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Authors

Musara, Petina
Montgomery, Elizabeth T
Mgodi, Nyaradzo M
et al.

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How Presentation of Drug Detection Results Changed Reports of Product Adherence in South Africa, Uganda and Zimbabwe

Petina Musara[1], **Elizabeth T. Montgomery**[3], **Nyaradzo M. Mgodi**[1], **Kubashni Woeber**[2], **Carolyne A. Akello**[6], **Miriam Hartmann**[3], **Helen Cheng**[3], **Lisa Levy**[4], **Ariana Katz**[3], **Cynthia I. Grossman**[5], **Z. Mike Chirenje**[1], **Ariane van der Straten**[3,7], and **Barbara Mensch**[8] **On behalf of the Microbicide Trials Network-003D Study Team**

[1]University of Zimbabwe-University of California San Francisco Collaborative Research Programme, 15 Phillips, Belgravia, Harare, Zimbabwe [2]HIV Prevention Research Unit, South African Medical Research Council, Cape Town, South Africa [3]Women's Global Health Imperative; RTI International, San Francisco, CA, USA [4]FHI-360, Durham, NC, USA [5]DAIDS/NIH/NIMH, Bethesda, MD, USA [6]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda [7]Center for AIDS Prevention Studies, UCSF, San Francisco, CA, USA [8]Population Council, New York, NY, USA

Abstract

Accurate estimates of study product use are critical to understanding and addressing adherence challenges in HIV prevention trials. The VOICE trial exposed a significant gap between self-reported adherence and drug detection. The VOICE-D qualitative study was designed to better understand non-adherence during VOICE, and was conducted in 2 stages: before (stage 1) and after (stage 2) drug detection results were provided to participants. Transcripts from 44 women who participated in both stages were analysed to understand the effect of presenting drug detection data on narratives of product use. Thirty-six women reported high adherence in stage 1, yet admitted non-use in stage 2, three reported high adherence in both stages (contrary to their drug detection results) and five had consistent responses across both stages and drug results. Presenting objective measures of use may facilitate more accurate product use reporting and should be evaluated in future prevention trials.

Keywords

Drug detection results; Adherence measures; Pre-exposure prophylaxis; Microbicides; HIV prevention

Correspondence to: Petina Musara.

Compliance with Ethical Standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical Approval The study protocol was approved by the Institutional Review Boards at Research Triangle Institute International and at each of the study sites. Informed consent was obtained from all the participants enrolled in the study.

Background

Young women in Sub-Saharan Africa (SSA) remain at very high risk of HIV infection [1]. Current proven methods of HIV prevention, including condoms, require the participation or consent of a male partner and may not be an option for many women. There is an urgent need for HIV prevention methods that women can and will actually use [2]. Biomedical interventions such as vaginal microbicides and oral HIV pre-exposure prophylaxis (PrEP) containing antiretrovirals have demonstrated effectiveness at preventing HIV acquisition in women in some trials in the region, but not in others [2]. Similar to the other PrEP and microbicide trials that demonstrated no protective effects, VOICE revealed low product adherence based on retrospective drug level testing of biological samples. Specifically ≥50% of VOICE participants assigned to daily active oral tablets or vaginal gel had undetectable tenofovir in all tested plasma samples [2], despite the fact that product adherence was estimated at 90%, as measured by participants' report to study staff via face-to face interviews, Audio Computer Assisted Self Interview (ACASI), and by returned product counts [8]. Similar discrepancies were revealed in other trials of daily PrEP, such as FEM-PrEP, MTN-001 and iPrEX [6, 7, 9]. Unfortunately, demonstration of effectiveness is undermined when study products are not consistently and correctly used, even if they are biologically efficacious.

VOICE D, a qualitative 2-stage study, was conducted after trial completion in each of the 3 VOICE countries, Uganda, Zimbabwe, South Africa, in part, to better understand discrepant adherence results [10]. In stage 1, participants discussed adherence to study product during the VOICE trial, with no feedback on drug detection. In stage 2, which was limited to VOICE participants in the active arms, women were retrospectively provided with their plasma drug detection results. Based on participants' recommendations in stage 1, we hypothesized that providing an objective measure of drug detection might encourage more honest discussion of product non-use and challenges to adherence. This paper examines women's reports of study product usage before and after being presented with their drug level test results.

Methods

Study Design and Setting

VOICE-D was a qualitative sub-study of the VOICE trial, conducted between December 2012 and March 2014, in Kampala, Uganda; Durban, South Africa; and Chitungwiza, Zimbabwe, following completion of VOICE in August 2012. VOICE was a randomized, 5-arm, double-blind, placebo controlled trial that investigated the safety and effectiveness of daily vaginal 1% tenofovir (TFV) gel, oral tenofovir, and oral emtricitabine/tenofovir disoproxyl fumarate (FTC/TDF) for the prevention of HIV-1 infection in women in SSA. Participants who had provided permission to be re-contacted at the end of VOICE were approached for recruitment into VOICE-D. In stage 1, each participant provided informed consent, completed a brief demographic questionnaire, and underwent an in-depth interview (IDI), using a semi-structured guide. Interviews were conducted by trained non-VOICE female staff at neutral locations in the participant's preferred language. Stage 1 findings informed the design of stage 2. Despite the fact that in-depth interviews are thought to

encourage candid and open-ended discussion, in VOICE-D stage 1, participants did not personally admit to challenges with product use. The inability of the VOICE researchers to objectively identify non-users during trial implementation was mentioned by some VOICE-D stage 1 participants as one of the factors contributing to product non-use and inaccurate self-reports. VOICE-D participants recommended that drug monitoring and feedback would motivate women to candidly discuss their challenges with study product use. In stage 2, each participant provided informed consent, completed a brief demographic questionnaire, received their plasma drug detection results and as well completed either an IDI, a focus group discussion (FGD), or both. The interviews were conducted by social scientists with the required interviewing skills and experience in conducting qualitative research who were trained to provide the drug test results in a neutral manner using a visual tool [10].

Study Participants

VOICE-D enrolled 171 former VOICE participants across 3 sites in Kampala, Uganda (N = 61), Durban, South Africa (N = 45) and Chitungwiza, Zimbabwe (N = 65); 88 were enrolled in stage 1 and 127 in stage 2. Forty-four women who had been assigned to active products during VOICE, participated in both stages 1 and 2 and constitute the sample for this analysis. Stage 1 participants were recruited from a sample of potentially eligible participants and randomly pre-selected for participation in the study, after stratification by product assignment and HIV status. The eligibility criteria for stage 2 participants required, among other things, that participants had received active product during VOICE and had drug level data available from VOICE study. Some stage 1 participants who met the criterion were preselected for inclusion in stage 2; participants who had drug level data available but had not participated in stage 1 were also eligible for stage 2. Participants were then classified into one of three drug detection levels: (1) low (no plasma TFV detected at any available quarterly visit, N = 27), (2) inconsistent (plasma TFV detected at 1–74% of quarterly visits, N = 13) and (3) high (plasma TFV detected at 75–100% of quarterly visits, N = 4) and subsequently a randomized recruitment list for each of the three groups was generated by the MTN Statistical and Data Management Center and participants were systematically contacted as previously described [10]. (See Fig. 1).

Measures and Analysis

The stage 1 interview guide questions focused on HIV risk behaviors including anal sex (reported elsewhere [11]), women's motivation to join the trial, HIV risk perception, life events and other factors that might have affected product adherence, and views about how VOICE could have elicited more honest reporting of product use. In addition participants were asked about the methodology used in VOICE to assess women's product use, which included a self-reported adherence rating scale that asked: "Please rate your ability, over the past 4 weeks, to insert gel/take tablets, exactly as you were instructed". This self-ranking question which was administered in VOICE through face to face interviews and Audio Computer Assisted Self Interview (ACASI) at monthly, quarterly, annual and Product Use End visits, had six response categories: very poor, poor, fair, good, very good, excellent. In VOICE-D, we asked participants: "During your participation in VOICE, you were asked many questions about product use. One question asked you to "rate in the past 4 weeks your ability to (take the tablets/use the gel) exactly as instructed"… Now let's talk about the

different response options to this question-very poor, poor, fair, good, very good, and excellent. What was your typical answer? Why did you choose that answer?" In stage 2, topics for discussions included participants' plasma drug detection category (or levels), factors influencing (non-) adherence, women's experiences with product use and recommendations for future trials, intention for product use at trial start and seroconversion. The major difference between the two stages is that in stage 1 participants often framed their responses of product use around the self-ranking question that was administered in the VOICE trial, whereas in stage 2 participants received their drug detection levels privately, prior to the interviews and the questioning in the guides were based on the drug detection categories. Women with low drug detection levels were asked: "What are all the reasons you were not able to take your products?" Women with high/inconsistent drug detection levels were asked: "The drug data show that you took the product (some of/most of/all of) the time prior to coming to the study visits… What are all the reasons you were able to (some of/most of/all of) the time, take your products?" Follow-up questions in both groups probed around specific challenges to product use.

Interviews were audio recorded, transcribed verbatim, and translated into English by professional transcriptionists and translators who were familiar with the vernacular used during the interview. All transcripts, both local language and English, were reviewed by the study staff before they were finalized to check for completeness and accuracy. All transcripts were coded with NVIVO version 10 by the analysis team. The team developed codebooks for each stage which were very similar and guided the analysis of transcripts. Inter-coder reliability (≥80%) was established for 10% of the transcripts from a subset of 11 key codes for Stage 1 and 13 key codes for Stage 2, which were most representative of the main research questions. We used coding reports on the following codes related to product use: adherence, execution, initiation, intention, discontinuation and reporting, and investigated whether the 44 women enrolled in both stages modified their responses to study product adherence questions between stage 1 (with no provision of drug detection data) and stage 2 (following provision of drug detection data). Descriptive statistics were used to analyse the quantitative data. Women's responses to the adherence questions during IDIs and FGDs were quantified and stratified by product and drug detection category.

Results

Study Population Characteristics

The characteristics of the analytic sample (N = 44) at the time of implementing VOICE-D stage 1 are presented in Table 1. Participants' average age was 28 years old (range 21–40), 34% were married, 36% completed secondary school, 84% earned their own income, and 84% were HIV negative. An equal number of women were in the tablet (n = 22) and gel (n = 22) arms when in VOICE; 61% of the women were in the low drug detection group, 30% were in the inconsistent group, and 9% were in the high group.

Self-Report of Study Product Use

Thirty-six of 44 participants reported high product adherence at stage 1, yet described personal instances of non-use of product in stage 2, after they were provided retrospectively

with their plasma tenofovir results. The drug detection results indicated that for these 36 "modifiers", 25 were in the low drug detection group and 11 were in the inconsistent group with 20 in the gel arm and 16 in the tablet arm. (See Tables 2, 3).

The following excerpt is illustrative of narratives indicating modification of responses to study product adherence questions at stages 1 and 2:

> Stage 1 Response (IDI):
>
> I would take my tablets exactly as I was instructed …
>
> I didn't skip taking my tablets.

When re-interviewed as part of a focus group during Stage 2, her response changed:

> The waiting room was the source of all these problems … A lot of things came out from there … Some said the tablets can make you gain weight and some said they make you sick. After hearing all this you would think that this is true … we actually saw the participants who got sick … so I thought I was going to be sick as well. So I would drink my tablets here and there … The big one was difficult to swallow … There were those participants who had been in the study for a long time … Yes, they are the ones who discouraged others (Zimbabwe, Tablet, Low group).

Similarly, the following quote from a participant in South Africa who had inconsistent drug detection results demonstrates the typical shift from a vague overstatement of product use (in this case tablets) in Stage 1 to specific reasons that use was difficult.

> Stage 1 Response (IDI):
>
> It [product use] was never difficult with me… I used to choose "very good" [in the rating question] I did not have problems on using a product.
>
> Stage 2 Response (FGD):
>
> My problem was that they scared me since they looked like ARVs…. Another big problem … you find that these pills are big and they were not easy to swallow and they also caused nausea. So I would just think of the problems I will be causing to myself if I drank them and would get sick all over again and become nauseous and vomit…. I did not take them regularly any way so it happened whenever I took them (South Africa, Tablet, Inconsistent group).

The quote from a participant in Uganda demonstrates a shift from reporting high product use at stage 1, to acknowledging product non-use at stage 2.

> Stage 1 Response (IDI):
>
> I was using it everyday at 20h00. As soon as the Muslim prayer leader started the prayers, I would insert the gel.
>
> Stage 2 Response (FGD):
>
> That gel caused inflammation of the perineum … I am telling the truth, I did not use it. [Uganda, Gel, Low group]

Three of the 44 participants reported high adherence at stage 1 which they continued to assert at stage 2, despite drug test results indicating either low drug levels (N = 2) or inconsistent drug levels (N = 1).

> Stage 1 Response (IDI):
>
> There are some months I swallowed without skipping. I skipped like twice that day I vomited and that day I was sick of malaria and when I was stopped [due to HIV infection]. So when I was asked (to respond to the rating scale questions) I said "very good".
>
> Stage 2 Response (IDI):
>
> Since I missed a few times…What will I say, because I did swallow it…The number of times I missed were few…There is nothing I understand about it because I used to swallow; I only missed when I was sick … (Uganda, Tablet, Inconsistent group).

One woman who insisted that she used study product in both stages offered an explanation as to why the drug could not be detected in her blood. She reported that the husband did not like her study participation and would have sex quickly and immediately after gel insertion and that the gel would leak.

> Stage 2 Response (IDI):
>
> The moment you use the gel then he [husband] wants sex, the issue was that he just wanted to bother me …. He would just put it [penis] in and then take it out, and I would just wipe myself … I could feel that the stuff was coming out … It's not that I don't agree with the results, that in my blood … you didn't find the drug; I am just trying to explain what was happening in my life alright?… My side of things. (Zimbabwe, Gel, Low group)

Only five of 44 participants had consistent narratives of product use at both stages, which matched their drug detection results. Four were high adherers and one was an inconsistent user. Below is an illustrative quote of how one woman seemingly managed to maintain high use of study product.

> Stage 1 Response (IDI):
>
> I never went a day without using it… Most of the time I kept the product with my toiletries… Because sometimes I would go somewhere for a visit, thinking that I would come back, only to stay there and not come back. It was always in my bag.
>
> Stage 2 Response (IDI):
>
> I told myself to use the product because it might help me… I was interested in using it because I hoped that using it could help in finding something to treat the virus.
>
> (South Africa, Gel, High group)

At Stage 1, participants stated that it was possible for a woman to report excellent adherence when actually she did not use product. Women discussed that participants were more likely

to be honest in their reporting if presented with objective data on their product use. In fact, half of the women in the low and inconsistent groups (18/36) recommended that feedback of their drug level would be required in order to promote honest reporting. The following illustrative quotes highlight the challenges with self-report as a strategy to assess adherence in a clinical trial context given the inability of staff to detect product non-use in real time, as well as how drug testing and feedback may facilitate candid discussions on product non-use during research.

> Stage 1 response: (IDI)
>
> Interviewer: Okay. Do you think it was possible for a woman to miss taking the tablets on some days and rate herself as “very good”?
>
> Respondent: Yes, I think it was possible because it was a self-assessment … It was possible to rate myself as “good” while not taking the medication… It was a self-assessment without anyone supervising the taking of the medication … You are not present when I am taking the tablets; why don’t I say that I am good? I do not have any supervision, so why not? It would have been different if we had to come and take the medication at the clinic … the other thing is that the blood needs to be analysed immediately so that we know.
>
> Interviewer: How do we get them to tell the truth that they have not been using?
>
> Respondent: You cannot tell someone that ‘you did not use’ when the wall is your only witness. You cannot, unless they bring equipment that detects the quantity in a person who has taken the medication, so that we know how much is in a person who is taking the medication. For a person that does not take, that machine should be able to separate the blood from the medication before your very eyes. In that way, the person that does not take will think twice before telling a lie.
>
> (Uganda, Tablet, Low group)

A participant in South Africa also recommended drug monitoring to encourage honesty, and summed it up by saying “*blood-tests will show that you have defaulted*” (South Africa, Stage 1 IDI, Gel, Low group).

Changes Between Stages 1 and 2 in Reported Facilitators and Challenges to Product Use

The 36 women who modified their responses regarding product use between stages 1 and 2 also changed their reports of facilitators and challenges. In stage 1, 11 reported facilitators and no challenges, 13 reported challenges with no effect on product use and 12 reported challenges with minimal effect on product adherence. The most common factors facilitating adherence were regular use of reminders, supportive partner/family, perceived high HIV risk and gel enhancing sexual pleasure.

In stage 2, all the 36 women reported, not only significant challenges to product use, (with some expected variability depending on the product), but also acknowledged that these had a direct effect on their use of product. The following passage illustrates the multiple issues disclosed at stage 2, after the participant was presented with her drug test results, despite the fact that at stage 1 she had reported no issues affecting her ability to use the product.

> First of all that product looks exactly like the one for HIV patients. When I used it I got some effects on my body, first it made me gain weight … it made my skin turn dark … so how could I then swallow those products again after those changes on my body?… it would make you eat a lot and yet our income was small… Another thing is that you have to work but this product had a way of making you lazy after swallowing it … some of us did not tell our husbands and so we had to keep the drug very far for him not to see it… For me I really thought about, because those products were brought for trial … If the HIV virus is strong, they have to put high contents (drugs) in the product. If the contents are high, what is going to happen if I have sex with someone who does not have HIV yet the content (drug) in the product is meant to fight the HIV virus. So I ask myself what is to happen in such a case. Won't it burn me or bring me cancer?… Yeah haaa, it has not found what to fight… It was made for fighting the HIV virus … They are doing research, why would they do the research on you? What if after you get problems?
>
> (South Africa, Tablet, FGD, Low group)

The 25 women who reported challenges to use of product at stage 1, discussed strategies to overcome them.

> I struggled with the pills during the first days … so eventually I came up with a plan … to take the pill with a morsel of sadza [Sadza is Zimbabwe's staple food, a maize porridge] … and then I wash it down by drinking some water … It took me a whole month, struggling with swallowing the pills.
>
> (Zimbabwe, Tablet, IDI, Inconsistent group)
>
> In the beginning, I encountered some problems because I would get drunk and forget to use the gel. Later, I decided to first insert the gel before going to drink.
>
> (Uganda, Gel, IDI, Low group)

At stage 1, participants mainly discussed the reasons for other women not using study product but did not refer to themselves. At stage 2, a significant number of women (21/36) reported at least one reason for their own non-use of product, which matched their reports of other women's non-use in stage 1. The following matched stage 1 followed by stage 2 responses, from the same participants suggest that when a participant referred to "others" in Stage 1, she may actually have been talking about her own behavior, which she felt the need to disguise.

> Stage 1 response (IDI):
>
> Yes, others said that they couldn't stand pills …
>
> Drinking them [pills] every day, as if they are sick …
>
> But I didn't have a problem.
>
> Stage 2 response (IDI):
>
> I can only speak for myself and the pills. Sometimes, they became too much for me, when it came to swallowing them … There is a pill waiting for you, every day

you have to take a pill that was the problem … We were told here [at the clinic] that the pills are for preventing us from contracting the disease [HIV] … Yes, that is what we were told, but when you go outside, they say, "These pills are also found in ARVs". What are you going to do? Will you continue taking them?… Yes, that is how it was, I would say, "I'm not taking them anymore but I will say I take them only when I'm coming here [at the clinic]". (South Africa, Tablet, Low group)

Stage 1 Response (IDI):

I was determined and nothing would stop me from using the medication, but for the other women that I used to sit with during some of the meetings, they would say that sometimes they swallowed the medication, and at other times, they couldn't because they had nothing to eat. They had no money. I came to the conclusion that food… made it hard for those women.

Stage 2 Response (IDI):

If you hadn't gotten anything to eat … how would you swallow the tablets without eating anything first?… My reason for not swallowing is not because I do not want. It is because of the situation [financial situation]. If I had someone providing me with maize flour and beans, I would use the medication in the right way. (Uganda, Tablet, Low group)

Stage 1 Response: (IDI)

It was not difficult for me but I have heard that someone had said that she simply can't swallow a pill… Another said that it gets stuck in her throat … I never had that problem myself. I used to eat before swallowing the pills because they make you feel hungry.

Stage 2 Response: (IDI)

I also didn't like drinking them. I couldn't swallow those pills … I vomited them out.

(South Africa, Tablet, Low group)

Participant Characteristics and Reporting

We analysed several contextual factors including individual characteristics such as age, marital status, level of education and earning own income as well as participant relationship with staff, to determine if they might have accounted for the differences in the discussion of product use between the consistent and inconsistent reporters. No major differences were observed in the mean age of the consistent (28.4) and inconsistent reporters (29.1). Significant differences between the two groups were noted in marital status and level of education. The percentage of married women was higher in the consistent reporters group (60%) compared to the inconsistent reporters (28%) as was the proportion who completed secondary school, 80% in the consistent group versus 33% in the inconsistent group. The percentages of women who earned their own income were high in both groups (80% for the consistent and 86% for the inconsistent reporters) (See Table 4).

Participant rapport with study staff as it relates to ability to accurately report product use was also analysed. Four out of 5 consistent reporters and all the 36 inconsistent reporters described their relationship with study staff as good and believed that it had no bearing on reports on use of study product.

The following quote describes the relationship between the participant and study staff and illustrates how it apparently had no effect on reporting:

> Stage 1 (IDI):
>
> R: The staff at the research were very good at counselling and we felt free to talk to them about anything …
>
> I: Mmh, do you think that certain research staff may have been the reason why some participants felt that they couldn't tell the truth [about their product use]?
>
> R: I don't think they had any effect on them [participants'] not telling the truth. The workers made you feel free to say anything you wanted to say. It was up to you if you chose to lie.
>
> (South Africa, Tablet, Low group)

Discussion

This analysis of VOICE-D data, compares changes in responses to product adherence questions before and after provision of plasma drug detection results among former participants of the VOICE parent trial. Designed to gain insight into adherence challenges, and the effect of presenting drug data on adherence responses, our analysis strongly supports the hypothesis that providing drug level feedback to participants facilitates more candid and likely more accurate self-reports of product non-use and challenges with study product adherence in HIV prevention trials. The majority of participants (36/44) modified their stories about study product use, from high adherence at stage 1, to either low product use (N = 25) or inconsistent use (N = 11), at stage 2, after they were presented with their drug test results. Only three participants who reported high adherence at stage 1, did not accept their low drug level results at stage 2 insisting that they used the study product most of the time. The strength of these results suggests that the provision of drug level results should be considered in the design of future trials.

Our analysis elaborates on previous findings from this study [10], which observed that participants unwilling to reveal non-use and challenges in stage 1 were more candid about their product usage in Stage 2, following receipt of objective drug test results including discussion of various challenges to adherence. Many of the themes were similar to those found in VOICE-C, an earlier qualitative sub-study conducted concurrently with VOICE, in Johannesburg South Africa [12]. In VOICE-D, however, participants acknowledged that these perceptions about product use and social influences directly prevented their own consistent and correct use of product. A major strength of this analysis is the direct comparison of responses from the same participant before and after being provided her drug detection results (using both stage 1 and stage 2 data).

In stage 1, where only in-depth interviews and the best practice techniques for conducting qualitative in-depth interviews were employed (including establishing rapport and having non-VOICE staff to conduct the interviews away from the VOICE study clinics), most of the participants were not forthcoming about their own product non-use. Similar experiences have been observed in previous studies such as VOICE-C [12, 17]. The majority of women in VOICE-D reported product non-use at stage 2, only after they were retrospectively provided with their drug level results. The same staff interviewed women at both stages. While interviewer skills undoubtedly had an influence on whether the participant was able to openly discuss product non-use or not, given that women were interviewed by the same staff at both stages, we feel that it was the presentation of objective data and not staff skills that encouraged more candid accounts of trial related behaviors in the second stage.

The findings of this analysis support prior reports that self-reported product use may not be a reliable strategy of assessing product adherence in PrEP trials [13, 14]. The majority of participants in this analysis misreported product adherence; the reasons for not being truthful about product use are reported elsewhere [15], but in brief, were most commonly described as a result of human nature, fears of being removed from the trial or being reprimanded, not wanting to appear like a “bad participant” and simply because there was no consequence to concealing the truth.

The phenomenon of describing other women’s behavior as a means of communicating one’s own has been reported elsewhere [12, 16] and was clearly observed in this study as well. We noted that in stage 1, some women attributed challenges for non-use of product to other women and not themselves, but at stage 2, these same challenges matched their own reasons for product non-use. Future studies should consider training counselling and other staff to recognize that mention of other women’s challenges may be an important indicator of that individual’s own experiences. Equally important would be equipping counsellors with creative strategies to explore women’s reports of “perfect” adherence in more depth, as perfect use may be rare.

Providing drug level feedback to participants was generally well accepted; it was recommended by participants during stage 1 and endorsed in stage 2 [10]. Women more openly discussed product acceptability and use once presented with evidence of their product non-adherence. This increased willingness to disclose after presentation of drug feedback is consistent with results from previous studies such as iPrEx Open Label (OLE), where drug detection results were incorporated into the clinic study visit, acceptability of drug detection monitoring was assessed among a subset of participants and no drug detected results led to enhanced open discussion of missed doses [18]. The weight of all of these studies suggests that in the absence of a “gold standard”, it is recommended that HIV prevention trials use objective measures such as drug level tests to monitor adherence, and present participants with their results in real-time. Provision of drug tests feedback to participants is being implemented in the MTN-025 study, a phase 3B open-label follow-on trial, designed to assess the continued safety of and adherence to a vaginal ring containing dapivirine in women (ref: mtnstopshiv.org). Adherence is assessed through a combination of drug tests and self-reports. MTN-025 puts more emphasis on client-centered counselling and

participant's choice whether to use or not use the product and it is hoped that this approach will facilitate an open discussion of product use with study participants.

It is also noteworthy that in VOICE-D several participants reported side effects as a reason for not taking the study product. There is the potential that implementing drug detection tests may influence accrual and retention in future trials, as participants may refuse enrolment or withdraw from participation in anticipation or experience of side effects, if they fear that they will actually have to use the product. It is worth noting, however, that VOICE-D participants expressed a desire to receive the drug feedback, so we don't expect this to be a serious issue in MTN-025, which has put particular emphasis on training counsellors and monitoring counselling sessions.

One of the major limitations of the VOICE trial to which this ancillary study is attached, is that the drug level tests were infrequent, began after the first quarter and, because of the narrow window of tenofovir plasma detection, do not accurately summarize product use over time [19]. Hence, it is difficult to differentiate the true adherers from those who used the product proximal in time to their clinic visit due to a potential "white-coat" effect, whereby participants are adherent to product use in the few days preceding study clinic visits. Additionally, though there were discrepancies in responses to product use questions in stages 1 and 2 among most of the participants, women were not confronted with the inconsistencies in the two stages. Although this study exposed occurrences of and reasons for non-adherence, it is possible that in the data collection and analysis process some instances of non-use were missed. Finally, it is possible that some features of the qualitative methodology, for example differences in interviewing style and focus of questioning could have contributed to the large number of inconsistencies in reported adherence at stage 1 and 2.

It is interesting to note that three participants maintained reports of high adherence at both stages 1 and 2 despite the drug results indicating that two were in the low group and one was in the inconsistent use group. Though not common in this study, this finding indicates that not all participants will openly discuss their product non-use even after receiving their no-drug test results. It is possible, however, that there may be problems with the test, specifically that participants may have used the gel yet no product was detected. For example, one participant said as soon as she inserted the gel, her partner proceeded to have sex, causing the gel to spill out before the product was absorbed. The circumstances under which gel may be used yet the drug tests indicate non-use require further investigation.

New approaches to objectively assess product adherence in HIV prevention trials should be explored to augment self-reports. In this study, the majority of women recommended that real time drug monitoring and participant feedback would facilitate open discussions of product non-use in HIV prevention trials. While not an issue in open label trials where all women are on active product, providing individual drug level results in placebo controlled trials is not possible unless markers of product use can detect both active and placebo products. New strategies, which include an easily detectable marker in both the product and the placebo, should be considered in future HIV prevention trials [20].

Of note however, some of the adherence challenges highlighted by the women relate more to the clinical trial structure and implementation than to the products themselves, and thus would not be addressed through objective biomarkers. Strategies such as conducting laboratory tours for participants or community members, which were implemented after this study at one site to respond to rumors of Satanism and selling blood, can be implemented to increase transparency, build participants' trust and reduce trial-related fears.

Conclusion

The VOICE-D qualitative study demonstrated that participants were more likely to reveal and discuss product non-use when presented with objective drug detection data. Future research should explore novel objective approaches to measure and monitor adherence during clinical trials. Obtaining accurate reporting of study product use is critical to understanding challenges in product adherence in PrEP trials which, in turn, may inform efforts to help participants overcome these challenges, and improve the design of future prevention products.

Women's reports about challenges to product use cast light on dramatic life situations (e.g. not having sufficient food) that make it understandable why a participant might be hesitant to take pills. Also the rumors in the communities and waiting rooms, the concerns about negative consequences to taking the medication and the thought processes participants engage in when considering whether to use trial products—e.g. if the virus is strong, the drug must also be very strong and thus may affect me negatively—merit attention. Unless the reasons leading to poor adherence are addressed, the use of biomarkers alone will not guarantee improved adherence.

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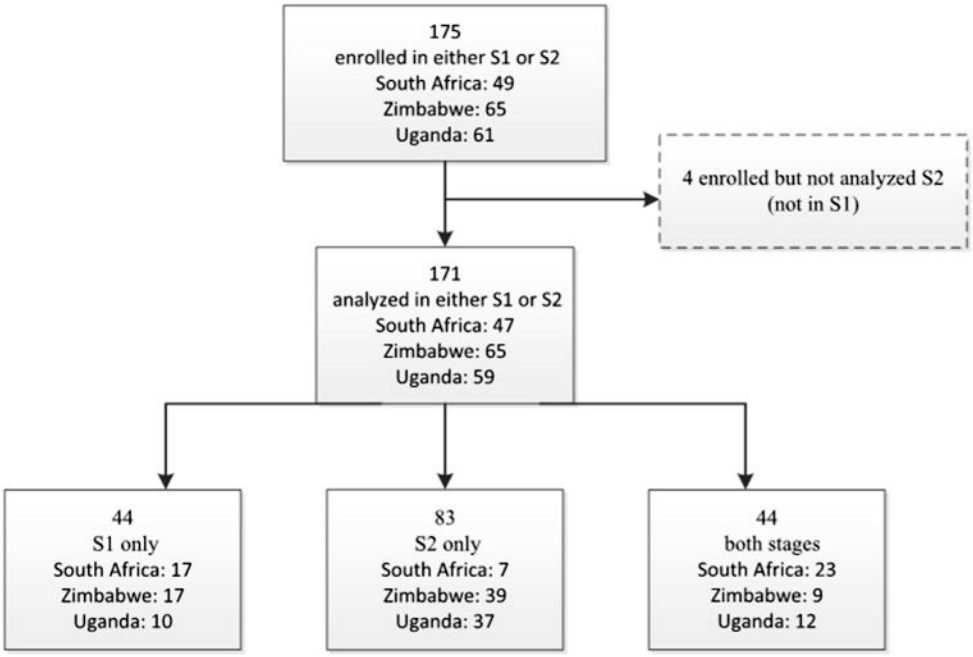

Fig. 1.
Sampling flow-chart for the study

Table 1

Characteristics of VOICE-D participants in this analysis at Stage 1

At time of VOICE-D interview	N = 44	Percent
Country (site)		
South Africa (Durban)	23	52%
Uganda (Kampala)	12	27%
Zimbabwe (Chitungwiza)	9	21%
Age: median (mean, range)	28 (29.2, 21–40)	
Currently married	15	34%
Completed secondary school	16	36%
Earns her own income	37	84%
HIV negative	37	84%
During VOICE trial		
VOICE study product group		
Gel	22	50%
Tablets	22	50%
Drug detection group		
Low	27	61%
Inconsistent	13	30%
High	4	9%

Table 2

Drug detection results stratified by study product type

	Tablet	Gel
Low adherence (N = 27)	(N = 13)	(N = 14)
Inconsistent adherence (N = 13)	(N = 6)	(N = 7)
High adherence (N = 4)	(N = 3)	(N = 1)

Table 3

Self-report adherence responses stratified by product type

	(N = 44)	Stage 1 response	Drug test result group	Stage 2 response
Tablet (n = 22)	(n = 12)	High adherence	Low adherence	Low adherence
	(n = 4)	High adherence	Inconsistent use	Inconsistent use
	(n = 1)	Inconsistent use	Inconsistent user	Inconsistent use
	(n = 3)	High adherence	High adherence	High adherence
	(n = 1)	High adherence	Low adherence	High adherence
	(n = 1)	High adherence	Inconsistent use	High adherence
Gel (n = 22)	(n = 13)	High adherence	Low adherence	Low adherence
	(n = 7)	High adherence	Inconsistent use	Inconsistent use
	(n = 1)	High adherence	High adherence	High adherence
	(n = 1)	High adherence	Low adherence	High adherence

Table 4

Participant characteristics stratified by reporter type

Participant characteristics	Consistent reporter (N = 5)	Inconsistent reporter (N = 36)
Mean age	28.4	29.1
Married	3 (60%)	10 (28%)
Completed secondary school	4 (80%)	12 (33%)
Earn own income	4 (80%)	31 (86%)
Good relationship with staff	4 (80%)	36 (100%)