Title
Characteristics Associated with HIV Drug Resistance Among Women Screening for an HIV Prevention Trial in KwaZulu-Natal, South Africa

Permalink
https://escholarship.org/uc/item/1nt7g30r

Journal
AIDS and Behavior, 19(11)

ISSN
1090-7165

Authors
Mensch, Barbara S
Gorbach, Pamina M
Kelly, Cliff
et al.

Publication Date
2015-11-01

DOI
10.1007/s10461-015-1056-4

Peer reviewed

Characteristics associated with HIV drug resistance among women screening for an HIV prevention trial in KwaZulu-Natal, South Africa

Barbara S. Mensch[1], **Pamina Gorbach**[2], **Cliff Kelly**[3], **Photini Kiepiela**[4], **Kailazarid Gomez**[5], **Gita Ramjee**[4], **Shayhana Ganesh**[4], **Neetha Morar**[4], **Lydia Soto-Torres**[6], and **Urvi M. Parikh**[7] **on behalf of the MTN 009 Protocol Team**

[1]Population Council, New York, USA

[2]Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles, California, USA

[3]Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[4]HIV Prevention Research Unit, South African Medical Research Council, Durban, South Africa

[5]FHI 360, Research Triangle Park, Durham, North Carolina, USA

[6]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

[7]Department of Medicine, Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Abstract

While the expansion of antiretroviral therapy (ART) in sub-Saharan Africa has reduced morbidity and mortality from HIV/AIDS, it has increased concern about drug resistance. The Microbicide Trials Network (MTN) 009 study assessed the prevalence of drug resistance mutations among women at clinical sites in Durban, South Africa who tested seropositive for HIV-1 at screening for the VOICE trial. The objective of this paper was to identify characteristics and behaviors associated with drug resistance. Factors found to be significantly associated with increased resistance were high perceived risk of getting HIV and prior participation in a microbicide trial, a likely proxy for familiarity with the health care system. Two factors were found to be significantly associated with reduced resistance: having a primary sex partner and testing negative for HIV in the past year. Other variables hypothesized to be important in identifying women with resistant virus, including partner or friend on ART who shared with the participant and being given antiretrovirals during pregnancy or labor, or the proxy variable—number of times given birth in a health facility—were not significantly associated. The small number of participants with resistant virus and the probable underreporting of sensitive behaviors likely affected our ability to construct

Corresponding Author: Barbara S. Mensch, Population Council, One Dag Hammarskjold Plaza, New York, NY 10017, Tel: 212-339-0640, Fax: 212-755-6052, bmensch@popcouncil.org.

a comprehensive profile of the type of HIV-positive women at greatest risk of developing resistance mutations.

Introduction

While the expansion of antiretroviral therapy (ART) in sub-Saharan Africa has reduced morbidity and mortality from HIV/AIDS, it has increased concern about drug resistance. HIV drug resistance is characterized as acquired or transmitted. Acquired resistance occurs when a person infected with wild type virus develops resistance by exposure to antiretrovirals (ARVs) at a level that is insufficient to stop viral replication, such as with inconsistent adherence to therapy or to ARVs used for HIV prevention. Acquired resistance is the major cause of antiretroviral treatment (ART) failure, which limits therapeutic options for those on first-line therapy and raises the cost of treatment. In a study of 13,288 patients from sub-Saharan Africa on first-line ART, 33% had failed treatment within 2 years [1, 2]. A multi-country 13-site cohort study in Africa by the PharmAccess African Studies to Evaluate Resistance (PASER) group found that 70% of patients achieved RNA suppression, but among those that did not, 71% had HIV drug resistance; 96% of cases were acquired resistance from the treatment regimen, and only 4% were due to transmitted resistance [3].

Transmitted resistance occurs when a person who has never used ARVs is infected with a drug resistant virus from a partner who had acquired resistance or from a partner who was infected with a drug resistant virus (secondary transmission). Recent surveys conducted among counseling and testing clinic attendees in the KwaZulu-Natal province of South Africa have found the prevalence of transmitted HIV drug resistance to be low, ranging from <5% to 5% [4-6] but increasing in recent years to moderate levels of resistance (5-15%) to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class [7]. While relatively low rates of transmitted drug resistance among HIV-positive individuals have been observed in studies conducted in the region, the scale-up of ART and the new WHO guidelines [8] that recommend ART be initiated with CD4 counts of <500 cells/mm3, may lead to an increase in the prevalence of resistance. Indeed, there is evidence that transmitted drug resistance appears to be rising in Eastern and Southern Africa [9].

A high rate of either transmitted or acquired resistance could compromise the effectiveness of antiretroviral agents used for pre-exposure prophylaxis (PrEP) to prevent HIV infection in individuals in high prevalence settings, because some of the same agents tested in prevention trials—Tenofovir (tenofovir disoproxil fumerate or TDF, known by the brand name Viread®) and Truvada (TDF combined with emtricitabine, whose use as PrEP was recently approved by the U.S. Food and Drug Administration)—are currently included in first-line treatment regimens in South Africa. Transmitted resistance is a concern if the circulating strains of HIV in the community are resistant to the product being tested for HIV prevention. More importantly, acquired resistance from the use of product by individuals in

the pre-seroconversion window period of infection, who are not yet aware of their HIV status, poses a greater risk to developing resistance than in participants who seroconvert on active product arms. Results from seven completed PrEP trials—Bangkok Tenofovir, CAPRISA 004, Fem-PrEP, iPrEx, Partners PrEP, TDF2 and VOICE—showed that resistance was rare and occurred predominantly in participants who were in the acute phase of infection (i.e. seronegative but HIV RNA positive). Only 1.5% of seroconverters on active product arms in the trials developed HIV drug resistance to tenofovir or emtricitabine, while 22% of participants who were already HIV infected at enrollment developed HIV drug resistance to these products [10-16]. Yet, at least in the case of the VOICE trial where pharmacokinetic results revealed drug in fewer than 30% of those in the active arms, resistance may have been low in part because many participants did not use the products; with better adherence, resistance may become more of a problem in PrEP trials.

Behavioral data may provide insights into risk factors for drug resistance. For example, data on sexual behavior might help identify women more likely to be infected with a resistant strain of HIV from their partner; having sex with an HIV-positive partner who is on ART but not fully adherent will increase risk and the more partners reported, the more likely it is that someone with resistant virus will be encountered. Acquired resistance may occur in sexual partners or family members of trial participants if the HIV-positive partner or family member shares PrEP trial participants' tablets, apparently to treat their illness, but at an inadequate dosage [17]. A sexual partner could then transmit resistance to the trial participant or other partners in his sexual network. Thus, data on HIV-positive members in women's social and sexual networks who are on treatment might help identify those more likely to develop resistance, whether acquired or transmitted. Data on substance use of women and their partners could be useful assuming those who use illegal drugs are more likely to be intermittent users of ARVs whether they were prescribed ART or because they obtained ARVs some other way. Information on prior participation in a PrEP trial or a microbicide trial, in which ARVs were being tested, could be illuminating as prior exposure to ARVs might elevate the risk of acquired resistance or indicate that the sexual network of the participant included members who have had exposure to ART through previous trial participation. Finally, information on Nevirapine use during labor for prevention of mother-to-child transmission (PMTCT) is of particular interest because such exposure has been identified as also being associated with acquired resistance. However, some HIV+ women may not be aware of whether they were given medication during labor. Thus, information on births in health facilities as compared with births at home may also be indicative of risk because it is likely that only when an infected woman gives birth at a health facility is she provided with ARVs for PMTCT.

While research has been conducted on the prevalence of resistance and the clinical correlates [1-9], very few data exist on the behavior or characteristics of HIV-infected African women of reproductive age with drug-resistant HIV infection. MTN-009 assessed the prevalence of drug resistance mutations among women at clinical sites in Durban, South Africa who tested positive at screening for the VOICE trial, a phase 2b safety and effectiveness study of three antiretroviral products: two different oral tablets, Tenofovir and Truvada, and Tenofovir gel, a vaginal formulation of Tenofovir. Information on the characteristics and behaviors of this group of women, who were interested in participating in a prevention trial but were already

infected with HIV may shed light on factors associated with resistance. Therefore, a secondary objective of the MTN-009 study and the objective of this paper is to identify characteristics and behaviors correlated with drug resistance. HIV positive women enrolled in MTN-009 could have gotten: 1) transmitted resistance by becoming infected with HIV via a sexual partner with drug-resistant virus; 2) acquired resistance if they were unaware of their status, and used ARVs at a dose intended for prevention [18]; 3) acquired resistance after being tested for HIV during labor and, when found positive, been given single-dose Nevirapine [19]; 4) acquired resistance if they were prescribed ARVs, but were non-adherent or poorly adherent as indicated by lack of viral suppression, and the virus mutated; 5) acquired resistance if they were aware of or suspected their status and obtained ARVs from an HIV-positive friend, acquaintance or family member, who shared pills, or obtained ARVs from some other source.

Methods

Design

MTN-009 was conducted at seven sites of the HIV Prevention Research Unit, Medical Research Council of Durban, South Africa between August 2010 and June 2011: Botha's Hill, Chatsworth, Isipingo, Overport, Tongaat, Umkomaas, and Verulam, all located in semi-rural and urban areas. Participants were not recruited directly for MTN-009; rather a subsample of those who presented for screening for VOICE were asked if they were interested in participating in MTN-009. Since the clinic staff could not handle the potential influx of participants in both studies simultaneously; the opportunity to screen for 009 was offered to a few participants each day, generally those coming to the clinic in the morning. The recruitment of participants during morning clinic hours was the result of practical operational constraints; such a recruitment process would be unlikely to affect the selection of participants based on behavioral factors and/or HIV status, and thus resistance. While there is no reason to believe that those who screened were selective, we do know that trial participants are not a random sample of reproductive-aged women in the communities. In order to enroll 350 HIV-positive evaluable participants, 1000 women aged 18–40 were targeted. However, when we reached 1000 participants, we only had 300 evaluable HIV-1 positive participants because of insufficient viral load in some positive participants. Thus we continued to enroll until we had 350 evaluable participants. In total, 1075 women were enrolled prior to knowing their HIV status.

After obtaining written informed consent, a demographic form was administered via a face-to-face interview. To establish whether the woman had a partner, we asked: "Do you currently have a primary sex partner? By primary sex partner, I mean a man you have sex with on a regular basis or whom you consider to be your main partner." This was followed by questions on the age of the primary partner, whether he was living with the participant, whether he had any sex partners other than the participant, whether he provided the participant with financial and/or material support, his average monthly income, his level of education, and his circumcision status. The interview included background questions on the participant's date of birth, her marital status, education, residence, income, number of

children to whom she gave birth, ownership of the house in which she lived, number of rooms in the house, and ethnic or tribal affiliation.

After the demographic form was administered women underwent an audio computer-assisted self-interview (ACASI) before rapid testing for HIV. Given the exploratory nature of the study, the ACASI instrument contained questions on a broad array of behaviors and attitudes; the type of variable and, where relevant, the response categories (in parentheses) are indicated here: number of times participant gave birth in a health facility (1-5+); whether the participant had been given medication to prevent mother-to-child transmission of HIV during pregnancy or labor (yes/no); sexual behavior, including number of lifetime partners (continuous), number of partners in the past year (continuous), whether there was a concurrent partner in the past year[1] (yes/no), use of condoms at last vaginal sex (yes/no), use of condoms at last anal sex (yes/no); risk perceptions (high/medium/low/no risk); concern about transmitting HIV to future children[2] (very worried/worried/not worried at all); knowing someone with HIV or AIDS (yes/no); recency of last HIV test and recency of last negative HIV test (for both variables; 0-6 months ago/7-12 months ago/more than a year ago/don't remember/never); prior experience in HIV prevention trials including microbicide trials[3] (yes/no/don't know), and most important reason to join an HIV prevention trial (to receive the financial reimbursement/to be provided with free health care during the trial or to get faster or better quality health care/to be tested for HIV/to get information about HIV prevention/to help test a product that may prevent women from getting HIV/none of these reasons); participant and partner substance use, including injection drug use (yes/no); HIV status of partner (negative/positive/don't know); partner use of ARVs (yes/no) including length of time taking ARVs (less than 6 months/6 months-3 years/3 years+) and ever skipped a day and not taken his ARVs (yes/no/don't know), whether he shared ARVs with participant; whether friend, acquaintance or family member was prescribed ARVs (yes/no/don't know) and whether those ARVs were shared with participant (yes/no/don't remember); participant prescribed ARVs (yes/no/don't know), including ever skipped a day and not taken ARVs (yes/no/don't know); ever taken a medicine (modern and traditional) or a vaginal product that participant thought might prevent HIV (yes/no).

Note that for the two questions on sexual partners: "In your lifetime with how many different male partners have you had sex?" and "Now, thinking about the past year, with how many male partners have you had sex?", an image of a male partner appeared on the computer screen for the participant to click on to provide a numerical response. In addition there were two other response options: "Never had vaginal or anal sex with a male partner," and "Don't remember." Each time a participant tapped the image on the screen in response to the questions on number of partners, a new face appeared to indicate a different partner. A similar interactive screen for reporting of partners had been successfully implemented in a prior MTN study in Malawi. While experimental data demonstrating the effectiveness of graphics to generate more accurate data within ACASI are lacking, this format resulted in

---

[1] The question was worded: "You indicated you have had vaginal or anal sex with 2 or more male partners in the past year. Were you still having a sexual relationship with one partner during the time when you had a sexual relationship with another partner?"
[2] The question was worded: "How worried are you about transmitting HIV to future children you may have?"
[3] The questions were worded: "Have you ever participated in any research studies or HIV prevention trials?" If yes, "Have you ever participated in a microbicide trial?"

more women reporting more partners and no partners (a protocol violation) compared to face-to-face interviews with the same women [20].

Two simultaneously conducted rapid tests (Determine, Abbott Laboratories, Johannesburg, SA; Unigold, Trinity Biotech, Wicklow, Ireland; or Oraquick, OraSure Technologies, Bethlehem, PA) were used to identify HIV status. Infection was confirmed by the Bio-Rad GS HIV-1/2+O Enzyme Immunoassay (Hercules, CA). In addition, Bio-Rad GS HIV-1Western blot was used to confirm status for participants with either discordant rapid tests or dual positive tests and undetectable HIV-1 RNA (<40 copies/ml). HIV-1 genotyping was performed on plasma from all confirmed HIV-positive participants with RNA levels >200 copies/ml using the ViroSeq 2.0 Genotyping Method (Celera, Alameda, CA) with kit-provided or alternative primers provided by Celera. Resistance mutations were identified using the Stanford Calibrated Population Resistance Tool [21]. Samples were considered resistant if they contained one or more mutations as defined by the Bennett WHO transmitted drug resistance list [22]. Note that there is no lagged effect of acquiring resistance except insofar as there is a window period for detecting HIV infection. While resistance can be detected once there are sufficient RNA levels, it can fade over time. All HIV-positive participants received post-test counseling; those with resistance mutations were also counseled about the results of their resistance tests.

The protocol, informed consent forms, and all study materials were reviewed and approved by the National Institute of Allergy and Infectious Diseases Division of AIDS (NIAID/DAIDS) in the United States, and by the Medical Research Council Ethics Committee in South Africa. All participants provided written informed consent to participate in this study. The MTN-009 study was registered at www.Clinical-Trials.gov (NCT01204814) and the protocol can be found at http://www.mtnstopshiv.org.

Analysis Plan and Statistical Methods

We first compared the demographic and behavioral characteristics of women enrolling in MTN-009 who tested seropositive for HIV-1 with those who tested negative. Second, among those who tested positive, we compared those with insufficient viral load levels for resistance testing with those who were sequenced. Third, among women who tested positive and were sequenced, we compared the characteristics of those with resistant and nonresistant virus.

Logistic regression with a dichotomous outcome indicating the presence of resistant virus was used to estimate the models. Given that few data exist on the correlates of HIV resistance, we assessed the significance of a broad array of demographic and behavioral risk factors. A variable was included in the multivariable resistance model if overall factors (continuous and ordinal variables) or individual categories (nominal variables) were significant at p<0.20 in the univariate models. Because the analysis is exploratory, we retained nonsignificant variables in the models to show which factors are unrelated to the outcomes of interest. Those nonsignificant factors are listed at the bottom of the regression table. We were particularly interested in the odds ratios for several variables for which there are theoretical reasons to suspect an association with resistance:

1. Frequency of birth in a hospital/primary health care clinic or polyclinic, which may reflect prior exposure to Nevirapine.

2. Medication given in labor to prevent HIV, a more direct measure of Nevirapine exposure than in #1.

3. HIV status of the primary partner and, if positive, whether the partner has been prescribed ARVs, which would potentially elevate the risk of transmitted resistance.

4. Number of male partners; the greater the number of partners, the more likely the woman is exposed to someone who has resistant virus.

5. Prior participation in an HIV prevention trial. Even if seroconverters in prior PrEP trials rarely developed resistance, prior participation in such trials may signal increased access to treatment and thus exposure to ARVs. Former trial participants are familiar with the health care system and it is likely that members of their immediate social and family circle who are HIV positive are linked to care.

6. Substance use of the woman and her partner, which may be associated with inconsistent use of ARVs.

Note that "don't know" responses were generally treated as a separate category for nominal variables. For several variables, however, "don't know" was grouped as a referent category.

Results

Of the women who presented for screening for VOICE, 1075 were enrolled into MTN 009, of whom 1073 were evaluable (one had an enrollment violation, and one did not provide any samples for testing). A total of 400 of the 1073 (37.3%) were HIV positive. Of those 400, HIV-1 RNA was detectable in 352 (88.0%). An additional 47 participants (11.8%) had detectable HIV-1 RNA levels that were at or below 200 copies/ml and therefore could not have HIV genotyping performed. For one participant, HIV sequencing was not successful. Of the 352 plasma samples that were analyzed for resistance, 26 or 7.4% had drug-resistance mutations (Figure 1). These results have been published previously [18].

Table 1 provides the distribution of selected demographic and behavioral factors for: 1) the enrolled sample, 2) participants who tested positive and, 3) HIV-positive participants whose plasma samples were able to be analyzed for resistance. The table indicates that reporting of some of the hypothesized risk factors is too low to explain variability in resistance observed in the sample. For example, only 1% of HIV-positive participants report that someone shared ARVs with them. In addition, while having an infected partner is also a risk factor for resistance, too few women report HIV-positive partners — only 3% of those tested for resistance — for this variable to be an important correlate in this analysis. On the other hand, some of the substance use variables are reported with sufficient frequency, e.g. 8% of women who were tested for resistance report cocaine use and 17% report taking "other" drugs. Although participants often underreport multiple partners [20], over one-quarter of women who were tested for resistance report having more than one partner in the past year,

a prevalence considerably higher than that reported nationally among females in South Africa in 2012 [23].

Other than participant age (AOR=1.15, 95% CI 1.07–1.23), no variable was significantly associated with having a viral load sufficient for resistance testing, suggesting that the sample of HIV-positive participants available for the resistance analysis is not selective for any measured behavioral factors (results not shown). That is, the sample of HIV-positive participants with a viral load sufficient for testing is similar to the entire sample of HIV-positive participants.

Factors significantly associated with resistance in the multivariable model are shown in Table 2; high perceived risk of getting HIV (AOR=3.47, 95% CI 1.15–10.47), and prior participation in a microbicide trial (AOR=5.36, 95% CI 1.17–24.51) increase the likelihood of resistance. Two factors are negatively associated: having a primary sex partner (AOR=0.03, 95% CI 0.002–0.59) and testing negative for HIV in the past year (AOR= 0.16, 95% CI 0.03–0.89). Notably, while having a husband/partner who has been prescribed ARVs substantially raises the likelihood of having a drug-resistance mutation in the unadjusted model (OR=10.46, p=0.01), this factor, which has an extremely large confidence interval likely because so few report this, becomes insignificant in a multivariable model (AOR=7.04 95% CI 0.59–83.58). Other variables that we hypothesized might be important in identifying those who have resistant virus, including sharing of ARVs and being given ARVs during pregnancy or labor or the proxy variable—number of times given birth in a health facility—were not significant.

Discussion

To the best of our knowledge, this study is the first to examine demographic and behavioral factors associated with resistant virus among a sample of HIV-positive women in a high prevalence setting in South Africa. Several findings warrant additional discussion: First, women who report previous participation in a microbicide trial were significantly more likely to have resistant virus. As noted earlier, less than 2% of seroconverters in seven PrEP trials developed HIV drug resistance [10-16]; thus it is highly improbable that a woman acquired resistance while enrolled in a microbicide trial. More likely, women who previously participated in a microbicide trial may have learned in that trial that they acquired HIV, and yet not have accessed care since the trial ended, instead choosing to obtain ARVs elsewhere or illicitly. They may have decided to screen for the VOICE trial hoping that they would be linked to care when they tested positive. Indeed qualitative data from a sub-sample of VOICE participants suggest that a primary reason for enrolling in the trial was to access health care [24]. Alternatively, women's partners, if positive, could have accessed treatment because of a referral from the trial or after the trial ended because of familiarity with the health care system as a result of the participant's prior trial experience; thus infection with resistant virus may have occurred via a partner but be associated with prior trial experience. Finally, these women may have previously joined a trial because they had a partner known to be HIV positive and were hoping for protection from acquiring HIV but instead were infected during or after the trial [25]. In short, former trial participants may be more likely to have exposure to ARVs either directly or through a partner and it is that increased exposure

to ARVs outside, and not within, the trial but related to trial participation that may have led to resistance. Second, women who perceive themselves to be at high risk of acquiring HIV are more likely to have resistant virus perhaps because they or their partners are substance users or engage in other high risk behaviors (e.g. commercial sex work) associated with inconsistent access or adherence to ARVs [26]. Alternatively, perhaps those who are at "higher risk" for HIV know they are HIV positive and thus are more likely to have taken ARVs. Third, of the 26 women with resistant virus, 15 (58%) reported that a friend or family member had been prescribed ARVs compared with 41% of those who were HIV positive who did not have resistant virus. Because of reluctance to report "borrowing" ARVs from friends or acquaintances, we think this variable may serve as a proxy for actual sharing. While not significant in the multivariable model, it does suggest that such behavior may contribute to the development of drug-resistant HIV infection.

This analysis has several limitations that affect the credence that we can give to our results: 1) The variables associated with resistance do not suggest a specific behavioral "profile" such as being a substance user or having multiple sexual partners; however, because only a small number of women have resistant virus (N=26) it is difficult to identify risk factors for resistance and to shed light on whether it is likely acquired or transmitted. 2) Given the exploratory nature of the analysis, we considered over 50 univariate factors in our analyses. For the resistance analysis, four showed significance at the 0.05 level, which is what we would also expect by chance when investigating this many factors. 3) It is likely that many of the risk and ARV exposure variables were not significant in our models because of underreporting. Proxy variables, such as prior participation in a microbicide trial, may be picking up that exposure; it is more likely that participants will disclose prior participation in a microbicide trial, a behavior which is not sensitive in the context of screening for another trial, than that a friend or partner is HIV positive and shared ARVs. Similarly, it is more likely that a participant will report being at high risk of HIV rather than report engaging in risky behavior.

Finally, much of our discussion about mechanisms underlying resistance was speculative. In order to identify which behaviors and characteristics are associated with resistance and to determine if it is acquired or transmitted, more extensive behavioral and social data should be collected from a larger sample of HIV positive individuals with resistant virus as well as more in-depth information from a sub-sample of respondents and their partners. We suggest that global surveillance efforts for HIV-1 drug resistance include behavioral assessments, which may provide a better understanding of the risk factors underlying resistant virus. With a sufficiently large sample and comprehensive information on potential behavioral and social correlates, it may be possible to develop a profile of the type of HIV-positive women at greatest risk of developing ARV-resistance mutations, although these analyses may be limited by underreporting of sensitive behaviors. As ART coverage increases in sub-Saharan Africa, efforts to minimize resistance will surely benefit both from the development of such a profile and from qualitative explorations of the behaviors linked to acquired and transmitted resistance.

Author Manuscript

Acknowledgments

References

1. Abbas UL, Glaubius R, Mubayi A, Hood G, Mellors JW. Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. J Infect Dis. 2013; 208(2):224–234. [PubMed: 23570850]

2. Barth RE, van der Loeff MF, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. Lancet Infect Dis. 2010; 10(3):155–166. [PubMed: 20185094]

3. Hamers RL, Sigaloff KC, Wensing AM, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis. 2012; 54(11):1660–1669. [PubMed: 22474222]

4. Hamers RL, Wallis CL, Kityo C, et al. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infect Dis. 2011; 11(10):750–759. [PubMed: 21802367]

5. Parboosing R, Naidoo A, Gordon M, Taylor M, Vella V. Resistance to antiretroviral drugs in newly diagnosed, young treatment-naive HIV-positive pregnant women in the province of KwaZulu-Natal, South Africa. J Med Virol. 2011; 83(9):1508–1513. [PubMed: 21739439]

6. Manasa J, Katzenstein D, Cassol S, Newell ML, de Oliveira T. Primary drug resistance in South Africa: data from 10 years of surveys. AIDS Res Hum Retroviruses. 2012; 28(6):558–565. [PubMed: 22251009]

7. Hunt GM, Ledwaba J, Basson AE, et al. Surveillance of transmitted HIV-1 drug resistance in Gauteng and KwaZulu-Natal Provinces, South Africa, 2005-2009. Clin Infect Dis. 2012; 54(Suppl 4):S334–338. [PubMed: 22544199]

8. World Health Organization. Executive Summary: Consolidated ARV Guidelines 2013, June, 2013. Geneva, Switzerland: World Health Organization; 2013. Available at: http://www.who.int/hiv/pub/guidelines/arv2013/intro/executivesummary/en/index.html [Accessed January, 2014]

9. Hamers RL, Sigaloff KC, Kityo C, Mugyenyi P, de Wit TF. Emerging HIV-1 drug resistance after roll-out of antiretroviral therapy in sub-Saharan Africa. Curr Opin HIV AIDS. 2013; 8(1):19–26. [PubMed: 23143140]

10. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013; 381(9883):2083–2090. [PubMed: 23769234]

11. 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(5996):1168–1174. [PubMed: 20643915]

12. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367(5):411–422. [PubMed: 22784040]

13. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363(27):2587–2599. [PubMed: 21091279]

14. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367(5):399–410. [PubMed: 22784037]

15. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012; 367(5):423–34. [PubMed: 22784038]

16. Parikh, UM.; Eskay, KA.; Hardesty, R., et al. HIV-1 resistance outcomes in seroconverters from the MTN 003 (VOICE) Study. Poster presented at: 21st Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA.

17. van der Straten A, Stadler J, Luecke E, et al. Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: The VOICE-C qualitative study in Johannesburg, South Africa. J Int AIDS Soc. 2014; 17(Suppl 2):19146. [PubMed: 25224610]

18. Parikh UM, Kiepiela P, Ganesh S, et al. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009). PLoS ONE. 2013; 8(4):e59787. [PubMed: 23585827]

19. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. N Engl J Med. 2004; 351(3):229–240. [PubMed: 15247339]

20. Gorbach P, Mensch BS, Husnik M, et al. Effect of computer-assisted interviewing on self-reported sexual behavior data in a microbicide clinical trial. AIDS Behav. 2013; 17(2):790–800. [PubMed: 23054034]

21. Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. Clin Infect Dis. 2006; 42(11):1608–1618. [PubMed: 16652319]

22. Bennett DE, Camacho RJ, Otelea D, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS ONE. 2009; 4(3):e4724. [PubMed: 19266092]

23. Shisana, O.; Rehle, T.; Simbayi, LC., et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. Cape Town, South Africa: HSRC Press; 2014.

24. van der Straten, A.; Musara, P.; Etima, J., et al. Disclosure of pharmacokinetic (PK) drug results promotes open discourse on non-adherence among women in VOICE. Oral presentation at: HIV Research for Prevention (R4P) Conference. Session on PrEP and Microbicide Adherence in Women; October 29, 2014; Cape Town, South Africa. OA15.04

25. Woodsong C, Alleman P, Musara P, et al. Preventive misconception as a motivation for participation and adherence in microbicide trials: evidence from female participants and male partners in Malawi and Zimbabwe. AIDS Behav. 2012 Apr; 16(3):785–790. [PubMed: 21863339]

26. Grelotti DJ, Closson EF, Smit JA, et al. Whoonga: Potential recreational use of HIV antiretroviral medication in South Africa. AIDS Behav. 2014; 18(3):511–518. [PubMed: 23955659]
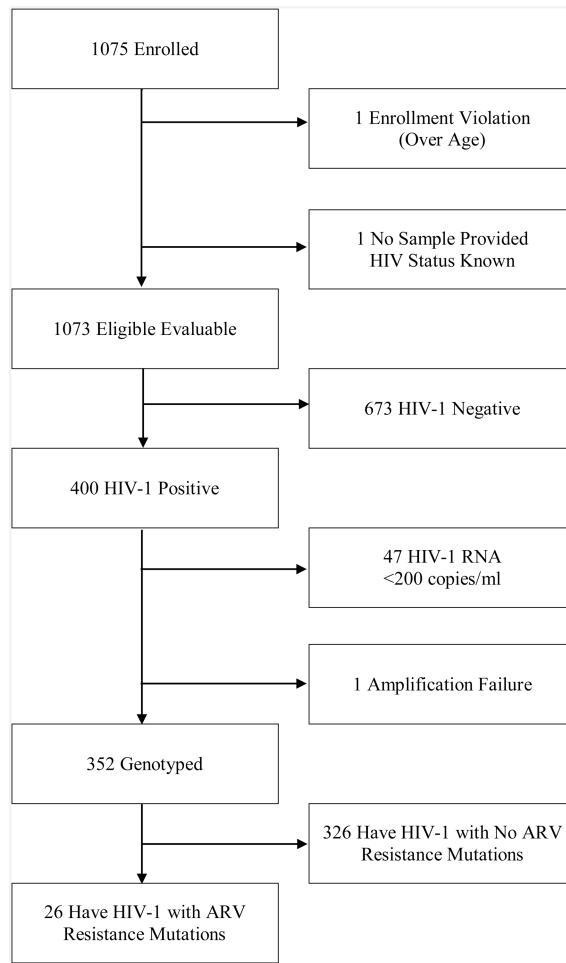
Figure 1. Consort diagram

Table 1

Demographic and behavioral characteristics of participants enrolled, HIV positive, and tested for resistance.

Factor	Enrolled (N=1073)	HIV Positive (N=400)	HIV+ and Tested for Resistance (N=352)
Site			
Botha's Hill	135 (13%)	39 (10%)	34 (10%)
Isipingo	133 (12%)	39 (10%)	34 (10%)
Overport	321 (30%)	141 (35%)	122 (35%)
R.K. Khan	91 (8%)	31 (8%)	26 (7%)
Tongaat	184 (17%)	62 (16%)	55 (16%)
Umkomaas	88 (8%)	34 (9%)	33 (9%)
Verulam	121 (11%)	54 (14%)	48 (14%)
Mean age, years (SD)[a]	25.6 (5.6)	27.2 (5.5)	26.8 (5.4)
Has at least some secondary school education	987 (92%)	350 (88%)	315 (89%)
Race			
Zulu	931 (87%)	342 (86%)	300 (85%)
Xhosa	111 (10%)	50 (13%)	45 (13%)
Other	12 (1%)	0 (0%)	0 0%)
Indian	17 (2%)	7 (2%)	7 (2%)
Formally employed	110 (10%)	30 (8%)	27 (8%)
Mean number of rooms in house (SD)[a]	3.3 (1.9)	3.1 (1.8)	3.2 (1.8)
Participant does not currently have a primary sex partner	15 (1%)	9 (2%)	7 (2%)
Participant currently married	43 (4%)	12 (3%)	11 (3%)
Participant ever been widowed	95 (9%)	65 (16%)	54 (15%)
Participant ever been separated or divorced	49 (5%)	14 (4%)	12 (3%)
Given birth in a hospital, primary health clinic or polyclinic	869 (82%)	327 (83%)	284 (81%)
When pregnant or in labor, given HIV prevention medication for baby			
Yes	64 (6%)	42 (11%)	38 (11%)
No	676 (64%)	223 (57%)	194 (56%)
Never been pregnant	152 (14%)	47 (12%)	44 (13%)
Don't remember/unsure	169 (16%)	82 (21%)	71 (20%)
Lifetime number of male sex partners			
None	38 (4%)	17 (4%)	15 (4%)
One	388 (36%)	92 (23%)	85 (24%)
Two or more	462 (43%)	201 (51%)	173 (50%)
Don't remember	140 (13%)	69 (17%)	60 (17%)
Skipped	38 (4%)	17 (4%)	16 (5%)
Number of male sex partners, past year			
None	100 (9%)	35 (9%)	29 (8%)
One	675 (63%)	220 (56%)	195 (56%)
Two or more	219 (21%)	102 (26%)	90 (26%)
Don't remember	54 (5%)	30 (8%)	26 (7%)

Factor	Enrolled (N=1073)	HIV Positive (N=400)	HIV+ and Tested for Resistance (N=352)
Skipped	19 (2%)	9 (2%)	9 (3%)
Participant has had concurrent sexual relationships with >1 partner in past year			
Yes	131 (12%)	69 (18%)	61 (18%)
No	104 (10%)	40 (10%)	36 (10%)
Don't remember	54 (5%)	30 (8%)	26 (7%)
Has one or no partner	775 (73%)	255 (65%)	224 (65%)
Partner has had sexual relations with another partner in the past year			
Yes	398 (37%)	181 (46%)	157 (45%)
No or no partner	212 (20%)	66 (17%)	57 (16%)
Don't know	454 (43%)	149 (38%)	135 (39%)
Perceived risk of getting HIV			
High	432 (41%)	190 (48%)	167 (48%)
Medium	317 (30%)	126 (32%)	114 (33%)
Low	183 (17%)	54 (14%)	45 (13%)
No risk	131 (12%)	25 (6%)	22 (6%)
How worried about transmitting HIV to future children			
Very worried	749 (70%)	295 (74%)	259 (74%)
Worried	201 (19%)	74 (19%)	68 (19%)
Not worried at all	116 (11%)	27 (7%)	22 (6%)
Participant knows someone with HIV			
Yes	699 (66%)	257 (65%)	227 (65%)
No	189 (18%)	61 (15%)	56 (16%)
Don't know	178 (17%)	78 (20%)	66 (19%)
Participant last tested for HIV within past year	460 (43%)	93 (23%)	83 (24%)
Participant ever participated in any research studies or HIV prevention trials			
Yes	161 (15%)	36 (9%)	33 (9%)
No	823 (77%)	315 (80%)	279 (80%)
Don't know	81 (8%)	44 (11%)	36 (10%)
Participant ever participated in a microbicide trial			
Yes	38 (4%)	17 (4%)	16 (5%)
No	932 (88%)	347 (88%)	307 (88%)
Don't know	95 (9%)	31 (8%)	25 (7%)
Most important reason to join an HIV prevention trial			
Financial reimbursement	25 (2%)	6 (2%)	4 (1%)
Free/better health care	302 (28%)	126 (32%)	111 (32%)
To be tested for HIV	90 (8%)	41 (10%)	33 (9%)
Learn about HIV prevention	212 (20%)	74 (19%)	62 (18%)
Help test a product for HIV prevention	429 (40%)	146 (37%)	136 (39%)
None of these reasons	6 (1%)	2 (1%)	2 (1%)
Ever injected drugs not prescribed	17 (2%)	6 (2%)	5 (1%)

Factor	Enrolled (N=1073)	HIV Positive (N=400)	HIV+ and Tested for Resistance (N=352)
Ever taken Tik/methamphetamine	27 (3%)	10 (3%)	9 (3%)
Ever taken E/Ectasy/Sugars	44 (4%)	15 (4%)	11 (3%)
Ever taken Heroin/dope/brown sugar	25 (2%)	13 (3%)	12 (3%)
Ever taken Coke/cocaine	64 (6%)	30 (8%)	28 (8%)
Ever used drugs but does not know the name	61 (6%)	24 (6%)	21 (6%)
Ever taken other drugs	154 (14%)	66 (17%)	59 (17%)
Husband/partner has ever been tested for HIV			
Yes	411 (39%)	88 (22%)	81 (23%)
No	230 (22%)	103 (26%)	88 (25%)
No husband/partner	9 (1%)	7 (2%)	4 (1%)
Don't know	411 (39%)	195 (50%)	173 (50%)
Husband/partner HIV status			
HIV negative	342 (34%)	60 (16%)	55 (17%)
HIV positive	25 (2%)	13 (4%)	11 (3%)
Don't know	647 (64%)	296 (80%)	261 (80%)
Husband/partner has been prescribed ARVs			
Yes	10 (1%)	7 (2%)	5 (1%)
No or no partner	765 (72%)	241 (62%)	217 (63%)
Don't know	277 (26%)	138 (36%)	120 (35%)
Husband/partner has ever shared ARVs with participant	0 (0%)	0 (0%)	0 (0%)
Friend/family member has been prescribed ARVs			
Yes	418 (39%)	162 (41%)	148 (43%)
No	330 (31%)	108 (27%)	91 (26%)
Don't know	316 (30%)	124 (31%)	108 (31%)
Friend/family member has ever shared ARVs with participant	7 (1%)	4 (1%)	4 (1%)
Participant has ever been prescribed ARVs			
Yes	7 (1%)	2 (1%)	2 (1%)
No	1029 (97%)	377 (96%)	334 (96%)
Don't know	28 (3%)	15 (4%)	11 (3%)
Participant ever taken a medicine she thought might prevent HIV	25 (2%)	14 (4%)	10 (3%)
Participant ever used a vaginal product she thought might prevent HIV	107 (10%)	27 (7%)	23 (7%)
Participant ever taken traditional medicine she thought might prevent HIV	41 (4%)	34 (9%)	26 (7%)

[a]SD=Standard Deviation.

Table 2

Factors associated with the presence of a drug resistance mutation among HIV⁺ participants — multivariable logistic regression model results (N=337)

Factor	OR	p-value	AOR (95% C.I.)	p-value
Site				0.190[a]
Isipingo vs. Botha's Hill	1.00	NS[b]	0.67 (0.02, 26.1)	0.831
Overport vs. Botha's Hill	1.06	NS[b]	3.79 (0.27, 53.45)	0.323
R.K. Khan vs. Botha's Hill	1.31	NS[b]	9.29 (0.56, 154.61)	0.120
Tongaat vs. Botha's Hill	0.87	NS[b]	7.60 (0.46, 125.78)	0.157
Umkomaas vs. Botha's Hill	0.21	0.16	1.30 (0.05, 35.52)	0.876
Verulam vs. Botha's Hill	0.85	NS[b]	1.13 (0.06, 19.89)	0.936
Participant age, years	1.14	<0.01	1.07 (0.98, 1.17)	0.160
Participant Some Secondary School Education or Higher	0.32	<0.01	0.40 (0.10, 1.62)	0.197
Participant has a primary sex partner	0.19	0.05	0.03 (0.002, 0.59)	0.020
High perceived risk of getting HIV	3.26	<0.01	3.47 (1.15, 10.47)	0.028
Participant knows someone who has HIV				0.191 [a]
Yes	2.75	0.18	2.63 (0.52, 13.24)	0.240
Don't know	1.29	NS[b]	0.75 (0.10, 5.60)	0.780
No	Ref	--	Ref	--
Participant last tested negative for HIV within past year	0.39	0.14	0.16 (0.03, 0.89)	0.036
Participant ever participated in a microbicide trial	4.76	0.01	5.36 (1.17, 24.51)	0.030
Participant ever taken other drugs	0.18	0.10	0.20 (0.03, 1.64)	0.134
Husband/partner has ever been tested for HIV				
Yes	1.82	0.17	2.35 (0.72, 7.67)	0.158
No, Don't Know or No partner	Ref	--	Ref	--
Husband/partner has been prescribed ARVs				0.235 [a]
Yes	10.46	0.01	7.04 (0.59, 83.58)	0.122
Don't know	1.43	NS[b]	1.65 (0.58, 4.73)	0.353
No	Ref	--	Ref	--
Friend/family member has been prescribed ARVs				0.810 [a]
Yes	3.31	0.06	1.62 (0.38, 7.02)	0.517
Don't know	2.35	NS[b]	1.47 (0.32, 6.83)	0.624
No	Ref	--	Ref	--

[a]For nominal variables with more than 2 categories, e.g. site, the overall p-value comes from the Type 3 analysis Wald Chi-Square test, which assesses whether all categories of that variable are the same. For each category, p-values are also provided from an analysis of maximum likelihood estimates Wald Chi-Square tests for a comparison to a reference, as indicated.

[b]NS = Non-significant p-value >0.20.