



DATA AND SAFETY MONITORING BOARD REPORT

OPEN REPORT APPENDIX

HPTN 052

A Phase III, 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

Review Date:

July 12, 2006

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Letter of Amendment # 1 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 2.0, May 24, 2004

FINAL Version: 23 December 2004

The following information impacts the HPTN 052 study and must be forwarded to your institutional review board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Please file this letter and any IRB/EC correspondence in your regulatory file and other pertinent files. You are NOT required to submit these documents to the Protocol Registration Office unless the changes result in a change to the informed consent for your site.

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

1. Table 3 in the Regimens and Administration section has been revised to remove the use of 400 mg QD dosing of nevirapine, as Boehringer-Ingelheim, Inc. does not recommend this frequency of dosing.
 2. The Study Procedures, Clinical Procedures, and Laboratory Evaluations section has been updated to reflect that the Two Week visit should only be scheduled for couples after the index case begins ART, or if a female index case becomes pregnant (as she must be placed on ART at the start of the 2nd trimester). This change is being made as the purpose of the Two Week visit is to assess participant safety after ART initiation.
 3. The Expedited Adverse Event Reporting section has been updated to reflect the new name of the DAIDS Toxicity Table.
 4. The Statistical Considerations section has been changed to remove the specific number of couples enrolled per site since the distribution of couples per clinic may vary within one site or across sites.
 5. Appendix I A and I B have been updated per item 2 above, to reflect that the Week Two visit should only take place for couples once the index case initiates ART.
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Implementation

Modifications outlined below are indicated by ~~strike through~~ or **bolded** text.

Revision 1 Section 4.2 Regimens and Administration, Table 3

Only the nevirapine section from Table 3 has been included here:

Medication	Class	Formulation	Daily Dose	Frequency	Storage
Nevirapine NVP Viramune®	NNRTI	200 mg tablet	200 mg (initial for 14 days) then 400 mg	200 mg QD for first 2 weeks (lead-in), 200 mg BID or 400 QD thereafter, with or without food.	25°C 77° F Excursions permitted between 15-30° C (59-86° F)

Revision 2 Section 5.3.1 Week Two (**only for couples after the index case begins ART, or if a female index case becomes pregnant, as she must be placed on ART at the start of the 2nd trimester**)

Revision 3 Section 6 Expedited Adverse Event Reporting

For ease of reference, only the paragraphs where the changes appear are provided below.

This study will follow standard reporting requirements (Grade 4 and higher) throughout the study period and will follow the Manual for Expedited Reporting of Adverse Events to DAIDS and the Division of AIDS Table for Grading **the Severity of Adult and Pediatric Adverse Experiences Events, December 2004**. ~~This The document~~ **Manual for Expedited Reporting of Adverse Events to DAIDS** is included in Appendix VI and in the SSP Manual. The SSP Manual also will provide more detailed instructions regarding expedited reporting.

These adverse events must be documented on the Division of AIDS Expedited Adverse Event (EAE) Form found in the SSP Manual and submitted to the DAIDS Safety Office as described in the reporting guidelines. The Division of AIDS Table for Grading **the Severity of Adult and Pediatric Adverse Experiences Events, December 2004**, must be used for determining and reporting the severity of adverse events. **This table is available on the RCC website at <http://rcc.tech-res-intl.com/>** and can be found in the SSP Manual.

Revision 4 Section 7.3 Accrual, Follow-up, and Sample Size

In order to achieve sufficient statistical power, a total of 1750 serodiscordant couples in which the index case has a CD4+ cell count of 300-500 cells/mm³ will be enrolled in this study over a period of 27 months. As mentioned in Section 7.1, up to 90 couples (~~6-10 couples for each of the 9 sites~~) will be enrolled in the first 3 months during the run-in phase of the trial. A total of 1660 couples will be enrolled from month 9 to 27 after the completion of the run-in phase. All couples will be followed until the end of the trial at 7.25 years (87 months).

Revision 5 Appendix I A. Schedule of Procedures and Evaluations – Index Case

Only the column headers and Footnotes are provided here.

	Screening	Enrollment	Week 2 ⁸	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
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BV, bacterial vaginosis; CBC, complete blood count; IFA immunofluorescence assay; LFT (liver function tests); O&P (ova and parasites); PBMC (peripheral blood mononuclear cells); TV (*Trichomonas vaginalis*). [] = If clinically indicated, or site specific

1 = Women only

2 = Refer to SSP for specific instructions.

3 = Perform at the first two months following initiation of antiretroviral therapy. When starting NVP, perform LFTs at week 2, 4, 6, then monthly for first 20 weeks.

4 = Administer/perform only if index case is on study medication.

5 = Perform at Study Month 1 and 2 only

6 = U.S. sites only: obtain PPD first. If > 5mm induration then chest x-ray is obtained.

7 = A swab should be taken for multiplex PCR at any time an ulcer is observed upon examination for shipment to the HPTN CL.

8 = The two-week visit should be conducted once the index case initiates ART.

Appendix I B. Schedule of Procedures and Evaluations – Partner

Only the column headers and Footnotes are provided here.

	Screening	Enrollment	Week 2 ⁵	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
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1 = Perform only if index case is on ART.

2 = Refer to SSP for specific instructions.

3 = Perform at Study Month 1 and 2 only

4 = A swab should be taken for multiplex PCR at any time an ulcer is observed upon examination for shipment to the HPTN CL.

5 = The two-week visit should be conducted once the index case initiates ART.

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 2.0, May 24, 2004

FINAL Version: 13 July 2005

The following information impacts the HPTN 052 study and must be forwarded to your institutional review board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Please file this letter and any IRB/EC correspondence in your regulatory file and other pertinent files. You are NOT required to submit these documents to the Protocol Registration Office unless the changes result in a change to the informed consent for your site.

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

1. The Inclusion Criteria has been revised to update information concerning efavirenz in response to a recent change in the pregnancy category of the drug. The category has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk). The new category classification requires a change to the inclusion criteria regarding reproductive documentation requirements.
2. The Study Procedures section and the corresponding schedule of evaluations have been corrected to collect demographic information at enrollment instead of at screening. This corrects a minor mistake in the protocol.

Implementation

Modifications outlined below are indicated by ~~strikethrough~~ or **bolded** text.

Revision 1 Section 3.1.1 Inclusion Criteria, Index Case

THE FOLLOWING INCLUSION CRITERIA MARKED WITH AN ARROW WILL APPLY ONLY DURING THE RUN-IN PERIOD:

- For female participants of reproductive potential, a negative serum or urine pregnancy test performed within 48 hours before initiating study treatment.

NOTE: “Reproductive potential” is defined as ~~girls~~ **females** who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months) or have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, or salpingotomy).

- Female participants who are participating in sexual activity that could lead to pregnancy (BUT not receiving EFV) must use at least one reliable method of contraception while receiving the protocol-specified drugs and for 6 weeks after stopping the medications.
- Female participants ~~who are~~ participating in sexual activity that could lead to pregnancy and are receiving EFV must agree to use two reliable methods of contraception: a barrier method of contraception (condoms or cervical cap) together with another reliable form of contraception (condoms, with a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormonal-based contraception) while receiving the protocol-specified drugs and for 6 weeks after stopping the drugs. Another ART drug may be substituted for EFV if participants are not able, or willing, to use two concurrent forms of contraception, or they will be excluded (if another ART drug is not available).
- Female participants who are without reproductive potential, as defined above, or whose male partner(s) have undergone successful vasectomy ~~with documented azoospermia or have documented azoospermia for any other reason,~~ are eligible without requiring the use of contraception. ~~Participant reported history is acceptable documentation of menopause, hysterectomy, bilateral oophorectomy, or tubal ligation.~~ **Acceptable documentation for sterilization or menopause for female participants would include written communication of a procedure signed by a licensed clinician or clinical staff, an operative report, a discharge summary, or a FSH measurement elevated into the menopausal range as established by the site laboratory. For male participants, a laboratory report of azoospermia to document successful vasectomy is required. If only self-reported history is available for sterilization (male or female) or menopause, the female participant must use a barrier method of contraception with a possible second method required at the discretion of the site study physician.**

Revision 2 Section 5 STUDY PROCEDURES, CLINICAL PROCEDURES, AND LABORATORY EVALUATIONS

5.1.1.1 Administrative, Behavioral, and Regulatory Procedures Both Index Case and Partner

- Screening informed consent
- ~~Demographic information~~

5.2.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner

- Study informed consent
- **Demographic information**

Appendix I. A. Schedule of Procedures and Evaluations – Index Case

	Screening	Enrollment	Week 2	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Serocoverts	Confirmed Virologic Failure
Administrative, Behavioral and Regulatory Procedures								
Informed consent (screening or study informed consent form)	X	X						
Demographic information	X	X						

Appendix I. B. Schedule of Procedures and Evaluations – Partner

	Screening	Enrollment	Week 2	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Serocoverts	Confirmed Virologic Failure
Administrative, Behavioral and Regulatory Procedures								
Informed consent (screening or study informed consent form)	X	X						
Demographic information	X	X						

Clarification Memo # 1 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 2.0, May 24, 2004

FINAL Version: 24 September 2004

Summary of Revisions and Rationale

- 1(a, b, c, d, e). The protocol roster is updated to add a new title and address information for Dr. Kumarasamy, a correct email address for Marybeth McCauley, a new mail code for Dr. Gary Thal, and to add Melissa Kaufman and Carolyn Yanavich.
 - 2(a, b). The Antiretroviral Drugs section is clarified to reflect that Reyataz[®] (atazanavir [ATV]) is now a registered trademark and is designated as [®]. In addition, the section is further clarified to reflect the recommended dosing of TDF when co-administered with didanosine enteric-coated (ddI-EC). This clarification does not reflect a correction to information already included in the protocol, but provides further instruction for use.
 3. The Inclusion and Exclusion Criteria is clarified to reflect that breastfeeding is not allowed during the pilot while using ATV. This clarification corrects a minor inconsistency in the protocol.
 - 4(a, b). The tables contained in the Concomitant Medications section are clarified to match the same tables in AACTG A5175. These clarifications correct minor inconsistencies between the tables included in the two protocols.
 - 5(a, b, c). The Precautionary Medications section is clarified to reflect the dosing amounts used for co-administration of tenofovir (TDF) and ddI-EC, and that ATV must not be co-administered with TDF *without* ritonavir (the protocol mistakenly states "...or ritonavir"). In addition, a paragraph is removed from the section as it is a repeat of a paragraph appearing earlier in the section.
 - 6(a, b). The Toxicity Management section is clarified to state that, in general, with an AST or ALT elevation, a protease inhibitor (PI) may be substituted for an NNRTI, and to not specify a particular PI, as is currently reflected in the protocol. This clarification results in a minor change to the existing wording. It is also clarified to reflect that ddI-EC and stavudine (d4T) are not restricted from use during pregnancy, and that they should not be co-administered (as already stated throughout other sections of the protocol).
 - 7(a, b, c, d). The Study Procedures, Clinical Procedures, and Laboratory Evaluations section is clarified to reflect that ATV is being provided by the study and that it is prohibited during pregnancy or breastfeeding in the run-in period of the study. In addition, the section is clarified to reflect that a pregnancy informed consent be obtained for those female index cases not on ART, in order to be consistent with the Pregnancy Informed Consent. The sentence reflecting this guidance was inadvertently missing from the section.
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Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB approval of HPTN 052 Protocol Clarification Memorandum #1 is not required by the sponsor; however, sites may submit the clarification memo to the responsible IRBs/ECs for their information.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1a Protocol Roster

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Revision 2a Section 1.3.4.1, Antiretroviral Drugs, Atazanavir (ReyatazTM, ATV)

Atazanavir (ReyatazTM, ATV)

Refer to the ATZ (ReyatazTM) package insert and the Investigator Brochure (if not registered in country) for more information.

Revision 2b Section 1.3.4.1, Antiretroviral Drugs, Didanosine (Videx[®], ddI-EC)

TDF - ddI-EC Pharmacokinetic Interaction

Once daily ddI-EC 400 mg (all individuals ≥ 60 kg) given 2 hours before TDF 300 mg with a light meal, resulted in an approximately 46% increase in ddI exposure relative to the administration of ddI-EC alone in the fasted state, as measured by AUC ddI concentration. Coadministration of ddI-EC and TDF 300 mg with a light meal resulted in an approximate 60% increase in ddI exposure relative to the administration of ddI-EC alone in the fasted state. Coadministration of ddI EC capsules had no effect on the AUC of TDF. **The recommended dosing is ddI EC 250 mg (if ≥ 60 kg), or 200 mg (if < 60 kg), with TDF 300 mg, administered as a single daily dose with or without food.**

Revision 3 Section 3.2.1, Index Case (Exclusion Criteria)

- Pregnancy (run-in period only). NOTE: Breastfeeding is allowed at enrollment; however, during the run-in period, women may not be on a regimen containing ~~study provided~~ ATV the entire time they are breastfeeding.

Revision 4a Section 4.3, Concomitant Medications

The existing Table 4 in Section 4.3.2, and Table 5 in section 4.3.3 will be replaced with the following two tables, and will be labeled as Table 4a and 4b, and be placed in Section 4.3.2.

Table 4a. Prohibited Concomitant Agents with EFV, NVP, ATV

Agent Class	Prohibited with EFV, NVP, ATV
Antihistaminics	Astemizole (Hismanal®)
	Terfenadine (Seldane®)
GI Motility	Cisapride (Propulsid™)
Psychiatric Medications	St. John's Wort (<i>Hypericum perforatum</i>)
Sedatives/Hypnotics	Midazolam (Versed®) (Can be used with caution as a single dose, when given in a monitored situation for procedural sedation.)
	Triazolam (Halcion®)
Other	Dihydroergotamine
	Ergonovine
	Ergotamine
	Methylergonovine

Table 4b. Prohibited Concomitant Agents with ATV

Agent Class	Prohibited with ATV
Antiarrhythmics	Amiodarone (Cordarone™)
	Lidocaine (Xylocaine®)
Anti-infective	Quinidine (Quinaglute®, Quinidex®)
	Rifampin (Rifadin™, Rimactane™)
Antineoplastic agent	Irinotecan (Camptosar®)
Calcium channel blockers	Bepidil (Vascor®)
HMG CoA reductase inhibitors	Lovastatin (Mevacor®)
	Simvastatin (Zocor®)
H2 blockers	Cimetidine (Tagamet®),
	Ranitidine (Zantac®).
	Nizatidine (Axid®)
	Famotidine (Pepcid®, Pepcid AC®)
Neuroleptic	Pimozide (Orap®)
Protease inhibitors	Indinavir (Crixivan®)
Proton pump inhibitors	Rabeprazole (Aciphex®)
	Esomeprazole (Nexium®)
	Omeprazole (Prilosec®)
	Lansoprazole (Prevacid®)
	Pantoprazole (Protonix®)

Revision 4b Section 4.3.3, Concomitant Medications

Table 5 in the protocol will be replaced with the following table, and will continue to be labeled as Table 5.

Table 5. Precautionary Agents

Agent Class	Precautionary Concomitant Medications
Anticonvulsants	Carbamazepine (Tegretol®)
	Phenobarbital
	Phenytoin (Dilantin™)
Anti-infectives	Artenolil
	Atovaquone (Mepron)
	Atovaquone/proguanil (Malarone®)
	Caspofungin (Cancidas®)
	Clarithromycin (Biaxin®)
	Dapsone
	Fluconazole (Diflucan®)
	Systemic itraconazole (Sporonox®)
	Proguanil (Malarone®)
Alternative/Complementary	Milk thistle (Silymarin, Silybum, Marianum)
Hormonal Agents	Glucocorticoids
Hypoglycemics	Pioglitazone (Actos®)
Sedatives/Hypnotics	All benzodiazepines (e.g.,)
	Alprazolam (Xanax®)
	Diazepam (Valium®)
	Estazolam (ProSom®)
	Flurazepam (Dalmane®)
	Oxazepam (Serax®)
	Temazepam (Restoril®)
	Buspirone (BuSpar®)
	Zaleplon (Sonata®)
	Zolpidem (Ambien®)
Other Agents	Theophylline
	Warfarin (Coumadin®)
	Antacids and other buffered products

Revision 5a Section 4.3.3, Precautionary Medications, bullet Tenofovir

In addition, ~~when TDF and ddI are coadministered, ddI doses should be adjusted as follows: reduce 400 mg QD to 250 mg QD for subjects who weigh ≥ 60 kg; and reduce 250 mg QD to 200 mg QD day for subjects who weigh < 60 kg.~~ **when co-administered, ddI EC 250 mg (if ≥ 60 kg) or 200 mg (if < 60 kg), with TDF 300 mg, should be administered as a single daily dose with or without food.**

Revision 5b Section 4.3.3, Precautionary Medications, bullet Atazanavir

When taken with TDF, ATV plasma levels may be decreased and result in reduced virologic efficacy. When coadministered with TDF, ATV 300 mg with ritonavir (RTV) 100 mg and TDF 300 mg should be given all as a single daily dose with food. ATV should not be coadministered with TDF ~~without or~~ RTV. It is required that a drug combination other than TDF + ATV be used if ritonavir-boosted ATV is not available.

Revision 5c Section 4.3.3, Precautionary Medications, bullet Atazanavir

~~When taken with TDF, ATV plasma levels may be decreased and result in reduced virologic efficacy. It is required that a drug combination other than TDF + ATV be used if ritonavir boosted ATV is not available. Low dose ritonavir must be used whenever ATV is given with TDF.~~

Revision 6a Section 4.5.5.4, AST and ALT Elevation

For asymptomatic elevation 5-10× ULN (Grade 3) believed secondary to study medications, all agents should be held until levels are Grade ≤ 2, at which time therapy may be reintroduced with the substitution of ~~a PI~~ **PI** ~~EFV or NVP, if applicable.~~ For asymptomatic or symptomatic elevation of AST or ALT >10 × ULN (Grade 4), all medications should be discontinued and held until levels are Grade ≤ 2, at which time therapy may be reintroduced with the substitution of a PI for EFV or NVP. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. If the subject was receiving an NNRTI (EFV or NVP), either of these medications should be considered the most likely cause of the elevations. The medications should be substituted and the NRTI medications can be resumed. If elevations >10 × ULN (Grade 4) recur in the absence of an NNRTI drug, all current ART and INH (if subject is receiving INH) should be discontinued. Alternative ART and TB prophylactic regimens may be considered, at the discretion of the study investigator.

Revision 6b Section 4.5.7.2, Pregnant Women on a Regimen Containing ddI and d4T

~~ddI will be replaced with 3TC, and d4T will be replaced with ZDV. Women in this case may return to their secondary regimen following pregnancy at the discretion of the study clinician.~~

Pregnant women may remain on or be given a regimen containing ddI-EC or d4T (but not co-administered).

Revision 7a Section 5.4.1, Procedures for Pregnancy or Breastfeeding at Enrollment

In the run-in period, pregnant women are not eligible for enrollment. In the full study, pregnant or breastfeeding women are eligible for enrollment, and must agree to be randomized. Breastfeeding or pregnant women on Arm 1 (immediate ART arm) should be prescribed ART drugs that are known to be safe during pregnancy or breastfeeding. (*e.g.* EFV, and the combination of ddI and d4T together should not be prescribed to these women.). During the run-in period, women who are breast-feeding should not receive ~~study provided~~ ATV as part of their regimen.

Revision 7b Section 5.4.2, Procedures For Female Index Case on ART Who Becomes Pregnant During Study

A pregnancy informed consent must be obtained. If the pregnant index case is already on a regimen containing EFV, EFV will be discontinued immediately and replaced with another NNRTI or PI during the remainder of the pregnancy, chosen at the discretion of the study clinician. However, during the run-in period pregnant women must not receive a regimen containing ~~study provided~~ ATV. At the time the site becomes aware a participant is pregnant, ~~study provided~~ ATV must be stopped and an appropriate drug given as substitution. In addition, during the run-in period women not already on ART who become pregnant ~~should~~ must not be given ~~study provided~~ ATV at any time during their pregnancy. ~~If during the run in period the site has access to ATV outside of the study, it may be provided per study clinician discretion and/or package insert guidelines.~~ It should be noted that ddI-EC and d4T must not be coadministered during pregnancy.

Revision 7c Section 5.4.3, Procedures for Breastfeeding Women on ART

Changes in ART for women who are breastfeeding will be at the study clinician's discretion. EFV is an evaluable drug for use in HIV-exposed infants and HIV-infected children. For this reason, breastfeeding women receiving EFV will be allowed to continue study drugs while breastfeeding. If a woman is breastfeeding during the run-in period, she must not be provided a regimen containing ~~study-provided~~ ATV.

Revision 7d Section 5.4.4, Procedures for Women Not on ART Who Become Pregnant

A pregnancy informed consent must be obtained. Pregnant index cases not on ART (Arm 2) will be followed per study procedures, and placed on a triple regimen of ART regardless of CD4 + cell count at approximately the beginning of the 2nd trimester of pregnancy (e.g. 12-14 weeks of pregnancy), and for 4-6 weeks following birth. The ART will be provided through the study. The choice of regimen for such women should be documented in the study participant's chart and on any applicable CRF's. The choice of the regimen must NOT include ~~study-provided~~ ATV, ~~unless the site has access to it outside of the study.~~ It should be noted that ddI-EC and d4T ~~should~~ **must** not be coadministered.

Clarification Memo # 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 2.0, May 24, 2004

FINAL Version: 14 December 2004

Summary of Revisions and Rationale

1. The Study Procedures, Clinical Procedures, and Laboratory Evaluations section has been updated to remove the collection of plasma and serum from the index case at the screening visit. The collection of these samples is not necessary at the screening visit, and was inadvertently included in the protocol.
2. Appendix I A has been updated to remove the collection of plasma and serum from the index case at the screening visit. The collection of these samples is not necessary at the screening visit, and was inadvertently included in the protocol.

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB approval of HPTN 052 Protocol Clarification Memorandum #2 is not required by the sponsor; however, sites may submit the clarification memo to the responsible IRBs/ECs for their information.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Text noted below by strikethrough will be deleted; text appearing below in **bold** will be added.

Revision 1 Section 5 Study Procedures, Clinical Procedures, and Laboratory Evaluations

5.1.1.3 Laboratory Evaluations – Index Case

- Urine pregnancy test (women only)
- HIV EIA antibody test/Western blot/IFA
- CBC (including hemoglobin and platelets)
- Blood chemistry (defined as sodium, potassium, chloride, phosphate, bicarbonate, creatinine, and albumin)
- LFTs (defined as AST [SGOT], ALT [SGPT], alkaline phosphatase, and total bilirubin)

- CD4+ cell count
- ~~Sample storage:~~
 - plasma
 - serum

Revision 2 Appendix IA Schedule of Procedures and Evaluations – Index Case

For Appendix IA, only the rows for plasma and serum sample storage are included here.

	Screening	Enrollment	Week 2 ⁸	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
Sample Storage								
Plasma	X	X ²			X	X	X ²	X ²
Serum	X	X			X	X		

HPTN 052 Study Monitoring Committee Review
Review Date: 26 May 2006
10:00am – 12:00pm ET

Participating SMC Reviewers:

Tom Fleming, SMC Chair, University of Washington
Jim Hughes, SMC Co-Chair, University of Washington
Ward Cates, HPTN CORE, Family Health International (FHI)
Mary Fanning, Division of AIDS (DAIDS), National Institutes of Health
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HPTN 052 Protocol Chairs/Site Representatives:

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David Celentano, Johns Hopkins University/RIHES, Baltimore MD
Sheela Godbole, National AIDS Research Institute, Pune, India
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James Hakim, University of Zimbabwe Clinical Research Center, Harare, Zimbabwe
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SUMMARY OF COMMENTS AND RECOMMENDATIONS:

The following are comments and recommendations from the Study Monitoring Committee:

- **The PIs and team members have achieved significant success in the run-in period of HPTN 052.**
- **All international sites have completed enrollment.**
 - It was noted that some sites (*e.g.* Blantyre and Porto Alegre) took longer than the intended 3 months for full accrual and that other sites achieved enrollment targets in much less than 3 months. Some of this diversity in accrual may be reflective of a site's ability to pre-screen couples for enrollment. Sites are encouraged to continue to identify couples as appropriate in preparation for the full study.
- **Fenway Community Health Center (located in Boston, MA, USA) has had difficulty fully enrolling into the run-in period primarily due to the unwillingness of potential participants to be randomized to immediate or delayed treatment (lack of equipoise).**

- The SMC strongly encourages the site to continue with all reasonable efforts to fully enroll participants into the run-in period.
- The SMC encourages the team to seek clarification from DAIDS regarding whether the site will be allowed to initiate its enrollment into the full study at the time the international sites begin.
- **It is important to enroll a population with the intended risk level so that the study will be adequately powered to meet its primary objectives.**
 - Early data reflect that, at some sites, the Index Case and Partners are somewhat older than anticipated and, in some cases, the couples are reporting less sexual activity and higher condom use than expected.
 - It appears that sites are identifying cohorts that will achieve the targeted levels of risk over the full duration of the trial.
- **The data show some discrepancies between screening and enrollment CD4+ cell count values for some Index Cases, with all meeting the eligibility criteria of 300-500 cells/mm³ at screening, followed by a higher or lower value at enrollment.**
 - Two to three of the sites are more heterogeneous in their enrollment CD4+ cell count values than others, which may be due to cofactors such as malaria.
 - CD4 cell counts can be highly variable, and this kind of fluctuation is not necessarily reflective of a true difference in values.
 - The SMC encourages the team to continue monitoring this issue so that proper accommodations can be made, if necessary, to ensure that there is an adequate time difference between ART initiation in the two groups.
- **The retention rates are as expected at this early point in the study, with some sites experiencing a 100% retention rate.**
 - It is important for the sites to achieve the protocol target of 2-4% lost-to-follow-up on an annual basis.
 - There is some early indication that the targeted level of retention might not be achieved for individual clinic visits; however, in most of cases, the couples are facing temporary difficulties that have been subsequently resolved. The site-specific teams expect to recover the participants at future visits.
 - The SMC reiterates the importance of high levels of retention of both the Index Cases and the Partners.
- **The most recent data indicates a very high adherence to study drug (ART).**
- **The team has achieved significant successes since the time of the last meeting in the area of drug procurement.**

- It appears now that Efavirenz will be available and that, while Kaletra is still being pursued, all drugs required for the full study will be available.
- **The team intends to initiate the full study by late summer 2006.**
- **Two sites (Blantyre and Harare) have experienced on-going laboratory-related issues; however, efforts are underway at both sites to implement corrective action measures in order to resolve the issues.**

General Commentary on the Report:

The run-in period is well underway and approaching completion. All sites have been activated and all international sites have completed enrollment. Fenway Community Health Center (located in Boston, MA, USA) has enrolled one couple and, thus, has not completed enrollment to date. The study was to have 86 couples enrolled into the run-in period across all sites; however, total enrollment to date is 81 couples.

Table 2: This table provides the number of participants enrolled per site as well as the number of person-years follow-up at each site. Enrollment at Blantyre and Porto Alegre took considerably longer than the intended 3 months.

Table 4a: This table shows the age of both Index Cases and Partners. Some sites are enrolling participants that are considerably older than anticipated. The SMC was reminded that the sample size is small at this point and that once enrollment numbers increase, the demographics may be more in line with expectations.

Table 6a & b: The decrease in risk behaviors was noted in the run-in cohort, based on the decreased numbers of non-primary partners and increased use of condom use. These factors may not be optimal for a study looking for transmission. It was noted that numbers are small at this time and that as the full study proceeds, it will be important to enroll a population with the intended risk level so that the study will be adequately powered to meet its primary objectives.

Table 7: The SMC asked and was informed that HSV serology is not being measured in this study.

Table 9: This table reports the screening and enrollment CD4+ cell count values. CD4+ cell counts between 300-500 cells/mm³ are required for screening, and the sites are adhering to this requirement. Two or three of the sites in particular are more heterogeneous in their enrollment CD4+ cell count values than others, which may be due to cofactors such as malaria. It was noted that CD4+ cell count values can be highly variable, even over short periods of time, and this kind of fluctuation is not necessarily reflective of a true difference in values. It was suggested that CD4+ percent might be added to this table in order to help analyze the importance of the variable CD4+ cell count values. Of note is the issue of whether the time of initiation algorithm needs to be refined in the delay arm of the study based on variability in the baseline CD4+ cell count values.

Table 10: The SMC noted that these data look very encouraging regarding HIV counseling attendance.

Table 11: The SMC asked whether this table indicated if a visit was missed. SCHARP representatives clarified that the table only reflects participants who attended their appropriate visits.

Table 13: At the time of the last SMC review, one couple had already been terminated at the Lilongwe site. There is now a second couple in Thailand that has permanently separated. In this case the Index Case will stay in the study, but the Partner will be terminated.

Table 14a & b: These tables indicate that Index Cases were retained at a very high level out to 6 months. A few sites have reported retention issues with a small number of their couples. Retention is targeted at 2-4% LFU per year and sites are reminded of the importance of retaining both Index Cases and Partners.

General Issues:

Predictors of incidence and retention will be followed closely by the SMC over time.

Regarding the fact that the site in Blantyre, Malawi took longer to complete enrollment than other sites, it should be noted that some of the other sites had a pre-screened cohort that they had been following and were able to enroll from quickly once activated. It may be that the situation in Blantyre will be more reflective of enrollment for the full study. It is anticipated that V. 3.0 of the protocol will be available in July, 2006 and sites can begin obtaining IRB site approval and then perhaps start enrolling in August, 2006. With this in mind, sites should take time now to identify couples who may become potential participants in the full study.

Merck has indicated that efavirenz will be provided to the study and Kaletra is being pursued from Abbott. If Kaletra is obtained, all the drugs that are required for the full study will be available.

Two sites (Blantyre and Harare) have experienced on-going laboratory-related issues; however, efforts are underway at both sites to implement corrective action measures in order to resolve the issues.

Input from the Sites:

Fenway Community Health Center, Boston, MA, U.S.A. (update given by K. Mayer): K. Mayer reported that Fenway continues efforts to screen and enroll into the run-in period of the study. The team is considering expanding to Miriam Hospital in order to attempt to identify couples in Providence. There is a question of whether Fenway will move into screening for the full study prior to enrolling their targeted number of participants for the run-in period.

YRG CARE, Chennai, India (update given by K. Mayer): K. Mayer indicated that the study is progressing well at YRG CARE. The site team has a list of pre-identified couples ready to be screened and enrolled into the full study.

RIHES, Chiang Mai, Thailand (update given by D. Celetano): D. Celetano reported that extensive pre-screening and community orientation activities have continued and as a result, there are a number of couples lined-up for enrollment into the full study.

University of Zimbabwe Clinical Research Center, Harare, Zimbabwe (update given by J. Hakim): J. Hakim reported that pre-screening efforts are continuing at the Harare site. It was noted that in Harare, the couples that have been enrolled are in their upper 40s (age), report to have less sexual activity and increased condom use than expected. J. Hakim indicated that the team will look at the situation as a group and attempt to develop some strategies to ensure that participants that are enrolled will exhibit the behaviors that are necessary to achieve the end-points of the trial. The Zimbabwe site has been having difficulty with critical value reporting. The site is working on updating their SOPs and representatives from the Central Lab are working with the site to resolve the issues. Considerable time has been invested in management of the Zimbabwe lab as well.

UNC Project, Lilongwe, Malawi (update given by M. Hosseinipour): M. Hosseinipour reported that the variability of CD4+ cell count values at Lilongwe may in part be due to the presence of malaria. Regarding retention of the couple in question at this site, M. Hosseinipour reported that during times that the couple is having marital difficulties, one member of the couple may leave the home for a period of time, but the team makes the effort to bring them back in for their required visits and provides extensive counseling. The lapse in retention is not permanent, but rather sporadic, given marital issues that occasionally arise.

Johns Hopkins/Malawi College of Medicine Project, Blantyre, Malawi (update given by T. Taha): T. Taha reported that the variability in CD4+ cell count values has been observed for several years and may be due to concurrent infections and other underlying factors such as nutrition. The Blantyre site is still working on getting their RNA panels completed for validation so that they can stop sending their samples to Lilongwe. The site is working on updating their SOPs and representatives from the Central Lab are working with the site to resolve lab-related the issues. It was reported that there have been changes in lab management at the Blantyre site and it is anticipated that these changes will have a positive impact on lab operations and results.

NARI, Pune, India (update given by S. Godbole): S. Godbole reported that the site continues with recruitment strategies and pre-screening activities in order to get started on the full study as soon as possible.

Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil (update given by B. Santos): B. Santos reported that the study is progressing smoothly. The site has recently completed enrollment into the run-in period, and they have a number of pre-screened couples waiting to be screened and enrolled into the full study. The CAB is publicizing the study throughout the city.

HPTN 052 Protocol Events Report Listing
Reporting Period: September 2005- Present

Study Site Name	Date(s) of Event	Event Category*	Brief Description of Event	No. Participants Involved
Fenway Community Health, USA	12 APR 06	ART- Protocol Violation	Following his rapidly declining CD4, a participant has been prescribed by his Primary Care Physician, an ART regimen not approved or recommended by the HPTN 052 protocol (TDF/FTC/EFV).	1
Fenway Community Health, USA	24 OCT 05	Eligibility determination	The site did enroll a couple with a previously undisclosed prior history of PEP use.	2
YRG CARE, Chennai, INDIA	10 NOV- 13 DEC 05	Informed consent	Lack of witness Signature Erroneous Completion of Specimen Storage ICFs	16
Hospital Dos Servidores do Estado, Rio de Janeiro, BRAZIL	14 &17 OCT 05	Laboratory	Excess blood (ranging from 5-20 mls) mistakenly collected at screening and enrollment visits.	4
IPEC, Rio de Janeiro, BRAZIL	22 SEP 05	Eligibility determination	A female participant , reported receiving previous ZDV monotherapy for pMTCT, but nonetheless was mistakenly enrolled by the site staff who follow the incorrect version of SSPs.	1
JHP, Blantyre, LILONGWE	05 AUG 05	Laboratory	Inadvertent additional testing was performed at screening, and at enrollment visit	5
RIHES, Chiang Mai, THAILAND	18-27 July 05	Informed Consent	The site has given additional reimbursement to some participant to cover the cost of transportation, as the price of petrol has risen steadily since the ICFs were written. As a result, the total reimbursement for those participants was above the reimbursement listed in the ICFs.	4
UNC , Lilongwe, MALAWI	15 JUL 05	Informed Consent	Between 12 June 2005 and 29 July, a total of 7 participants provided a version of written informed Consent that had been approved by the NHSRC (local IRB), but had not been approved by the UNC IRB.	7

HPTN052 Protocol Safety Review Committee Summary

14 June, 2006

Claude Drobnes

All PSRT conference calls have been cancelled to date due to no emerging safety concerns. Prior to each scheduled PSRT conference call, all PSRT members received an e-mail indicating that I was canceling the call and inviting them to send me via e-mail any questions/concerns that they may have. I never received any feedback, which I interpreted as consensus that there was no apparent safety issue.

Pharmacy Affairs Branch Summary

15 June, 2006

Eva Purcelle, PAB

Some of the sites were still dealing with the same issues addressed in the previous summary, i.e., giving back used study product to the same participant when dispensing at the next visit, but I do believe this may be an ongoing concern because it is a procedure outside of the general scope of some pharmacy practices.

I would anticipate that there may be issues or questions from the sites as they begin to prepare and enroll into the full study. With the increased numbers of enrolled participants in HPTN 052 in combination with the increasing enrollment in other studies, this may uncover some new and unforeseen situations.

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HIV Specialty Lab

HPTN 052 Central Laboratory Summary report for SMC call Updated 6/13/06

Chiang Mai

- No proficiency problems noted
- Wet mount proficiency test-passed
- Submitted revised Critical Value reporting SOP
- Performing Weekly LDMS –Clinic reconciliation checks

Pune/NARI

- Problems noted with microbiology proficiencies – PRFs returned. Has shown improvement in this area
- Wet mount proficiency test- passed
- Submitted revised Critical Value reporting SOP
- Performing Weekly LDMS –Clinic reconciliation checks
- Site ran out of space in their liquid nitrogen freezer. PBMC samples were being stored at -70. Cells were frozen down correct. Consensus is that viability will still be good.
- Site found one possible sample mis-labeling between partner and index. Samples were destroyed.

Chennai

- No proficiency problems noted
- Wet mount proficiency-passed
- Pending Enrollment QA shipment
- Submitted revised Critical Value reporting SOP
- Performing Weekly LDMS –Clinic reconciliation checks

Lilongwe

- Minor proficiency problems noted for malaria smear and rpr titers (last round)
- Wet mount proficiency-passed
- Pending final review of revised Critical Value SOP
- Performing Weekly LDMS –Clinic reconciliation checks

Blantyre

- Problems noted with TAT
- Problems with last round of hematology proficiency – differential portion
- Wet mount proficiency- passed
- Pending final review of revised Critical Value SOP
- Problems noted with RNA VQA panels – site is not certified
- Site had some initial LDMS specimen management issues that have been resolved.
- Now performing Weekly LDMS –Clinic reconciliation checks
- No problems with QA sample testing

Harare

Problems noted with critical value reporting and TAT
Problems noted with some microbiology proficiency
Problem with last round of hematology – differential portion
Wet mount proficiency – received results from some staff members, pending results from remaining
Pending review of updated Critical Value SOP
Now performing Weekly LDMS –Clinic reconciliation checks
Problem with QA sample testing. One of the partner samples tested HIV positive. It was determined that there was a specimen mix-up. Both the index and partner enrollment samples were destroyed.

Rio de Janeiro sites

HIV validation completed for new test kit
Wet mount proficiency- received results from 4 staff members, re-training performed for some site personnel
Critical Value SOP has not been received for review
TAT has been received
Now performing Weekly LDMS clinic reconciliation

Porto Alegre

Problems noted with last round of hematology proficiency – granulocytes
Wet mount proficiency- passed
Critical Value SOP has not been received for review
TAT has been received
Pending report on performance of LDMS clinic weekly