

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.
-

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

Nagalingeswaran N. (Kumar) Kumarasamy, M.D.
~~Chief Medical Officer & Clinical Researcher~~
~~YRG CARE, VHS Centre for AIDS Research~~
~~and Education~~
Principal Investigator - Chennai Site
~~1, Raman St. T Nagar~~
Tharamani,
~~Chennai, India 6000137~~ India

Revision 1b Protocol Roster

Marybeth McCauley, M.P.H.
Senior Clinical Research Manager
HIV Prevention Trials Network
Family Health International
HIV/AIDS Prevention Trials Division
2101 Wilson Boulevard, Suite 700
Arlington, VA 22201
Phone: (703) 516-9779
Fax: (703) 516-9781
Email: ~~mccauley@fhi.org~~ **mmccauley@fhi.org**

Revision 1c Protocol Roster

Gary D. Thal, M.D.
Associate Director, Scientific Operations
Bristol-Myers Squibb Company
777 Scudders Mill Road
Mail Code: P11- ~~14-20~~
Plainsboro, NJ 08536
phone: 609-897-4423
fax: 609-897-6068
email: gary.thal@bms.com

Revision 1d Protocol Roster

Melissa Kaufman, M.A.
Protocol Operations Coordinator
Statistical Center for HIV/AIDS Research and Prevention
Fred Hutchinson Cancer Research Center
phone: 206-667-4152
fax: 206-667-6888
email: mkaufman@scharp.org

Revision 1e Protocol Roster

Carolyn Yanavich, M.S.
Clinical Research Manager
HPTN CORE Operations Center
Family Health International
2101 Wilson Boulevard, Suite 700
Arlington, VA 22201
phone: 703-516-9779, x 377
fax: 703-516-0295
email: cyanavich@fhi.org

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** ~~NVP~~ for 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.
