

MTN-009

**Prevalence of HIV-1 Drug Resistance within a Female Screening Population for
HIV Prevention Trials**

Microbicide Trials Network

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

**Grant #:
5-U01-AI068633-04**

DAIDS Protocol #: 10791

A Non-IND Study

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Version 1.0

November 3, 2009

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LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	audio computer-assisted self interview
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
BRWG	Behavioral Research Working Group
CAB	Community Advisory Board
CD4	cluster determinant 4
CTU	Clinical Trials Unit
CWG	Community Working Group
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
FDA	(United States) Food and Drug Administration
FHI	Family Health International
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus – type 1
HIVDR	HIV drug resistance
IoR	Investigator of Record
IRB	Institutional Review Board
LAASER	Linking African and Asian Societies for an Enhanced Response
LDMS	Laboratory Data Management System
MRC	Medical Research Council
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NL	Network Laboratory
OHRP	Office for Human Research Protections
PASER	PharmAccess African Studies to Evaluate Resistance
PCR	polymerase chain reaction
PMTCT	preventing mother-to-child transmission
PrEP	pre-exposure prophylaxis
PSP	Prevention Sciences Program
PTID	Participant ID
RCC	Regulatory Compliance Center
RNA	Ribonucleic acid
SDMC	Statistical Data Management Center
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SMC	Study Monitoring Committee
SOP	Standard Operating Procedure
SSP	study specific procedures
UNAIDS	Joint United Nations Programme on HIV/AIDS
US	United States
WHO	World Health Organization

MTN-009

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MTN-009

**Prevalence of HIV-1 Drug Resistance within a Female Screening
Population for HIV Prevention Trials**

INVESTIGATOR SIGNATURE FORM

**Version 1.0
November 3, 2009**

A Study of the Microbicide Trials Network (MTN)

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institutes of Health

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Investigator of Record Agreement which I have also signed. I agree to maintain all study documentation for a minimum of three years after the study is closed, unless otherwise specified by the Division of AIDS (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 for review prior to submission and will be made available to DAIDS.

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-009

Prevalence of HIV-1 Drug Resistance within a Female Screening Population for HIV Prevention Trials

PROTOCOL SUMMARY

- Short Title:** HIV-1 Drug Resistance Study
- Chair:** Urvi Parikh, PhD
Co-Chair: Photini Kiepiela, PhD
- Sample Size:** Approximately 1000 women may be enrolled in order to achieve enrollment of 350 evaluable HIV-positive women
- Study Population:** Women presenting for screening for HIV prevention trials
- Study Sites:** Study sites will be part of the South African Medical Research Council (MRC) HIV Clinical Trials Unit (CTU) - Durban
- Study Design:** Cross-sectional study
- Study Duration:** Approximately 1-3 study visits per participant with projected two years of accrual

Primary Objective:

- To assess the frequency of HIV-1 drug resistance mutations among women who test HIV-positive when presenting to screen for participation in HIV prevention trials

Primary Endpoint:

- Major and minor mutations in HIV-1 reverse transcriptase and protease known to be associated with drug resistance as measured by standard and sensitive genotypic methods

Secondary Objectives:

- To identify and evaluate behavioral indicators including self or sexual partner(s) exposures to antiretroviral (ARV) drugs as risk factors for drug resistant HIV-1 infection in women who present for screening to participate in HIV prevention trials

- To characterize the degree of immunodeficiency and risk of disease progression by quantifying plasma HIV-1 RNA and CD4-positive T cells among women who test HIV-positive when presenting for screening to participate in HIV prevention trials

Secondary Endpoints:

- Participant self-reported ARV drug exposures and other behaviors of herself or sexual partner(s) that may be associated with risk of drug resistant HIV-1 infection
- Plasma HIV-1 RNA levels and CD4-positive T-cell counts

Exploratory Objective:

- To identify polymorphic or subtype-specific sequence changes in HIV-1 that may impact susceptibility to ARV drugs
- To estimate the proportion of HIV-positive women who have chronic versus recent HIV-1 infection

Exploratory Endpoint:

- Sequence changes in HIV-1 protease, reverse transcriptase or other viral genes in HIV-1 that may be associated with ARV resistance
- Classification of HIV-positive participants as having chronic or recent infection based on current incidence estimation algorithms

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Prevalence of HIV-1 Drug Resistance within a Female Screening Population for HIV Prevention Trials

Protocol Number: MTN-009

Short Title: HIV-1 Drug Resistance Study

Date: 3 November 2009

1.2 Sponsor Identification

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2 INTRODUCTION

Women are disproportionately burdened by human immunodeficiency virus (HIV) infection, particularly in sub-Saharan Africa, where 76% of new HIV-1 infections are in young women of reproductive age [1]. Widespread implementation of HIV-1 prevention services, including behavioral strategies, has had only a modest impact on the rate of new HIV-1 infections in most populations, thus continued efforts to identify effective preventative modalities are needed. Microbicide clinical trials in HIV-uninfected participants conducted by the Microbicide Trials Network (MTN) will include Phase 2B randomized trials of promising new compounds that include antiretroviral (ARV) agents for topical application or oral administration with specific HIV-1 inhibitory activity.

There are many reasons women choose to participate in HIV prevention trials. Though free medical care and a modest reimbursement are cited as reasons for participation, finding out HIV status and altruism are also strong motivators [2-4]. Some women may have an HIV infected partner and are seeking an alternative to condoms to protect against HIV infection. Inevitably, some women who present to the clinic intending to participate in an HIV-prevention trial discover they are HIV-positive for the first time. This cohort of women is critical to understand both from a virologic and behavioral perspective, because the future success and large scale implementation of an ARV product for HIV prevention largely depends on targeting the appropriate population for its use.

One of the major concerns of using ARV-based products for HIV prevention is the potential for drug resistance, both in trial settings with women who seroconvert while on study product and in future product roll-out settings by women who may be HIV-positive but unaware of their status.

MTN-009 aims to evaluate the prevalence of drug resistance in women who are ineligible for participation in HIV prevention trials because they are identified as HIV positive. This study will also collect limited behavioral data in both HIV-positive and HIV-negative individuals to help interpret any drug resistance identified, in the context of participants' prior ARV exposures and their motivations for participating in a prevention trial.

The primary goal of MTN-009 is to understand the current status of HIV resistance in newly diagnosed HIV-positive women of reproductive age. The finding of significant resistance to ARV-based study products delivered vaginally or taken orally may guide decisions related to future microbicide and pre-exposure prophylaxis (PrEP) studies.

2.1 Possible Causes of Drug Resistance in Presumed Treatment-Naïve Populations

HIV is considered to be resistant when it is no longer sensitive or has reduced sensitivity to one or more ARV drugs that are used to treat it. Drug resistance in HIV-infected individuals who are treatment-naïve can be polymorphic, transmitted or selected.

The high diversity of HIV-1 subtypes might have implications for patterns of resistance development, such as the presence of naturally occurring polymorphisms that facilitate evolution of resistant mutants or affect the susceptibility or magnitude of resistance to some ARVs [5-8]. For example, recent studies have suggested that the tenofovir-resistance K65R mutation is selected more readily in subtype C HIV-1 as compared to subtype B HIV-1 [9, 10]. The impact of subtype on resistance caused by other mutations has not been fully evaluated. Current algorithms for interpreting drug resistance mutations are predominantly based on studies with subtype B virus [11, 12]. Most of southern Africa has a predominately subtype C epidemic (98.3%), with the exception of Uganda whose epidemic is primarily subtypes A and D [13, 14]; subtype B accounts for only 0.2% of HIV-1 infections in southern Africa [14]. This study will contribute to the collection of sequence data from non-subtype B virus to continue improving the interpretation of drug resistance data.

Resistant strains of HIV can also be transmitted person-to-person. Individuals with recent HIV-1 infection often have high viral loads and may be highly infectious [15-17]. Among serodiscordant couples, the risk of HIV transmission was found to be seven times higher during the first five months after seroconversion as compared to later stages of infection when measured prospectively [15]. Risky sexual behavior soon after infection carries high potential for HIV transmission to others, including transmission of drug resistance. Where antiretroviral therapy (ART) is widely used, between 5 and 20% of new HIV-1 infections include virus that have drug resistance mutations [18-20]. Therefore, knowledge of whether infection is recent or chronic may be informative.

Finally, a major concern about ARV-based prevention is the possibility that the use of topical microbicides or oral chemoprophylaxis by those who are unknowingly already infected could select for drug resistant HIV-1. Although ART has been highly successful in slowing disease progression in HIV-infected individuals, drug resistance can develop in an infected person who is exposed to ARVs in doses insufficient to completely suppress HIV replication. Drug resistance could occur when HIV-positive women use single or dual ARVs intended for HIV prevention, because at least three drugs in combination are required to sufficiently suppress actively replicating HIV in an untreated, infected person. There are currently no data describing the resistance status of infected women presenting for participation in HIV prevention trials.

ARV resistance is a concern both for treatment and prevention; high rates of drug resistance in a population could facilitate spread of drug resistance and eventually compromise the effectiveness of ARVs. For this reason, the current study will analyze

drug resistance data in the context of information about ARV exposure and characteristics of the infection, including an estimation of whether seroconversion occurred recently and degree of disease progression as indicated by plasma viral ribonucleic acid (RNA) levels and CD4-positive T cell counts. These correlations will aid in assessing the risk of drug resistance transmission in predominantly treatment-naïve populations with increasing access to ARVs.

2.2 ARV Access in Sub-Saharan Africa

It is estimated that 33 million people worldwide were living with HIV in 2007, and that 22 million were living in sub-Saharan Africa [21]. Of the estimated 2 million people who died of acquired immunodeficiency syndrome (AIDS) in 2007, 1.5 million lived in sub-Saharan Africa [21]. Several African countries have in recent years begun rapid scale-up ARV treatment programs as a result of the global commitment to increase access to ARV therapy. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimates that one third of adults in South Africa living with HIV/AIDS need ART (1.7/5.7 million adults). As of 2007, only about one third of those that need ART (460,000 adults) were currently receiving it [22]. ART coverage in South Africa has increased from 15% in 2005 to 28% in 2007, with a goal of reaching up to 70% by 2010 [23]. Similarly, by the end of December 2006 over 85,000 HIV-positive patients in Malawi had begun a standard regimen of stavudine plus lamivudine and nevirapine [24]. Scale-up is expected to continue at a rate of 45,000 additional patients per year until 2010, with 14-25% of the enrollees from Lilongwe [24, 25]. In sub-Saharan Africa overall, it is estimated that 2.1 million people were receiving ART as of December 2007 as compared with 1.38 million in December 2006 [26].

Access to ARVs has also increased with their use for the prevention of mother to child transmission (PMTCT). In South Africa, an estimated 57% of pregnant women living with HIV received ARV for PMTCT in 2007 compared to only ~15% in 2005 [22]. Globally, infected mothers have been given short courses or single doses of multiple ARVs, including combinations of stavudine, zidovudine, didanosine and nevirapine to identify the best modality and dose to reduce infant HIV infection rates at birth [27]. An unintended consequence has been the development of nevirapine resistance in 25% to 69% of mothers who used single dose nevirapine [28, 29]. Even the existence of minority variants (mutants present at a frequency of <20%) generally missed by standard genotyping methods have been shown to reduce treatment efficacy [30, 31]. However, waiting 6 months to treat after using single dose nevirapine may restore nevirapine effectiveness [32-34]. Continued surveillance of drug resistance in infected women is critical for evaluating the success of PMTCT programs and the lessons learned from PMTCT will help manage resistance and guide use of ARVs for preventing horizontal transmission.

An increasing number of clinical trials under consideration for preventing sexual transmission of HIV include the use of ARVs. Of the 15 microbicide and PrEP candidates currently in clinical trials, 6 are ARV-based [35]. These candidates include Food and Drug Administration (FDA)-approved reverse transcriptase inhibitors also in

use for treatment such as tenofovir and emtricitabine, and investigational RTIs such as dapivirine (TMC-120) and UC781 [36-38]. The MTN has two studies with sites in sub-Saharan Africa to assess the safety and effectiveness of tenofovir-based regimens for HIV prevention.

In the face of expanding access to treatment and potential for introduction of ARV-based prevention methods, collection of drug resistance data will be increasingly valuable in gauging the public health and virologic impact of treatment and prevention strategies.

2.3 Current Surveillance of HIV-1 Drug Resistance in Africa

As ARV usage increases both in the context of HIV treatment and HIV prevention, routine surveillance of drug resistance is essential for minimizing selection and transmission of resistant strains and preserving ARV-based treatment and prevention options. In the United States, some physicians recommend genotypic testing prior to initiation of therapy, regardless of duration of infection or need for treatment [39, 40]. However, in resource-limited settings, HIV resistance genotyping in newly diagnosed or treatment-experienced individuals is rarely available [41, 42].

There are limited population data regarding HIV drug resistance rates in African countries. In 2002, Tarin et al published results of a study that was performed in South Africa in preparation for the introduction of ARV treatment. They found that 3 of 46 cases (7%) had primary resistance mutations [43]. One meta analysis reported the rate of resistance to any drug among treatment-naïve individuals to be 5.5% in Africa, but did not focus on specific regions [44]. Geretti reviewed results from six small HIV drug resistance surveys, 3 in Cameroon, 1 in Burkina Faso, 1 in the Democratic Republic of Congo and 1 in Nigeria. The prevalence reported from these surveys ranged from zero in Nigeria (from 18 samples tested) to 14.8% in Western Cameroon (from 54 samples tested) [45].

In the absence of routine testing for drug resistance prior to initiating ART, WHO, in collaboration with HIVResNet, a global network of clinical, laboratory, epidemiology and research experts and organizations, has developed an HIV Drug Resistance (HIVDR) prevention and assessment strategy to be implemented by National HIVDR Working Groups in resource-limited countries that are scaling up ARV treatment [46, 47]. This drug resistance threshold survey method classifies resistance to each relevant drug class at a threshold of <5%, 5-15% or >15%, to guide public health actions [47]. The survey is to be repeated in 2 years if drug resistance prevalence is found to be less than 5%. In the absence of other concerns, no further public health action would be deemed necessary regarding investigation of resistance for regions under the 5% cutoff. This includes countries such as Tanzania, Uganda, Swaziland, Malawi and the Gauteng Province of South Africa [24, 48-51]. This lower 5% cutoff is statistically determined and based on cost-effectiveness of implementing a large scale surveillance program in resource-constrained settings. Mathematical modeling studies disagree on whether

resistance at <5% prevalence is sufficiently low to prevent a future epidemic of drug resistant HIV [52, 53].

The PharmAccess African Studies to Evaluate Resistance (PASER) program is also performing monitoring and surveillance of HIV-1 drug resistance in sub-Saharan Africa in coordination with the WHO Global Resistance Surveillance Network. PASER is part of the Linking African and Asian Societies for an Enhanced Response to HIV/AIDS (LAASER-HIV/AIDS) program, funded largely by a grant from the Dutch Ministry of Foreign Affairs. The PharmAccess program is monitoring acquired resistance as well as transmitted resistance in six countries in sub-Saharan Africa: Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe, and has plans to include approximately 3500 patients over a 5-year period. Preliminary results of a monitoring study that included 260 of the expected 533 samples from chronically HIV-1 infected adults who were eligible to initiate first-line ART in Lusaka, Zambia, were recently presented [54]. Ninety-eight percent of these were classified as subtype C, and 13 of 242 samples (5.4%) from people who were ARV-naïve demonstrated HIV-1 drug resistance mutations. Accrual is expected to be completed by the end of 2010.

To date, most studies conducted in sub-Saharan Africa have identified low rates of transmitted ARV resistance, and the rate of increase may be low until ART coverage increases as predicted by mathematical modeling and experience from resource-rich countries [41]. However the current surveillance of drug resistance prevalence in ARV-naïve people is inadequate. The data are primarily based on “threshold” methods that rely on statistical cut-offs, and minority variants (those present at <20%) are not detected or accounted for; however, several recent studies have highlighted the importance of this minor population [31, 55, 56]. In addition, the existing drug resistance data are only population based for the purpose of developing policy and are not linked to information about behavior, estimates as to how recently infection occurred, or degree of immunodeficiency. These data can enhance surveillance data to allow better targeting and implementation of a microbicide should a parent trial identify one as successful.

2.4 Impact of Behavior on Risk and Acquisition of Drug Resistant HIV-1

HIV-negative and HIV-positive women have different risks for infection with drug resistant HIV.

One way HIV-negative women can be at risk of acquiring resistant virus is from infected sexual partners. Studies conducted in the United States have indicated that transmission of resistant virus could be facilitated by specific risk behaviors such as the use of certain illicit substances, repeated exposure by the same partner, concentration of resistant HIV in certain sexual networks, or the practice of specific sexual acts during substance use. [57, 58]. This information is important for understanding the causes and spread of drug resistance, but parallel studies in sub-Saharan Africa have yet to be done. In this study, responses to the behavioral questions from HIV-negative women

will help to better understand what risks HIV-negative women face in becoming infected with drug resistant HIV (transmitted resistance).

HIV-positive women may be at risk of developing drug resistance if they take ARVs with incomplete adherence. For instance, availability of prescribed ARVs may be inconsistent, or drug sharing could occur in situations where a loved one is very sick. Also of concern in the region is that women who have delivered children in hospital settings may have been treated with ARVs without knowledge of their HIV status. Women may not realize that they were treated with ARVs due to confusion at a time when multiple medications were being administered. Resistance could occur with use of single dose nevirapine, or if courses of PMTCT were not completed.

Little is known about the behavioral indicators of transmitted or selected drug resistance risk in women of reproductive age. The findings from the behavioral data interpreted in the context of resistance data from MTN-009 may help to understand resistance risk in future prevention trials or product roll-out.

2.5 Study Summary

The current study proposes to assess ARV resistance or risk of ARV resistance in an important and vulnerable population: women of reproductive age who are interested in participating in HIV prevention trials.

All women who enroll in MTN-009 will be asked to complete a behavioral questionnaire (audio computer-assisted self interview (ACASI) or interviewer-administered) designed to determine the participant's and her sexual partner(s)' previous exposures to ARVs, as well as other potential risk factors for acquisition of drug resistant virus. All women who enroll in MTN-009 will also be tested for HIV infection.

Since the primary aim of this study is to assess the prevalence of ARV resistance in HIV-positive women, women who test HIV positive may have additional blood collected for further testing, which includes standard resistance testing, CD4-positive T cell counts, and levels of plasma HIV-1 RNA. Results of these three tests will be reported back to participants. In addition, sensitive resistance testing and a laboratory test to estimate how recently the infection occurred will be performed for research purposes.

Women that test HIV negative will not participate in any further MTN-009 study visits, and may be referred to any ongoing prevention trials. The results of their behavioral questionnaire will be used to further understand the risk of HIV-negative women in acquiring drug resistant HIV infection.

Data from MTN-009 will provide a current estimate of the prevalence of ARV resistance, a comprehensive analysis about the potential spread of resistance if found, and an examination of the possible relationship between drug resistance and risk behaviors. This study will also provide information for comparison analyses of seroconverter resistance data from prevention trials, will be a model for future drug resistance

surveillance efforts, will provide evidence for improved mathematical modeling for the risk of drug resistance when ARVs are used for HIV prevention, and will inform implementation policy for both HIV treatment and prevention programs.

2.6 Study Hypothesis

The prevalence of HIV-1 drug resistance in the population of women interested in participating in HIV prevention trials who are found to be HIV positive will be low and underestimated by standard genotyping methods.

2.7 Rationale for Study Design

ARV agents have been highly successful in slowing disease progression in HIV-infected individuals and are now at the forefront of HIV prevention efforts, including their use in PMTCT and their evaluation as oral or topical pre-exposure prophylaxis (PrEP). A consequence of widespread ARV use is the risk of drug resistance, particularly in high prevalence resource-limited settings where monitoring of HIV-1 RNA or HIV-1 genotyping in persons in treatment roll-out programs is not routinely performed. In sub-Saharan Africa, women of reproductive age face the greatest risk for HIV acquisition, which could include transmission of resistant strains.

To date, a comprehensive surveillance of HIV-1 drug resistance in newly diagnosed women of reproductive age has yet to be undertaken. As the potential exposure to ARVs both in women and their partners increases in communities with concurrent ARV treatment programs and ARV-based HIV prevention trials, it is essential to gain a better understanding of the existence of ARV resistance within this population.

The results of this study may inform the implementation of PMTCT programs, ARV-based HIV prevention research, and community roll-out of ARV-treatment for HIV-infected persons. This study will also provide ARV resistance information for future drug resistance surveillance efforts, as well as studies designed to evaluate resistance in women who become HIV-infected while participating in HIV prevention trials of ARV agents.

Study Participation Prior to Screening for HIV Prevention Trials in High-Prevalence Settings

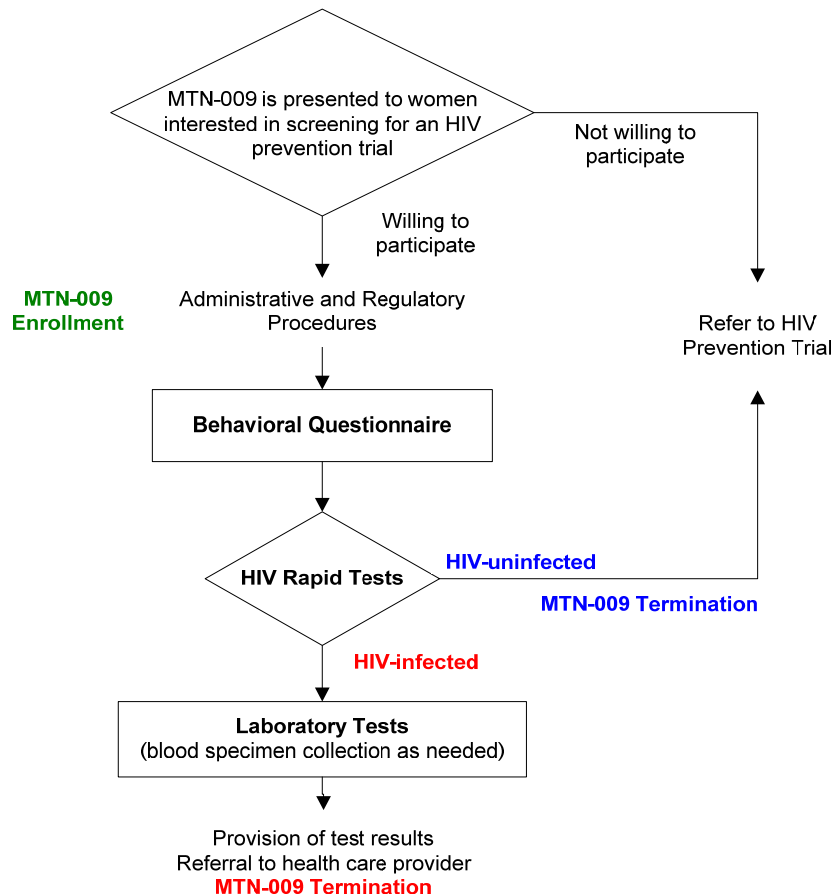
Wide-scale implementation of a successful ARV-based prevention product will require targeting confirmed HIV-negative women for its use. To better understand the population of women interested in using a product to prevent HIV, particularly women who may not know their HIV status, MTN-009 will enroll women prior to initiating the screening procedures for available HIV prevention trials.

There are several benefits to undertaking MTN-009 procedures in women who do not yet know their HIV status. Asking a woman to participate in a drug resistance study after learning she is HIV-positive may cause undue burden to her. A woman may be

saddened or anxious, and unable to provide informed consent to study procedures. Collecting behavioral data prior to the HIV test results being known will reduce the risk of any reporting biases that might arise and would enable inclusion of results from both HIV positive and HIV negative participants. All participants will be tested for HIV, but further testing on blood will be done only if the participant is confirmed to be positive.

In addition to providing better data for the current study, conducting MTN-009 prior to screening for HIV prevention trials may benefit sites located in areas with a high HIV prevalence. For sites that do not have pre-screening procedures, MTN-009 may help serve as one way women can be pre-screened for HIV infection. Referring only HIV-negative women for potential participation in HIV prevention trials may streamline lengthy and complex screening procedures often necessary for consenting women for studies that involve product use and long-term commitments. However, participation in MTN-009 is not a pre-requisite to screening for HIV prevention trials ongoing at the same site. Women who do not consent to participation in MTN-009 are not specifically prohibited from directly screening for any ongoing HIV prevention trials. Figure 1 outlines the schema for presenting MTN-009 to potential participants, describes the timing of protocol procedures, and notes when to refer participants to other HIV prevention trials.

Figure 1. Summary Schema for MTN-009 Study Procedures



3 OBJECTIVES

Primary Objective:

- To assess the frequency of HIV drug resistance mutations among women who test HIV-positive when presenting to screen for participation in HIV prevention trials

Primary Endpoint:

- Major and minor mutations in HIV-1 reverse transcriptase and protease known to be associated with drug resistance as measured by standard and sensitive genotypic methods

Secondary Objectives:

- To identify and evaluate behavioral indicators including self or sexual partner(s) exposures to ARV drugs as risk factors for drug resistant HIV infection in women who present for screening to participate in HIV prevention trials
- To characterize the degree of immunodeficiency and risk of disease progression by quantifying plasma HIV-1 RNA and CD4-positive T cells among women who test HIV-positive when presenting for screening to participate in HIV prevention trials

Secondary Endpoints:

- Participant self-reported ARV drug exposures and other behaviors of herself or sexual partner(s) that may be associated with risk of drug resistant HIV-1 infection
- Plasma HIV-1 RNA levels and CD4-positive T cell counts

Exploratory Objective:

- To identify polymorphic or subtype-specific sequence changes in HIV-1 that may impact susceptibility to ARVs
- To estimate the proportion of HIV-positive women who have chronic versus recent HIV infection

Exploratory Endpoint:

- Sequence changes in HIV-1 protease, reverse transcriptase or other viral genes in HIV-1 that may be associated with ARV resistance
- Classification of HIV-positive participants as having chronic or recent infection based on current incidence estimation algorithms

4 STUDY DESIGN

4.1 Identification of Study Design

This study will provide an estimate of the prevalence of ARV resistance in the population of women who present to study sites to be pre-screened or screened for participation in an HIV prevention trial. This study uses a cross-sectional design. Descriptive characteristics of the infection and behavioral information, including self-reported ARV exposure of the participant and her sexual partner(s) will be collected. All participants who present to MTN-009 study sites for pre-screening or screening for HIV prevention trials will be offered participation in MTN-009 (see Section 2.7 and Figure 1). Based on local estimates of the HIV-1 prevalence rates, approximately 1000 participants may need to be recruited in order to reach 350 evaluable HIV-positive participants for the primary endpoint. When enrollment of 350 HIV-positive participants is reached, the study recruitment will be stopped, regardless of the number of HIV-negative participants enrolled. It may be necessary to continue recruitment beyond 1000 in order to reach 350 evaluable HIV-positive participants.

Study assessments (detailed in Section 7) are scheduled to be completed at the screening and enrollment visit of MTN-009. However, if for some reason any study procedure is not completed on the day of enrollment, participants will be asked to return within a designated timeframe to complete the procedure as specified in the MTN-009 Site-Specific Protocol (SSP). HIV-positive participants will be asked to return for follow-up visits to receive the results of their CD4-positive T cell counts, plasma viral HIV RNA levels (viral load) and standard HIV-1 resistance testing.

4.2 Description of Study Population

The study population will consist of women between the ages of 18 and 40 years old who meet eligibility criteria outlined in Section 5.

4.3 Time to Complete Accrual

Accrual is expected to be completed in approximately 2 years.

4.4 Expected Duration of Participation

All study procedures at the Screening and Enrollment Visit are expected to be completed in one visit. Results of the CD4-positive T cell counts, plasma viral HIV RNA levels (viral load) and standard resistance testing for participants found to be HIV-positive will be communicated to them over approximately two follow-up visits, when the test results become available.

4.5 Sites

Study sites will be part of the South African Medical Research Council (MRC) HIV CTU – Durban.

5 STUDY POPULATION

5.1 Selection of the Study Population

The study population will consist of women who meet the eligibility criteria listed below.

5.2 Inclusion Criteria

Women must meet all of the following criteria to be eligible for inclusion in MTN-009:

1. Present to an MTN-009 study site to pre-screen or screen for an HIV prevention trial
2. Age 18-40 years, verified per site standard operating procedures (SOP)
3. Able and willing to provide written informed consent for participation in MTN-009
4. Able and willing to provide adequate locator information, as defined in site SOPs

5.3 Exclusion Criterion

Women who meet the following criterion will be excluded from MTN-009:

1. Any condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achievement of the study objectives

6 STUDY PRODUCT

No study product considerations are applicable for MTN-009.

7 STUDY PROCEDURES

Women who present to an MTN-009 study site to pre-screen or screen for participation in an HIV prevention trial will first be offered enrollment in MTN-009. Once it is determined a participant is eligible for MTN-009, the participant may be enrolled. For this study, enrollment is the act of assigning a MTN-009 Participant ID (PTID). Eligibility determination, enrollment and study procedures at the Screening and Enrollment Visit are anticipated to take place during one visit. However, if for some reason any study procedure is not completed on the day of enrollment, participants will be asked to return within a designated timeframe to complete the procedure (as specified in the MTN-009 SSP). HIV-positive participants will have approximately two additional follow-up visits to receive test results.

7.1 Screening and Enrollment (Visit 1)

An overview of the Screening and Enrollment Visit and procedures is presented below. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-009 SSP Manual available at www.mtnstopshiv.org.

7.1.1 Administrative and Regulatory Procedures

- Informed consent for Study Screening, Enrollment, Storage and Future Testing of Specimens
- Collection of locator information
- Eligibility verification
- Assignment of PTID
- Collection of demographic information
- Administration of behavioral questionnaire
- HIV pre-test and risk reduction counseling
- Provision of HIV-1 rapid test results
- Participant reimbursement

For participants who test HIV-negative:

- Post-test counseling (as needed)
- Referral to HIV prevention trial

For participants who test HIV-positive:

- Post-test counseling
- Referral to health care provider

- Schedule next visit

7.1.2 Clinical Procedures

- Blood specimen collection

7.1.3 Laboratory Procedures

- Rapid HIV testing as described in Appendix II
- For participants who test HIV-positive
 - CD4-positive T cell counts
 - Plasma viral HIV-1 RNA levels (viral load)
 - Identification of drug resistance mutations in HIV-1 by standard and sensitive assays
 - Categorization of infection as recent or chronic using current incidence testing algorithms

Further information on each assay is included in the MTN-009 SSP Manual, available at www.mtnstopshiv.org.

7.2 Follow-up (Visits 2-3)

Follow-up visits are only required for participants who are found to be HIV-positive.

7.2.1 Follow-up (Visit 2): Administrative and Regulatory Procedures

- Update locator information
- Pre/post-test result counseling
- Provision of CD4-positive T cell count
- Provision of plasma viral HIV-1 RNA level (viral load), if available
- Schedule next visit, if applicable
- Reimbursement

7.2.2 Follow-up (Visit 3): Administrative and Regulatory Procedures

- Pre/post-test result counseling
- Provision of plasma viral HIV-1 RNA level (viral load) (if needed)
- Provision of HIV-1 standard resistance test result by trained staff
- Resistance counseling (as needed)
- Reimbursement

7.3 Laboratory Evaluations

Evaluations will be conducted at local, regional, network, and/or approved reference laboratories according to site capacity and guidelines outlined in the MTN-009 SSP Manual.

Local Laboratory

- Rapid HIV-1 tests and, if needed, Western blot for confirmation of HIV-1 infection
- CD4-positive T cell counts
- Specimen storage for shipment to the NL

Local, Regional or Network

- Plasma HIV-1 RNA polymerase chain reaction (PCR)

Network Laboratory

- Standard HIV-1 resistance testing using an FDA approved assay
- Sensitive HIV-1 resistance testing using an in-house PCR-based assay
- Categorization of infection as chronic or recent using current incidence testing algorithms as defined in the MTN-009 SSP is available at www.mtnstopshiv.org

7.4 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements

(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Laboratories.htm>),

MTN-009 SSP Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories and shipping information will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.5 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials

(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Laboratories.htm>).

7.6 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

The HIV Drug Resistance Study is a cross-sectional study involving no investigational products or procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation. No safety events will be captured in the study database.

The Manual for Expedited Reporting of Adverse Events to DAIDS will not be used for this study for the following reasons: 1) this study is observational in nature; 2) this study does not involve a study drug or intervention; and 3) adverse events are not endpoints in the study.

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 Investigator of Record (IoR) to be serious or unexpected will be reported to responsible site Institutional Review Boards (IRB)/Ethics Committees (EC) at least annually, or according to their individual requirements. 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.

Relationship to study participation or procedures will be assessed by the site IoR, or designee according to current DAIDS guidelines.

Any unanticipated problems will be reported to the DAIDS Medical Officer at the same time as the problems are reported to the responsible site IRB/Ethics Committees (ECs) overseeing the research according to pre-established procedures as required by 45 CFR 46.

9 CLINICAL MANAGEMENT

Study site staff will make every reasonable effort to ensure that the resistance testing results, along with the plasma HIV-1 RNA levels (viral load), and CD4-positive T cell counts, are communicated to the participant at approximately two study follow-up visits. Health care referrals will be coordinated by the site to local clinics, hospitals and/or health providers. ARVs will not be provided by the study, however resistance information provided to the site may be forwarded to physicians managing care with participant permission. Study sites may also provide study test results to non-study health care providers who are responsible for management of participant care with participant permission.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a cross-sectional study conducted in volunteers who are pre-screened or screened for potential participation in an HIV prevention trial. The study will enroll participants until 350 evaluable participants have been identified as HIV-infected. To reach the target of 350 evaluable HIV-positive participants, approximately 1000 participants may need to be enrolled. Therefore, a total of 350 evaluable HIV-infected and approximately 650 HIV-uninfected may be enrolled into this study. However the number of HIV-uninfected participants might be lower or higher depending on the prevalence of HIV-1 in the targeted population at the site. Enrollment will continue until 350 HIV-positive evaluable participants have been enrolled. Blood collection and the administration of a brief questionnaire are expected to be completed in one visit.

10.2 Study Endpoints

10.2.1 Primary Endpoints

The primary endpoint will be evaluated using two different methods for assessing drug resistance, namely, standard and sensitive methods.

Consistent with the primary objective, the primary endpoint will only be assessed among the participants that are HIV-infected. An HIV-infected participant will be considered '*resistant according to the standard method*' if any major or minor mutations in HIV-1 reverse transcriptase and protease known to be associated with drug resistance are identified via the standard genotypic assessment method. If no such mutations are identified, an HIV-infected participant will be considered '*not resistant according to the standard method*'.

Similarly, HIV-infected participants will be considered '*resistant according to the sensitive method*' if any major or minor mutations in HIV-1 reverse transcriptase and protease known to be associated with drug resistance are identified via the sensitive genotypic assessment method. If no such mutations are identified, an HIV-infected participant will be considered '*not resistant according to the sensitive method*'.

10.2.2 Secondary Endpoints

Consistent with the secondary objectives, the following secondary endpoint will be assessed among HIV-infected participants:

Immunologic and Virologic Assessments

From the sample taken at the time of the HIV screening test, CD4-positive T cell counts and plasma HIV-1 RNA levels will be measured.

The following secondary endpoints will be assessed on all participants (HIV-infected and uninfected):

Behavioral and Basic Demographic Assessments

Participant self-reported behavioral indicators including current and past ARV exposures will be assessed via a brief questionnaire. These assessments will include comparisons of resistance risk between HIV-negative and HIV-positive participants and between HIV-positive participants with and without drug resistance.

10.3 Sample Size Justification and Accrual

For the primary analysis, drug resistance will be assessed via the proportion of drug resistant participants among the 350 HIV-infected women. The proportion is expected to be low and less than 10%. The power of the study can be characterized as follows: with a true proportion of drug resistance of 10%, a sample size of 350 will provide 89% power to exclude a proportion greater than 15%. Furthermore, if no drug resistance is identified among the 350 HIV-infected participants, the upper limit of the (exact) 95% confidence interval for the proportion of resistant participants is 1% (this upper limit is 14%, if 10% of the HIV-infected participants are resistant).

Based on the anticipated accrual rate at the sites, we anticipate that it will take approximately 2 years to reach the target number of HIV-infected participants.

10.4 Data and Safety Monitoring and Analysis

10.4.1 Study Monitoring Committee (SMC)

No Data and Safety Monitoring Board (DSMB) oversight is planned for this cross-sectional study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, target number of HIV-infected participants and completion of primary and secondary endpoint assessments. These reviews will take place approximately every 6 months, or as needed or required by the SMC. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor.

10.4.2 Data Analyses

Primary Analyses

The proportion of drug resistance among the 350 HIV-infected participants will be computed for both the standard and sensitive methods along with (exact) 95% confidence intervals (using the Clopper-Pearson method). Furthermore, the proportion

of drug resistance along with 95% confidence intervals will be computed for ART-naïve and non-naive HIV-infected participants.

In addition, frequencies and proportions of specific mutations (e.g., K65R) will be computed and presented.

Secondary and Exploratory Analyses

Descriptive analyses among the HIV-infected participants will include the mean, the median, standard deviation, quartiles, and range (minimum and maximum) of plasma HIV-1 RNA (log-transformed) levels and CD4-positive T cell counts. Proportion of recently infected participants and of past and current ART use will be computed as well as 95% confidence intervals.

Behavioral indicators and basic demographics among all participants (i.e., HIV-infected and –uninfected) will be summarized using the mean, the median, standard deviation, quartiles, and range (minimum and maximum) for continuous variables, proportions for binomial responses, and contingency tables for categorical variables. Analyses will be performed using logistic regression to explore differences between sub-groups including HIV-infected and HIV-uninfected participants and HIV-positive participants who are drug resistant or not drug resistant. Additionally, analyses will be performed using logistic regression to identify potential predictors of resistance among the HIV-infected participants.

Resistance data obtained from standard resistance testing will undergo exploratory analysis to identify polymorphic or subtype-specific sequence changes in HIV-1 that may be associated with ARV resistance.

HIV-infected participants will be classified as having a chronic or recent infection based on current incidence estimation algorithms. These results will be interpreted in the context of viral load, CD4-positive T cell counts and HIV-1 resistance data for each participant. Results will not be used to estimate incidence of HIV-1 infection in the study population.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries will routinely be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all case report forms to be used as source documents. Study data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

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://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/>).

Each IoR/designee will maintain, and store securely, complete, accurate, and current study records throughout the study. In accordance with US regulations, the IoR/designee will maintain all study documentation for at least two years after study closure.

Study records must be maintained on site for the entire period of study implementation. 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.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites. This can be found on the following website:

(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm>).

12 CLINICAL SITE MONITORING

Site monitoring visits may be conducted to assess compliance with applicable non-US and/or US regulatory requirements, including US Department of Health and Human Services (DHHS) regulations, and CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks of study procedures to human participants. Volunteers will take part in a thorough informed consent process. Before beginning the study, the investigators will have obtained IRB/EC approval. The investigators will permit audits by the NIH or any of their appointed agents, local authorities, site IRBs/ECs, representatives of the MTN and/or SDMC, and OHRP.

Participants whose HIV test results are positive will be provided referral to HIV-1 primary care and psychosocial support. Those HIV-positive participants who are identified as having drug resistant infection will be offered additional counseling.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that the protocol and the associated informed consent documents and study-related documents are reviewed by an IRB/EC prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study-related documents must be approved by the IRB/EC, CORE, and DAIDS prior to implementation.

13.2 Protocol Registration and Study Activation

Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/protocolregistration/>. Protocol registration must occur as a condition for site-specific activation; no participants may be screened or enrolled in the study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

Protocol registration material can be sent electronically to epr@tech-res.com. For questions regarding protocol registration, contact the Protocol Registration Office via e-mail at protocol@tech-res.com, fax (800-418-3544 or 301-897-1701), or phone (301-897-1707).

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRBs/ECs and the RCC prior to implementing the amendment.

13.3 Risk Benefit Statement

13.3.1 Risks

Participants may become worried about their privacy and confidentiality, and may become embarrassed or worried while waiting for results of their tests if they decide to participate. Every effort will be made to protect privacy and confidentiality. Participant visits will take place in private. Although study sites make every effort to protect participant privacy and confidentiality, it is possible that others may learn of participant study involvement and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection).

Study site staff will be trained to counsel participants regarding these issues.

Phlebotomy may lead to discomfort or pain, feelings of dizziness or faintness, and/or bruising, swelling, small clot and/or infection.

13.3.2 Benefits

Participants may experience no direct benefit from participation in this trial. Results of lab tests may be released, if permitted by the participant, to her health care provider and thus may assist in management of medical care. Participants may appreciate the opportunity to contribute to the field of HIV research.

13.4 Informed Consent Process

Written informed consent for screening, enrollment, and storage and future testing of leftover specimens for MTN-009 will be obtained from study participants prior to screening and enrollment procedures. The combined consent form is preferable so as not to unduly burden the participant after receiving HIV test results. A shortened consent form is also appropriate for a cross-sectional study and will avail staff of performing a long consent process.

13.5 Participant Confidentiality

All study-related information will be stored securely at the study sites. All participant information will be stored securely in areas with access limited to study staff. To maintain participant confidentiality a coded number will identify all study specific laboratory specimens, reports, study data collection, and administrative forms and folders.

All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate area with limited access.

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

- DAIDS, and/or its contractors
- Local authorities
- Site IRBs/ECs
- Representatives of the MTN and/or SDMC
- OHRP

13.6 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, OHRP, site IRBs/ECs, or other applicable government or regulatory authorities.

14 PUBLICATION POLICY

DAIDS 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 and DAIDS for review prior to submission.

15 APPENDICES

**APPENDIX I: SAMPLE INFORMED CONSENT (SCREENING, ENROLLMENT,
STORAGE AND FUTURE TESTING OF SPECIMENS)**

**SAMPLE INFORMED CONSENT FORM
DAIDS, NIAID, NIH**

MTN-009

**Prevalence of HIV-1 Drug Resistance within a Female Screening
Population for HIV Prevention Trials**

**Version 1.0
November 3, 2009**

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

Short Title for the Study: HIV Drug Resistance Study

INTRODUCTION

You are being asked to volunteer for the research study named above. This study is for women who want to screen for participation in an HIV prevention study at this site. HIV is the virus that causes AIDS. Before you decide whether to be in the HIV Drug Resistance Study, we would like to explain its purpose, review the risks and benefits, what is expected of you, and what you can expect from the study site.

This consent form might contain words that are unfamiliar. Please ask questions about anything you do not understand or want to learn more about.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the blood test(s) that will be done during this study and about a questionnaire you will be asked to complete. This form will also ask whether or not you agree to the storage and future testing of any leftover blood. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important to know the following:

- It is your choice whether or not you join this study
- You may decide not to join this study, or you may choose to leave this study at any time, without losing the benefits of your regular medical care
- If you decide not to join this study, you can still choose to join another study later, if you qualify, and if one is available

PURPOSE OF THE STUDY

The main purpose of the HIV Drug Resistance Study is to find out if blood samples from women being screened for HIV prevention trials, who are found to be HIV-positive, have signs of drug resistance. Drug resistance is when one or more medicines that usually work to treat HIV, called antiretrovirals or ARVs, no longer work as well. This study will help researchers understand drug resistance in HIV prevention trials. This is important to understand since more people now have access to ARVs through HIV treatment programs and in HIV prevention trials. Information from this study will help researchers plan for future HIV prevention studies and HIV treatment programs.

The United States National Institutes of Health (US NIH) is funding this study.

Approximately 1000 women may be enrolled in this study. It may take up to about 2 years to enroll all participants.

STUDY PROCEDURES

If you decide to join this study, after you read, discuss, and sign or make your mark on this form, you will have one visit, continuing today, to complete blood collection and a questionnaire. Approximately two additional visits may be scheduled at a later time if you are found to be HIV-positive. Study staff will help you understand the form and answer your questions before you sign or mark this form.

If you decide to join this study, you will be asked to tell study staff about where you live and how they may contact you. Study staff will ask you about the best way to contact you to schedule another visit if necessary. You will also be asked to complete a questionnaire about whether you or your sexual partner(s) ever took medicines used to treat HIV, and other questions about sexual practices that you may have engaged in. Some of these questions may be about your sexual behavior, sexual partner(s), and medications you may have been given. The responses from HIV-positive and HIV-negative women to the behavioral questionnaire will be used for research purposes, to better understand HIV infection and HIV drug resistance.

[SITES TO INCLUDE FOLLOWING TEXT IF APPLICABLE]: You will be asked to use a computer to answer these questions. The questions will be shown on the computer screen and read to you through earphones. The study staff will show you how to use the computer. You can practice using the computer and ask the study staff any questions you may have. Then you will answer questions using the computer by yourself. You will answer each question by marking your answer on the computer screen.

You will talk with counselors about HIV, HIV testing and ways to avoid contracting HIV.

We will also collect a blood sample from you [insert local specific method of collection] that will not exceed [depending upon collection method insert local equivalent; if blood draw, please insert XX mL or if finger stick please insert the following; < 0.5 mL of blood or about 2 droplets]. This blood sample will be tested for HIV infection.

Your samples will never be sold or used to make products that could be sold.

Your HIV test results will be shared with you today, unless, in the unlikely event that we are not able to determine your HIV status. If we are not able to determine your HIV status we will make arrangements with you to share the results of your HIV test as soon as they become available.

If your HIV test is found to be **negative**:

- You will receive counseling
- No additional blood sample testing will be performed

If your HIV test is found to be **positive**:

- You will receive counseling and we [may] need to collect additional blood from you, not to exceed XX mL [insert local equivalent] to run the following tests:
 - A test to find out how changes in HIV may affect how well some HIV drugs work (HIV drug resistance)
 - A CD4-positive T cell count, which will measure the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections
 - A test for the amount of virus in your blood (viral load)
 - Finally, one additional test for research (not medical) purposes which will help researchers learn more about your HIV infection
- You will need to return for approximately two additional visits so staff can explain the results of the following tests to you when they become available, these results may take up to 6 months:
 - CD4-positive T cell count
 - Viral load
 - HIV drug resistance
- If you test positive for HIV, this study will not provide you with treatment, but study staff will provide you with immediate counseling and also refer you to available sources of medical care, counseling, and other services you may need. Study staff also will be available to talk with doctors who oversee your medical care. Because the results of study tests may help your doctors make the best medical choices for you, study staff will give the results of your study tests to your doctors if you wish and with your permission

RISKS AND/OR DISCOMFORTS

This is a minimal risk study. We do not expect you to experience any additional risks or discomforts above and beyond what you would normally experience as part of a routine doctor's visit.

Risk of Blood Draws

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your arm.

Other Possible Risks

You may become worried while waiting for your blood test results. If you have HIV or drug resistant HIV, knowing this could make you worried. Trained study counselors will help you deal with any feelings of anxiety or embarrassment or any questions you have.

You may also become embarrassed and/or worried when answering questions about any possible exposure to medicines used to treat HIV or other behavioral questions.

We will make every effort to protect your privacy and confidentiality while you are in the study. Your visit(s) here will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. Discrimination may also occur from others learning that you are participating in this study or the results of your HIV test; however every precaution has been made by study staff to ensure that test results will not be shared with anyone other than those individuals listed in the Confidentiality Section of this form. If you have any problems like this, counselors will talk with you to try to help resolve them.

NEW INFORMATION

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

BENEFITS

You may get no direct benefit from being in this study. You or others may benefit in the future from information learned in this study. The information from your tests may help your health care team to make the best choices for you in the event your HIV test is positive. You may also get some personal satisfaction from being part of research on HIV resistance.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from this study without your consent for the following reasons:

- This HIV Drug Resistance Study is stopped or canceled
- The study staff feels that this HIV Drug Resistance Study would be harmful to you
- Other administrative reasons

ALTERNATIVES TO PARTICIPATION

There may be other studies going on here or in the community that you may be eligible for or other ways you could obtain the same kind of test results available through this study. If you wish, we will tell you about other studies and locations for testing that we know about.

COSTS TO YOU

There is no cost to you for being in the HIV Drug Resistance Study.

REIMBURSEMENT

[Sites to insert information about local reimbursement:]

You will receive [insert amount] for your time and effort in this study. You will also receive compensation for activities affected by your participation [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME-SITES TO COMPLETE].

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute (complete) 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.

Your records will not be given to anyone without your permission except as needed for review by any or all of the following:

- The Division of AIDS (DAIDS), and/or its contractors
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff

If during the course of the study, we find out that you have [insert applicable reportable diseases (e.g. HIV)], we must report it to [insert the name(s) of the local health authorities], however your name will not be reported to the agency. [Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of participating in this minimal risk study. If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. The US NIH does not have a program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or if you have a research-related injury, 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].

STORAGE AND FUTURE TESTING OF LEFTOVER SPECIMENS

The researchers would like to keep leftover blood from participants who are found to be HIV-positive to use for research in the future. If you agree to this, no additional blood samples will be taken from you. Only leftover blood samples from the samples already taken for this study will be kept and used for future research. This consent form gives you information about the collection, storage and use of your samples. If you agree to the Storage and Future Testing of Specimens you will not be compensated for your donated leftover blood samples.

If you choose not to have your leftover blood stored for future testing you will still be able to participate in this study. Any leftover blood will be destroyed after all research related tests have been performed.

How will you use my leftover samples?

The specific research to be done on your samples is not known at this time. Your leftover blood will only be used to look for additional evidence of infection with HIV, damage caused by infection, or your body's response to infection. Tests may also include examining your genes (DNA), since they might affect your response to HIV in important ways. For example, your genes may make you more or less susceptible to make HIV progress faster or slower, or may affect your response to treatment. No other kinds of genetic testing unrelated to HIV will be done by anyone on your stored specimens without first explaining the test to you and getting your permission.

(Storage and Future Testing of Leftover Specimens Continued)

Research studies wishing to use your blood must gain approval by the United States National Institutes of Health (NIH) and a special committee at the researcher's institution (an Institutional Review Board or Ethics Committee). The role of this committee is to protect you and other research volunteers from harm.

How long will you keep my leftover samples and how will they be stored?

There is no time limit on how long your samples will be stored. Your blood will be stored safely and securely in a storage facility at this site. [Sites should modify the previous sentence to identify where long-term samples are being stored.] Only the people who work at the facility and approved researchers will have access to your samples. The people who work at the facility will not have any information that identifies you. The approved researchers may be given information about you such as your age and sex, but they will not be given your name or any other information that identifies you. Your samples may be shipped to approved researchers who work outside of your country. There is no time limit on how long your samples will be stored. Storage of the specimens will be handled in the same manner for both the study-specific testing (CD4 count/viral load/resistance) and the future separate research. [Sites should add language here if local regulations put a restriction on the length of time samples may be stored.]

Does storage of my leftover samples benefit me?

There are no direct benefits to you. The benefit of doing research on stored samples includes helping researchers learn more about HIV infection and its prevention.

What are the risks related to storage of leftover samples?

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible but unlikely that if others find out information about you that is learned from tests, it could cause you problems with your family, getting a job or insurance.

What about confidentiality related to storage of leftover samples?

To keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information, they will only be given the code.

The research staff will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential, but absolute confidentiality cannot be guaranteed.

(Storage and Future Testing of Leftover Specimens Continued)

People who may review your records include:

- DAIDS, and/or its contractors
- [insert applicable local authorities, e.g. Ministry of Health]
- [insert names of applicable IRBs/ECs]
- study staff

Will the results of future tests be shared?

The results of future tests will not be included in your health records nor will the results of these tests be shared with you or your doctors. Also, any publication of the research will not use your name or identify you personally.

What are my rights regarding storage of leftover samples?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time.

If you change your mind about the storage of your samples you must contact a member of the study staff by telling them or writing a letter to them letting them know that you do not want your samples used for future research. Your samples will not be used and will be destroyed as per laboratory guidelines.

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 HIV Drug Resistance Study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature (or Mark)	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name	Witness Signature	Date
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Please initial or make your mark to indicate if you choose to allow your test results from this study (CD4-positive T cell count, viral load, and HIV drug resistance) to be shared with your regular doctor:

_____ I agree and give the study staff permission to give my test results to my regular doctor

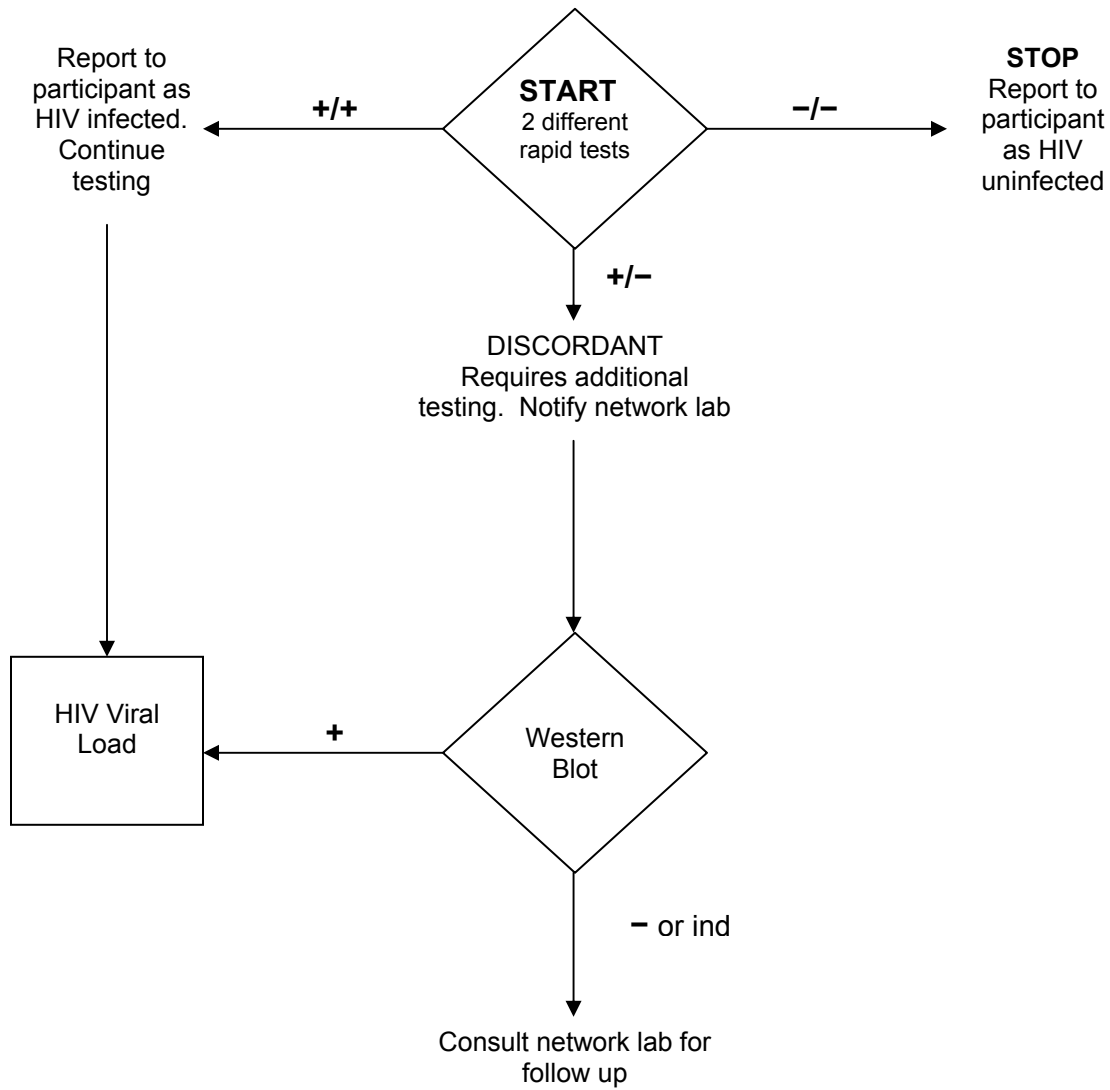
_____ I do not agree for the study staff to give my test results to my regular doctor

Please initial or make your mark to indicate whether or not you give your permission to the use and future testing of leftover blood samples labeled with a unique number. If you agree, you acknowledge that you understand that this research will be done at a later date, that you will not be informed of the results of these future studies, and that you do not have to agree to this testing in order to participate in this study.

_____ I agree to allow my leftover blood samples to be stored and used for future testing

_____ I do not agree to allow my leftover blood samples to be stored and used for future testing

APPENDIX II: MTN-009 Algorithm for Determination of HIV Infection



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