

Microbicide Trials Network

Clarification Memorandum #01 to:

MTN-001

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir, Version 1.0, dated 12 November 2007

DAIDS PROTOCOL #10617

IND # 55,690

Date of Clarification Memorandum: 17 April 2008

Section 1: Summary of Clarifications and Rationale

The procedures in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB overseeing the study at their site for information. This CM is official MTN-001 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-001. No change in informed consent is necessitated or included in this CM.

The goals of this CM are to update the Team Roster and clarify the nature of tenofovir assays in Exploratory Endpoints, Study Procedures, and Statistical Considerations. Study Procedures and Appendix 1 are edited to omit behavioral assessments at the 7- and 14-Week Visits. Section 7.9.1 clarifies that creatinine clearance will be calculated for every creatinine result. Section 9.3 is edited to clarify product hold for Grade 3 or Grade 4 Adverse Events. Section 9.5.1 is edited to clarify treatment and product hold in the event of nausea and/or vomiting. Section 13.5 is edited to allow for site-specific approaches to confidential storage of study documents.

Section 2: Implementation

Text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

1. The Protocol Team Roster has been updated.

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2. Protocol Summary, Exploratory Endpoints, first bullet is modified to reflect collection of blood PK measures.

PK measures (~~plasma~~, **blood**, intracellular, and tissue values for C_{min}, C_{max}, and AUC)

3. In Section 7.3 Follow-Up Visits, Table 7: 7-Week and 14-Week Study Visit, the behavioral assessment is omitted.

Behavioral	<ul style="list-style-type: none"> • Administer behavioral assessment
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4. In Appendix 1, Schedule of Study Visits and Evaluations, behavioral assessments are omitted at the 7-and 14-Week Visits.

Behav. Assessment		X	X	X	✗	X	X	✗	X	X	X	
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5. Section 7.8.3 Pharmacokinetic Procedures: Intensive PK Participants (US Sites), fifth paragraph, last sentence is modified to reflect analysis of blood samples.

Blood (~~plasma~~) and intracellular samples will be analyzed for routine PK parameters - C_{max}, T_{max}, AUC, and C_{min}.

6. Section 7.9.1 Local Laboratory Testing, second bullet, second sub-bullet is edited to clarify that creatinine clearance will be calculated every time creatinine is performed.

- o Creatinine (**creatinine clearance calculated for every creatinine result**)

7. Section 9.3 Discontinuation of Study Product(s) in the Presence of Toxicity, Grade 3, first paragraph last sentence is edited to clarify product hold for Grade 3 AEs.

If documentation is not available within 2 weeks to show that the adverse event is ~~less than~~ **≤** Grade 2, the current study product must be permanently discontinued.

8. Section 9.3 Discontinuation of Study Product(s) in the Presence of Toxicity, Grade 4, fourth sentence is edited to clarify product hold for Grade 4 AEs.

If documentation is not available within 2 weeks to show that the adverse event is ~~less than~~ **≤** Grade 2, the study product(s) must be permanently discontinued.

9. Section 9.5.1 Nausea and Vomiting, first sentence is edited to clarify treatment of nausea and/or vomiting. Section 9.5.1, Nausea and Vomiting, Oral Study Product, first sentence is edited to clarify product hold for Grade > 3 nausea and/or vomiting.

Participants with Grade 1 or 2 nausea **and/or** vomiting may be treated symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories.

Participants with Grade ≥ 3 nausea and/or vomiting must hold the study product until the toxicity grade returns to Grade ≤ 2 and be treated symptomatically.

10. Section 10.7.2 Primary Analysis, third paragraph, first and last sentences are modified to clarify that blood tenofovir levels will be measured.

~~Plasma~~**Blood** and intracellular samples will be analyzed for routine PK parameters - C_{\max} , T_{\max} , AUC, C_{\min} - and described using descriptive statistics.

Model building will be attempted to relate ~~plasma~~**blood** and intracellular model drug levels if sufficient samples have detectable drug levels.

11. Section 13.5 Participant Confidentiality, second paragraph, fourth sentence is omitted to permit site-specific strategies for confidential storage of study documents.

~~All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.~~