SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-003D

DAIDS Protocol #:11893

An Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/May 29, 2013

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-003D study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-003D.

Summary of Revisions

To ease in the review process, all revisions are displayed below. A summary of revisions is provided below:

- The cover page has been revised to include all funding agencies for the study
- The Protocol Team Roster is updated to reflect current members. The roster format is also modified to list members by affiliation.
- The list of Abbreviations and Acronyms has been updated
- The Investigator Signature form has been revised
- The background section is updated to include additional and up-to-date information regarding clinical studies. Related sections have been updated accordingly
- Section 4, *Study Design*, has been modified to enhance study clarity and maintain consistency
- Section 5, *Study Population*, has been revised to include a Stage 1 and Stage 2 as well as eligibility criteria for both
- In Section 7, *Study Procedures,* the formatting and organization has been revised. Modifications include Stage 2 procedures. The Sample Informed Consent documents are updated accordingly
- Section 9, *Clinical Management*, has been revised to include sub-section 9.1, *Criteria for Early Termination of Study Participation*
- Section 10, *Analytical Considerations*, is modified to reflect the revised number of participants, inclusion of Focus Group Discussions (FGDs) and Interim Reviews

- Section 13, *Human Subjects Protection,* is updated to reflect the confidentiality risks involved due to participation in FGDs. Also, the Participant Confidentiality and Study Discontinuation sections have been revised

- Section 14, *Publication Policy,* is updated to more accurately describe the DAIDS/NIAID and MTN publication policy

- Appendix II: *Sample Informed Consent Document,* has been added to reflect and explain study procedures for Stage 2 participants

- Other minor updates, corrections, and clarifications are incorporated

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Rationale

The primary purpose of this full version amendment is to explore participants' motivation for study product use/non-use and adherence reporting within the context of actual MTN-003 PK results. Participants will be provided with their MTN-003 (VOICE) PK results, and these results will be used as a tool to further discuss product non-adherence and related behaviors. The study design and study procedures will be modified to allow for additional points of contact with participants to be included in-depth interviews (IDIs) and/or FGDs. FGDs rely on peer-interactions and a different social dynamic to explore normative rather than individual behaviors. Furthermore, FGDs may provide a more natural interview setting, and thus may facilitate candid discussions of the topics of interest.

Stage 1 of this study was conducted under MTN-003D Version 1.0 and included 88 women who underwent IDIs. As per Version 1.0 procedures, these IDIs did not include discussions about participants' PK results. Stage 1 participants with available individual PK results will be re-contacted and invited to participate in Stage 2. Additionally, former VOICE participants with PK data available who did not take part in Stage 1 will also be invited to enroll in Stage 2. This will allow for adequate numbers of women to conduct FGDs as well as provide the opportunity to interview MTN-003D-naïve participants.

Modifications throughout the protocol, including updates to the sample size, study design, study duration, introduction, study procedures, analytical considerations, and the sample informed consent have been incorporated for clarity and consistency. The overall scientific priorities, primary and secondary objective and study endpoint remain consistent with Version 1.0.

Implementation

This amendment is now official MTN-003D protocol documentation. Prior to implementing the revisions listed below, MTN-003D study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs/ECs. Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented.

With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions). Unless otherwise stated section numbers reflect the current version of the protocol.

Detailed Listing of Revisions New to Version 2.0

1. The protocol title, version number, table, section and page numbers, as well as the date, are updated throughout the protocol document.

2. Correction of minor editorial and typographical edits and updates are made throughout the protocol document.

3. Cover Page, the Funding Agencies and grant number have been updated:

~~Sponsored by~~**Funding Agencies**:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US ***Eunice Kennedy Shriver*** **National Institute of**
Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health

Grant #:

~~5-U01-~~**5UM1** AI068633-~~05~~**07**

4. LIST OF ABBREVIATIONS AND ACRONYMS has been updated:

FGD	**Focus Group Discussion**
FTP	**File Transfer Protocol**

5. The Protocol Team Roster is updated to reflect current Protocol Team members and contact information:

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

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The following individuals have been removed from the protocol: Stephanie Horn, Nyaradzo Mgodi, Gita Ramjee

6. The last sentence of the first paragraph on the Investigator Signature Form has been revised:

Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, ~~and made available to~~ **DAIDS,** NIMH and ~~DAIDS,~~ **other entities** for review prior to submission**, as required by the MTN Publication Policy**.

7. The following revisions have been made to the Protocol Summary:

Sample Size:	~~Up to 80 women~~**Stage 1: 88 Participants** **Stage 2: Approximately 108-144 Participants**
Study Design:	Exploratory sub-study of VOICE using qualitative in-depth interviews (IDIs**) and focus group discussions (FGDs**).
Study Duration:	**Stage 1: Approximately two months for recruitment and follow-up at each site** **Stage 2:** Approximately seven months for recruitment and follow-up~~.~~ **at each site**

8. Section 2.1, *MTN-003 Study*, the last sentence of the first paragraph has been revised, the first sentence of the second paragraph has been revised, a third paragraph has been added, and the last paragraph has been modified:

[...] Approximately 5000 participants were randomized to the five study arms in a 1:1:1:1:1 ratio. The VOICE study ~~is being~~**was** implemented in sub-Saharan Africa. [...]

While the trial ~~is continuing~~**continued** to examine the safety and efficacy of oral Truvada **through the entire trial period**, two separate reviews of data by an independent Data Safety and Monitoring Board (DSMB), in September and November 2011, respectively, resulted in the oral and vaginal tenofovir arms being dropped from the study **early**. [...]

Upon completion of the trial and final analysis, oral Truvada was also found to be ineffective. Therefore none of the three active products tested in the VOICE study – tenofovir gel, oral tenofovir and oral Truvada®– proved to be effective among the 3017 women who were assigned to

them. One potential reason may be that participants did not use them daily as recommended.[1] Drug was detected in less than a third of blood samples from women who were assigned to use either Truvada or oral tenofovir and in less than a quarter of samples from women designated to use tenofovir gel. Moreover, those least likely to use their assigned products, single women under the age of 25, were also the most likely to acquire HIV. Yet, adherence to product use was calculated to be about 90 percent based on what the participants themselves had reported to trial staff (or by ACASI) and on monthly counts of unused gel applicators and leftover pills. In sharp contrast to this low level of product adherence (based on drug levels), participants' retention in the trial was very high (>90%).[40] Given these results, continued exploration of the reasons for the widespread low adherence is warranted (Stage 2), as well as a better understanding of the context and reasons that motivated women to enroll and remain in the trial despite low use of study products, and this, in the face of a very high HIV incidence rate.

In light of VOICE's divergent results, we propose to explore the potential factors that may have contributed to efficacy dilution in the ~~VOICE~~**trial. MTN-003D, was initially designed after the early closure of the oral and vaginal tenofovir arms, and sought to explore those factors contributing to the dilution of efficacy using qualitative methods (Stage 1). Given the subsequent release of VOICE results in February of 2013 and the availability of drug PK data, Stage 2 of MTN-003D has been designed to explore factors influencing adherence in greater depth, including HIV risk perception and motivation to join the** trial.

9. Section 2.2.1, *Adherence*, the last sentence of the first paragraph has been revised, the fifth sentence has been revised and an eighth sentence added to the second paragraph, and the last sentence of the third paragraph has been modified:

[...]It will do this in two ways**, during Stages 1 and 2**: by using VOICE data on adherence to engage participants in an open discussion of non-use and by delving further into the role of the contextual and trial environment in adherence and reporting.

[...] Any potential differences in reported adherence across measures raises questions around true levels of product adherence as well as the measures themselves. For instance, which adherence measure (self-reported use, pharmacy records **,** or self-ranking) most accurately reflects actual product use **and/or drug detection by PK measurement**~~)?~~**?**[8] [...]**Are participants more forthcoming in discussing non-adherence in one-on-one or group interviews, and does the number of interactions with interviewers, a possible proxy for greater trust and rapport, improve accurate reporting? Also, does presentation of final VOICE findings, including individual PK results to participants alter their adherence reporting?** [...]

[...]By conducting this study outside of the VOICE trial context and including additional VOICE sites, MTN-003D will expand upon the VOICE **and VOICE**-C study results, especially in ~~its~~**the** ability to explore the contribution that the trial environment may have had on VOICE participants' use of study products.

10. Section 2.2.2, *HIV Risk Perception and Motivation for Trial Participation*, the first paragraph has been revised:

One possible factor that may contribute to low adherence is participant~~'s~~**'** varying perception**s** of HIV risk, as well as reasons for joining the trial. These factors ~~are being~~**were** assessed quantitatively in a VOICE exit questionnaire; however MTN-003D, using qualitative exploration, will seek to more thoroughly expand our understanding of their relationship to product use **in both Stages 1 and 2**.

11. Section 2.2.3, *Anal S*ex, the last sentence of the second paragraph has been modified:

[...] ~~This~~**Stage 1 of this** study ~~will therefore explore not only~~**explored both** the socio-cultural context that may contribute to anal sex practices and reporting of these practices among VOICE participants~~, but also~~

~~examine~~ **as well as** perceptions of rectal gel efficacy and use within the trial context in order to better understand how anal sex may contribute to dilution of efficacy.

12. Section 2.3.4, *Study Hypothesis*, has been revised:

This study is primarily exploratory and is designed to **both** identify factors that may have affected participant adherence to study product in VOICE, ~~as well as to~~**and** describe how sexual behaviors, ~~specifically~~**such as** anal sex, may have had an effect on product efficacy. As such there is no specific hypothesis that is being tested.

13. Section 2.3.5, *Rationale for Study Design*, the first sentence of the first paragraph has been revised and a second and third paragraph have been added:

MTN-003D will use qualitative in-depth interviews ~~with exited~~**and/or focus group discussions with** VOICE participants to explore study product adherence and**/or** anal sex behaviors in greater depth than was measured quantitatively during trial participation. [...]

The rationale for adding a second stage to this study is that it offers an opportunity to continue to explore the critical issue of participant product adherence within the context of available biological data on drug use (PK results). Specifically, it will allow us to examine whether participants will be more forthcoming about their personal experience with products, including motivations/reasons for use and non-use, when presented individually with biological data on drug use. We aim to understand reasons and motivations for participants' adherence level to the study regimen, especially nonuse of product, despite high study retention and high levels of reported product use. It is anticipated that the provision of PK results to participants will generate more candid discussions of product use during VOICE, compared to discussions in VOICE-C or MTN003D Stage 1.

In Stage 2 of the study, we will also leverage the opportunity to explore how responses to PK results may differ among participants who do and do not have an existing relationship with MTN-003D staff, by enrolling and comparing results from, Stage 1-experienced and Stage 1-naïve participants. It is possible that previously interviewed MTN-003D participants may feel that they cannot contradict their previously reported level of adherence during Stage 1 interviews for fear of negatively impacting their relationship with study staff. Alternatively, lack of rapport may hinder candid discussion with participants not previously interviewed by MTN-003D staff. Additionally, in Stage 2, FGDs will be included. FGDs rely on peer-interactions and a different social dynamic to explore normative rather than individual behaviors. Furthermore, FGDs may provide a more natural interview setting, and thus may facilitate candid discussions of the topics of interest.

14. Section 4.1, *Identification of Study Design*, has been modified:

MTN-003D ~~will be~~**is** a sub-study of VOICE. It is an exploratory study using qualitative research methods, which will be conducted at sites selected by the MTN Executive Committee (EC). VOICE participants will be offered participation in MTN-003D during or after their final VOICE visit. ~~Participation will involve one in-depth interview.~~ **Participants who took part in Stage 1, agreed to one in-depth interview. Participants in Stage 2 of MTN-003D will take part in an in-depth interview and/or a focus group discussion.**

15. Section 4.3, *Time to Complete Accrual*, has been modified:

- ~~The accrual period is planned to occur over approximately 28 weeks.~~
- **Stage 1: Approximately two months for recruitment and follow-up at each site**
- **Stage 2: Approximately seven months for recruitment and follow-up at each site.**

16. Section 4.4, *Expected Duration of Participation*, has been modified:

~~The~~ **For Stage 1 participants, the** expected duration of participation ~~for each participant~~ is up to three hours total, including administrative and data collection procedures.

For Stage 2 participants, the total duration of study participation is not anticipated to exceed six hours, including administrative and data collection procedures. The duration of participation is dependent upon the scheduling of IDIs and/or FGDs. Each IDI and/or FGD is expected to take up to three hours.

17. Section 5.1, *Selection of Study Population and Recruitment*, has been revised:

In collaboration with the MTN Statistical Data Management Center (SDMC), a sample of potentially eligible women will be pre-selected for participation in this study. ~~They will be recruited during or after their final VOICE visit, and up to 80 will be~~**Stage 1 of this study** enrolled **88 participants** into **MTN-**003D and interviewed **them** after they ~~have~~ completed their final VOICE visit. **Approximately 108-144 participants will enroll into Stage 2 of MTN-003D.**

~~Table 1 below presents the estimated overall study sample stratified by target populations of interest. The stratification procedure will ensure that approximately 10% of participants will have reported engaging in anal sex while enrolled in the VOICE study, and approximately 10% will have acquired HIV during the VOICE trial. The overall sample will be evenly distributed among tablet and gel users. Table 1 below includes a 20% oversampling to account for those who are unwilling to be recontacted, refuse participation or are found to be ineligible.~~

~~**Table 1. Estimated** OVERALL STRATIFIED RECRUITMENT SAMPLE~~

~~**Study Group:**~~	~~**Tablet Users**~~	~~**Gel Users**~~	~~**Total**~~
~~Reported Anal Sex~~	~~5~~	~~5~~	~~**10**~~
~~Acquired HIV while enrolled in VOICE~~	~~5~~	~~5~~	~~**10**~~
~~All other women~~	~~49~~	~~49~~	~~**78**~~
~~**Total**~~	~~**59**~~	~~**59**~~	~~**98**~~

18. Section 5.2, *Inclusion Criteria*, an inclusion criteria has been added:
4) Stage 2 participants must have pharmacokinetic data available

Note: Women from Stage 1 who have PK data available will be considered eligible for Stage 2.

19. Section 7, *Study Procedures*, the second paragraph has been modified:

Given that the study objectives seek to gain insight into the influence of the trial culture and the environment on behaviors that contribute to efficacy dilution (i.e., non-adherence and**/or** unprotected anal sex), we will conduct all interviews in an environment ~~which~~**that** feels safe and neutral to participants. Study staff and participants will identify a mutually agreeable location, which feels safe, private and comfortable for the study participant. This location may be ~~the participant's home,~~ a designated neutral study interview**/FGD** location, **the participant's home (for IDIs),** or, if ~~requested by the participant, the~~**needed, a** VOICE site may be used. Additionally, interviews will be conducted by researchers who have had no prior interaction with the VOICE participant**, while they were enrolled in the VOICE study**.

20. Section 7.1, the section title has been modified:

Section 7.1 **Stage 1** ~~Screening and Enrollment~~

21. Section 7.2., *Stage 2*, has been added:

7.2 Stage 2

22. Section 7.2.2, Table 2 *Screening and Enrollment Procedures*, has been added:

Table 2. Screening and Enrollment Procedures

Screening and Enrollment	
Component	**Procedures**
Administrative and Regulatory	• **Confirm eligibility** • **Obtain written informed consent** • **Collect demographic data** • **Provide reimbursement for study visit**
Behavioral	• **Provision of overall VOICE results and individual PK results*** • **Administer questionnaire (Case Report Form (CRF)*** • **Conduct in-depth interview (IDI)***

***=if indicated**

23. Section 7.3, *Stage 2 Follow-up Visit(s)*, has been added:

7.3 Stage 2 Follow-up Visit(s)

24. Section 7.3.1, Table 3, *Follow-up Visit Procedures*, has been modified:

Table 3. Follow-up Visit Procedures

Follow-Up Visit(s)	
Component	**Procedures**
Administrative and Regulatory	• **Provide reimbursement for study visit**
Behavioral	• **Provision of overall VOICE results and individual PK results*** • **Administer questionnaire (Case Report Form (CRF)*** • **Conduct in-depth interview (IDI)*** • **Conduct focus group discussion (FGD)***

***=if indicated**

Combining the Screening and Enrollment Visit with Follow-up Visits is permitted. In addition, multiple visits may be conducted to complete all required procedures, if necessary.

25. Section 7.3, *Demographic and Behavioral Data*, has been revised:

A brief questionnaire will be completed **on a CRF** to capture and/or update demographic ~~and~~**,** sexual behavior data **and current involvement in any trial or HIV-related study** (e.g., to allow for descriptive statistics to assess the characteristics of MTN-003D participants). **The questionnaire will also capture a participant's reaction and comments after provision of overall VOICE results and of her PK results.**

26. Section 7.4, *Stage 1*, has been modified:

7.4 Stage 1

7.4.1 In-depth Interview Procedures

~~Qualitative~~**Stage 1, qualitative** interviews ~~will cover~~**covered** two main topics, adherence and anal sex. In-depth interview guides ~~will be~~**were** developed, ~~which will be~~**and** administered by qualified female social scientists. Guides ~~will contain~~**contained** key research questions relating to the main topics of interest, and suggested probes. Interviews ~~will be~~**were** audio-recorded and transcribed and translated into English (if applicable).

Adherence

Discussions on adherence ~~will focus~~**focused** on exploring 1) potential discrepancies between actual and reported product use, and 2) reasons underlying actual and reported product use as they are influenced by the socio-cultural environment.

Motivations to join the trial, and risk perception in particular, ~~will be~~**were** explored as one of the explanatory factors contributing to suboptimal adherence. This topic ~~will serve~~**served** as an icebreaker and a way to encourage the participant to engage in the interview process. We ~~will investigate~~**investigated** participant risk perception, how the socio-cultural environment contributes to that perception, and the way perceptions may have influenced product usage. We ~~will~~ also ~~explore~~**explored** other reasons for joining the trial and their effect on motivation to use the product and actual product use. The discussion ~~will move~~**moved** progressively from a general discussion of risk perception to how risk perception and other factors ~~relate~~**related** to participant interest/willingness to use study products during the trial.

~~Following~~**For Stage 1 participants, following** the discussion of risk perception/motivations, several qualitative tools, such as short scenarios, visual **VOICE study timeline** displays, **show cards** and/or open-ended questions ~~may be~~**were** used to explore participant's understanding of the adherence questions, including the qualitative rating scale that was administered in VOICE. ~~Questions will be~~**Probes were** designed to help understand how women interpreted these questions in general, and in relation to their experience of product use. ~~In the case of scenarios, short descriptive examples of hypothetical participants' product use would be developed in advance by the team, to explore different response categories. Culturally appropriate visual displays (e.g., pie or bar charts, images of object piles, etc.) representing aggregate levels of adherence based on self-rating scores of adherence, product dispensation and return, and/or self-reported product use at the site level, may be used to further explore reported adherence.~~ Participants ~~will~~**were** also ~~be~~ asked to provide their opinions about why differences ~~may exist~~**existed** between the various **adherence** measures.

Finally, additional questions and probes ~~will be~~**were** designed to delve further into the social and cultural norms that ~~may play~~**might have played** a role more broadly in both reported and actual adherence levels. Larger contextual issues that ~~affect~~**might have affected** participants' actual and reported product use such as culture, community, and the social environment, as well as the trial-specific context (e.g., power issues between research staff and participants, trial procedures, interviewing modes, and counseling, including the Voice Adherence Strengthening Program), ~~will be~~**were** a focus of this investigation.

Anal ~~sex~~**Sex**

~~A discussion of~~**Stage 1 discussions about** anal sex and rectal gel use ~~will follow~~**followed** the discussion of product adherence, using an interview guide developed by the investigators. Similar to the discussion of adherence, ~~several~~**an** additional qualitative ~~tools~~**tool** (e.g., ~~short scenarios,~~ body mapping~~, etc.) may be~~ **activity) was** used to supplement this discussion. While a subset of participants who reported having anal sex ~~will be~~**were** purposefully sampled for this study, all participants ~~will be~~**were** asked about the topic. Those who reported the behavior ~~will~~**were** not ~~be~~ alerted that this was a stratification criterion and

the interview ~~will~~**was** not ~~be~~ targeted towards their specific reporting of the behavior. The interviewer ~~will~~**did** not know what participants reported about anal sex behavior during the VOICE study.

Participants ~~will~~**were** first ~~be~~ asked to describe in their own words and/or demonstrate using techniques such as body mapping what is meant by anal sex to verify their understanding of the question administered during VOICE using Audio Computer-Assisted Self-Interviewing (ACASI). Depending on their understanding, participants ~~will be~~**were** provided an accurate definition of anal sex. Given the sensitivity of the topic, this clarification ~~may be followed by either open-ended questions, normative statements, or hypothetical scenarios, based on existing empirical data (e.g., from VOICE-C) and published data on anal sex behaviors. The use of scenarios to elicit community norms and behaviors has been shown to be effective when collecting data on sensitive topics.33,34 These statements/scenarios or other techniques for eliciting sensitive information will be used to probe participants about the context in which anal sex occurs in their community, in a neutral, non-personally threatening way. Personal experiences will be discussed only if the participant acknowledges~~**was followed by open-ended questions. Personal experiences were discussed only if the participant acknowledged** engaging in this behavior.

The occurrence of rectal gel application among VOICE participants in the vaginal gel group ~~will~~**was** also ~~be~~ investigated using a similar methodology. ~~For example, since not all participants will have participated in the gel arm, hypothetical scenarios may be presented that require the participants to speculate on a character's rectal use of gel when engaging in anal sex.~~ Participants ~~may~~**were** also ~~be~~ probed on **other women's and** their own ~~hypothetical~~**potential** non-vaginal use of study gel ~~within the given scenario~~ and the reasons for use or non-use.

27. Section 7.5, *Stage 2*, as well as, Figure 1: *Stage 2 Behavioral Mode Assignment* have been added:

7.5 Stage 2

Participant Selection:

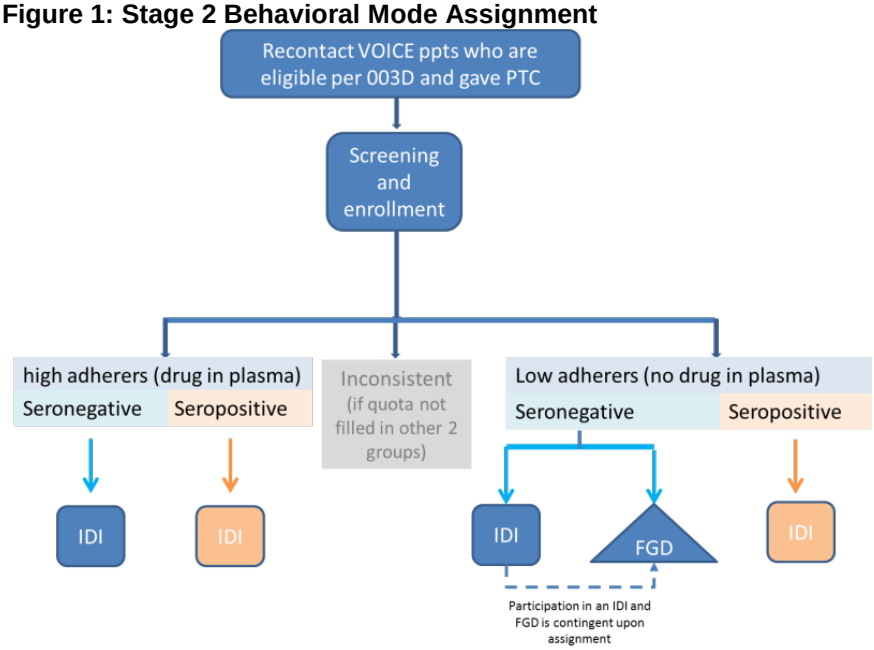
In addition to the study eligibility criteria, Stage 2 participants will be systematically selected and approached for participation based on several characteristics, including, but not limited to: PK-defined adherence-level, VOICE study product assignment, HIV status, previous enrollment in MTN 003D and age, see MTN-003D SSP for additional details.

HIV-positive women will be invited for a single IDI. The number of seroconverters at each site will be too small to consider a HIV-positive only FGD, and mixing seronegative and seropositive participants in the same group may introduce various biases (e.g., social acceptance bias, sensitivity bias), in addition, participant confidentiality regarding serostatus may be compromised in such a group setting. Therefore, HIV-positive women will not be included in the FGDs.

HIV-negative women will be invited for either a single IDI and/or an FGD. We will aim to interview a set number of HIV-negative "high adherers" per treatment assignment at each site. In addition, drawing from both women who participated in 003D Stage 1 and those who did not, we will aim to enroll a set number of HIV-negative women classified as "low adherers" per treatment assignment and conduct IDIs. HIV-negative "low adherer" participants who are identified by site staff to be "forthcoming" when presented with PK results regarding their actual product experience and challenges may be invited to participate in a subsequent FGD. In these cases, staff will ask these participants if they are willing to a) discuss their adherence challenges with their peers, and b) help FGD facilitators encourage other participants to be forthcoming regarding their experiences and challenges with study products. As such FGDs will be limited to participants who are low adherers. As described above, FGDs are an important data collection method in which to capture group attitudes and norms. The goal is for women to openly share stories and discuss product experiences within a setting where they are not being individually questioned by a researcher.

Ideally, FGDs will be homogenous by treatment assignment. In addition to any IDI participants invited to participate, FGD participants will be recruited in sequential order from a list provided by the Data Coordinating Center, see Section 10 for additional details.

Figure 1: Stage 2 Behavioral Mode Assignment



7.5.1 IDI and FGD Procedures

Qualitative interviews will cover participant adherence (see Section 7.6.2). Stage 2 in-depth interview guides will be administered by qualified female social scientists. Guides will contain key research questions relating to the main topics of interest, and suggested probes. Interviews will be audio-recorded and transcribed and translated into English (if applicable).

7.5.2 Topics to be explored during the IDIs and FGDs

Discussions on adherence will focus on exploring 1) potential discrepancies between actual and reported product use, and 2) reasons underlying actual and reported product use as they are influenced by the socio-cultural environment.

Motivations to join the trial, and risk perception in particular, will be explored as one of the explanatory factors contributing to suboptimal adherence. This topic will serve as an icebreaker and a way to encourage the participant to engage in the interview process. We will investigate participant risk perception, how the socio-cultural environment contributes to that perception, and the way perceptions may have influenced product usage. We will also explore other reasons for joining the trial and their effect on motivation to use the product and actual product use. The discussion will move progressively from a general discussion of risk perception to how risk perception and other factors relate to participant interest/willingness to use study products during the trial and challenges to follow study instructions for product use.

Various tools will be used to facilitate interviews and discussion of sensitive topics with Stage 2 participants. These may include visual displays of PK data/results, timelines (also used in Stage 1), show-cards listing topics and themes previously elicited in other studies, including Stage 1 MTN-003D qualitative interviews, and newspaper clippings of VOICE results, when appropriate. These tools can help to deepen our exploration of adherence/non-adherence issues, trial

experience and socio-cultural context influencing product use and sensitivity around disclosure to staff of actual product-related behavior. The topics of discussion will include systemic non-use of study products in VOICE (for the majority – those with no to very few samples with drug present) and/or ability to sustain consistent product use as part of the VOICE trial (for the minority – those with drug in most their samples, i.e. high adherers) particularly among younger women.

Questions were/are designed to help understand how women interpreted these questions in general, and in relation to their experience of product use. Culturally appropriate visual displays (e.g., pie or bar charts, images of object piles, etc.) representing aggregate levels of adherence based on self-rating scores of adherence, product dispensation and return, and/or self-reported product use at the site level, may be used to further explore reported adherence. Participants will also be asked to provide their opinions about why differences may exist between the various measures.

Finally, additional questions and probes will be designed to delve further into the social and cultural norms that may play a role more broadly in both reported and actual adherence levels. Larger contextual issues that affect participants' actual and reported product use such as culture, community, and the social environment, as well as the trial-specific context use of products prompted by imminent study visits ("white coat effect"), will be a focus of this investigation. Further potential power issues between research staff and participants, trial procedures, interviewing modes, and counseling, including the Voice Adherence Strengthening Program may be explored.

28. Section 8.1, *Safety Monitoring*, the last sentence of the first paragraph has been modified:

Since the safety risks are minimal in this study, if any such unexpected concerns arise, the team will notify an appropriate on-site staff member (e.g., site clinician, counselor, **and/or** nurse) affiliated with the clinical research site (CRS) for follow-up.

29. Section 9.1, *Criteria for Early Termination of Study Participation*, has been added:

> **Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study funder, the MTN, government or regulatory authorities, including the Office for Human Research Protections (OHRP), other government or regulatory authorities, site IRBs/ECs terminate the study prior to its planned end date. Study staff members will record the reason(s) for all withdrawals in participants' study records.**

30. Section 10.1, *Overview and Summary of Design*, has been revised:

MTN-003D is an exploratory sub-study of VOICE using qualitative research methods, specifically in-depth interviews **and focus group discussions**.

31. Section 10.4, Number of Participants, has been revised:

MTN-003D will include a stratified sample of ~~up to 80~~ **88** participants **in Stage 1 and approximately 108-144 participants in Stage 2**. Participants will be systematically selected from former VOICE participants at participating VOICE sites. ~~Approximately~~**In Stage 1, approximately** half of the study sample ~~will represent~~**represented** gel users (both active and placebo) and half ~~will represent~~**represented** tablet users (either tenofovir, Truvada, or placebo). At each site, selection of participants ~~will be~~**were** stratified to ensure that ~10% of the sample include**d** women who reported engaging in anal sex and another ~10% of the sample encompasse~~s~~**d** women who acquired HIV during the trial. Valid data from all women interviewed will be considered in the primary analysis.

In Stage 2 of this study, participants with PK drug results available will be considered eligible. Assignment to either a FGD or IDI or both is dependent upon participants' level of product adherence, see SSP for the definitions of high and low adherers.

While the number of participants in each group at a given site is relatively small, we anticipate they will still be sufficient to reach theoretical saturation.[41] Furthermore, diversity across participants and representativeness of the overall VOICE trial will be ensured by enrolling participants at each of the three participating VOICE countries, Uganda, Zimbabwe, and South Africa.

Table 4. Estimated Overall Stage 2 Sample per Country

		Approximate Number of IDIs/FGDs to be Conducted within Each Country*		
Adherence Level**	**Study Group**	**HIV(+)**	**HIV(-)**	**Total N**
Low Adherence per PK results	**Gel**	**2 IDI**	**4 IDI/2 FGD⌂**	**18**
	Tablet	**2IDI**	**4 IDI/2 FGD⌂**	**18**
High Adherence per PK results	**Gel**	**2IDI**	**4IDI**	**6**
	Tablet	**2IDI**	**4IDI**	**6**
Approximate Total N		**8**	**40**	**48**

⌂ Approximately 6 participants will take part in each FGD
***At the discretion of MTN-003D leadership, and in consultation with DAIDS and NIMH, these projections may be modified**
****Women will be drawn from Stage 1 and 003D naïve participants. If quota for low and high adherence cannot be filled we will recruit women with inconsistent adherence (some drug detected in their plasma). See the SSP for additional details.**

32. Section 10.5.1, *Study Monitoring Committee (SMC)*, the following last paragraph has been added:

Interim Reviews: The study team will suspend data collection after ~12 IDIs and ~3 FGDs with low-adherers provided that at least 2 countries have contributed data, to determine whether to: a) proceed with full data collection per protocol; b) limit data collection activities; or c) terminate data collection activities. This decision will be made amongst the Protocol Chairs and key members of the protocol team, based on an evaluation as to whether the interviews are successful in yielding new data and insight into VOICE non-adherence.

33. Section 10.5.2, Data Analysis, the following modifications have been made to the Qualitative Analysis section:

Qualitative Analysis

Data Sources

The qualitative data from MTN-003D will include two main data sources:

- Handwritten notes and summaries of IDIs **and FGDs**
- Transcripts from audio-recorded IDIs~~.~~ **and FGDs**

34. Section 13.4.1, *Risks*, the following last paragraph has been added:

Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions. All FGD participants will be asked and strongly encouraged to respect each other's confidentiality, but participants who participate in the FGDs may still disclose what other participants said during the group discussion. Furthermore, all FGD participants will be asked to use pseudonyms for themselves and for anyone they may talk about during the course of the FGD.

35. Section 13.6, *Participant Confidentiality*, the second paragraph has been modified:

All study-related information will be stored securely at the study site ~~or designated location. All participant information will be stored in locked areas with limited access. All study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. Forms, lists, logbooks, appointment books, informed consent and any other documents that link participants' ID numbers to identifying information will be stored in a separate, locked file in an area with limited access to identifiable information. All local databases will be secured with password-protected access systems.~~**. All participant information will be stored in locked areas with access limited to study staff.** Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following: [...]

36. Section 13.9, *Study Discontinuation*, has been modified:

> This study may be discontinued at any time **if the study funder,** the MTN, **government or regulatory authorities, including** the Office for Human Research Protections (OHRP)**, other government or regulatory authorities,** ~~other government or regulatory authorities,~~ site IRBs/ECs **terminate the study prior to its planned end date**.

37. Section 14, *Publication Policy*, has been modified:

DAIDS/NIAID and MTN policies will govern publication of the results of this study. ~~Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, and NIMH for review prior to submission.~~

38. Appendix II, *Sample Informed Consent Document*, has been added for Stage 2 participants:

APPENDIX II: Sample Informed Consent Document

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

MTN-003D
An Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial
Version 2.0

STAGE 2 PARTICIPANTS

May 29, 2013

PRINCIPAL INVESTIGATORS:
PHONE:

INFORMED CONSENT
You are being asked to take part in this research study because you are a woman who took part in the VOICE trial and received study product for at least three months. As you consented to during your VOICE participation, blood specimens were drawn for the purposes of understanding how much of the study drug was present in your body. We would like to take the opportunity to discuss those test results with you. Approximately 108-144 women will participate in this study at multiple sites. Before you decide if you want to join this study, we want you to know about the study. This Screening/Enrollment consent form gives you information about this study. MTN-003D staff will talk with you about the study and answer any questions you may have.

YOUR PARTICIPATION IS VOLUNTARY

Participation in this study is voluntary. You will be asked to sign or make your mark on this form to indicate whether you agree to participate in this study. Before you decide whether to be in MTN-003D, we would like to explain the purpose of the study. If you decide to enroll in this study, you may decide to withdraw from the study at any time. There will be no penalty for refusing to participate or choosing to withdraw from this study.

PURPOSE OF THE STUDY

The main goal of this study is to better understand VOICE participants' experience with study product and sexual behavior while participating in VOICE.

STUDY PROCEDURES

There are no medical procedures or drugs involved in this research study. If you agree to join this study, you will be informed of the VOICE study results and of your study product use as determined by a blood test. You may be asked to participate in in-depth interviews (IDIs) in the presence of one or two MTN-003D research staff members and/or you may be asked to participate in a focus group discussion (FGDs) with other study participants about opinions that you and other participants have. It is important that you know that that by signing this informed consent you are agreeing to take part in both an IDI and an FGD; however you may be selected to take part in an interview and not a focus group discussion or vice versa. If you agree to take part in this study, the interviewer will ask you some brief questions and write your responses on a form. During the IDIs, the interviewer will also ask more in-depth questions, during which time notes may be taken and the conversation will be audio-recorded. During the FGD, you will join other women who participated in the VOICE trial and who are also aware of how much of the study drug was present in their bodies. During the FGD a discussion about the study products, study product use, and overall study experience will occur. These discussions will also be audio-recorded. You will be asked to use a fake name for yourself and for anyone you may talk about during the FGD.

You will be asked some general questions, such as your age, education, living situation, relationship status, and health. The interviewer will also ask questions about your experiences while participating in the VOICE trial. These will include questions about different ways women used their study product, your use of the study products and your understanding of the questions in VOICE that asked about product use and sexual behaviors. The interviewer will discuss your opinions about sexual behavior in your community. You will not be required to discuss your personal sexual behavior. You will also be informed of the VOICE trial results and of your study product use as determined by a blood test. Your response to receiving these results will also be recorded.

We expect the interview and focus group procedures will take approximately 3 hours each. If you are selected to have an IDI it will be completed at a place agreed upon by you and the study staff, which may be your home, a designated neutral study interview location, the clinic you went to for your VOICE visits or another convenient place of your choice. Clinic staff will let you know where the FGD will take place.

The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. The information that links you to the research data will be kept in a secure location that will be accessed only by members of the MTN-003D study team for the purposes of this research.

To obtain information about your participation in VOICE, the MTN-003D study team will need to access your VOICE research records. By signing this form, you are giving the MTN-003D study team permission to look up and record the needed information from your research record.

RISKS AND/OR DISCOMFORTS

During the interview we may ask you some questions that cause you to feel embarrassed or uncomfortable. You can choose not to answer questions in the interview at any time. It is also possible that people or family members may find out you are participating in this study. As a result, they may ask questions about the study, treat you unfairly, or you may encounter problems in being accepted by your family and/or community.

If you choose to participate in the group discussion, other participants will hear what you say. We will not reveal your full name to other participants. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

Another possible risk of this study is loss of confidentiality of the information you give. Every effort will be made to protect your confidential information, but this cannot be guaranteed. To reduce this risk, we will strictly protect the information recorded during your interview. The audio recording, notes, and analyses from these materials will be kept confidential. This means that no one other than the MTN-003D interview team will have access to your responses. The information that links you to the research materials will be kept in a secure location. Your audio recordings will also be kept in a secure location and only people involved with the study will have access to these recordings. When the information on the audio recording is typed onto paper and fully checked, the recording will be destroyed. Study leaders will make sure this happens.

In the unlikely event that you get injured as a result of your study participation, it is important that you know the US National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research-related injury.

NEW INFORMATION
You will be told about new information from this or other studies that may affect your, welfare or willingness to stay in this study.

BENEFITS
There are no direct benefits to participating in this study. However, the information you provide may help researchers improve the design of future studies.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT
You may be removed from this study without your consent for the following reasons:

- **The study is stopped or canceled**
- **The study staff feels that staying in the study would be harmful to you**
- **The study is stopped by NIAID, the MTN, the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs**
- **Other administrative reasons**

ALTERNATIVES TO PARTICIPATION
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies we know about.

COSTS TO YOU
There is no cost to you for being in this study.

REIMBURSEMENT
[*Sites to modify/insert text as necessary for planned local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for each MTN-003D visit. At visits in which you complete an in-depth interview and/or focus group discussion, you will receive [Site to insert amount $xx].

CONFIDENTIALITY
We will do our best to make sure that the personal information gathered for this study is kept private, and it will not be shared with VOICE site staff. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

The Microbicide Trials Network (MTN) study is sponsored by the US NIH.

Your records may be reviewed by any or all of the following:

- **The MTN-003D study staff**
- **[insert applicable local authorities, e.g., Ministry of Health, medicine control authority]**
- **Site IRBs/ECs**
- **Representatives of the US OHRP, NIH, National Institute of Allergy and Infectious Diseases (NIAID), and/or contractors of the NIH, and other local or US regulatory authorities, and of the MTN**

PROBLEMS OR QUESTIONS
If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or community advisory board (CAB) member [staff will decide which] at [insert telephone number and/or physical address].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] **If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.**

Participant Name (print)	**Participant Signature or Mark**	**Date**
Study Staff Conducting Consent Discussion (print)	**Study Staff Signature**	**Date**
Witness Name	**Witness Signature**	**Date**