Microbicide Trials Network

LETTER OF AMENDMENT #01 TO:

MTN-003B
Bone Mineral Density Substudy
Ancillary Study to MTN-003 (VOICE)

Version 1.0/14 July 2008
DAIDS Document ID 10709
IND # 55,690

Date of Letter of Amendment: 30 April 2010

Instructions to Study Sites from the Division of AIDS

The following information impacts the MTN-003B 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.

Upon receiving final IRB/EC and any other applicable regulatory entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Compliance Center (RCC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003B. Changes previously noted in Clarification Memo (CM) #01 and CM #02, are also included in this LoA.

The primary goal of this LoA is to increase the sample size to include all eligible participants. The safety data on the use of tenofovir in healthy individuals is quite limited. Among the ongoing PrEP studies, only VOICE and two others include bone density substudies. The other studies with BMD are the iPrEX study (all men) and the Botswana CDC trial (TDF2). The Botswana trial and bone density substudy includes both men and women; the number of women in the substudy is less than 200 (randomized 1:1 to FTC/TDF or placebo). Evaluation of BMD at baseline in African women is hampered by the lack of sufficient normal population data, but a preliminary analysis of the Botswana

participants (N=114 women) indicated a higher than expected proportion with osteopenia or osteoporosis (Paxton abstract, IAS 2009). However the classification of osteopenia or osteoporosis is based on comparison to the African-American database which is not the appropriate comparison. This will allow us for the first time, to begin to gather an appropriate database from sub-Saharan African women for future analyses and studies.

MTN-003B has the potential to contribute substantially to the safety profile of TDF in healthy women, to discern the degree of BMD loss and, if it is significant, to determine the risk factors and pathophysiologic mechanism for bone loss. The expansion of the sample to include all eligible women will allow participation of all interested women at the MTN-003B study sites. This provides the opportunity to establish reasonable data on baseline (and longitudinal) bone mineral density in sub-Saharan African women in view of several reports of potential effects from prolonged Depoprovera exposure, nutritional deficiencies, differences in activity, and other competing co-morbidities. Increasing the sample size also improves the ability to evaluate the impact of multiple potential confounders, including age, type and duration of contraception, history of pregnancy and prolonged breastfeeding, and to compare BMD change between the two countries.

Additionally, this LoA provides clarification on the following items:

1. Protocol Team Roster, to reflect updates to the Protocol Team
2. List of Abbreviations and Acronyms
3. Update to Study Procedures to reflect that the SDMC, not the sites, will calculate the average of the DXA scans
4. Adverse event reporting requirements, to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS
5. Protocol Registration requirements, to reflect recent updates to the Protocol Registration template language

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Implementation

This LoA is official MTN-003B protocol documentation. The DAIDS Regulatory Affairs Branch will submit the LoA to the US Food and Drug Administration for inclusion in Investigational New Drug application # 55,690. Upon receipt of all required regulatory and IRB/EC approvals, the revisions listed below will be implemented. Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions from CM #01 (26 January 2009) and CM #02 (16 September 2009)

1. The following modifications have been made to the Protocol Team Roster:

The following individuals have been added to the Protocol Team Roster:

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The following individuals have been removed from the Protocol Team Roster: Nomapondo Barnabas, Missy Cianciola, David Humiston, Corey Kelly, Morenike Ukpong.

2. In Section 5.3, Exclusion Criteria, text is edited as follows:

2. Has a medical condition known to affect bone (e.g., hyperparathyroidism, bone cancer) or taking any medication known to affect bone (e.g., glucocorticoids, heparin, warfarin, cyclosporine, ~~medroxyprogesterone acetate,~~ cancer drugs, and thyroid hormone).

3. The following sections have been updated to allow height and weight measured at VOICE Study Visits to be used at MTN-003B Study Visits.

Section 7.1, Schedule of Study Visits, Table 1: Schedule of BMD Substudy Visits and Evaluations

Nutrition Assessment – Anthropometric (height and weight)****	X	X	X

***** *Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

Section 7.2.2, Anthropometric and Clinical Procedures, third bullet:

- Nutrition assessment - anthropometric (height and weight) ***Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

Section 7.3.2, Anthropometric and Clinical Procedures, second bullet:

- Nutrition assessment - anthropometric (height and weight) ***Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

4. The timing of the DXA scan is further clarified in Section 7.1, Schedule of Study Visits, end of first paragraph:

As indicated in the SSP Manual, all MTN-003B visits may be conducted as split visits.

Detailed Listing of Revisions New to MTN-003B, LoA #01

1. The Protocol Team Roster is updated. Note that some of these updates include modifications to some listings included in CM #02:

The following individuals have been added to the Protocol Team Roster:

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The following individuals are removed from the Protocol Team Roster: Anne Coletti, Nancy Connolly, and Laura McKinstry.

2. The List of Abbreviations and Acronyms is updated:

DAIDS PRO DAIDS Protocol Registration Office

3. The sample size has been increased to include all eligible participants in the following sections:

Protocol Summary:

Sample Size: All eligible participants

Section 4.1, Identification of Study Design, second sentence:

All VOICE participants randomized to oral study product at selected sites will be offered participation in the BMD Substudy and will be accrued, ~~using competitive enrollment,~~ until ~~300~~ **all eligible** participants have been enrolled.

Section 10.1, Overview of Study Design, second and third sentences:

A**ll** ~~total of approximately 300~~ **eligible** participants randomized to oral study product will be enrolled via competitive enrollment at selected substudy sites. ~~Accrual will stop once the target enrollment of 300 is reached.~~

Section 10.4, Sample Size and Power Calculations, second paragraph:

For the purpose of sample size determination, we are conservatively assuming that a minimum of 300 women will enrolled in the study (i.e. 100 women per oral arm). Given that at the selected sites all women enrolled into oral arms will be asked to participate in this study, ultimately approximately 300 to 540 women could be potentially enrolled into this study.

Appendix I: Sample Informed Consent (Bone Mineral Density), PURPOSE OF THE STUDY section, first sentence:

~~About 300 w~~**W**omen **who take oral tablets in the VOICE study** will be ~~in this~~ **offered enrollment into the** BMD Substudy, which will take about 3 years to finish. **Up to 540 women will join this study.**

4. Section 7.4, DXA Scan, second paragraph, first sentence is modified to reflect that the SDMC will calculate the average of both DXA scans.

To reduce measurement error, all DXA scans of the hip (total hip, femoral neck) and PA spine (L1-L4) will be performed in duplicate at each visit, and ~~an average of both measurements~~ results will be recorded on case report forms. **The SDMC will use this data to calculate the average of the two scans for a given visit.**

5. Section 8.2, Adverse Event Definitions and Reporting Requirements, sixth paragraph, is updated to reflect the revised Manual for Expedited Reporting of Adverse Events to DAIDS:

The relationship of AEs involving bone mineral loss will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated ~~may 6, 2004~~ **January 2010** (DAIDS EAE [expedited adverse event] Manual), the VOICE Study oral product Package Inserts and the clinical judgement of the IoR designee.

6. Section 13.2, Protocol Registration is updated to reflect revised Protocol Registration template language, second paragraph:

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS Protocol Registration Office (DAIDS PRO) and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.