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Disclosure of pharmacokinetic drug results to understand nonadherence: results from a qualitative study

Ariane VAN DER STRATEN^{1,2}, Elizabeth T. MONTGOMERY¹, Petina MUSARA³, Juliane ETIMA⁴, Sarita NAIDOO⁵, Nicole LABORDE¹, Miriam HARTMANN¹, Lisa LEVY⁶, Thola BENNIE⁷, Helen CHENG¹, Jeanna PIPER⁸, Cynthia I. GROSSMAN⁹, Jeanne MARRAZZO¹⁰, and Barbara MENSCH¹¹ on behalf of the Microbicide Trials Network-003D Study Team

¹ Women's Global Health Imperative (WGHI), RTI International, San Francisco, CA, USA ² Center for AIDS Prevention Studies (CAPS), University of California, San Francisco, CA, USA ³ University of Zimbabwe-University of California San Francisco Collaborative Research Programme, Harare, Zimbabwe ⁴ Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda ⁵ HIV Prevention Research Unit, South African Medical Research Council, Durban, South Africa ⁶ FHI360, Durham, NC, USA ⁷ Desmond Tutu HIV Centre, Department of Medicine, University of Cape Town, South Africa ⁸ National Institute of Allergy and Infectious Diseases, Division of AIDS, Bethesda, MD, USA ⁹ National Institute of Mental Health, Bethesda, MD, USA ¹⁰ University of Washington, Division of Allergy and Infectious Diseases, Seattle, WA, USA ¹¹ Population Council, New York, NY, USA

Abstract

Objectives—In VOICE, a phase IIB trial of daily oral and vaginal tenofovir for HIV prevention, 50% of women receiving active products had undetectable tenofovir in all plasma samples tested. MTN-003D, an ancillary study using in-depth interviews (IDIs) and focus group discussions (FGDs), together with retrospective disclosure of plasma tenofovir pharmacokinetic (PK) results, explored adherence challenges during VOICE.

Methods—We systematically recruited participants with PK data (median 6 plasma samples), categorized as low (0%, N=79), inconsistent (1%-74%, N=28), or high (>75%; N=20) based on frequency of tenofovir detection. Following disclosure of PK results, reactions were captured and adherence challenges systematically elicited; IDIs and FGDs were audio-recorded, transcribed, coded, and thematically analyzed.

Results—We interviewed 127 participants from South Africa, Uganda, and Zimbabwe. The most common reactions to PK results included surprise (41%; low PK), acceptance (39%; inconsistent PK), and happiness (65%; high PK). Based on participants' explanations, we developed a typology of adherence patterns: noninitiation, discontinuation, misimplementation (resulting from

Correspondence and reprints: Ariane van der Straten, PhD, MPH, RTI International, 351 California Street, Suite 500, San Francisco, CA 94104-2414, Tel: 415-848-1324, Fax: 415-848-1330, ariane@rti.org.

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visit-driven use, variable taking, modified dosing or regimen), and adherence. Fear of product side effects/harm was a frequent concern, fueled by stories shared among participants. Although women with high PK levels reported similar concerns, several described strategies to overcome challenges. Women at all PK levels suggested real-time drug monitoring and feedback to improve adherence and reporting.

Conclusions—Retrospective provision of PK results seemingly promoted candid discussions around nonadherence and study participation. The effect of real-time drug monitoring and feedback on adherence and accuracy of reporting should be evaluated in trials.

Keywords

microbicide; HIV pre-exposure prophylaxis; adherence; pharmacokinetic drug detection; women; VOICE-D Study

Introduction

Despite considerable progress in HIV prevention, young women in sub-Saharan Africa experience the highest HIV incidence rates globally. Suitable prevention approaches for this vulnerable population are critically needed [1]. Oral tenofovir (TFV)-based pre-exposure prophylaxis (PrEP) is now approved as a highly effective HIV prevention strategy when used consistently and proof of concept for investigational antiretroviral-based microbicides was demonstrated with pericoital dosing of TFV vaginal gel in the CAPRISA [Centre for the AIDS Programme of Research in South Africa] 004 trial [2]. However, because of low product adherence, the FACTS-001 [Follow-on African Consortium for Tenofovir Studies] confirmatory trial was unable to demonstrate effectiveness [3]. Indeed, suboptimal adherence explains divergent results across oral and vaginal PrEP trials, and adherence to product regimen—particularly in women—is critical for PrEP effectiveness [3-13].

The VOICE [Vaginal and Oral Interventions to Control the Epidemic] Study investigated the effectiveness of daily oral tenofovir, oral tenofovir-emtricitabine (TDF-FTC), and 1% vaginal TFV gel for preventing male-to-female sexual transmission of HIV-1 in Africa. Based on self-reports and returned products at the clinics, product adherence was high (>90%). However, 50% of women assigned to active products in a representative subcohort had undetectable TFV in all plasma samples tested, likely explaining the lack of protection observed in the intent-to-treat analyses [12]. Specifically, 30% of plasma samples had detectable TFV levels among women assigned to active tablets; 25% of plasma samples and 49% of cervicovaginal fluid (CVF) samples had detectable TFV levels among those assigned to active gel [12].

In addition to *achieving* adherence to study products, accurately *measuring* adherence has been a challenge in HIV prevention trials. Behavioral and electronic measures are known to overestimate product use, and biological measurements have limitations, too [14, 15]. Nevertheless, pharmacokinetic (PK) measures have provided clear evidence of an association between plasma drug concentration and recent TFV dosing, and additional techniques are in development to improve detailing patterns of product use over time [13, 16-20].

VOICE participants' engagement and adherence, or lack thereof, have previously been examined, including the role of visit retention and of male partners [21-23]. This study took a different approach, by providing individualized plasma TFV results to former active-arm VOICE participants, to elicit greater details about their varying levels of adherence. It is among the first to provide trial participants with direct feedback on their drug levels and to explore their reactions and explanations.

Methods

VOICE trial: behavioral and pharmacological measures of adherence

The VOICE trial (MTN-003; ClinicalTrials.gov identifier: NCT00705679) was conducted from 2009 to 2012 at 15 sites among 5029 women from Uganda, South Africa, and Zimbabwe. The trial design, population, procedures, and primary findings were previously published [12]. Behavioral adherence assessments included face-to-face interviews (FTFI), audio computer-assisted self-interviewing (ACASI), and pharmacy product counts (PC). Post-trial analysis of TFV in plasma and in CVF was conducted in samples collected at selected quarterly visits in a random subcohort of active-arm participants [12]. The lower limit of quantification (LLOQ) for TFV in plasma (0.31 ng/ml) corresponded to no tablet used in the prior 7 days or no gel used in the prior 2-3 days [16, 17].

VOICE-D study design and setting

VOICE-D (MTN-003D) was a two-stage multisite qualitative ancillary study conducted in Kampala, Uganda; Durban, South Africa; and Chitungwiza, Zimbabwe [24]. This article includes data collected from November 2013 through March 2014 during the second stage of the study, when participants were retrospectively presented with their PK results. The findings related to sexual behaviour captured during the first stage have been published elsewhere [25-27]. Former VOICE participants were recruited from among those who had provided permission to be recontacted and had plasma TFV data. Recruitment was stratified by VOICE HIV-seroconversion status, tablet or gel assignment, and one of three PK detection levels: low (no plasma TFV detected at any visit), inconsistent (plasma TFV detected at 1%-74% of visits), and high (plasma TFV detected at 75%-100% of visits). Participants in each recruitment group were randomly selected and contacted in ascending order from a list generated by the Data Coordinating Center until target numbers were reached (Figure 1).

Procedures

Following written informed consent, participants completed a short demographic questionnaire. Trained female research staff who had not interacted with participants during VOICE, privately presented participants with their plasma PK results using a pretested pictorial tool (Supplemental Digital Content 1) [28]. Participants were informed of the category (0, 1%-49%, 50%-74%, 75%-99%, and 100%) corresponding to the frequency of TFV plasma detection from quarterly samples tested in VOICE, and were told that TFV detection only indicated recent product use. Because of the novelty of presenting PK results and our uncertainty regarding how participants would react, staff assessed and recorded participants' immediate response on a Case Report Form (CRF) according to a list of basic

emotions [29], with an option for other responses. In-depth interviews (IDIs) and Focus Group Discussions (FGDs) were conducted at a location intended to be neutral and unaffiliated with the VOICE clinic site. Interviews followed a standardized guide, were conducted in the participants' language of choice, audio-recorded, transcribed, and translated into English. The guides focused on product experiences and adherence challenges and included a card pile sort and ranking exercise with IDI participants [28, 30] (Supplemental Digital Content 2). Staff received in-person training from the investigators on how to present PK results in a nonjudgmental manner.

Data analysis

Transcripts were coded in NVivo 10 by the multisite analysis team; high (80%) inter-coder reliability was maintained and calculated as previously described [21]. Coded data were concatenated into reports by thematic area, then summarized into memos [30]. Memos were further analysed to reveal patterns related to PK results and adherence, contrasting findings from participants displaying low/inconsistent and high PK levels as well as those in tablet and gel groups.

VOICE-D participants were compared to VOICE participants not enrolled in VOICE-D at the same sites using Fisher's exact test for the following baseline characteristics: age, marital status, education, income, parity, sexual partners, and sexual behavior. The rank-order for which each adherence challenge card was selected was assigned a weighted score, averaged, and presented in descending order of relevance [28].

The study protocol was approved by the Institutional Review Boards at RTI International and at each of the study sites, and was overseen by the regulatory infrastructure of the U.S. National Institutes of Health and the Microbicide Trials Network.

Results

The study sample (N=127) included 49 participants from Uganda, 48 from Zimbabwe, and 30 from South Africa, with similar numbers of women in the active tablet and gel groups. PK groups included 79 classified as low (62%), 28 as inconsistent (22%), and 20 as high (16%), based on an average of 6.7 VOICE visits among the 114 HIV-negative participants and 4.2 visits among the 13 HIV-positive participants (Table 1). IDIs were conducted with 68 women (13 women also joined an FGD) and the remainder participated only in an FGD (Figure 1). VOICE-D participants were younger and less well educated than other VOICE participants at the same sites (Supplemental Digital Content 3).

Product adherence during VOICE

Table 2 presents plasma TFV detection rates at the first quarterly visit, last visit with PK testing, and average across VOICE visits in women assigned to each of the PK groups. Women with low PK had no detectable TFV at any visit; for those classified with high PK, 85% had TFV detectable at first quarterly visit, and an average of 90% across visits. Among those with inconsistent PK, the average was 31% across visits; TFV detection was 46% at first visit and 18% at last visit, with evidence of decreased detection over time (McNemar test; $p=0.04$). Assessments based on self-reports and product counts during VOICE

suggested 90% product adherence among VOICE-D participants of all PK levels, as previously described for the entire VOICE sample [12].

Disclosure of PK results

Provision of plasma PK results generated a variety of reactions, including surprise (41%) and disbelief (37%) among women with low PK and acceptance (39%) among women with inconsistent PK. Women with high PK expressed happiness (65%) and most agreed with their results (Table 2). During the IDIs, a majority of women with low/inconsistent PK also came to accept their results (63%); participants in the FGDs reacted similarly. When objecting, many provided detailed explanations of why they felt their results were erroneous (e.g., intentionally dosing prior to study visits, or using products some of the time). A few attributed nondetection to problems with the PK testing (i.e., inaccuracy, interference with other medications, or alcohol consumption) or being randomized to placebo as an explanation (Supplemental Digital Content 4).

Typology of product use

Participants described a variety of reasons and circumstances that influenced nonadherence. A typology was developed that depicted four main adherence patterns: (1) *noninitiation*, whereby participants never engaged with the product regimen; (2) *discontinuation*, whereby participants stopped temporarily or permanently following product initiation; (3) *misimplementation* whereby participants persisted but exhibited various behaviors resulting in incorrect use; and (4) *adherence* defined as using product daily as instructed during the trial (Supplemental Digital Content 5). Discontinuation and misimplementation may or may not be intentional. Furthermore, misimplementation included four subpatterns based on participants' explanations: *visit-driven use*, or white-coat compliance, described dosing prompted by an upcoming visit to the clinic; *variable-taking* referred to skipping doses when the set time for taking products was missed; *modified dosing* occurred when participants took extra or partial doses (e.g., emptying only part of a gel applicator) or engaged in other behaviors that impacted administration of a full dose (e.g., vaginal wiping or cleansing); a *modified regimen* described variability in frequency of intake, such as missing product use for single or sequential days (e.g., skipping, episodic use; product holiday), which was sometimes described as intentional, and more often as unintentional, such as forgetting or being unable to use on a given day or for a given period. Table 3 provides additional descriptions of each typology with supporting quotations. Based on their explanations, women often displayed several subpattern types concurrently or consecutively, highlighting the dynamic and complex nature of adherence-related behaviors (see case studies, Table 4).

Adherence challenges, motivation to be in the study, and strategies for study participation

Among the 20 statement cards related to study participation and adherence challenges, IDI participants ranked the following statements as most salient: "I experienced or was worried about side effects"; "The products may be harmful"; and "I joined the study for health services provided by the clinic" (see Supplemental Digital Content 3). These rankings were similar for women in tablet or gel groups, and for those with low/inconsistent and high PK. The adherence issues raised in the card pile ranking activity were consistent with challenges

commonly discussed in the FGDs. As noted by one participant, fear of side effects and/or harm from the product was fueled by waiting room stories:

A lot of women stopped taking their tablets because they listened to others. People who experienced side effects might not have been that many, but some of us just copied what others were saying, when you heard someone say “The tablets are dangerous” [or] “They make me feel weak” [or] they do this and that, you would also stop using them too.

(FGD, Zimbabwe, low/inconsistent PK, tablet)

Women with high PK reported similar challenges; however, several indicated how they overcame negative comments from other participants, partners, or family members by ignoring them, avoiding situations where their trial participation would be questioned or exposed to criticism (i.e., avoiding interactions with others, using product discreetly), maintaining their internal motivation as “it really comes from your heart” (IDI, Uganda, high PK, tablet), reminding themselves of the care provided at the clinic, and trusting and feeling encouraged by the staff:

“While at home, the words of the counsellors would resound in your ears. If you did not forget, it made it a lot easier.”

(IDI, Uganda, high PK, tablet).

All participants emphasized that access to quality health services, free treatments, and regular HIV testing were motivations to join and remain in the trial, even when not taking study products. The education they gained, as well as curiosity about trial results also kept women involved. Reimbursement was appreciated but typically not reported to be a main reason for staying in VOICE. Participants also mentioned remaining in the trial after discontinuing product use, because they felt obligated from having signed a “contract” (the informed consent), they felt trapped and pursued if they decided to stop, or feared being alleged as seroconverters if they terminated early. Several women worried about being discontinued from the study if they reported or were found to be nonadherent. Others stated not wanting to “fail” or feared being reprimanded by staff if they reported adherence challenges. Conversely, some women said that it was easier to appear adherent as no one could detect their nonuse. Thus, women chose to maintain an appearance of high adherence. To return the correct number of unused products to the clinic, women described counting, decanting, stock-piling, burning, burying, dumping, or throwing extra products in toilets or trash cans or sharing surplus with others.

To encourage honest response and product use, participants at all sites and across PK levels recommended real-time product use monitoring and feedback in future trials:

“I think if the results of the blood tests came out immediately, then it can also be immediately established whether you were using the product or not. Then, they should tell you, your blood test results. This approach will make you feel more compelled to use the products properly.”

(IDI, Zimbabwe, low PK, gel)

Other strategies mentioned to improve motivation and adherence outcomes in future trials included the study providers administering the product rather than participants, not requiring daily use, fewer opportunities for waiting room conversations among participants, rewards for high adherence, more fun and social activities, and improved staff-participant interactions.

Discussion

VOICE-D was a qualitative study among 127 participants from Uganda, South Africa, and Zimbabwe that aimed to provide insight into women's motivations, experiences, and behaviors regarding product use during the VOICE trial through retrospective provision of plasma PK results collected during the trial. Three important findings emerged from this study. First, presenting women with their PK results was acceptable, understood, and elicited open discourse on product nonuse. Second, individual patterns of product nonuse and the reasons behind them, were complex and underscored the need for multipronged and tailored approaches to adherence support. Third, participants suggested that real-time product adherence monitoring and feedback be used in future trials.

During the design and ethical review of this study, discussion focused on how to present women with their PK results in a clear and neutral manner, how women might feel and respond when presented with objective information about product nonuse [31]. Although women's reactions to receiving PK results varied, few were negative, and the majority who initially disagreed with or denied their results ultimately accepted them, implying that provision of adherence results was acceptable and understood. Importantly, participants—the majority of whom had low or inconsistent plasma TFV detected during VOICE—openly discussed their product experiences, suggesting that feedback using objective measures may effectively bridge an important gap in reporting, which historically has posed a challenge in prevention trials. In VOICE-C, a qualitative study conducted concurrently with VOICE, women were unwilling to personally acknowledge nonadherence [21]. In VOICE-D, only after provision of PK results did women acknowledge nonuse as well as other socially undesirable behaviors [32].

Women's complex accounts of product nonuse during VOICE suggested a variety of circumstances and patterns that informed a typology—based on participants' descriptions and existing adherence literature definitions [33, 34]—that is useful insofar as it demarcates different patterns of use, informs interpretation of overall trial and drug PK results, clarifies challenges that inhibit correct and sustained product use, and identifies points of entry for tailored approaches to support adherence. Women often reported intertwined patterns, underscoring the situational, social, and temporal complexities affecting product adherence. Indeed, a variety of factors operating at different socioecological levels influenced participants' product use [21, 35]. Although several physical attributes of the gel and tablets and the daily regimen were discussed as hurdles for sustained use, many adherence challenges and reported patterns were not directly related to the type of product. This suggests that low use in the context of this effectiveness trial was less affected by the products themselves than by contextual influences, including fear of side effects/harm propagated through waiting room stories and concerns about receiving an investigational

drug. These negative influences were experienced in the gel and tablet groups and across PK levels, although those with high PK indicated strategies to overcome these challenges. The typology also suggests that developing combination adherence support interventions that address multiple needs and levels of influence might be more effective. Adherence support for HIV prevention methods will likely evolve as effective products progress from research trials to demonstration projects and into real-world settings. Notably, in a recent oral PrEP demonstration project, high adherence to daily use of Truvada™—whose efficacy is now established—was achieved among young South African women, with robust adherence monitoring and support [36].

Participants recommended real-time monitoring and feedback as a way to motivate product use and encourage greater honesty in self-reports. A tailored adherence support intervention based on unannounced pill counts achieved near perfect adherence among HIV-serodiscordant couples in Uganda [37]. Notwithstanding the cost and logistical challenges of providing near or real-time monitoring, recommendations from VOICE-D participants have been incorporated into the next generation of MTN trials to the extent that study designs permit, including provision of aggregated site-level drug results in placebo-controlled trials and individual drug results in open label studies [38, 39]. Moreover, to accommodate a range of study designs, as well as real-world implementation, more creative approaches are needed to objectively monitor and provide feedback to participants in a straightforward yet culturally sensitive and cost-effective manner.

This study has several limitations. First, the sample was selected based on predetermined criteria; consequently, the adherence information derived may be different from that of women who did not join VOICE-D, and may not represent challenges faced by all women in the surrounding communities. The VOICE-D sample was demographically and behaviorally similar to the VOICE sample at the same sites, except for being younger and less educated. Second, plasma TFV testing cannot determine patterns of product use and fluctuating behavior as described by VOICE-D participants; given the narrow window of detection it cannot distinguish either between visit-driven use and adherence. Other trials have used different biological measures to assess use over longer periods and circumvent white-coat compliance [5, 11, 16]. Although women with high PK described fewer adherence challenges compared with women with low PK [40] and described strategies to overcome challenges, we cannot rule out that women with high PK were exhibiting white-coat compliance, a behavior also observed in HIV treatment trials [41]. Hence, the focus of this study was on women with low and inconsistent PK who had documented nonadherence. Finally, although participants were forthcoming about nonuse and discussed a range of socially undesirable behaviors (e.g., vaginal practices, techniques for counting and discarding products, white-coat compliance), social desirability bias may have been present and women may have underreported nonuse. Of note, in the subset of gel group participants whose CVF was tested at Month 6 (first vaginal swab collection time), a higher proportion of women had TFV detectable in CVF than in plasma, as might be anticipated based on the longer TFV detection window in CVF. Hence, the CVF data support the descriptions from the interviews, suggesting that varied incorrect or inconsistent patterns were more dominant compared to noninitiation or early discontinuation.

This study successfully elicited more honest reporting of adherence challenges and product nonuse during VOICE by providing women with their drug-level data and interviewing in a neutral and nonjudgmental manner. Improved relationships between staff and participants to support use and address ongoing challenges, without fearing negative consequences for honestly reporting nonadherence could contribute to more effective support interventions in future studies, although implementation is not necessarily straightforward [42-44]. Given the role of peer interactions and social influences on adherence, interventions could be designed to promote a positive social discourse around product use and supportive norms fostering commitment toward the study and its objectives. Initiatives to promote participants' engagement are being implemented in the next generation of prevention trials [45]. Finally, real-time product use monitoring and feedback to participants should be further evaluated in future trials for improving accuracy of self-reports and motivating high product adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. VOICE-D participants study flow

VOICE-D enrolment target was 144 participants, and at each site, we aimed to conduct two to four in-depth interviews (IDIs) with women from each recruitment group: seronegative (HIV-negative) and seropositive (HIV-positive) low or inconsistent PK gel, high PK gel, low or inconsistent PK tablet, high PK tablet and four gel or tablet-specific focus group discussions (FGDs) with HIV-seronegative participants with low or inconsistent PK levels. A total of 127 women who were all on active products during VOICE were interviewed and analysed. This represents 88% of the original target of 144 former VOICE participants. 68 IDIs and 12 FGDs were conducted, 6 FGDs with gel users and 6 FGDs with tablet users, with a range of 4–10 participants in each FGD. Seronegative: HIV(–) and seropositive: HIV(+); pharmacokinetic (PK). * Does not include those attempted to contact, but unable to reach.

Table 1

Characteristics of VOICE-D Participants

At time of VOICE-D interview		N=127	Percent
Country (site)	South Africa (Durban)	30	24%
	Uganda (Kampala)	49	39%
	Zimbabwe (Chitungwiza)	48	38%
Age: median (mean, range)		28 (29.3, 21-41)	
Currently married		72	57%
Has current primary sex partner or is married		118	93%
Lifetime partners: median (mean, range) ¹		3 (11.8, 1-99+)	
Completed secondary school or more		47	37%
Earns her own income		94	74%
Religion	Christian	108	85%
	Muslim	14	11%
	Other/None	5	4%
During VOICE trial			
VOICE study product group			
	Gel	63	50%
	Tablets	64	50%
Median number of visits with PK data (mean, range)		6 (6.4; 1-11)	
	Among HIV negatives (N=114)	6 (6.7; 3-11)	
	Among seroconverters/HIV positives (N=13)	4 (4.2; 1-9)	
Median month of follow-up in VOICE (mean, range)		17 (17.5; 7-27)	
Pharmacokinetic (PK) group			
	Low	79	62%
	Inconsistent	28	22%
	High	20	16%

¹ Participants with 99 or more sex partners were checked as "99." All those who reported 99+ partners came from Uganda.

Table 2

Participants' Adherence Level in VOICE and Reaction to PK results, by Plasma PK Level and Overall

	Plasma PK level			Total n=127 (%)
	Low n=79 (%)	Inconsistent n=28 (%)	High n=20 (%)	
VOICE biological measures of adherence (drug detection)				
VOICE plasma tenofovir (TFV) PK data				
TFV detected at first quarterly visit ^(*)	0	13(46%)	17(85%)	30(24%)
TFV detected at last visit with PK testing ^(**)	0	5(18%)	15(79%)	20(16%)
Median % visits with TFV detected (mean, range) ¹	0(0, 0-0)	25(30.8, 11-71)	95(89.9, 75-100)	0(21, 0-100)
TFV detected in cervicovaginal fluid at Month 6 in gel subset [N=42] ^(***)	10(42%)	8(62%)	5(100%)	-
VOICE behavioral measures of adherence (matching for visits where plasma PK results were available)				
ACASI: average adherence(%) across visits, ² median (mean, min-max)	100(94, 0-100)	100(89, 25-100)	100(98, 81-100)	100(93, 0-100)
FTFI: Average adherence (%) across visits, ² median (mean, min-max)	100(95, 33-100)	100(91, 25-100)	100(100, 93-100)	100(95, 25-100)
PC: Cumulative adherence (%), ³ median (mean, min-max)	99(93, 40-114)	99(93, 58-102)	99(92, 35-103)	99(93, 35-114)
VOICE-D: Reactions to PK results upon category disclosure (multiple answers allowed)				
Surprise	32(41%)	7(25%)	4(20%)	43(34%)
Disbelief	29(37%)	7(25%)	-	36(28%)
Neutral	15(19%)	4(14%)	4(20%)	23(18%)
Acceptance	8(10%)	11(39%)	2(10%)	21(17%)
Happiness	-	-	13(65%)	13(10%)
Distress/Unhappiness	7(9%)	1(4%)	1(5%)	9(7%)
Sadness	7(9%)	1(4%)	-	8(6%)
Other ⁴	7(9%)	1(4%)	-	8(6%)

ACASI, audio-computer assisted self-interviewing; FTFI, face-to-face interview; PC, pharmacy product count (monthly returns of unused products at the clinic).

^(*) 117 (92%) has their first visit with PK results at Month 3, for the remaining 10, it was at Months 4 to 6;

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mean monthly visit for last PK result was Month 17 (low PK) and Month 16 (inconsistent and high PK).
(***)
(***) Subset in gel group with swab test.
1 Excluding post-seroconversion visits for seropositives;
2 Assessed product use in past 7 days, denominator is women;
3 Cumulative adherence across visits, denominator is women;
4 Other: anger (N=2), embarrassed/uncomfortable (N=3), confused (N=1), laughed (N=1) in low group, fear (N=1) in inconsistent group.

Table 3

Typology of Women's Reported Product Use Patterns: Descriptions and Illustrative Quotes

Noninitiation	<p>This pattern was uncommon and stemmed from a stated lack of interest in the products. Very few acknowledged disinterest from the start. Some described these participants as “greedy” for not using products and coming to the visits solely for the reimbursements.</p> <ul style="list-style-type: none"> <i>I was not interested. Honestly at that time, I was not interested. However, at the end after we received our results, I realized that many of us women were wrong in not honoring the commitment we had made to the VOICE study. (IDI, Zimbabwe, Low PK, Gel)</i> <i>I would explain it easily; I am one of those who did not drink it. I only drank the ones we were given at the clinic to drink while we were being taught. (IDI, South Africa, Low PK, Tablet)</i>
Discontinuation	<p>This common pattern represents women who reported initiating product use but then stopped temporarily or permanently. Circulating stories generated fear or mistrust of the research and led to discontinuation. Other negative influences were unsupportive partners, family members, or community rumors. Waning motivation, driven by a burdensome daily regimen, unpleasant experience using products (e.g., leaky gel, tablets too big), side effects, unknown efficacy, and believing oneself to be on placebo also resulted in discontinuation. Some restarted using product toward the end of the trial because they realized they “worked,” that they should not believe rumors, or when they felt an immediate risk from a promiscuous sexual partner.</p> <ul style="list-style-type: none"> <i>Haaa. I can say that I used it diligently, till about half way through the study. But when I started to hear that other women experienced side effects from the products and they started to question what would happen when you stopped using the products, I reduced the number of times I used the gel. At times, I used it thrice a week, maybe twice; and at times, not at all. (FGD, Zimbabwe, Inconsistent PK, Gel)</i> <i>My parents were concerned that I might use this thing and then get ill since this was a study... I was afraid of it when I had just started using it, when I also lacked understanding. I was afraid that they were testing it on us. [...] I then stopped [after 2 months]. (IDI, South Africa, Low PK, Tablet)</i>
Misimplementation	<p>This pattern describes women who remained persistent with the regimen, but used their products incorrectly or inconsistently. Misimplementation stemmed from various behaviors described by these subpatterns:</p> <p>Visit-driven use: Product use prior to coming to the study visits was mentioned occasionally – across all PK levels – either because the visit acted as a reminder, or because women wanted to ensure products would be detectable in their blood. Indeed, a majority – but not all – of the women understood that their blood was tested for presence of the study drug during VOICE, but they were not given the test results since testing occurred after study's end.</p> <ul style="list-style-type: none"> <i>I used it whenever I was due to come to the clinic, maybe 2 days before I had to come to the clinic. (IDI, South Africa, Low PK, Gel)</i> <i>When I know that the day after tomorrow I am going for my visit, I then took my tablets consistently for those 3 days. I was afraid of what was said about the staff tracing the products in the blood. (FGD, Zimbabwe, Low PK, Tablet)</i> <p>Variable taking: Several women mentioned that often they missed their “set time,” which often led them to just skip a dose, as they understood that product had to be taken at the same time each day.</p> <ul style="list-style-type: none"> <i>Coming home late, you would find that the time that I plan to take it has passed when I come back [from work], and I would forget to put it in my bag, do you see that? [...] When I come back, the time has already passed. Yes, I would end up not using it. (IDI, South Africa, Low PK, Gel)</i> <i>And sometimes when we asked the study staff questions they might give unsatisfactory answers. Sometimes you fail to tell them that you didn't understand because some of them were known to be impatient and didn't entertain a lot of questions. If you then have a question or you didn't understand, you will be afraid to ask; for example, if you forgot to take your tablets on time. Because you are afraid to ask you end up just flushing them down the toilet. Because you can't ask the study staff. (IDI, Zimbabwe, High PK, Tablet)</i> <p>Modified dosing: Specifically mentioned by those assigned to gel, some women used only a fraction of the single dose applicator to manage side effects or unpleasant product attributes: leakage, oozing, wetness, coldness, or excessive moisture during sex. Women also mentioned vaginal practices like washing or cleaning to remove excess gel that may have interfered with correct dosing. Few tablet users mentioned taking only one of the two pills assigned or taking two of the smaller pills.</p> <ul style="list-style-type: none"> <i>The prostitutes, they used to insert only a fraction of it before going to have sex with a man. They could not insert the whole applicator because they would need to carry a whole box and move with it. It was helpful for the lubrication it provided [...] That is what I know about it because that is what I used to do. (FGD, Uganda, Low PK, Gel)</i> <i>Like with the tablets, you were supposed to take 2 per day...A dark one and a light one... So a person with doubts would think let me just take the light one and leave the other. Or maybe just take 2 light ones and leave the dark ones. (IDI, Zimbabwe, High PK, Tablet)</i> <p>Modified regimen: Women with low/inconsistent PK levels commonly reported inconsistent or intermittent use. They described managing side effects or concerns about harm from high-level drug exposure or adjusting use to suit their</p>

	<p>sexual life and partners: some women selectively used products when their partner was around for coitally-dependent protection, others avoided using product when their partner was present – specifically gel users – if he was unsupportive or disliked its feeling during sex. Situational and logistic reasons were provided as well: women refrained from carrying products. around (e.g., to work or when travelling) and skipped use, because of bulkiness, lack of privacy, or concerns about HIV stigma. Menses was a common reason for skipping gel use, across all PK levels. Forgetting was mentioned across all PK levels as well, because of a hectic life, unpredictable events (funerals, unexpected travels, job change) that made daily use challenging. The burden of a “boring” daily regimen also provided an explanation for forgetting doses.</p> <ul style="list-style-type: none"> • I just applied it because I heard them say it works [...] At that time when I know I’m going to get together with my partner, but if we’re not going to do anything [not have sex], I didn’t use it. (IDI, South Africa, Low PK, Gel) • It depends on how you are going to swallow. You only swallow when you feel like [...] Yes, you might swallow about three times [per week]...Yes, so that the product concentration reduces. (IDI, Uganda, Low PK, Tablet) <p>It was just not nice. I didn’t enjoy it every day. That’s why, even though I would tell myself that I was going to apply it, I would sometimes forget to. I would sometimes just stop applying it because it is not nice to put something into the vagina. (FGD, South Africa, Inconsistent PK, Gel)</p>
Adherence	<p>This pattern was commonly described among women with high PK level, but also among those with low/ inconsistent PK levels who denied their results. These women described strong internal motivations, because they were committed or felt an obligation toward the study, they wanted to contribute to the study’s results, they trusted the researchers and products, wanted to protect themselves, or for altruism. Some assigned to gel also mentioned gel lubricating properties, and improved sexual experiences as beneficial.</p> <ul style="list-style-type: none"> • <i>I swear in the name of Jesus I used the gel and I have told you my reasons were two: The [Depo] injection is making me dry and when I used the gel, it worked for me very well. And another reason was fearing to get AIDS because I know my husband is a womanizer</i> (IDI, Uganda, Low PK, Gel) • <i>So I didn’t care if it would harm me because I was committed. [...] I used to tell them [others] to look at me, I took the tablets and I never changed. I didn’t have any side effects. I tried to encourage the others; I used to invite some of them to my house just to see that I was telling the truth. I was actually taking my tablets.</i> (IDI, Zimbabwe, High PK, Tablet)

Table 4

Case Studies

Case 1. Ugandan gel participant, low PK level, 34 years old, married, financially dependent on husband	
<ul style="list-style-type: none"> • <i>Why joined/stayed in trial:</i> Joined the trial after a friend told her about the study. She felt at risk for HIV because of her husband's extramarital affairs and was tempted by the reimbursements offered in the study. She felt bound to her commitment to stay in the trial. She said <i>"It was like signing a contract, you could not leave until you had finished with the study."</i> • <i>Adherence highlights:</i> Was disturbed by the feeling of coldness and the volume of gel. It would soil her underpants and <i>"give the feeling of being in your periods."</i> At one point, she developed a rash, which when combined with other participant's fear of uterine cancer, increased her concerns. She said, <i>"I was badly affected by it and it got me thinking, if it does cause itching, what happens when it gets deeper.....into the uterus? Will it not cause cancer?"</i> Her fear of HIV kept her using gel. She also faced challenges with her husband. She felt obligated to tell him about her participation. He was the breadwinner of the household, paying for rent, food, and school fees - support that outweighed the reimbursements provided at the VOICE clinic: <i>"I had to be more obedient to him than to MU-JHU [referring to the research center]."</i> His reaction was to tell her <i>"that the products would either make me sick or kill me."</i> Balancing her obedience to her husband with her commitment to the trial, her fear that her husband may infect her, and her concerns about harm and the gel's physical attributes, she began to insert only a little bit of gel each night at the introitus. • <i>Product disposal:</i> She would flush the remaining gel that she did not use down the toilet. Occasionally she shared gels with a prostitute friend. 	
Case 2. South African tablet participant, low PK level, 26 years old, unmarried, one sexual partner in past 3 months	
<ul style="list-style-type: none"> • <i>Why joined/stayed in trial:</i> She heard about the study when other women began talking about the benefits they were receiving from VOICE, including the visit reimbursements. She was interested in knowing her HIV status. She continued in the study because she began to see the benefits of the counseling, which she described as caring and comprehensive. • <i>Adherence highlights:</i> The same ability to be influenced by others that led her to join the trial, began to challenge her participation during the study. Her partner, family, friends, and others around her created fear of the study and products. Her family and friends told her <i>"death is waiting"</i> if she continued to use the tablets. Other participants told her things that confused her, such as <i>"drinking the pills would cause me to have AIDS."</i> People around her questioned the study and <i>"said that our blood was being taken to be sold somewhere else. That is when things started to be hard for me."</i> In this context of little support, her product use became difficult. She would take the pills when she remembered and suggested that her visit date was a prime reminder: <i>"I would drink it when the time for my visit was close."</i> • <i>Product disposal:</i> She counted her tablets and removed those that she calculated she should have taken, returning the rest to the clinic. If she did not bring back enough by accident, she would claim someone stole them from her cupboard. 	
Case 3. Zimbabwean tablet participant, low PK level, 24 years old, married, lives separately from partner	
<ul style="list-style-type: none"> • <i>Why joined/stayed in trial:</i> Was experiencing some health issues and heard that the VOICE study offered health care and testing: <i>"So that was my major reason for joining VOICE, the health services provided."</i> She continued in the study, in part, because she feared being labelled as HIV positive if she dropped out. • <i>Adherence highlights:</i> She was motivated and excited to participate at the start. She began to lose interest as women in the waiting rooms stirred up fear about the tablets. They said the tablets were ARVs, that they would cause cancer, and that they would cause your future children to be born with disabilities: <i>"We also experienced fear, you know that fear that grows from hearing what others were saying would happen if you used the products."</i> Later she received abnormal liver test results from the clinic and was put on product hold. Her fear increased: <i>"So when they told me about the liver function being affected, I got really scared."</i> She continued to avoid the tablets, even a month after she was able to restart. At this point, the challenge of regaining her motivation, her growing fear, her annoyance with the size, taste, and daily schedule of taking tablets made reengaging with the product regimen difficult. • <i>Product disposal:</i> She was scared to return tablets to the clinic for fear she would be kicked out of the study, so she flushed unused tablets down the toilet instead. 	

Legend: The three case studies were selected to demonstrate the complexity and interplay of issues described by VOICE participants as impacting their adherence. These particular cases were selected to represent participants from each country in the low PK group, with representation of those assigned to gel and to tablets. They were also emblematic of the common themes identified throughout VOICE-D in terms of motivation to join and stay in the trial and reported challenges associated with product use, while displaying a diversity of incorrect product implementation patterns (modified dosing; modified regimen, visit-driven use, discontinuation).