

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.**