MTN-003D

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

Microbicide Trials Network

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

Grant #:

5-U01-AI068633-05

DAIDS Protocol #: 11893

A Non-IND Study

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Version 1.0

May 15, 2012

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List of Tables

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LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audio Computer-Assisted Self-Interviewing
AIDS	Acquired Immunodeficiency Syndrome
BRWG	Behavioral Research Working Group
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CAB	community advisory board
CFR	Code of Federal Regulations
CORE	Coordinating and Operations Center
CRF	case report form
CRS	clinical research site
CWG	Community Working Group
DAIDS	Division of AIDS
DSMB	Data Safety Monitoring Board
EC	Executive Committee
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HIV	human immunodeficiency virus
ICF	Informed Consent Form
IDI	in-depth interview
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
IT	information technology
MTN	Microbicide Trials Network
MO	Medical Officer
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
NIMH	National Institute of Mental Health
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
QA	quality assurance
QC	quality control
RE	regulatory entity
RSC	Regulatory Support Center
RTI	Research Triangle Institute
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	Standard Operating Procedure
SSP	study specific procedures
TDF	tenofovir disoproxil fumarate
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WRHI	Wits Reproductive Health and HIV Institute

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MTN-003D

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Version 1.0

May 15, 2012

A Study of the Microbicide Trials Network

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Mental Health
US National Institutes of Health

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by DAIDS or the Microbicide Trials Network (MTN) Coordinating and Operations Center. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, and made available to NIMH and DAIDS, for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-003D

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

PROTOCOL SUMMARY

Protocol Chair:	Ariane van der Straten, PhD, MPH
Protocol Co-Chairs:	Barbara Mensch, PhD; Elizabeth Montgomery, PhD
Sample Size:	Up to 80 women
Study Population:	Former VOICE participants at selected MTN-003D sites
Study Sites:	VOICE site(s) in sub-Saharan Africa as designated by the MTN Executive Committee
Study Design:	Exploratory sub-study of VOICE using qualitative in-depth interviews (IDIs).
Study Duration:	Approximately seven months for recruitment and follow-up.

Primary Objectives:

- To explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants' actual and reported product use.
- To explore the reasons, motivations and context of engaging in receptive anal intercourse (and rectal use of gel among VOICE participants in the gel group).

Secondary Objective:

- To explore participants' risk perceptions and motivations to participate in VOICE and the association of these factors with product use or non-use in a prevention trial setting.

1 KEY ROLES

1.1 Protocol Identification

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

Protocol Number: MTN-003D

Date: May 15, 2012

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2 INTRODUCTION

2.1 The MTN-003 Study

The Vaginal and Oral Interventions to Control the Epidemic (VOICE) Study (MTN-003), was designed to assess the safety and efficacy of daily dose oral and vaginal formulations of tenofovir and oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), also known as Truvada, in preventing human immunodeficiency virus (HIV) acquisition. The VOICE study, a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial, was open-label with respect to the randomly assigned mode of administration (vaginal or oral), and subsequently double-blinded within each mode. Approximately 5000 participants were randomized to the five study arms in a 1:1:1:1:1 ratio. The VOICE study is being implemented in sub-Saharan Africa.

While the trial is continuing to examine the safety and efficacy of oral Truvada, 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. Although no safety concerns were identified, neither the daily dosing regimen of oral tenofovir nor the 1% tenofovir gel used in the VOICE study was shown to be associated with reduced rates of HIV acquisition. Therefore the VOICE DSMB recommended that these arms of the study be stopped for futility. The closure of these study arms was in contrast to the previously reported positive results from the Partners PrEP study and Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004. Partners PrEP, which tested both daily dosing of tenofovir and Truvada, found that participants taking a daily regimen of oral tenofovir had an average of 62% fewer HIV infections than those taking placebo.[1] The coital dosing regimen of 1% tenofovir gel used in the CAPRISA 004 study was also associated with a significant reduction in HIV acquisition.[2] 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.

2.2 Dilution of Efficacy

Many factors may contribute to dilution of efficacy results within the context of an HIV prevention clinical trial, including several participant-related behaviors, such as product adherence and sexual practices. Generally, trials attempt to discourage those behaviors that may have a detrimental effect on outcomes through participant-focused counseling. For example, they may provide guidance and support to participants to maintain high levels of product use. However, despite a trial's best efforts to support adherence and/or discourage sexual behaviors that may contribute to dilution of efficacy, the socio-cultural context,[3] including the trial context, organization of the participant's social environment (i.e., importance and role of partners, family members, and the larger social network), and individual beliefs and attitudes about HIV risk and/or the trial may influence these behaviors. Furthermore, a trial's efforts to discourage behaviors that contribute to efficacy dilution – through ongoing counseling and messaging – may promote social desirability bias in participant responses about these behaviors. This may in turn limit the accuracy of behavioral measures that might otherwise contribute to an understanding of effectiveness results. In light of this, we propose conducting a qualitative ancillary study, which would explore potential sources of efficacy dilution in the VOICE clinical trial among exited VOICE participants. Based on preliminary data from VOICE, two potential sources of efficacy dilution that currently warrant additional exploration are product adherence and anal sex.

2.2.1 Adherence

Adherence to a trial product and accurate reporting of one's adherence are both essential to determining a product's effectiveness. It is unknown what level of participant adherence is needed in order to achieve sufficient levels of drug to provide efficacy. Even with adherence levels as high as 60%, the effectiveness of a product can be reduced to less than half of its true biological efficacy, resulting in a significant decrease in a trial's ability to detect efficacy.[4] Reported use also plays an important role in estimating product effectiveness. If participant use of a product does not match reported use, a trial will be unable to determine whether lack of effectiveness is due to inefficacy of the actual product or simply lack of use by participants.[5] While VOICE-C, another qualitative ancillary study of VOICE, has been actively exploring factors affecting adherence of VOICE participants at one site in Johannesburg, South Africa, Wits Reproductive Health and HIV Institute (WRHI), results are limited in their ability to explain VOICE futility results. This study plans to build on VOICE-C by more specifically exploring the impact of adherence on VOICE product effectiveness. It will do this in two ways: 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.

In the absence of a "gold standard," it is recommended that HIV prevention trials use multiple measures to capture adherence.[6] However, the use of multiple adherence measures often results in some level of discrepancy between measures.[7] It is therefore likely that VOICE participants may have varied their product adherence responses depending on the question and question modality that was used. 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)?[8] Do participants feel more comfortable revealing difficulties with adherence via the qualitative rating scale than when asked directly how much product they used? And, how were the various items on the rating scale interpreted by participants in terms of actual levels of use? Qualitatively exploring questions such as these has been shown to be useful to resolving differences in adherence results [5] and will be essential to better understanding how adherence was understood and reported by participants in VOICE.

In addition to exploring self-reported adherence, this study will examine the role of the contextual environment in adherence. As suggested previously, elements of participants' socio-cultural environment — e.g. the trial context, cultural norms and attitudes around HIV and research, living arrangements and partner relationships — may play a role in both actual and reported adherence. This study complements and expands upon VOICE-C, which is exploring factors influencing adherence at the community and household levels but is limited to a single VOICE site (WHRI, RSA). Here the topics for exploration will include these elements, but will focus more directly on individual experiences, the dynamic between trial participants and trial staff, and will solicit input from participants at multiple sites. Additionally, VOICE-C's integration into the VOICE trial may have limited its ability to effectively explore the role of the trial context on adherence and self-reported use. By conducting this study outside of the VOICE trial context and including additional VOICE sites, MTN-003D will expand upon the VOICE-C study results, especially in its ability to explore the contribution that the trial environment may have had on VOICE participants' use of study products.

2.2.2 HIV Risk Perception and Motivation for Trial Participation

One possible factor that may contribute to low adherence is participant's varying perception of HIV risk, as well as reasons for joining the trial. These factors are being 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.

A woman's perception of HIV risk is influenced by her individual level behaviors, such as engagement in high-risk sex, as well as the social-cultural context in which she lives. This perception of risk has often been linked to willingness to participate in hypothetical HIV prevention trials [9-20] and occasionally to interest in and acceptance of an HIV prevention product.[21] Despite these linkages, the question remains: how does one's perception of HIV risk contribute to product adherence once enrolled in a trial? One might expect that a higher perception of risk would lead to more consistent product use due to a greater desire for protection. However, a recent study in India found that contrary to this hypothesis, increased HIV risk perception was negatively associated with consistent gel use. Indeed, women at higher risk may be less able to adhere to product use for a host of contextual reasons.[22] Further, it is not well understood how regular (e.g., monthly) HIV testing may change individual risk perception and adherence behavior over time. By investigating how the socio-cultural environment influenced perception of risk and ultimately product use among VOICE participants, this study hopes to contribute to a greater understanding of the relationship between these issues.

Other motivations for joining an HIV prevention trial, such as increased access to quality health care, altruism, and financial incentives, and their contribution to product adherence will also be explored.

2.2.3 Anal Sex

Anal sex, whether occurring in a heterosexual or homosexual relationship, is a high-risk sexual activity.[23] A meta-analysis estimated that HIV transmission per sex act is higher for heterosexual anal sex than vaginal sex (1.7% vs. 0.182%)[24] and that condom use during anal sex is often lower.[25-27] Engaging in heterosexual anal sex has also been shown to be associated with participation in other high-risk sexual activities, including having multiple sexual partners, transactional sex, and sex under the influence of drugs or alcohol.[28,29] While not widely reported, it is estimated that worldwide more people engage in heterosexual anal sex than homosexual anal sex[25] and there is growing concern that underreporting of heterosexual anal sex may be playing a hidden role in the HIV epidemic in sub-Saharan Africa.[30]

As early as 1998, Karim and Ramjee[31] warned that HIV prevention studies should consider the effect anal sex may have in the context of a microbicide trial, lest a vaginally-applied gel be perceived by participants as protective during anal intercourse. Evidence that anal sex may be preferred over vaginal sex to prevent pregnancy, confer intimacy, or enhance male sexual pleasure may exacerbate this risk.[32] This study will therefore explore not only the socio-cultural context that may contribute to anal sex practices and reporting of these practices among VOICE participants, but also examine 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.

2.3 Study Hypotheses and Rationale for Study Design

2.3.4 Study Hypothesis

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

2.3.5 Rationale for Study Design

MTN-003D will use qualitative in-depth interviews with exited VOICE participants to explore study product adherence and anal sex behaviors in greater depth than was measured quantitatively during trial participation. The study approach is designed to encourage honesty and to minimize socially desirable responses, which may have affected participants' ability/willingness to accurately report during the trial. An in-depth and candid understanding of the various behavioral factors that contribute to the dilution of efficacy may assist in the interpretation of VOICE trial results and inform future studies.

3 OBJECTIVES

3.1 Primary Objectives

- To explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants' actual and reported product use.

- To explore the reasons, motivations and context of engaging in receptive anal intercourse (and rectal use of gel among VOICE participants in the gel group).

3.2 Secondary Objective

- To explore participants' risk perceptions and motivations to participate in VOICE and the association of these factors with product use or non-use in a prevention trial setting.

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-003D will be 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.

4.2 Description of Study Population

The MTN-003D study population will consist of former VOICE participants.

4.3 Time to Complete Accrual

The accrual period is planned to occur over approximately 28 weeks.

4.4 Expected Duration of Participation

The expected duration of participation for each participant is up to three hours total, including administrative and data collection procedures.

4.5 Sites

MTN-003D participants will be recruited from VOICE sites in sub-Saharan Africa as designated by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population and Recruitment

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 enrolled into 003D and interviewed after they have completed their final VOICE visit. The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used to ensure the appropriate selection of study participants.

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**

5.2 Inclusion Criteria

Potential participants must meet all of the following criteria to be eligible for inclusion in the study:

1) Able and willing to perform the study procedures

2) Able and willing to provide informed consent in one of the MTN-003D study languages

3) Participated in VOICE and received at least three consecutive months of study product at any time during VOICE trial participation

5.3 Exclusion Criteria

Potential participants who meet the following criteria will be excluded from the study:

1) Has any condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

6 STUDY PRODUCT

MTN-003D will not involve the administration of any study product.

7 STUDY PROCEDURES

Additional information on visit-specific study procedures are presented in this section. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-003D Study Specific Procedures (SSP) Manual located at http://www.mtnstopshiv.org.

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 unprotected anal sex), we will conduct all interviews in an environment which 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 location, or, if requested by the participant, the VOICE site may be used. Additionally, interviews will be conducted by researchers who have had no prior interaction with the VOICE participant.

7.1 Screening and Enrollment

7.1.1 Administrative, Behavioral and Regulatory Procedures

Table 2. Screening and Enrollment Procedures

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

Multiple visits may be conducted to complete all required procedures, if necessary.

7.2 Demographic and Behavioral Data

A brief questionnaire will be completed to capture and/or update demographic and sexual behavior data (e.g., to allow for descriptive statistics to assess the characteristics of MTN-003D participants).

7.3 In-depth Interview Procedures

Qualitative interviews will cover two main topics, adherence and anal sex. In-depth interview guides will be developed, which 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).

7.2.1 Adherence

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.

Following the discussion of risk perception/motivations, several qualitative tools, such as short scenarios, visual displays, and/or open-ended questions may be used to explore participant's understanding of the adherence questions, including the qualitative rating scale that was

administered in VOICE. Questions will be 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 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 (e.g., power issues between research staff and participants, trial procedures, interviewing modes, and counseling, including the Voice Adherence Strengthening Program), will be a focus of this investigation.

7.2.2. Anal sex

A discussion of anal sex and rectal gel use will follow the discussion of product adherence, using an interview guide developed by the investigators. Similar to the discussion of adherence, several additional qualitative tools (e.g., short scenarios, body mapping, etc.) may be used to supplement this discussion. While a subset of participants who reported having anal sex will be purposefully sampled for this study, all participants will be asked about the topic. Those who reported the behavior will not be alerted that this was a stratification criterion and the interview will not be targeted towards their specific reporting of the behavior. The interviewer will not know what participants reported about anal sex behavior during the VOICE study.

Participants will 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 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 engaging in this behavior.

The occurrence of rectal gel application among VOICE participants in the vaginal gel group will 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 also be probed on their own hypothetical non-vaginal use of study gel within the given scenario and the reasons for use or non-use.

8 ASSESSMENT OF SAFETY

MTN-003D is a minimum-risk research: it does not involve a study product and does not involve any clinical, laboratory or other procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation. The study site IoR is responsible for continuous monitoring of all study participants and for alerting the protocol team if unexpected safety events arise. Study sites will have written procedures for ensuring prompt reporting to the Institutional Review Board (IRB)/Ethics Committees (EC), of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database.

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if unexpected concerns arise. 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, nurse) affiliated with the clinical research site (CRS) for follow-up.

The Manual for Expedited Reporting of Adverse Events to Division of AIDS (DAIDS) will not be used for this study for the following reasons: 1) this study does not involve a study drug and is non-invasive; and, 2) adverse events are not primary or secondary objectives of the study. Untoward clinical or medical occurrences reported by study participants to have been experienced during study participation will be recorded in participant file notes.

8.2 Social Harms Reporting

Participants may experience social harms — non-medical adverse consequences — as a result of their participation in the study. Social harms that are judged by the IoR to be serious or unexpected will be reported to responsible site IRB/ECs at least annually, or according to their individual requirements. In the event that a participant reports a social harm, a Social Harms Report CRF will be completed and the participant will be referred to a counselor at the research site. Every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Research Triangle Institute (RTI) will provide listings of social harms reported by study participants to the protocol team on an ongoing basis. Additionally, a Standard Operating Procedure (SOP) for emergency procedures will be developed for the MTN-003D research team to be used in situations of social harm and when situations that require immediate attention are identified, including domestic violence, suicidal ideation or behavior. The procedures will provide clear guidelines for researchers to refer participants in these situations to the relevant institution/body and to provide feedback to the protocol team.

9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in this study. Participants who express concerns with social, psychological or clinical issues will be referred for appropriate care to services available at the CRS, or at nearby partnering facilities.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

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

10.2 Study Endpoints

The main outcome of interest in MTN-003D is the effect of the trial culture and a participant's environment on VOICE study product adherence and anal sex practices.

10.3 Primary Study Hypotheses

This is a descriptive and exploratory study, which is not designed to test a hypothesis.

10.4 Number of Participants

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

10.5 Data, Study Monitoring and Analysis

Demographic and behavioral data will be captured by CRF and entered in an electronic database (e.g., CSPRO). Qualitative data will be audio-recorded, transcribed, translated and coded for qualitative analyses, using NVivo or a similar qualitative software. RTI will function as the overall data coordinating center for quantitative and qualitative data and will lead all analyses.

10.5.1 Study Monitoring Committee (SMC)

No SMC review will be performed for this study given the short study timeline and the nature of the study. Protocol team members from RTI International and FHI 360 will provide oversight of study operations and ensure the study is implemented in accordance with MTN standards, as defined in the MTN Manual of Operating Procedures.

10.5.2 Data Analysis

Quantitative Analysis

While MTN-003D will not include formal quantitative analysis, we will use the following descriptive statistics to assess the characteristics of MTN-003D participants: the number and percent in each category for categorical variables, (e.g., marital status, employment, oral vs. vaginal group, self-reported product use and anal sex per VOICE CRF and ACASI data), and the mean or median and range for continuous variables (i.e., age, education). No formal statistical testing will be conducted.

Qualitative Analysis

Data Sources

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

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

Analysis Overview

The following section provides a brief overview of the analysis process; however, a more detailed description of the qualitative analysis will be presented in the study analysis plan.

Qualitative analyses from MTN-003D study will use a variety of techniques to provide exploratory findings that will describe, in depth, contextual factors that affected participants' actual and reported product use, as well as engagement in anal intercourse. The primary source of qualitative data used in the MTN-003D analysis will consist of raw textual data. Qualitative data will be audio-recorded, transcribed, translated and coded for qualitative analyses, using NVivo or a similar qualitative software. Data coding will be used as a primary analytical approach, for data reduction, that is, to summarize, extract meaning, and condense the data.[35,36] MTN-003D transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook (see section on Codebook Development and Coding Process below).[37] Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified accordingly. In addition to descriptive codes, pattern codes, which achieve a greater level of abstraction, will be used to start linking themes and topics together in order to explore the relationship between contextual factors and sources of efficacy dilution.[35] Whenever possible, we will also compare study sites and explore differences or similarities in response to the trial and the study regimen due to different socioeconomic, cultural and geographical contexts. The analysis will be done by the investigative team, working interactively through emails, and regular phone or face-to-face meetings. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data.[38]

The primary final output of the qualitative analysis will include a synthesized report with representational quotes that will describe the subjective contextual experiences of trial participants and how they influenced adherence, anal sex, and reporting of these behaviors. Any emerging differences in results by "stratifying" groups or variables will be described.

The findings from MTN-003D may contribute to our understanding of the VOICE futility results and in turn inform future trials of this nature. Specifically, the data may suggest strategies to

minimize behaviors that contribute to dilution of efficacy, such as non-adherence and anal sex, as well as strategies for improving the accuracy of measurements of these behaviors.

Codebook Development and Coding Process [39]

Coding is an essential process for data reduction necessary for the management and interpretation of large amounts of qualitative data. To ensure the quality of the coding, staff at RTI in collaboration with site staff and other MTN-003D team representatives will develop a codebook and study procedures for coding and analysis of all of the qualitative data. Each code will be operationally-defined and refined in an iterative way, as needed. Transcripts will be coded using a qualitative software package such as Nvivo.

During the study development stage, a set of preliminary codes will be developed based on the research questions of this study. The analysis coding structure will be hierarchical, and will reflect the topics/themes covered in the interview guides. After the first 2-3 rounds of interviews are completed, each group member will apply this initial set of thematic codes to a common transcript, discuss their coding experiences (via email, a meeting, or conference call), and agree on expanding and modifying code names and definitions when necessary. We will generate substantive and conceptual categories through an iterative process of reading the data, and generating codes based on the data and on key themes or topics identified *a priori*, applying the codes to the data, and refining these as we continue to read and code the data. Thus, codes will be centered on the main topics of interest (product reported and actual use and anal intercourse) and the hypothesized contextual spheres of influence. However, by nature, the qualitative research process is iterative, and the Nvivo software allows for the generation of new codes for emergent themes that were not identified *a priori* by the research team. The software also allows for coders to insert descriptive comments and memos to themselves and others as they are working, and to code for concepts not spelled out in verbatim text, such as "contradiction," when a participant contradicts oneself.

Once finalized, the codebook will be used for a final recoding all of the transcripts. Comprehensive listings of all coded quotations for every code (as well as "families" of related codes) will be generated in Nvivo. We will consider the coded dataset in entirety, and "stratify" the coded quotations by the site, self-reported adherence levels, reported anal sex, and study product group (e.g. oral vs. vaginal) when applicable. Depending on findings from the cluster analysis, we may conduct additional grouping and stratifications of the data.

The coding process will involve a core group of 2-3 analysts who will frequently communicate (via email, phone or in person meetings) and discuss their use of the codebook and application of the codes during the coding process. A pre-selected number of transcripts will be double-coded by two coders to establish intra-coder and inter-coder reliability. These measures can be automatically generated in Nvivo. Following this process, the coding team will discuss (in person or via teleconference) the coding discrepancies, which will ultimately be resolved through consensus. This process will continue until the inter-coder reliability is sufficiently high, defined as 80% or above. Thereafter each remaining text will be coded by one analyst only within Nvivo. Regular discussions among the coding team will ensure that coding remains standardized and reliable.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by RTI in conjunction with the protocol team and will be manually double-entered in an electronic database. Quality control reports and queries will be routinely generated and distributed by RTI for verification and resolution. As part of the study activation process, each study site must identify all materials to be used as source documents. Transcriptions of interviews will be generated in the field and electronically transferred to RTI using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using the qualitative software package Nvivo.

RTI will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Original language and translated transcripts will be transferred to RTI as they are completed. RTI will save all versions of all files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. (http://rsc.tech-res.com/policiesandregulations/)

For MTN-003D, source documentation may include recruitment logs, enrollment records, visit checklists, CRFs, interview data, participant file notes, and electronic audio files. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and key communication with the protocol team. In accordance with U.S regulations, each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. Thereafter, instructions for record storage will be provided by DAIDS. No study records, may be moved to an off-site location or destroyed prior to receiving approval from DAIDS. Audio files will be transcribed and immediately destroyed following a transcription quality assurance check. The site IoR or designee will be responsible for ensuring that these files have been destroyed.

11.3 Quality Control (QC) and Quality Assurance (QA)

At the field level, the study coordinator(s) will check the quality of the transcripts and translations to ensure that they reflect the content of the interview, and then send each transcript to RTI for additional quality control. CRFs will be reviewed at the site and transmitted to RTI where they will be reviewed and queried. All queries will be resolved through a standardized QC reporting mechanism.

All study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies. (http://rsc.tech-res.com/policiesandregulations/)

12 CLINICAL SITE MONITORING

FHI 360 staff or designee will review study records during the course of the study, however no formal clinical monitoring will be conducted. FHI 360 staff or designee will examine the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312.
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized 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 representatives of the MTN. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTION

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval. The IoR will permit audits by the National Institutes of Health (NIH) or any of their appointed agents, local authorities, site IRBs/ECs, representatives of the MTN, and Office for Human Research Protections (OHRP).

13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent form, and study-related documents as required, are reviewed by an IRB/EC responsible for oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Each IoR/designee will make progress reports to the IRBs/ECs within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the most current DAIDS policies at the time of registration.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

The site-specific informed consent form (ICF) *will not* be reviewed or approved by the DAIDS PRO, and the site will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Study Coordination

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS Medical Officer. Study implementation will also be guided by a common Study Specific Procedures (SSP) manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Standardized study-specific training will be provided to all sites by RTI, FHI 360, or other designated members of the Protocol Team.

13.4 Risk Benefit Statement

13.4.1 Risks

Psychological Harms

MTN-003D will ask questions that may cause individuals discomfort given the personal nature of questions. Stress and feelings of guilt or embarrassment may arise simply from thinking or

talking about one's own behavior or attitudes on sensitive topics. This could result in undesired changes in thought and emotion.

While the risk of psychological harm is anticipated to be minimal, and study staff will inform participants that they can choose not to answer questions at any time, study staff will collect information on participants who report a change in mood as a result of study participation. In addition, study staff will ensure that participants have access to proper clinical resources to address psychological harms.

Social Harms

Participation in research includes the risk of loss of confidentiality. Although the study site will make every effort to ensure that safeguards are in place that protect participant privacy and confidentiality, it is possible that participants' involvement in the study may result in study-related social harms.

Data on the occurrence of potential social harms will be collected from all participants. These data will be reported via CRF and analyzed on an ongoing basis and the protocol team will monitor, evaluate and adjust operations to reduce the potential for such occurrences.

13.4.2 Benefits

There are no direct benefits to participating in this study. However, the information that participants provide may help health professionals develop better ways to improve communication and understanding between researchers and participants in HIV prevention studies.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to completing any study procedures. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://rsc.tech-res.com/policiesandregulations/). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

13.6 Participant Confidentiality

All study procedures will be conducted in a location agreed upon by the participant, and every effort will be made to protect participant privacy and confidentiality. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives will be obtained to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

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. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Study staff
- 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

After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, electronic documents and audio files.

13.7 Special Populations

13.7.1 Pregnant Women

Pregnancy is not exclusionary. Due to the nonclinical nature of this study, no pregnancy-related risks are anticipated in MTN-003D.

13.7.2 Children

MTN-003D will enroll former VOICE participants who were age 18 through 45 years (inclusive) at the time of screening, as verified per site SOPs, thus children will not be considered eligible for this trial.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in accordance with requirements and standards set forth by local IRBs.

13.9 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

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.

APPENDIX I: Sample Informed Consent Document

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-003D

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

Version 1.0

May 15, 2012

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. Approximately 80 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
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' use of 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 have an interview in the presence of one or two MTN-003D research staff members. If you agree, the interviewer will ask you some brief questions and write your responses on a form. The interviewer will also ask more in-depth questions, during which time she may take notes and will audio-record your conversation. None of the clinic staff who worked with you when you participated in VOICE will be involved with this study nor will they will have any knowledge of the specific responses that you provide.

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, including anal sex. Anal sex is

when a male inserts his penis into a woman's anus. You will not be required to discuss your personal sexual behavior.

We expect the interview procedures will take up to 3 hours and 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.

To obtain information about your participation in VOICE, the MTN-003D study team will need to consult 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.

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 voice 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 voice recording is typed onto paper, 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 health, 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 counseling materials about product use and sexual behavior, and ways to improve reporting these behaviors in 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 insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your MTN-003D visit.

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

REFERENCES

1. Pivotal study finds that HIV medications are highly effective as prophylaxis against HIV infection in men and women in Africa. In: University of Washington International Clinical Research Center; 2011.
2. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010;329:1168-74.
3. Barnett E, Casper M. A definition of" social environment". American Journal of Public Health 2001;91:465a.
4. Weiss HA, Wasserheit JN, Barnabas RV, Hayes RJ, Abu-Raddad LJ. Persisting with prevention: the importance of adherence for HIV prevention. Emerg Themes Epidemiol 2008;5:1-7.
5. Pool R, Montgomery CM, Morar NS, et al. Assessing the accuracy of adherence and sexual behaviour data in the MDP301 Vaginal Microbicides Trial using a mixed methods and triangulation model. PLoS One 2010;5:e11632.
6. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of PrEP Trials for HIV Prevention. AIDS in press.
7. Pool R, Montgomery CM, Morar NS, et al. A mixed methods and triangulation model for increasing the accuracy of adherence and sexual behaviour data: the Microbicides Development Programme. PLoS One 2010;5:e11600.
8. Lu M, Safren SA, Skolnik PR, et al. Optimal recall period and response task for self-reported HIV medication adherence. AIDS and Behavior 2008;12:86-94.
9. Bekker LG, Jaspan H, McIntyre J, Wood R, Gray G. Adolescents and HIV Vaccine Trials. Journal of the International Association of Physicians in AIDS Care (JIAPAC) 2005;4:93-7.
10. De Bruyn G, Skhosana N, Robertson G, McIntyre J, Gray G. Knowledge and attitudes towards HIV vaccines among Soweto adolescents. BMC research notes 2008;1:76.
11. De Souza CTV, Lowndes C, Szwarcwald CL, Sutmöller F, Bastos F. Willingness to participate in HIV vaccine trials among a sample of men who have sex with men, with and without a history of commercial sex, Rio de Janeiro, Brazil. AIDS care 2003;15:539-48.
12. Jaspan HB, Berwick JR, Myer L, et al. Adolescent HIV prevalence, sexual risk, and willingness to participate in HIV vaccine trials. Journal of adolescent health 2006;39:642-8.
13. Li Q, Luo F, Zhou Z, et al. Willingness to participate in HIV vaccine clinical trials among Chinese men who have sex with men. Vaccine 2010;28:4638-43.
14. McGrath JW, George K, Svilar G, et al. Knowledge about vaccine trials and willingness to participate in an HIV/AIDS vaccine study in the Ugandan military. JAIDS Journal of Acquired Immune Deficiency Syndromes 2001;27:381.
15. McGrath JW, Mafigiri D, Kamya M, et al. Developing AIDS vaccine trials educational programs in Uganda. JAIDS Journal of Acquired Immune Deficiency Syndromes 2001;26:176.

16. Ruzagira E, Wandiembe S, Bufumbo L, et al. Willingness to participate in preventive HIV vaccine trials in a community-based cohort in south western Uganda. Tropical Medicine & International Health 2009;14:196-203.
17. Smit J, Middelkoop K, Myer L, Seedat S, Bekker L, Stein D. Willingness to participate in HIV vaccine research in a peri-urban South African community. International journal of STD & AIDS 2006;17:176-9.
18. Suhadev M, Nyamathi AM, Swaminathan S, Suresh A, Venkatesan P. Factors associated with willingness to participate in HIV vaccine trials among high-risk populations in South India. AIDS Research and Human Retroviruses 2009;25:217-24.
19. Suhadev M, Nyamathi AM, Swaminathan S, et al. A pilot study on willingness to participate in future preventive HIV vaccine trials. Indian Journal of Medical Research 2006;124:631.
20. Yin L, Zhang Y, Qian HZ, et al. Willingness of Chinese injection drug users to participate in HIV vaccine trials. Vaccine 2008;26:762-8.
21. Bentley ME, Fullem AM, Tolley EE, et al. Acceptability of a microbicide among women and their partners in a 4-country phase I trial. American Journal of Public Health 2004;94:1159.
22. Tolley EE, Tsui S, Mehendale S, Weaver MA, Kohli R. Predicting Product Adherence in a Topical Microbicide Safety Trial in Pune, India. AIDS and Behavior 2011:1-8.
23. Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. International journal of epidemiology 2010;39:1048-63.
24. Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. The Lancet infectious diseases 2009;9:118-29.
25. Halperin DT. Heterosexual anal intercourse: prevalence, cultural factors, and HIV infection and other health risks, Part I. AIDS Patient Care and STDs 1999;13:717-30.
26. Jones R. Sex scripts and power: A framework to explain urban women's HIV sexual risk with male partners. Nursing Clinics of North America 2006;41:425-36.
27. Priddy FH, Wakasiaka S, Hoang TD, et al. Anal Sex, Vaginal Practices, and HIV Incidence in Female Sex Workers in Urban Kenya: Implications for the Development of Intravaginal HIV Prevention Methods. AIDS Research and Human Retroviruses 2011;27:1067-72.
28. Kalichman SC, Simbayi L, Cain D, Jooste S. Heterosexual anal intercourse among community and clinical settings in Cape Town, South Africa. Sexually transmitted infections 2009;85:411.
29. Lane T, Pettifor A, Pascoe S, Fiamma A, Rees H. Heterosexual anal intercourse increases risk of HIV infection among young South African men. AIDS 2006;20:123.
30. Brody S, Potterat JJ. Assessing the role of anal intercourse in the epidemiology of AIDS in Africa. International journal of STD & AIDS 2003;14:431-6.
31. Karim SS, Ramjee G. Anal sex and HIV transmission in women. American Journal of Public Health 1998;88:1265.
32. Duby Z, Colvin C, Kitungulu B. Heterosexual anal sex: knowledge, attitudes, and practice in 5 East African communities. In: 1st International HIV Social Science and Humanities Conference; 2011 12 June 2011; Durban, South Africa; 2011.

33. Hughes R. Considering the Vignette Technique and its Application to a Study of Drug Injecting and HIV Risk and Safer Behaviour. Sociology of Health & Illness 1998;20:381-400.
34. Schoenberg NE, Ravdal H. Using vignettes in awareness and attitudinal research. International Journal of Social Research Methodology 2000;3:63-74.
35. Miles M, Huberman A. Qualitative Data Analysis: An Expanded Sourcebook. 2nd ed. Thousand Oaks: Sage Publications; 1994.
36. Denzin N, Lincoln Y, editors. Handbook of Qualitative Research. Thousand Oaks: Sage Publications; 2000.
37. MacQueen KM, McLellan-Lemal E, Bartholow K, Milstein B. Codebook development for team-based qualitative analysis. In: Guest G, MacQueen M, eds. Handbook for team-based qualitative research. Lanham: AltaMira Press; 2007.
38. Ryan GW, Bernard RH. Data Management and Analysis Methods. In: Denzin N, Lincoln Y, eds. Handbook of Qualitative Research. 2nd ed. Thousand Oaks: Sage Publications; 2000:769-802.
39. McLellan E, MacQueen KM, Niedig J. Beyond the qualitative interview: data preparation and transcription. Field Methods 2003.