money you will receive.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are or your baby is injured as a result of being in this study, (*insert name of delivery facility*) will provide immediate necessary treatment for your/your baby's injuries. You will be told where you/your child can go to receive additional treatment for injuries. This will be applied in accordance with the principles of the Association of the British Pharmaceutical Industry. There is no program for monetary compensation or other forms of compensation through this facility or through the NIH. You will not be giving up any of your legal rights by signing this consent form.

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INTRAPARTUM GROUP

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave the study at any time. You and your baby will be treated the same no matter what you decide.

WHAT DO I DO IF I HAVE PROBLEMS OR QUESTIONS?

For questions about this study or a research-related injury, contact:

- *name of the investigator or other study staff*
- *telephone number of above*

For questions about your/your baby's rights as a research subject, contact:

- *name or title of person on the Institutional Review Board (IRB)*
- *telephone number of above*

SIGNATURE

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

\_\_\_\_\_  
Participant's Name (print)

\_\_\_\_\_  
Participant's Signature and Date

\_\_\_\_\_  
Participant's Legal Guardian (print)  
(as appropriate)

\_\_\_\_\_  
Legal Guardian's Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness' Name (print)  
(as appropriate)

\_\_\_\_\_  
Witness's Signature and Date

APPENDIX IX

DIVISION OF AIDS  
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)  
SAMPLE INFORMED CONSENT

FOR PROTOCOL:

PACTG P1031A, Version **3.0**: Mother Infant Rapid Intervention At Delivery  
(MIRIAD), **dated 01/18/06**

SHORT TITLE:

PACTG P1031A, Version **3.0**: MIRIAD

POSTPARTUM GROUP

INTRODUCTION

You are being asked to take part in this research study because you have just delivered your baby and you do not know if you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. This study is sponsored by the National Institutes of Health (NIH) in the United States, in collaboration with the Centers for Disease Control (CDC). The doctor in charge of this study at (*insert name of delivery facility*) is (*insert name of Principal Investigator*). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

HIV can be passed from a pregnant woman to her baby during delivery. If a woman finds out she has HIV, then she and/or her baby can take an anti-HIV medicine around the time of delivery to decrease the risk of passing HIV to the baby. The current South African guideline for women who do not know their HIV status is to offer HIV counseling and testing during pregnancy, where available. For women who miss being offered HIV counseling and testing during pregnancy and are in labour, HIV counseling and testing is offered after the baby is born, where available. Another approach, offering HIV counseling and testing during labour, is recommended in the United States and other countries for women who miss being offered HIV counseling and testing before labour.

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In this study, there will be two groups of women:

- women who are offered HIV counseling and testing during labour, and
- women who are offered HIV counseling and testing after delivery.

You will be in one group or the other depending on when you came to the hospital to have your baby. Women who have a positive test during labour will be offered anti-HIV medicine before delivery. Their babies will also be offered anti-HIV medicine. Women who have a positive test after delivery will not be offered anti-HIV medicine, but their babies will be. How well anti-HIV medicine works when given only to babies is not known.

To help us decide which approach is better for South Africa, the study will:

- look at how women feel about HIV counseling and testing during labour compared to HIV counseling and testing after delivery
- see if women who have positive HIV test results accept anti-HIV medicine for themselves and/or their babies

This study will also compare two rapid HIV tests, called OraQuick<sup>®</sup> and Determine<sup>®</sup> on blood and on oral fluid. These tests will be compared to standard HIV tests, called ELISA and Western blot. All of these tests are approved for use in South Africa.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Once you agree to participate in this study:

- you will receive HIV counseling by a trained counselor.
- the OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid HIV tests will be done on a small amount of blood taken by pricking your finger.
- the OraQuick<sup>®</sup> rapid test will also be done on a small amount of your saliva, taken by rolling a swab on the inside of your cheek.
- the standard HIV tests will be done on a small amount of blood (about 1 teaspoon) taken from a vein in your arm. The purpose of these tests is to make sure the results of the rapid tests are right.
- you will have a physical examination.
- you will be asked some questions about your medical history. Your medical records may be reviewed by the study staff, but all personal information will be kept as confidential as possible.
- A small amount of blood will be taken from the umbilical cord to test for HIV. This cord blood sample and the test result will not be linked to you in any way.

The rapid test results will be ready within 30 minutes.

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POSTPARTUM GROUP

If your OraQuick® and Determine® rapid test results are positive for HIV:

1. Your baby will be offered anti-HIV medicine as soon as possible after your test results are available. The kind of anti-HIV medicine that is offered to your baby will depend on the medicines available at the delivery facility. Your baby will probably be offered **two** medicines called nevirapine (**NVP**) and **azidothymidine (AZT)**.
2. About 2 teaspoons of blood will be taken from a vein in your arm to do a routine blood check and to determine the amount of HIV and CD4/CD8 cells (cells that fight HIV) in your blood.
3. You will receive counseling about what a positive test result means for you and for your baby. The midwife, nurse, or counselor will tell you where you can go for treatment and social services.
4. You may be asked some questions about how you feel about receiving HIV counseling, testing, and treatment during labour. All of your answers will be kept as confidential as possible.
5. Your baby will have a physical examination. A few drops of blood will be taken from **either** your baby's heel **or from a vein in your baby's arm** to test your baby for HIV. If this test is not done or if the results are not clear, the study staff will ask you to bring your baby back to the clinic as soon as possible to repeat this test.
6. You and your baby will be asked to come back in about 6-10 weeks. At this time, you will be told the result of the ELISA and Western blot standard tests and the results of the special blood tests. You may be asked to be interviewed again about how you feel about receiving HIV counseling, testing, and treatment just after delivery. All of your answers will be kept as confidential as possible.

A few drops of blood will again be taken from **either** your baby's heel **or arm** to test your baby for HIV. The result of your baby's HIV test at birth and the result of your baby's HIV test at this visit are both needed to determine if your baby is really infected with HIV. You will be asked to bring your baby back in two weeks to get this test result. Sometimes the mother's antibodies to HIV (proteins that fight HIV infection) can still be in the baby's blood at birth, making it seem that the baby is infected with HIV. So it is very important to come back for the second test result.

7. If your baby's second test result is positive for HIV, another few drops of blood will be taken from **either** your baby's heel **or arm** to repeat the tests and make sure this result is right. You will be asked to bring your baby back in another two weeks to get this test result.
8. You may be asked to be interviewed again at 6 months after you deliver your baby. If you agree to this, a nurse will visit you at your home to do the interview(s). The purpose of the interview(s) is to see if your feelings about HIV counseling, testing and treatment just after delivery have changed since you delivered your baby.

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You can decide at any time that you don't want to be part of the study anymore, or that you don't want your baby to be part of the study anymore. If you decide this, there won't be any other tests or questions for you or your baby.

If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are negative for HIV:

1. You will receive counseling about HIV, and told about some things you can do to keep from getting HIV.
2. You may be asked some questions about how you feel about HIV counseling and testing just after delivery. All of your answers will be kept as confidential as possible.
3. There are no further study requirements for you or for your baby, **unless both of the standard HIV tests are positive for HIV. If this happens, the study staff will contact you and ask you and your baby to come back to the clinic as soon as possible. If this is within 72 hours of birth, the study staff will arrange for your baby to start anti-HIV medicine. The kind of medicine that is offered to your baby will depend on the medicines available at the delivery facility. Your baby will probably be offered both NVP and AZT. You and your baby will then follow steps 3-8 listed under "If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV."**

If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are not the same:

There is a chance that one of your rapid test results will be positive and one will be negative. If so, the rapid HIV tests will be repeated on a small amount of blood taken by pricking your finger to determine which rapid test result is the correct one.

1. If both of your repeat test results are positive, your baby will be offered anti-HIV medicine. You and your baby will follow steps 2-8 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV.*
2. If both of your repeat test results are negative, then your baby does not need anti-HIV medicine. You will follow steps 1-3 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are negative for HIV.*
3. If one repeat test result is positive and one is negative, your baby will be offered anti-HIV medicine. The standard HIV tests will determine which result is the right one. You and your baby will follow steps 2-8 listed under *If your OraQuick<sup>®</sup> and Determine<sup>®</sup> rapid test results are positive for HIV.*



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Storage of Blood Specimens

If you have a positive test result, some of your blood (about 1 teaspoon) and your baby's blood (about ½ teaspoon) will be taken right after delivery and stored (with usual protectors of identity) for use in specified, PACTG-approved, HIV-related research studies. These studies have been approved by NIH, and the *(insert name of delivery facility)* Institutional Review Board (IRB). An IRB is a special committee that watches over the safety and rights of research subjects.

The research studies include genetic testing, which is a study of your/your baby's genes (DNA). Genetic testing will determine if you or your baby have genes which make it more likely that your baby will be infected with HIV. If you would like to know more about other studies that will be done with your/your baby's blood samples, ask the study staff.

Your/your baby's blood samples will be **shipped to and** stored at a special facility **in the United States** where only approved researchers will have access to them. People who work at the facility will also have access to your/your baby's samples to keep track of them, but these people won't have information that directly identifies you/your baby. As your/your baby's samples are needed, they will be sent to **CDC laboratories in the United States**, where the studies will be done. Your/your baby's samples will not be sold or directly used to produce commercial products. Once the CDC research is complete, your/your baby's samples will be discarded.

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

You may decide that you do not want your blood and/or your baby's blood stored for research studies. You and your baby can still participate in this study even if you make this decision. Please read the following statement, and mark your initials in the appropriate space provided.

I agree to have my blood stored for use in specified, PACTG-approved, HIV-related research studies.

\_\_\_\_\_ Yes                      \_\_\_\_\_ No                      \_\_\_\_\_ Date

I agree to have my baby's blood stored for use in specified, PACTG-approved, HIV-related research studies.

\_\_\_\_\_ Yes                      \_\_\_\_\_ No                      \_\_\_\_\_ Date

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*POSTPARTUM GROUP*

Other Information

The information collected in this study may be used for other PACTG-approved, HIV-related research.

HOW MANY WOMEN WILL TAKE PART IN THIS STUDY?

About **400-500** women will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

If you have a positive rapid test result, you will be part of this study until 6-10 weeks after you deliver your baby. If you are asked to be interviewed, you will be in this study until 6 months after you deliver your baby. Your baby will be part of this study for up to 3 ½ months.

If you do not have a positive rapid test result, you will be part of this study for only a few hours and your baby will not be part of this study at all.

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

Your doctor may need to take you/your baby off the study early without your permission if the doctor decides that staying on the study would be harmful to you/your baby, or if the study is cancelled by the NIH or the South African Research Ethics Committee. This is a committee that watches over the safety and rights of people in research studies.

WHAT ARE THE RISKS OF THIS STUDY?

Risks of HIV Testing

Rapid tests are not perfect. There is a very small chance that one or both of the rapid test results will not be correct. Thinking you have HIV when you really do not could make you anxious or upset. But we will not offer your baby anti-HIV medicine unless we are sure that you are infected with HIV and that you may have passed HIV to your baby.

Risks When Drawing Blood

You/your baby may feel some discomfort when you/your baby are having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of fainting or of a minor infection forming where the needle goes into the skin.

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ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Knowing whether or not you are infected with HIV is important to your health. If you are infected with HIV, anti-HIV medicine can be given to your baby right after delivery to decrease the risk of your baby having HIV. You can choose not to breastfeed your baby, because HIV can be passed to your baby through breast milk. The nurse or counselor will give you some advice on feeding your baby if you are infected with HIV.

If you are not infected with HIV, you can still receive counseling about HIV, and told about some things you can do to keep from getting HIV.

If you/your baby take part in this study, there may be a direct benefit to you/your baby, but no guarantee can be made. It is also possible that you/your baby may receive no benefit from being in this study. Information learned from this study may help other people with HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being part of this study, you could decide that you don't want to be counseled and tested for HIV, or have counseling and testing done but not as part of this study. The nurse or counselor will talk to you about your choice and what it means for you and your baby.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. The results of this study may be published, but your name would not be used.

Your records may be reviewed by the (*insert name of delivery facility*) IRB, the South African Research Ethics Committee, NIH, CDC, the study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost to you for any of the HIV tests, examinations, laboratory tests, or study-related visits. If you test positive for HIV, anti-HIV medicines will be provided at no cost for you and for your baby through the Prevention of Mother To Child Transmission (PMTCT) programs of the Western Cape Province and the Eastern Cape Province.

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WILL I RECEIVE ANY PAYMENT?

If you are found to be infected with HIV, you will be asked to bring your baby back to the hospital at 6-10 weeks after delivery. If you do so, you will receive some money for your time. If the study staff asks to interview you at **6 months** after you deliver your baby, you will receive some money for your time. The study staff will tell you how much money you will receive.

WHAT HAPPENS IF I AM/MYBABY IS INJURED?

If you are or your baby is injured as a result of being in this study, (*insert name of delivery facility*) will provide immediate necessary treatment for your/your baby's injuries. You will be told where you/your child can go to receive additional treatment for injuries. This will be applied in accordance with the principles of the Association of the British Pharmaceutical Industry. There is no program for monetary compensation or other forms of compensation through this facility or through the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave the study at any time. You and your baby will be treated the same no matter what you decide.

WHAT DO I DO IF I HAVE PROBLEMS OR QUESTIONS?

For questions about this study or a research-related injury, contact:

- *name of the investigator or other study staff*
- *telephone number of above*

For questions about your/your baby's rights as a research subject, contact:

- *name or title of person on the Institutional Review Board (IRB)*
- *telephone number of above*

APPENDIX IX  
*POSTPARTUM GROUP*

SIGNATURE

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

\_\_\_\_\_  
Participant's Name (print)

\_\_\_\_\_  
Participant's Signature and Date

\_\_\_\_\_  
Participant's Legal Guardian (print)  
(as appropriate)

\_\_\_\_\_  
Legal Guardian's Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness' Name (print)  
(as appropriate)

\_\_\_\_\_  
Witness's Signature and Date