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Pre-exposure Prophylaxis adherence measured by plasma drug level in MTN-001: comparison between vaginal gel and oral tablets in two geographic regions

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Abstract

Despite strong evidence that daily oral pre-exposure prophylaxis (PrEP) reduces HIV risk, effectiveness across studies has varied. Inconsistent adherence constitutes one explanation. Efforts to examine adherence are limited when they rely on self-reported measures. We examined recent adherence as measured by plasma tenofovir (TFV) concentration in participants of MTN-001, a phase 2 cross-over trial comparing oral tablet and vaginal gel formulations of TFV among 144 HIV-uninfected women at sites in the United States (US) and sub-Saharan Africa (SSA). Adherence to daily product use was higher in the US than in the SSA sites. Within region, however, adherence was similar between products. In the US, gel adherence was higher among married women, and lower among women using male condoms and injectable contraceptives. At the SSA sites, gel adherence was lower for younger women. Inconsistent adherence points to challenges in use of daily PrEP, even during a trial of short duration.

Keywords

pre-exposure prophylaxis; medication adherence; biomarker; HIV prevention

INTRODUCTION

Despite strong evidence that daily oral pre-exposure prophylaxis (PrEP) reduces HIV risk in multiple population groups, (1–4), and that pericoital tenofovir (TFV) 1% gel reduced HIV risk in women (5), the level of HIV protection across PrEP studies has varied. Three large trials in women found no evidence of effect (6–8). Inconsistent and low adherence to study products constitutes one central explanation for the varied findings (9, 10). Those trials

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reporting a positive effect have demonstrated that protection levels are consistently higher among participants with high adherence; in others, overall low product adherence appears to have provided insufficient coverage to confer adequate HIV protection (11). Indeed, in the VOICE and FEM-PrEP studies, both of which tested the effectiveness of daily PrEP regimens, TFV was detected in only 25% to 30% of quarterly plasma samples (7, 12); in VOICE, TFV was never detected in plasma samples for half the women in the three active product arms (range 49% to 58%). Yet, both self-reported adherence and adherence measures derived from clinic product counts indicated high adherence. Clearly, inadequate product use compromises the measurement of biological efficacy and safety and ultimately decreases product effectiveness.

Methodologically, these findings have prompted a call for more objective adherence measures, including real-time assessments that could be implemented alongside novel interventions to increase adherence (9, 13, 14). Their interpretation has informed several hypotheses proposed to explain the apparent low adherence found in some trials that, notably, achieved high study retention overall despite intensive study visit schedules. Adherence to daily PrEP has been particularly low among young adults (7), who continue to be at highest risk of HIV infection. In addition, both marital status and partner engagement may be influential (15–18). The high adherence achieved in Partners PrEP attributed to partner engagement, the VOICE finding that married women had higher adherence (as measured by plasma drug concentration), and qualitative research conducted as part of other Phase 2 and 3 trials of microbicides and herpes suppressive therapy, suggest the important role of partner engagement (15, 19). Others have proposed that HIV risk behaviors and risk perception may influence motivation to use products and patterns of adherence (20). In addition, understanding women's motivations for enrolling in biomedical prevention trials and sustained engagement over time, including attention to the sociocultural context in which trials are conducted, have been hypothesized to assume a critical role in adherence (21).

We explored these hypotheses using an objective adherence measure (i.e., plasma TFV concentration) to minimize the biases of self-reported adherence using data from MTN-001, a phase 2 cross-over trial comparing oral tablet and vaginal gel formulations of TFV among women at sites in the United States and sub-Saharan Africa. We assessed sociodemographic factors; self-reported HIV risk behaviors; partner engagement; HIV risk perceptions; and stated motivations for enrolling in the trial and remaining in the study over time. We examined whether predictors of adherence as measured by plasma drug level differed between the vaginal gel and oral tablet product formulations and between the two geographic regions in which we conducted the study.

METHODS

Study design and population

MTN-001 was a Phase 2 open label crossover study of adherence to and acceptability of daily tenofovir disoproxil fumarate (TDF) 300 mg tablet taken orally and tenofovir 1% gel used vaginally. During the 21-week study, participants received the oral tablet, vaginal gel, and both together (dual use regimen) in each of three six-week periods followed by a one

week washout before the regimen cross-over or final study visit. Participants were randomized equally to one of six study sequences of the three product regimens (all possible orders of the three products yielded six sequences). The study methods have been described elsewhere (17, 22). At enrollment, participants were told that the purpose of the study was to understand women's experiences in taking tenofovir in several different forms and that data collected through questionnaires and blood specimens would be used to examine the research questions. They were also told that tenofovir oral tablets and vaginal gel had not been approved by the FDA for HIV prevention. The study was conducted at four clinical sites in the US (Pittsburgh, Cleveland, Birmingham, New York City) and three clinical sites in sub-Saharan Africa (Kampala and Durban [2 locations]). All sites received ethics and regulatory approvals prior to implementation.

The study enrolled 168 women aged 18–45 who were HIV-negative, sexually active (vaginal intercourse at least four times in the four weeks prior to screening and intending to have intercourse at least once a week for the duration of study participation), not pregnant, and using highly effective contraception (hormonal [excepting vaginal ring], IUD or sterilization). This analysis includes 141 participants who completed both the oral tablet and vaginal gel product periods and had blood specimens available for TFV detection testing.

Study visits took place at enrollment, at the midpoint and end of each six-week product period, and after the final one-week washout period. At each visit, research staff administered face-to-face interviews that assessed product use, sexual behavior, partner engagement and product acceptability. At the final visit, participants were asked their preference among study products. A 25% random sample of participants (N=36) at five sites (2 in the U.S. and 3 in sub-Saharan Africa) completed an in-depth interview at their final study visit. The structured interview guide explored individual, product and partner-related factors associated with adherence and acceptability. All study instruments were developed in English, and translated into the local languages in the African sites and back-translated to English to ensure accuracy.

Measures

Outcome—Adherence measured by drug level constituted the primary outcome for this analysis. At the end-of-period visit for each product, plasma TFV concentrations were measured using a validated liquid chromatography/tandem mass spectrometry method (22). For the oral tablet period, TFV concentrations <=40 ng/mL were considered inconsistent with daily product use as this level is below the lower 95% confidence bound as determined through an observed dosing study (HPTN 066 (23)). Thus, values <=40 ng/mL indicate that the oral product was not taken in the 24 hours prior to the study visit. For plasma TFV detection for vaginal gel dosing we designated a cut-point of <0.31 ng/mL as a measure of non-adherence based on an observed dosing study (24) where this concentration level corresponded with the lower quartile 24 hours after dosing, indicating that no doses had been used in the previous day. This point is also the lower limit of quantification (the limit of detection). Because the available data to apply concentration thresholds differs in measure of spread between route of dosing arms (oral lower 95% confidence interval, vaginal lower interquartile range or 25th percentile) the definitions of recent adherence are imperfectly

matched. Specifically, persons in the 5th to 25th percentile of TFV concentration during the vaginal dosing period cannot be detected (below the lower limit of quantitation) and will result in misclassifying a few individuals in this range during the vaginal dosing period.

Predictors—We examined participants' sociodemographic characteristics (age, marital status, educational attainment) at screening; recent HIV risk behavior, including number of partners in the past three months and male condom use frequency in the previous three weeks (reported at enrollment and at the corresponding end-of-period visit); current contraceptive use (reported at the corresponding end-of-period visit); HIV risk perception ("how worried are you that you/your partner will become HIV-positive in the next year?" [note that perceived partner risk was asked only of those participants who reported their partners to be HIV negative or of unknown status]) and partner's HIV status (positive, negative, unknown); and two measures of partner engagement (assessments both of whether the partner accompanied the participant to the clinic during the study period and whether he knew she was using the study product) (18). In the structured in-depth interviews conducted among the random sub-sample at the final study visit we assessed reasons for joining the study and for remaining engaged over time.

Analysis

All analyses were performed using SAS Version 9.2. We compared the overall levels of adherence between study products and geographic regions using chi-squared statistics. We calculated proportions and means with standard deviations for all factors considered as predictors of adherence. To test for differences in adherence between product regimens, stratified by geographic region, we used fisher's exact tests. Owing to small sample sizes, we did not conduct multivariable analysis. In previous analyses of adherence in MTN-001 published elsewhere (17), we found that adjusting for period (1st, 2nd, or 3rd six-week period of product use) and product sequence (e.g., gel, tablet, dual vs. tablet, dual, gel) did not affect results; thus, we did not adjust the associations presented here for these design features. We coded in-depth interview transcripts (translated into English if they had been conducted in another language) in Atlas.ti, using a code list developed from the interview guide and through initial review of transcripts. Coded sections of text were reviewed and analyzed for dominant themes and illustrative quotes. For this analysis, we reviewed and summarized qualitatively the coded text that addressed reasons cited for study participation and continuation.

RESULTS

Self-reported adherence to each of the study products was high, with overall mean of 94% of daily doses taken that did not vary by product regimen (p=0.8). Recent adherence to the daily product use regimen, as measured by plasma TFV drug levels, was higher in the United States sites (83% for vaginal gel and 84% for oral tablets) than in the sub-Sahara African sites (41% for vaginal gel and 43% for oral tablets) (p<0.001). Within sites, adherence was similar between product regimens (Table 1). At the U.S. sites, recent adherence to vaginal gel use was higher among married compared to unmarried women (100% among married women vs. 78% among unmarried women; p=0.06). At the African

sites, adherence was lower during the vaginal gel regimen for young women aged 18–25 compared with older women (20% vs. 49%, p=0.03), but did not vary by marital status. Adherence did not vary by age in the U.S. sites nor for tablets at the African sites.

Current contraceptive use was associated with gel adherence among women at U.S. sites. Adherence was lower among women reporting current male condom use and among women reporting current use of injectable contraceptives. These associations did not hold for these same women during the oral tablet regimen, nor for women at the African sites. Though not statistically significant, adherence to oral tablets at the African sites was highest among women who reported never using condoms, (p=0.14). Nearly all (96%) women from U.S. sites and most (78%) of women from the African sites, reported that their partner was aware they enrolled in the study and using a daily oral tablet or vaginal gel product. The questions used to evaluate HIV risk perception did not reveal effects on product use. At the African sites, a higher proportion of women who reported that their primary partner's HIV status was unknown, compared to those reporting their partner was HIV negative, had biomarker evidence of recent product use, though these associations were non-significant (p=0.23 for the vaginal regimen and p=0.13 for the oral regimen).

Data from the sub-set of in-depth interview participants highlighted some variation across geographic regions in why women enrolled in the study and motivations for continued participation. Among women at the U.S. sites the predominant reasons for joining the study were altruism and the financial incentives offered. These perspectives were exemplified in statements such as: "I joined the study because I'm interested in helping prevent HIV transmission and I thought it was finally something that I could do as a person who does not have HIV to help the epidemic" (Cleveland participant); and, "The reasons I joined the study were mostly for money. That was like the main reason" (Pittsburgh participant).

No women selected for in-depth interviews from the U.S. sites cited access to medical care and testing as reasons for participation.

In contrast, women from the African sites identified a broader range of motivations, with access to regular HIV testing and medical care as the primary factor prompting trial enrollment. A woman from the Uganda site, for example, commented that the study "has been helping us with our health, knowing our status. They first checked us, things like the kidney, liver, whatever conditions they were in…my health was being helped." Similarly, a woman from Durban, South Africa stated, "I felt it was good for me to join because we were getting all our medical examinations done." Another Ugandan women described the access to health education as particularly valuable: "What brought me in this study is to research and find out how my health is standing. And it taught me on how a person can protect herself from acquiring an HIV/AIDS virus and how she must behave. It gave me knowledge and a lesson on how [I] am supposed to handle my health….When I was tested and found without the virus then learnt that I have to continue protecting myself so that I do not acquire the virus. And it gave me strength to learn and understand." Women from the African sites also noted the desire to participate in research and altruism as important.

Factors influencing ongoing participation were reportedly more diverse among women at the African sites. At the U.S. sites, a sense of responsibility and commitment to complete their obligations as a study participant motivated the high retention: “if I wasn’t gonna finish it through there wasn’t no sense in starting it, cause then they’d only get half the results” (Pittsburgh participant). Often, this sense of commitment was attached to receipt of financial payments to participate: “It didn’t really take too much out of my life to do it. And then the pay was also nice” (Pittsburgh participant). Some women at the African sites also noted a sense of responsibility to the research as motivating their ongoing participation. A Ugandan participant, for example, described her decision to participate as interest in: “research about the Tenofovir medicine, how it behaves inside a person’s body and what the person who has swallowed or used it gets inside the body, inside her body.” Nonetheless, testing and medical care access, alongside enjoying the experience of participating in the trial featured more prominently in their responses.

DISCUSSION

Adherence to daily regimens of oral and vaginal tenofovir, as measured through a biomarker indicating recent use, was imperfect across all study sites, but substantially lower in the African sites than in the U.S. sites. Overall adherence, nonetheless, was comparable between products within geographic region. The levels of adherence observed in MTN-001 add to the literature highlighting the heterogeneity of product use across recent trials that evaluated PrEP for HIV prevention in heterosexual women (e.g., VOICE, FemPrEP) (6, 7). Though definitions of biomarker-assessed adherence have varied in these studies (“recent” dosing in VOICE was defined as the past week whereas in Fem-PrEP it was the past two days and here we defined it as the previous day), there are clearly substantial differences in the levels of product use across these trials. Inconsistent adherence points to challenges in use of a user-dependent, daily product regimen even during a phase 2 trial of short duration.

Though few factors predicted adherence, several findings highlight directions for further research to inform development and scale-up of biomedical HIV prevention approaches. Among sociodemographic factors, adherence to daily use of vaginal gel, as measured by plasma TFV drug levels, was lower in women aged 25 and younger at the South African and Ugandan sites. Adherence at these sites, however, did not vary significantly by age for oral tablets. Similarly, in VOICE, adherence was lowest in women aged 25 and younger (7), a pattern found in multiple PrEP trials: adherence was lower among young men in the iPrEX study (25); and, younger age was associated with lower adherence among serodiscordant couples in the Partners PrEP study as well (13). Young women in sub-Saharan Africa experience the highest rates of HIV acquisition and, therefore, have the greatest need for effective HIV prevention strategies. Yet, as evidenced in this and other studies, young women may experience greater obstacles to adopting daily, on-demand prevention interventions (26). That this age effect was not seen for either product at the U.S. sites highlights potential regional differences in younger adults’ ability to adopt PrEP use.

We had hypothesized that partner engagement would be associated with higher product adherence. However, we found no significant associations, in large part due to the fact that the majority of women (nearly all in the U.S.) reported that their partner knew they were

using the product, which constituted one of our primary measures of partner engagement. Additional measures, including those related to male partner support for and interference with product use as well as perceptions regarding shared responsibilities for HIV prevention, could have permitted a more nuanced examination of this issue (18). Indeed, in qualitative interviews we conducted with participants at the conclusion of this study (findings are reported elsewhere (17)) women did discuss the importance of partner engagement and approval for multiple facets of product adherence, including uptake and sustained use. Other qualitative studies conducted as part of large biomedical HIV prevention trials underscore the importance of engaging partners, even for non-coitally dependent methods such as daily PrEP (27). A small qualitative examination of adherence in a trial of herpes suppressive therapy in Tanzania, for example, highlighted a key role for male partners both in impeding and facilitating adherence, with direct outreach to husbands resolving misinformation that led to restrictions on use (28). An examination of adherence among Partners PrEP participants in Uganda revealed the value of partners supporting one another in sustaining high levels of adherence (15). Considering that partnership patterns vary considerably among young women and that sexual activity may be intermittent, further work on how best to address partner engagement is warranted.

The contribution of risk perception has received considerable attention in examining how individuals make choices about adopting HIV prevention strategies, particularly in the context of combination prevention. Though our risk perception measures were not significantly associated with adherence, this analysis did yield suggestive evidence that unknown partner serostatus prompted increased adherence to the vaginal and oral regimens at the African sites. This finding is aligned with that for male condom use frequency among oral tablet users whereby use was highest among women who reported never using condoms during the previous three weeks. Nonetheless, the findings remain equivocal since the direct question of individual HIV risk perception was not associated with adherence. It may be that participants understood the uncertainty regarding the products' HIV prevention efficacy that motivated the need for safety and adherence data in this Phase 2 trial, and, thus, women did not adopt product use in response to individual perceived risk. Furthermore, there are likely multiple factors related to the product attributes and daily use regimen, as well as contextual influences ranging from perceived stigma regarding product use to family and partner reactions that may have been more important influences on adherence.

As reported in other trials, in MTN-001 a considerable proportion of women reported consistent product use without biological evidence supporting these self-reports (17), raising questions about the shared understanding of the social contract underlying trial participation. Ethics guidelines for conducting research with human participants stipulate clearly the obligations a researcher has to individual participants and these are detailed in the study's consent form. In MTN-001, as in numerous other HIV prevention trials, participants demonstrated tremendous commitment to the study through high participation and retention rates and completion of extremely rigid and demanding study procedures. Yet, the ability to offer definitive answers to fundamental research questions of product safety or efficacy is compromised when adherence is low. Greater attention to the social context underlying the enrollment and consenting of trial participants and accountability expectations for research participants are needed to guide community engagement efforts for future trials. Null

findings from previous biomedical HIV prevention trials conducted at these same research sites may also have affected participants' motivations to use the trial products of unknown efficacy, particularly in a trial where participants were tested repeatedly for HIV infection and where receipt of negative results may provide reassurance that their current behaviors confer sufficient protection.

One key question to address in considering how to achieve sufficiently high levels of adherence in future HIV prevention trials is that related to the motivation for enrolling in a trial. Our findings here are hypothesis generating only, but suggest that financial incentives played a prominent role in women's participation at the U.S. sites. Women reported that monetary payments for study visit completion functioned as a primary motivator for joining the trial and for sustaining participation over time; further, it seems that the payments themselves instilled a sense of obligation to adhere to product regimens. Yet, at the two African sites, the motivators were more diffuse – access to services was a central factor, and the barriers to use were more numerous and included reports of side effects, partners, mobility, and lack of privacy.

The examination of TFV concentration in plasma as a biological measure of recent product use demonstrated consistent levels of adherence between oral and vaginal PrEP formulations within geographic region. The study's cross-over design afforded a unique opportunity to compare biomarker evidence of recent adherence of two PrEP formulations directly within the same users in two geographic areas. Though the adherence measures for the oral and vaginal TFV concentration have an imperfect correspondence, and the plasma measure of adherence (adherent vs. non-adherent) reflects only very recent behavior from the prior day, these more objective measures constitute a vast improvement over past assessments that were dependent solely upon self-reported use. Nonetheless, these adherence estimates may be biased by women's use of the products daily only prior to the study visits when they knew biological specimens were collected. We found considerable heterogeneity in the factors associated with recent adherence in the two regions and between study products, indicating motivations and ability to use the products and the characteristics of users varied. Strategies to overcome adherence barriers and to promote use are clearly critical, particularly in populations where motivations for enrolling in a study may be overwhelmed by more pressing social constraints and economic and health care needs.

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TABLE 1

PrEP adherence and factors associated with adherence measured by plasma drug level in MTN-001

	United States				South Africa and Uganda			
	Vaginal gel (N=70)		Oral tablets (N=70)		Vaginal gel (N=71)		Oral tablets (N=68)	
	Adherent (83%)		Adherent (84%)		Adherent (41%)		Adherent (43%)	
	N (%)	p-value^	N (%)	p-value^	N (%)	p-value^	N (%)	p-value^
Sociodemographic factors								
Age								
18–25	17 (81)	0.74	15 (75)	0.27	4(20)	0.03**	6 (32)	0.29
26–45	41 (84)		44 (88)		25 (49)		23 (47)	
Married								
Yes	15 (100)	0.06*	14 (93)	0.44	16 (39)	0.81	18 (46)	0.62
No	43 (78)		45 (82)		13 (43)		11 (38)	
Educational attainment								
Completed secondary or higher	56 (85)	0.13	57 (86)	0.11	8 (35)	0.61	8 (38)	0.79
Less than secondary education	2 (50)		2 (50)		21 (44)		21 (45)	
Sexual behaviors								
Multiple partners last 3 months								
Yes	11 (85)	1.0	10 (91)	1.0	1 (20)	0.64	1 (20)	0.38
No	47 (83)		49 (83)		28 (42)		28 (44)	
Male condom use frequency past 3 weeks								
Never	26 (87)	0.91	28 (90)	0.48	10 (33)	0.48	16 (57)	0.14
Sometimes	16 (84)		15 (79)		8 (44)		7 (39)	
Always	16 (80)		15 (79)		11 (50)		6 (29)	
Current contraceptive use								
Male condom								
Yes	18 (62)	<0.001**	24 (83)	1.0	1 (50)	1.0	1 (50)	1.0
No	40 (98)		35 (85)		28 (41)		28 (42)	
Oral contraceptives								

	United States				South Africa and Uganda			
	Vaginal gel (N=70)		**Oral tablets (N=70)**		**Vaginal gel (N=71)**		**Oral tablets (N=68)**	
	Adherent (83%)		**Adherent (84%)**		**Adherent (41%)**		**Adherent (43%)**	
	N (%)	**p-value^**	**N (%)**	**p-value^**	**N (%)**	**p-value^**	**N (%)**	**p-value^**
Yes	25 (86)	0.75	23 (79)	0.51	4 (33)	0.75	3 (30)	0.50
No	33 (80)		36 (88)		25 (42)		26 (45)	
Injectable contraceptives								
Yes	5 (56)	0.04**	7 (88)	1.0	21 (40)	1.0	23 (45)	0.58
No	53 (87)		52 (84)		8 (42)		6 (35)	
Partner involvement								
Partner knew participant was using study product								
Yes	55 (82)	1.0	53 (83)	1.0	23 (43)	0.56	24 (45)	0.56
No	2 (100)		2 (100)		5 (33)		5 (36)	
Risk perception								
Partner's HIV status#								
Negative	57 (83)	n/a	54 (83)	n/a	20 (37)	0.23	20 (38)	0.13
Unknown	0		1 (100)		8 (57)		9 (64)	
Concern regarding HIV risk in next year								
Somewhat or very worried	0	n/a	2 (100)	1.0	17 (41)	1.0	16 (38)	0.45
Not very or not at all worried	58 (83)		57 (84)		12 (41)		13 (50)	

^ p-values derived from Fisher's exact tests.

No participants reported that their partner was HIV positive.

* p<0.1;

** p<0.05