Letter of Amendment # 4 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: 9 December 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 do not result in any changes to the informed consent forms. Therefore, subjects who previously provided informed consent and are enrolled in the study need not be re-consented unless otherwise specified by the IRB(s)/EC(s).

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

1. The protocol has been revised to add Gaborone, Botswana and Soweto, South Africa as new study sites.

2a-b. Sections 2.3 and 4.0 have been revised to indicate that viable combinations of study- and non-study provided ART may be used in primary, secondary and/or salvage regimens at the discretion of the site investigator.

3. Table 3 has been revised to include current nevirapine labeling information regarding dosing in patients experiencing rash.

4. Table 4a and Table 5 have been revised to include current labeling information regarding the midazolam warning. Table 5 has been revised to correct the spelling of Artemotil.

5. Section 4.3.2 has been revised to include current Kaletra labeling information regarding the midazolam warning.

6. Section 4.3.3 has been revised to include drug-drug interactions regarding the administration of atazanavir.

7. Section 6 has been revised to include information regarding the implementation of DAERS for Expedited Adverse Event (EAE) reporting.

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 1 **Schema**

Study sites:

Gaborone, Botswana

Soweto, South Africa

Revision 2a Section 2.3 Study Design

It is recommended that Combivir® and EFV or ATV be used as the primary regimen; however, **at the discretion of the site investigator,** study clinicians may use **any** other **viable combination of** study-provided ART. ~~after obtaining permission from the HPTN 052 CMC.~~ Secondary and salvage regimens are not defined by the protocol and may contain any viable combination of three or more of the HPTN 052-provided study drugs at the discretion of the site investigator. **Regimens containing** non-study-provided ART (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may also be used ~~in secondary and salvage regimens~~ if approved by the HPTN 052 CMC. If non-study ART is used during the study, it must be provided by non-study prescription.

Revision 2b Section 4.0 Study Treatment Considerations

The ART drugs provided for use in this study include Combivir® [3TC/zidovudine (ZDV)], efavirenz [EFV], atazanavir [ATV], nevirapine [NVP], tenofovir [TDF], lamivudine [3TC], didanosine [ddI-EC], stavudine [d4T], Kaletra®/Aluvia® [lopinavir(LPV)/ritonavir (r)], and Truvada® [emtricitabine (FTC)/tenofovir (TDF)]. It is recommended that Combivir® and EFV or ATV be used as the primary regimen; however, **at the direction of the site investigator,** study clinicians may **use** any other **viable combination of** study-provided ART. ~~after obtaining permission from the HPTN 052 CMC.~~ Secondary and salvage regimens are not defined by the protocol and may contain any viable combination of three or more of the HPTN 052-provided study drugs at the discretion of the site investigator. **Regimens containing** non-study-provided ART (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may also be used ~~in secondary and salvage regimens~~ if approved by the HPTN 052 CMC. If non-study ART is used during the study, it must be provided by non-study prescription.

Revision 3 Table 3

Table 3: Antiretroviral Therapies

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Nevirapine NVP Viramune®	NNRTI	200 mg tablets	200 mg for 14 days, then 400 mg	1 PO QD for first 14 days (lead-in), then 1 PO BID thereafter with or without food.	25°C 77°F Excursions permitted between 15-30°C (59-86°F)	Whenever NVP is initiated (even if as a substitution for EFV), it should be started with the lead-in of 200 mg PO QD for 14 days; then 200 mg PO BID. If the person tolerates NVP for ≥ 3 months, the dose may be changed to 400 mg PO QD. It is recommended that the QD dose be taken at bedtime, although this is not required. Health care providers must review signs and symptoms of NVP-related hypersensitivity and hepatitis with the participant prior to dispensing NVP. Participants should contact their site physician if they develop rash or signs and symptoms of hypersensitivity or hepatitis. If rash occurs during lead-in, do not increase dose until the rash has resolved. After reaching full dose, if NVP dosing is interrupted for >7 days NVP should be started with the lead-in of 200 mg PO QD for 14 days; then 200 mg PO BID. **The lead-in dosing period should not exceed 28 days; in these instances, an alternative regimen should be sought.**

Revision 4 Table 4a

Table 4a: Prohibited Concomitant Medications with Efavirenz, Nevirapine, and Atazanavir

Agent Class	Prohibited with EFV, NVP, ATV
Antihistaminics	Astemizole (Hismanal®)
	Terfenadine (Seldane®)
GI Motility	Cisapride (Propulsid™)
Psychiatric Medications	St. John's Wort (Hypericum perforatum)
Sedatives/Hypnotics	Midazolam (Versed®) **(**~~Can be used with caution as a single dose, when given in a monitored situation for procedural sedation.~~ **Oral midazolam is contraindicated.)**

Table 5. Precautionary Agents

Agent Class	Precautionary Concomitant Medications
Anticonvulsants	Carbamazepine (Tegretol®)
	Phenobarbital
	Phenytoin (Dilantin®)
Anti-infectives	~~Artenotil~~ **Artemotil**
	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
	Alprazolam (Xanax®)
	Diazepam (Valium®)
	Estazolam (ProSom®)
	Flurazepam (Dalmane®)
	Oxazepam (Serax®)
	Temazepam (Restoril®)
	Buspirone (BuSpar®)
	Trazodone (Desyrel)
	Zaleplon (Sonata®)
	Zolpidem (Ambien®)
	Midazolam (In subjects receiving protease inhibitors other than lipinavir/ritonavir or atazanivir, if midazolam is used for sedation in those undergoing procedures, close monitoring for respiratory depression and/or prolonged sedation should be exercised)
Triptan	Eletriptan (Relpax®)
Other Agents	Theophylline
	Warfarin (Coumadin®)
	Fluticasone (Flonase)
	Antacids

Revision 5 Section 4.3.2 Prohibited Medications

If lopinavir/ritonavir or atazanivir is co-administered with parenteral midazolam, close monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.

Revision 6 Section 4.3.3 Precautionary Medications

- ATV-Related Precautions

Do not coadminister ATV with nevirapine because nevirapine substantially decreases atazanavir exposures, and potential risk exists for nevirapine associated toxicity due to increased nevirapine exposures.

Efavirenz decreases atazanavir exposure, therefore, for treatment-naïve patients the recommended dose is atazanavir 400 mg with ritonavir 100 mg and efavirenz 600 mg once daily. Efavirenz should be taken on an empty stomach preferably at bedtime. For treatment-experienced patients, do not coadminister atazanavir with efavirenz because efavirenz decreases atazanavir exposure.

Use with caution if co-administration of atazanavir or atazanavir/ritonavir with oral contraceptives is considered. If a combined oral contraceptive is administered with atazanavir/ritonavir, it is recommended the oral contraceptive contain at least 35 mcg of ethinyl estradiol. If atazanavir is administered without ritonavir, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol.

Potential safety risks include substantial increases in progesterone exposure. The long-term effect of increases in concentration of the progestational agent are unknown and could include risk of insulin resistance, dyslipidemia and acne.

Coadministration of atazanavir or atazanavir/ritonavir with other hormonal contraceptives (eg, contraceptive patch, contraceptive vaginal ring, or injectable contraceptives) or oral contraceptives containing progestagens other than norethindrone or norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied; therefore, alternative methods of contraception (non-hormonal) are recommended.

Midazolam:
Coadministration of oral midazolam with atazanavir is contraindicated. Concomitant use of parenteral midazolam with atazanavir may increase plasma concentrations of midazolam. Coadministration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

H_2-receptor antagonists:
The package insert already contains the following dosing information for treatment naïve patients: atazanavir 300 mg with ritonavir100 mg once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. H_2-receptor antagonist dose comparable to famotidine 40 mg twice daily can be used with atazanavir 300 mg with ritonavir 100 mg in treatment-naïve patients.

For treatment-naïve patients unable to tolerate ritonavir, atazanavir 400 mg once daily with food should be administered at least 2 hours before and at least 10 hours after a dose of the H2-receptor antagonist. No single dose of the H_2-receptor antagonist should exceed a dose comparable to famotidine 20 mg, and the total daily dose should not exceed a dose comparable to famotidine 40 mg.

Substrates of CYP2C8:
Atazanavir is a weak inhibitor of CYP2C8. Caution should be used when atazanavir without ritonavir is coadministered with drugs highly dependent on CYP2C8 with narrow therapeutic indices (e.g. paclitaxel, repaglinide). When atazanavir with ritonavir is coadministered with substrates of CYP2C8, clinically significant interactions are not expected.

Revision 7 Section 6: ADVERSE EVENT (AE) AND EXPEDITED ADVERSE EVENT (EAE) REPORTING

This study will follow standard level 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 Events, Version 1.0, December 2004 (or most current version). The Manual for Expedited Reporting of Adverse Events to DAIDS (dated 6 May 2004 or most current version) can be found at http://rcc.tech-res-intl.com/eae.htm.~~ **The requirements and definitions for expedited reporting of adverse events (AEs) to the DAIDS RCC Safety Office are defined in "The Manual for Expedited Reporting of Adverse Events to DAIDS" (DAIDS EAE Manual) dated May 6, 2004. The DAIDS EAE Manual is available on the RCC website: http://rcc.tech-res-intl.com.**

> **Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.**

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: http://rcc.tech-res-intl.com and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC. The SSP Manual also will provide more detailed instructions regarding expedited reporting.

~~EAEs must be documented on the Division of AIDS Expedited Adverse Event (EAE) Form 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 Events, December 2004 must be used for determining and reporting the severity of adverse events. The ~~EAE reporting form and~~ DAIDS grading table ~~are both~~ is available on the RCC website at http://rcc.tech-res-intl.com/.