Letter of Amendment # 2 to:

HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples, Version 3.0, November 20, 2006, DAIDS Document ID: 10068

Final Version: 20 March 2008

The following information impacts the HPTN 052 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) as soon as possible for their information and review. This Letter of Amendment must be approved by all responsible IRBs/ECs before implementation.

The modifications in this Letter of Amendment result in changes to the informed consent forms. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

This Letter of Amendment and any IRB/EC correspondence must be filed in the site regulatory file and in other pertinent files. Any revised informed consent forms based on this LoA must be submitted to the DAIDS/RCC Protocol Registration Office for informational purposes.

If the HPTN 052 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

Summary of Revisions and Rationale

1a-b. Abbott Laboratories has been included in the protocol as they are now providing pharmaceutical support to the study.

2a-h. The protocol has been revised to add Francesca Conradie, Kristy Grimm, Amita Gupta, Richard Stryker, Jacqueline Talley, and Lei Wang as new protocol team members and Johannesburg, South Africa as a new site. Gary Thal's contact information has been updated.

3a-h. A secondary objective has been added to the protocol to include the collection and analysis of circumcision data. Sections 5.2.3, 5.2.5, 5.3.4.3 and 5.3.4.5 for Clinical Procedures for Index Case and Partner have been revised to include this addition.

4a-f. Sections 2.3, 4, 4.5.7, 4.5.7.1, and 4.5.7.3 have been revised to indicate that, for this protocol, as requested by Abbott Laboratories, a Kaletra®/Aluvia® (liponavir/ritonavir – [LPV/r])-based regimen is the preferred ART regimen to manage pregnancy for women with CD4+ cell counts of >250 cells/mm^3.

5. Section 4.2, Table 3 has been revised to indicate that for stavudine [d4T], participants >60 kg may be dosed at 30 mg orally BID, with or without food, at the discretion of the site investigator.

6 a-d. Sections 5.2.4, 5.2.6, 5.3.4.4, 5.3.4.6, Appendix I.A, Appendix I.B and Index Case and Partner Enrollment Informed Consent have been revised to indicate that for women, urine or endocervical swab samples may be used for *Neisseria gonorrhea* and chlamydia trachomatis analysis if an FDA–approved assay is used for testing.

7 a-b. Section 5.3.9 and the Index Case and Partner Enrollment Sample Informed Consent Forms have been revised to include a Termination Visit.

8. Section 5.4 has been revised to indicate that registration of pregnancies with the Antiretrovial Pregnancy Registry is now mandatory and that those pregnancies not already registered must be added to the registry retrospectively, as requested by Abbott Laboratories.

Implementation of the Protocol Modification

The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Revision 1a Title page
Pharmaceutical Support Provided by:
Abbott Laboratories
Boehringer-Ingelheim Pharmaceuticals, Inc.
Bristol-Myers Squibb
Gilead Sciences, Inc.
GlaxoSmithKline
Merck & Co., Inc

Revision 1b Investigator of Record Signature Page
Pharmaceutical Support Provided by:
Abbott Laboratories
Boehringer-Ingelheim Pharmaceuticals, Inc.
Bristol-Myers Squibb
Gilead Sciences, Inc.
GlaxoSmithKline
Merck & Co., Inc

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Revision 2g Schema

Johannesburg, South Africa

Revision 2h Protocol Roster

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Revision 3a Schema (secondary objectives)
Section 2.2, Secondary Objectives

- **Determine, characterize and compare the effect of circumcision on HIV transmission in different geographic settings and by antiretroviral treatment strategies**.

Revision 3b Section 5.2.3 Clinical Procedures – Index Case

- **Circumcision status (men only)**

Revision 3c Section 5.2.5 Clinical Procedures – Partner

- **Circumcision status (men only)**

Revision 3d Section 5.3.4.3 Clinical Procedures – Index Case

- **Circumcision status (men only - unless previously determined that participant has been circumcised)**

Revision 3e Section 5.3.4.5 Clinical Procedures – Partner

- **Circumcision status (men only - unless previously determined that participant has been circumcised)**

Revision 3f Section 7.6.1 Primary Analysis

In addition, the effect of potential confounding factors, e.g., adherence, and risk factors, e.g., **circumcision,** HIV risk behaviors, will be explored (see next section for more details.)

Revision 3g Section 7.6.2 Secondary Analysis

Given that the trial is unblinded, an important secondary analysis will focus on adherence to study treatment strategy, sexual behavior, **and circumcision**. Self-reported adherence and sexual behavior will be measured monthly and quarterly, respectively. The main self-reported sexual behavior outcome that will be used in the analysis is the proportion of sexual acts, vaginal and anal, unprotected by condom. **Circumcision data will be collected at baseline and on an annual basis, with the date of circumcision captured in the database.**

For adherence and circumcision, this data structure will permit the estimation of:

1. Adherence **and circumcision** rates
2. The testing of differences in adherence **and circumcision** between the two treatment strategies.
3. The testing of trends over time in adherence rates and
4. The examination of the relationship between adherence **and/or circumcision with** HIV infection.

Revision 3h Appendix I.A. Schedule of Procedures and Evaluations – Index Case
Appendix I.B. Schedule of Procedures and Evaluations – Partner

NOTE: Only actual changes to these Appendices are depicted below.

	Screening	Enrollment	Week 2[1]	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
Clinical Procedures								
Circumcision status (men)		X				X		

Revision 4a Section 2.3, Study Design

It is recommended that Combivir and EFV or ATV be used as the primary regimen, **except in the case of pregnancy. For this study, an LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used. In all cases,** study clinicians may use other study-provided ART for the primary regimen after obtaining permission from the HPTN 052 CMC.

Revision 4b 4, Study Treatment Considerations

It is recommended that Combivir and EFV or ATV be used as the primary regimen, **except in the case of pregnancy. For this study, an LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used. In all cases,** study clinicians may use other study-provided ART for the primary regimen after obtaining permission from the HPTN 052 CMC.

Revision 4c Section 4.5.7, Management of ART and Pregnancy, Contraception, and Breastfeeding**.**

While ART during pregnancy will be provided to participants on both arms of the study, prenatal care for women who become pregnant, postpartum testing, or care to infants born to women will not be provided through this study. **For this study, an LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ cell counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used.**

Revision 4d Section 4.5.7.1, Pregnant Women on a Regimen Containing EFV

Women who are taking EFV and become pregnant will immediately stop EFV and substitute a different ART drug for the full course of pregnancy. **For this study, an LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ cell counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used.** The study clinicians will determine ~~which ART drug should be substituted for EFV, and whether the woman should return to EFV~~ **the regimen to be used** following pregnancy.

Revision 4e Section 4.5.7.3, Pregnant Women on a TDF or ATV-Containing Regimen

If other ARV drugs are available and appropriate (e.g., ZDV)**,** women may be counseled to change therapy to an appropriate substitute. **For this study, an LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ cell counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used.**

Revision 4f Section 4.2, Table 3 Antiretroviral Therapies

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Lopinavir / Ritonavir* LPV/r Kaletra® or Aluvia®	PI	200 mg/50 mg tablets	800 mg/200 mg	2 PO BID with or without food	20°-25°C 68°-77°F Excursions permitted between 15-30°C (59-86°F)	An LPV/r-based regimen is the preferred regimen to manage pregnancies of women with CD4+ cell counts > 250 cells/mm^3 and for women with CD4+ cell counts < 250 mm/cells^3, an LPV/r-based or a nevirapine-based regimen may be used.

Revision 5 **Table 3: Antiretroviral Therapies**

NOTE: Only actual changes to this table are depicted below.

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Stavudine d4T Zerit®	NRTI	15 mg, 20 mg, 30 mg, and 40 mg capsules	**30*or** 40 mg, weight >60 kg 30 mg, weight ≤60 kg ***at the discretion of the clinician**	1 PO BID with or without food	15°-30°C 59°-86°F	None

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Revision 6a Section 5.2.4 and 5.3.4.4 Laboratory Evaluations – Index Case
Section 5.2.6 and 5.3.4.6 Laboratory Evaluation – Partner

- Urine PCR for chlamydia **trachomatis** (CT) and **Neisseria** gonorrhea (GC) for men, ~~vaginal~~ **endocervical** swab **or urine** for PCR for GC and CT for women **(An FDA-approved GC/CT assay for female urine must be used. If an FDA-approved assay is not available, an endocervical swab must be collected.)**

Revision 6b Appendix I.A. Schedule of Procedures and Evaluations – Index Case
Appendix I.B. Schedule of Procedures and Evaluations – Partner

NOTE: Only actual changes to these Appendices are depicted below.

	Screening	Enrollment	Week 2[1]	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
Laboratory Evaluations – Local Laboratory								
Urine PCR for GC and CT ~~(men only)~~		X				X		
PCR for GC and CT ~~(vaginal swab)~~ **(endocervical swab if FDA-approved assay for urine is unavailable)**		X				X		

Revision 6c Appendix I. B. Schedule of Procedures and Evaluation – Partner

	Screening	Enrollment	Week 2 [1]	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
Clinical Procedures								
Urine collection ~~(men only)~~ **For men and women, but only for women if urine will be used for PCR for GC and CT analysis (see Laboratory Evaluations below)**		X				X		

Revision 6d Index Case Enrollment Sample Informed Consent Form (Yearly Visit), and Partner Enrollment Sample Informed Consent Form (Enrollment and Yearly Visit)

- If you are a man, we will ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and chlamydia). **If you are a woman, we may ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and Chlamydia) rather than an endocervial swab.**

Revision7a Section 5.3.9 ~~Interim Visit (Ad Hoc).~~ **Additional Visits**

5.3.9.1 Interim Visits

5.3.9.2 Termination visits

Termination visits may be conducted when a participant, either Index Case or Partner, will no longer continue in the study. The termination visit should include as many procedures as possible from the yearly visit, unless a quarterly visit has been done within the previous 60 days. If a quarterly visit has been done within 60 days prior to the termination visit, only the STD components (syphilis, GC, CT, TV, BV, candida), circumcision data, and the stored blood samples from the yearly visit should be collected. The termination visit may be conducted at a regularly scheduled visit or at an interim visit.

Revision 7b Index Case Enrollment Sample Informed Consent Form
Partner Enrollment Sample Informed Consent Form.

Termination visits

If you are no longer able or willing to participate on the study, you will be asked to return to the clinic for a termination visit. During this visit, you will be asked to complete procedures that would be completed during a yearly visit, unless you have completed a quarterly visit within 60 days prior to your termination visit. In this case, you will be asked to provide samples for STD testing (syphilis, GC, CT, TV, BV, candida), as well as circumcision data and blood samples for storage.

Revision 8 Section 5.4. Procedures to be Followed in the Event of Pregnancy or Breastfeeding

Sites ~~or study participants are encouraged to prospectively~~ **must** register pregnancies that occur on study to The Antiretroviral Pregnancy Registry by fax at +44-1628-789-666 (for non-U.S. sites) or 1-800-800-1052 from within the U.S. More information is available at: www.apregistry.com. **If pregnancies exist or occur that are not included in the registry, sites must add those pregnancies to the registry retrospectively.**
