Published in final edited form as:
AIDS Behav. 2013 February ; 17(2): 737–747. doi:10.1007/s10461-012-0333-8.

Adherence and acceptability in MTN 001: A randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women

Alexandra M. Minnis[a,b], **Sharavi Gandham**[c], **Barbra A. Richardson**[d], **Vijayanand Guddera**[e], **Beatrice A. Chen**[f], **Robert Salata**[g], **Clemensia Nakabiito**[h], **Craig Hoesley**[i], **Jessica Justman**[j], **Lydia Soto-Torres**[k], **Karen Patterson**[d], **Kailazarid Gomez**[l], and **Craig Hendrix**[m] **on behalf of the MTN-001 Protocol Team**

[a]Women's Global Health Imperative, RTI International, San Francisco, CA [b]School of Public Health, University of California, Berkeley [c]SCHARP, Seattle, WA [d]University of Washington, Seattle, WA [e]South African Medical Research Council, Durban, South Africa [f]University of Pittsburgh, Pittsburgh, PA [g]Case Western Reserve University, Cleveland, OH [h]MU-JHU Research Collaboration, Kampala, Uganda [i]University of Alabama at Birmingham, Birmingham, AL [j]Mailman School of Public Health, Columbia University, New York, NY [k]Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD [l]FHI360, Research Triangle Park, NC [m]Johns Hopkins University, Baltimore, MD

Abstract

We compared adherence to and acceptability of daily topical and oral formulations of tenofovir (TFV) used as pre-exposure prophylaxis (PrEP) for HIV prevention among women in South Africa, Uganda and the United States. 144 sexually active, HIV-uninfected women participated in a cross-over study of three regimens: oral tablet, vaginal gel, or both. We tested for differences in adherence and evaluated product acceptability. Self-reported adherence for all regimens was high (94%), but serum TFV concentrations indicated only 64% of participants used tablets consistently. Most women in the U.S. (72%) favored tablets over gel; while preferences varied at the African sites (42% preferred gel and 40% tablets). Findings indicate a role for oral and vaginal PrEP formulations and highlight the importance of integrating pharmacokinetics-based adherence assessment in future trials. Biomedical HIV prevention interventions should consider geographic and cultural experience with product formulations, partner involvement, and sexual health benefits that ultimately influence use.

Keywords

anti-infective agents; HIV; patient compliance; sexual behavior; vaginal creams, foams and jellies; administration, oral; PrEP; microbicide

INTRODUCTION

Results of recent trials evaluating the effectiveness of antiretroviral drugs used as pre-exposure prophylaxis (PrEP) to prevent HIV acquisition offer evidence of a protective effect of both vaginal gel and oral tablet formulations, with some conflicting results (1, 2).

Corresponding Author: Alexandra Minnis, PhD, MPH, Women's Global Health Imperative, RTI International, 114 Sansome Street, Suite 500, San Francisco, CA 94104, USA, Phone: 415-848-1323, Fax: 415-848-1330, aminnis@rti.org.

Nonetheless, the Food and Drug Administration recently approved use of the antiretroviral combination tenofovir–emtricitabin as oral PrEP (3–10). Across all trials reporting a protective effect, results underscore the importance of achieving high levels of product adherence. In trials both of vaginal gel used pre- and post-coitally in women and of daily oral PrEP in MSM, higher effectiveness was found among the most consistent users (5, 6). Likewise, among heterosexual serodiscordant couples, HIV seroconverters had lower plasma drug concentrations compared to participants remaining HIV negative (11). In considering potential scale-up of PrEP for HIV prevention, product adherence and acceptability ultimately will affect population effectiveness; achieving and sustaining high levels of adherence will be critical.

Microbicide trials have employed self-reported assessments of adherence as the primary strategy to obtain data on product use. However, efforts to measure adherence accurately have faced challenges largely resulting from social desirability and recall biases (12). Despite tremendous attention to research team configuration and training, interview design and standardization, interview mode experiments to increase the privacy of the interview setting, and notifying participants that biomarkers will be used to assess adherence (13, 14), recent advances in measuring drug levels in plasma have highlighted the persistent and substantial over-reports of product use in recent HIV biomedical prevention trials (6, 9). Over-reported product use is likely to differ across products, populations, and geographic areas.

Acceptability has been regarded as important to the adoption and consistent use of products and, as a result, has constituted a standard component of microbicide development and research (15–18). Acceptability may reflect responses to product attributes, effects on sexual activity, and overall satisfaction and willingness to use a product in the future if proven effective. Further, beyond the product attributes and individual-level factors, acceptability may be influenced by partners, relationships, trial participation and community and cultural context (17). Acceptability measures may also include product use, though a product with high acceptability may not necessarily be used consistently (16); likewise, a product with known high effectiveness may be used despite moderate acceptability (19). Thus, accurate adherence assessment is important as a direct measure of patterns of use.

This paper reports adherence and acceptability data from the first study to compare directly two PrEP approaches for HIV prevention: vaginal tenofovir gel and oral tenofovir tablets. This Phase 2 trial, known as MTN-001, compared three regimens of tenofovir: vaginal gel, oral tablets, or dual use of both formulations among women from multiple sites in the United States, South Africa and Uganda. Specifically, we compared short-term adherence to and acceptability of the three product regimens; examined whether the product formulations had differential effects on sexual behavior and condom use; and, through qualitative interviews, evaluated factors influencing adherence and acceptability. In addition, we evaluated serum tenofovir drug concentrations during the oral and dual use regimens as an objective measure to compare with self-reported adherence.

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. The study also evaluated tenofovir concentrations in multiple anatomic locations across the product regimens (reported elsewhere (20)). During the 21-week study, participants received the oral tablet, vaginal gel, and both together (dual) in each of three six-week periods followed by a one week washout before the regimen cross-over or final

study visit (Figure 1). 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). Randomization, conducted by the data coordinating center, was stratified by site and blocks of size six and 12 were chosen randomly to distribute the six treatment sequences. Study sites received sealed, numbered randomization envelopes that were assigned in sequential order to each participant as she enrolled. The study was conducted at seven clinical sites in three countries: Umkomaas and Botha's Hill in Durban, South Africa; Makerere University-John's Hopkins University Research Collaboration in Kampala, Uganda; and Case Western Reserve University in Cleveland, University of Pittsburgh, University of Alabama at Birmingham, and Bronx-Lebanon Hospital Center in the United States. All sites received ethics and regulatory approvals prior to implementation. The study was conducted June 2008 through July 2010.

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 effective contraception (hormonal [excepting vaginal ring], IUD or sterilization). The analysis includes 144 evaluable participants (Figure 1), defined as women who were dispensed study product and completed at least one follow-up visit to report on product use in each of the three product regimen periods.

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 and sexual behavior. Product acceptability assessments took place at each end-of-period visit after participants had used the product regimen for six weeks. At the final visit, an additional acceptability interview was administered that assessed comparative acceptability and partner reactions to products. A 25% random sample of participants at five sites (N=36) completed an in-depth interview directed by a structured interview guide that 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. To minimize social desirability bias for self-reported behaviors, interviews took place prior to counseling procedures and were conducted by a different staff member from those providing counseling. During consent, participants were told that drug concentrations would be measured using blood, biopsies, and vaginal fluid specimens collected during the study.

Product use instructions were offered during each study visit. Participants were instructed to use their study product(s) once daily, before bedtime or the longest period of rest. One dose of vaginal gel consisted of the entire contents of one applicator inserted into the vagina. One TDF tablet taken orally by mouth constituted one dose of the oral product. During the dual use period, participants were asked to use both products at approximately the same time. Study products were dispensed by an on-site research pharmacy. Participants were instructed to return all unused study products to the site at each scheduled visit.

Measures

Self-reported adherence—The primary endpoint was the percent of daily doses reported taken during each product period, which was calculated as the number of daily doses reported taken divided by the number of expected doses if fully adherent (i.e., 42 days). Secondary endpoints included: 1) the percent of women ≥90% adherent; 2) an ordinal measure of frequency of use (5-point scale ranging from "never" to "once a day"); and 3) the number of days product was not used in the previous seven days.

Biomarker adherence measure—During the oral and dual use regimens, serum tenofovir concentrations were measured at the end-of-period visit using a validated LC-MS/MS method (21). Serum tenofovir concentrations prior to an observed dose in the clinic were used to assess adherence in the days prior to the clinic visit; serum tenofovir concentrations over 8 hours following the observed clinic dose were used to estimate individual tenofovir pharmacokinetics. Tenofovir 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 (22)). Thus, values <=40 ng/mL indicate that the oral product was not taken in the 24 hours prior to the study visit or that a dose in the last three days was missed. Serum tenofovir was also assessed after vaginal dosing, but no directly observed dosing reference data are available for a vaginal dosing regimen.

Acceptability—The primary acceptability evaluation assessed future willingness to use the product using a 4-point scale from “very unlikely” to “very likely”: “If daily use of tenofovir gel is found to protect people from HIV, how likely would you be to use it?” We also measured product preferences between vaginal gel and oral tablet, both for the participant and her primary partner as well as perceived support of the primary partner in using each of the products.

Sexual behavior—To examine the effects of product use on sexual activity and condom use, we assessed the frequency of vaginal and anal sex over the past seven days, as well as the frequency of male condom use (number of times used during sex in the past 7 days and whether one was used at last sex).

Descriptive population characteristics—At screening we assessed participants’ sociodemographic characteristics (age, marital status, parity, educational attainment) and at enrollment we assessed current sexual behavior (number of partners in the previous three months, sexual frequency and condom use) and contraceptive use.

In-depth interview guide—A structured in-depth interview guide was developed to permit exploration of factors affecting adherence and acceptability. The guide addressed the same content areas with greater attention to aspects of the products that were liked and disliked; factors that inhibited or facilitated use; and participant communication with partner(s) about the trial and products.

Analysis

All analyses were performed using SAS Version 9.2. Descriptive analyses of participant characteristics included calculating proportions and means with standard deviations for the study population overall as well as for individual sites and sites grouped by country and region. To assess differences between the total enrolled sample and the evaluable participants we compared baseline demographic and behavioral characteristics using t-tests and chi-square tests.

To test for differences in self-reported adherence we used a mixed effects model with adherence as a continuous outcome, including fixed effects for product regimen (vaginal gel, oral tablet or dual use), period (1st, 2nd, or 3rd six-week period) and sequence (one of six product sequences), and random effects for participant within sequence. We compared acceptability between treatment regimens based on a dichotomous endpoint defined as likely (“very likely” and “likely”) vs. unlikely (“unlikely” and “very unlikely”) future use of the product using a conditional logistic regression model (Wald test) that controlled for period and sequence. We evaluated the proportion of participants overall, and by country, with

biomarker evidence of non-adherence to the daily oral tablet regimen (tenofovir concentration <=40ng/mL), in both the oral and dual use regimen periods. Finally, we assessed the level of discordance between self-reported high adherence (defined through three measures, each indicating at least nearly perfect use as defined in Table 3) and biomarker evidence of recent non-adherence to product use using contingency table analysis. We also compared the relationship between stated method preference and serum TFV at the end of the oral tablet period.

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. We wrote country-specific memos to summarize major findings on acceptability, adherence, and male partner involvement. We also synthesized themes across sites to compare discussions of factors affecting adherence and acceptability.

RESULTS

Study population characteristics

One hundred sixty-eight women enrolled in the trial and were randomized to one of the product sequences (Figure 1) and we achieved the target sample size of 144 evaluable participants. We found no differences in socio-demographic factors or baseline sexual behaviors between evaluable and non-evaluable participants. Among evaluable participants, study retention was high with visit-specific retention ranging from 97% to 100%. Complete adherence data were collected at 98.3% of possible visits with no variations across sites.

Participants had a mean age of 30.8 years (Table 1); the proportion married ranged from 21% at the U.S. sites to 96% at the Uganda site. Sexual behaviors at enrollment varied between sites with Ugandan participants reporting a higher mean number of sexual partners in the previous three months (2.6 partners vs. 1 and 1.2 partners in South Africa and the U.S., respectively). No meaningful variations across sites within country were found.

Adherence and acceptability

Adherence—We found no significant difference in reported adherence by product regimen (Table 2). In general, reported adherence to each of the study products was high. The percent of daily doses taken ranged from 9.5% to 100%, with an overall mean of 94% that did not vary by product regimen (p=0.8). No differences in adherence across study sites were observed (data not shown given the presentation of multiple adherence measures). For oral product use during the oral and dual use regimen periods, however, biomarker adherence data indicate actual use was considerably lower and varied by geographic region (Table 2). Across all sites, 64% of participants concluding the oral tablet regimen and 62% of participants concluding the dual use regimen had serum tenofovir concentrations that were consistent with daily product use. Biomarker evidence of inconsistent use was 2.7–3.5 times higher in the African sites relative to in the U.S ($p < 0.01$). Among participants who reported not missing any doses of oral tablets in the previous three weeks, 59.4% in South Africa, 57.9% in Uganda, and 8.3% in the U.S. had serum tenofovir concentrations *inconsistent* with daily product use (Table 3). These discrepancies persisted across multiple measures of self-reported adherence. Furthermore, analysis of tenofovir concentrations after an observed oral dose indicated similar pharmacokinetics across sites (20).

Though overall reported adherence was high, during 35% of visits women nonetheless reported missing at least one product dose during the previous three weeks; with 28%

reporting three or more missed doses. The primary reason offered by U.S. participants for a reported missed dose was forgetting (reported at 31% of visits). Being away from home was the reason most commonly cited by participants from the three African sites (reported at 10% of visits). Additional reasons for missed doses included: challenges in storing products with a tension between wanting to keep them "out of sight" so they would not be found by others, but that leading to "out of sight, out of mind" (primarily a reason offered by women from the African sites); unplanned overnights; lack of privacy for insertion of product when away from home (gel only; African sites only); and menstruation, which made use messy (gel only).

Acceptability—Product acceptability, as measured by hypothetical future use, was high overall and varied both between products and by geographic region. Across all sites, a higher proportion of women reported that they would be likely to use oral tablets in the future if they were proven effective (93%) than reported they would be likely to use gel (83%) or the dual product regimen (82%) (p=0.002). At the two South African and and the Ugandan site, nearly all women reported that future use would be likely for all three product regimens if the products were proven effective. A higher proportion of women at the South African sites reported they would be *very likely* to use the individual products in the future, compared with those women at the Ugandan site (though the sample sizes are small). In contrast, U.S. participants reported a higher likelihood of future use for oral tablets (87%) than for gel (64%) or the dual product regimen (65%). This preference for oral tablets among women at the U.S. sites was evident as well through a direct question assessing method preferences (Table 4) where 72% indicated a preference for the oral tablets compared to 14% preferring the gel. Women at the South African and Ugandan sites, on the other hand, had more varied preferences, as 42% preferred gel, 40% preferred tablets and 14% liked both equally. Stated method preference and serum TFV at the end of the oral tablet period aligned, with a lower proportion of women who stated they preferred oral tablets having evidence of recent non-use of the oral product compared with those women who stated they preferred the vaginal gel (24.4% vs. 59.5%, p=0.001).

Effects of product use on sexual behavior and condom use

We found no evidence that product use affected the frequency of sexual activity and reported use of male condoms. The overall mean number of reported vaginal sex acts for the previous seven days was 2.7 (standard deviation 2.2), with minimal variation across products. Male condom use during last vaginal sex was reported at 61% of visits overall (58% for oral, 62% each for vaginal and dual). Sexual frequency was consistent with that reported at baseline, though reported male condom use at last sex was slightly higher than at enrollment for the Uganda and U.S. sites.

Despite finding no apparent effects of product use on sexual frequency or condom use, data from qualitative interviews suggested that women at all sites gave considerable thought to the use of vaginal gel in the context of their sexual relationships. Oral tablet use, in contrast, was not discussed as affecting sexual interactions directly (though some women in Uganda and in South Africa noted other partner-related concerns that affected use [discussed below]). Indeed some made calculated decisions related to timing of gel use with sex to address partner like or dislike of the product's lubricating properties during sex, partner concerns about exposure to the gel, and perceptions of the gel's HIV prevention effectiveness. Several women in Uganda and South Africa who had chosen to use gel without their partner's knowledge described inserting it early in the day so that it would be undetected by their partner when they had sex in the evening. A Ugandan woman whose partner disliked the gel and "refused her sex" altered the timing of use so that "when he comes for sexual intercourse [the gel] has decreased and he cannot know." Some U.S.

women tried to minimize their partner's exposure to the gel by inserting it after having sex. One described: "I would go in my room and I would look at him like see if he want to say something about sex. And if he don't say nothing about sex, then I'd just go ahead and do it." Others at the U.S. sites described uncertainty about whether to use gel before or after sex: "I'd be like should I have sex before or should I have sex after? Sometimes using the gel after I had sex like would hurt sometimes" (U.S., 28 years old). Finally, participants like this U.S. woman who hoped the gel was an efficacious product, commented: "I used to use the gel and then I would have sex. But I changed my hours a little bit to use the gel like an hour and a half to two hours before…so it would be absorbed….just in case it might actually help."

Factors influencing adherence and acceptability

In qualitative interviews participants described multiple factors that influenced product use and acceptability (Table 5). Among them, first and foremost, were product attributes. The preference for the oral tablet formulation among women at the U.S. sites clearly reflected cultural and personal familiarity with tablets. As a 33-year old participant in Cleveland described: "[Using the pill] was easy. I mean it was more like a birth control pill. So it was like bam! I'm not going to forget to take that pill." Furthermore, the oral tablet was perceived by some participants at each site to offer discreetness not afforded by the gel, a factor likely important to the one-third of Ugandan and 15% of South African participants whose partners did not know they were using study products (Table 4). In addition, not all male partners who knew about the product were supportive of its use (approximately 15% were perceived as unsupportive, with this proportion higher at the South African and Ugandan sites than at the U.S. sites). Thus partner support constituted another important factor in influencing use. A 30-year old Ugandan participant explained:

> My problem was that sometimes on using [gel] when the man is around and he sees you moving around with the applicator, he asks you what you are going to do, which in most cases you don't have a reply to it. But the tablet, I swallow it like swallowing a panadol [pain medication] even when he is there….will you know which tablet I have swallowed?

For others at the African sites, tablet-taking was associated with illness (and with HIV infection, in particular) so the product formulation itself was regarded as a barrier to use. One respondent commented: "I did not tell him [about tablet use] because he is a very tough man, he would ask me what I am doing. I feared…I thought it would distract our relationship and decided not to tell him. I didn't tell him because those tablets, I think, resemble ARVs so he would think that maybe we are sick….I have tried my best to make sure he does not get to know it and he has not known it" (Ugandan woman, 22 years old).

For Ugandan and South African women for whom product discreetness was less a concern, the lubricating properties of the vaginal gel were attractive. Gel was reported to offer sexual health benefits, including reduced vaginal dryness and pain during intercourse as well as improved sexual pleasure for the woman and/or her partner. As illustrated by a 28-year old Ugandan participant: "Before, you might have had some problems of having no vaginal fluids. But when you have that gel, it helps you not get much problems. He [your partner] might even start wondering whether you drunk too much millet porridge." Others at the Uganda site commented more directly about improved sexual pleasure: "Since I started using [the gel] the love with my husband increased…because he thinks I love him so much yet it's the gel" (Uganda, 20 years old). Likewise, a South African participant stated: "There are men who are lazy to perform foreplay, so that is where it helps."

DISCUSSION

This Phase 2 trial of oral and vaginal formulations of tenofovir used as a daily pre-exposure prophylaxis regimen offers unique comparative data on the adherence and acceptability of these two products, including tenofovir serum concentration data to assess recent use of oral tablets. With a cross-over design in which each product formulation was used individually and in combination, method preferences and factors affecting acceptability and use could be examined directly. Furthermore, the study design permitted comparison between women in the U.S. and from sites in two African countries. Experiences using the two product formulations varied considerably across geographic regions, with biomarker evidence of adherence to the daily oral regimen higher at U.S. than African sites. Most women in the U.S. favored the oral tablet over the vaginal gel, while preferences varied at the South African and Ugandan sites, highlighting a role for both PrEP formulations in HIV prevention.

Differences in method preferences and reactions to product attributes appeared to reflect both cultural familiarity with product formulations, partner support, and perceptions of the products' effects on sexual health. For women in the U.S., where prescription and non-prescription tablets are widely available and used, the oral tablet was regarded as familiar and generally easier to integrate into a daily routine. While some women at the Ugandan and South African sites remarked that they appreciated the oral tablet's discreetness relative to the vaginal gel, others described pill-taking as associated with illness, rendering its use more difficult. Despite cultural acceptance of intravaginal practices aimed at achieving "dry sex" in both the South African and Ugandan communities where the study was conducted, many at the South African and Ugandan sites noted that the gel improved their sexual relationship with their partner(s) by reducing vaginal dryness and enhancing sexual pleasure. Indeed, a prospective qualitative study among participants from KwaZulu-Natal in a Phase 3 trial of the vaginal microbicide PRO2000 found that use of a vaginal gel microbicide may not be at odds with intravaginal practices adopted to achieve "dry sex" (23). Further, across all study sites, the potential for broader sexual health benefits for couples was observed. Acceptability data from that trial highlighted the role that gel played in improving sex and increasing partner satisfaction, with this emerging as a more important (and empowering) benefit than product covertness (24). A microbicide product has the potential to be introduced as offering other sexual health benefits that may facilitate its use by women, particularly in the context of relationships where the introduction of a method perceived solely as a disease prevention device raises questions of relationship fidelity (25, 26). Indeed, adoption and use of condoms has been compromised in part because of such stigma.

This evaluation of adherence and acceptability has several important limitations. First and foremost, despite the high levels of self-reported adherence, an objective assessment using drug concentrations indicated a far lower degree of adherence in some subsets of the study cohort (20). One-third of women had serum tenofovir concentrations inconsistent with daily product use at the end of their six-week daily oral tablet use regimen, and this varied significantly between the U.S. and African sites. Tenofovir concentrations after an observed oral dose, however, did not indicate any pharmacokinetic differences across sites to account for the lower than expected or site-specific differences in pre-dose tenofovir concentrations (20). These differences, then, reflect differences in adherence in the few days prior to the research clinic visit. This variability in adherence was not captured through the self-reported adherence measures, highlighting persistent challenges in overcoming social desirability bias in reports of product use in the context of trial participation (12, 13, 27). This may be particularly heightened in settings where the economic and health care resources offered by the trial itself impart a strong sense of obligation to comply with study protocols to ensure continued participation. In qualitative interviews, women at each of the sites described using

the products because they felt a sense of obligation to the study from having agreed to participate, and, at the Ugandan site in particular, because they received health care not otherwise available. Further work on the ethical and contextual issues surrounding trial participation may make important contributions to improving the quality of self-reported behavioral data obtained through clinical trials, and, ultimately, of strategies adopted to increase adherence to prevention interventions to levels necessary to evaluate efficacy.

Several measurement and design constraints warrant mention. First, we were unable to measure the level of over-reporting of vaginal gel use through comparison with a biomarker of drug concentration, a technological limitation that merits priority for further research on gel-based microbicides. Second, the primary acceptability measure, willingness to use products in the future, though widely used in clinical trials, yielded little variability in response at the Ugandan and South African sites and was not aligned with biomarker data indicating recent use fell substantially below “perfect” during the trial. We advocate use of alternative and multidimensional measures of acceptability in future trials (17). The comparative product preference measure was associated with serum TFV data, suggesting that stated preference ultimately may be a good measure of acceptability. Third, in qualitative interviews we did not systematically assess product use within different types of partnerships. Ugandan participants reported a higher mean number of partners at baseline (2.6 in the previous three months), yet their experiences using the study products did not appear to differ meaningfully from women at the South African sites. Nonetheless, future research should pursue experiences of product use in both primary and non-primary partnerships. Finally, our findings may have limited generalizability owing to the stringent eligibility criteria and protocol requirements of this Phase 2 trial. However, they are consistent with larger phase 2B and phase 3 trials conducted at these and similar sites. Clearly the integration of behavioral data with more objective biomarkers of product use is essential and should be prioritized in future trials.

Adherence and acceptability findings in MTN 001 offer evidence that there is a role for both oral and vaginal formulations of tenofovir used daily as pre-exposure prophylaxis. The over-reporting of adherence documented through examination of the serum tenofovir concentrations highlights the importance of integrating pharmacokinetics-based adherence assessment in future trials. Findings underscore the need for consideration of geographic and cultural experience with product formulations, of male partner involvement, and of broader sexual health benefits that may ultimately increase product use. There exists a fundamental connection between behavior and biomedical prevention. Future introduction of PrEP approaches for HIV prevention will need to integrate behavioral and biomedical interventions to achieve high population effectiveness (28).

Acknowledgments

MTN-001 was sponsored by the US National Institutes of Health (NIH); and co-sponsored by CONRAD and Gilead Sciences, Inc. CONRAD supplied the tenofovir gel product and Gilead Sciences provided the tenofovir disoproxil fumarate (Viread) tablets. The study was designed and implemented by the Microbicide Trials Network (MTN), based at Magee-Womens Research Institute and the University of Pittsburgh. MTN principal investigator is Sharon Hillier, Ph.D., and co-principal investigator is Ian McGowan, M.D., Ph.D. The MTN (U01AI068633) has been funded by NIAID, NICHD, and NIMH. The trial is registered with clinicaltrials.gov (NCT00592124). The principal contributions of each author are as follows: AM Minnis (design of behavioral aims and measures; led manuscript development); S Gandham (statistical analysis); BA Richardson (study design development and lead statistician); V Guddera, B Chen, R Salata, C Nakabiito, C Hoesley, and J Justman (site investigators); K Patterson (data management oversight); K Gomez (study operations lead manager); L Soto-Torres (Division of AIDS medical officer); C Hendrix (protocol chair). All authors reviewed the manuscript. The authors are grateful to all site staff for rigorous implementation of the study as well as to the MTN core in Pittsburgh for leadership in numerous areas of protocol development and implementation. We would like to thank Ms. Arendevi Pather, site leader at Botha’s Hill, South Africa and Sherri Johnson at FHI360 for substantial contributions to study implementation.

REFERENCES

1. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012; 26(7):F13–F19. Epub 2012/02/16. [PubMed: 22333749]
2. Kashuba AD, Patterson KB, Dumond JB, Cohen MS. Pre-exposure prophylaxis for HIV prevention: how to predict success. Lancet. 2012; 379(9835):2409–2411. Epub 2011/12/14. [PubMed: 22153566]
3. Cohen M, Baden L. Preexposure prophylaxis for HIV--where do we go from here? N Engl J Med. 2012; 367(5):459–461. [PubMed: 22784041]
4. Grady D. FDA advisory panel backs preventive use of HIV drug. New York Times. 2012 May 10.:D5.
5. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329(5996): 1168–1174. Epub 2010/07/21. [PubMed: 20643915]
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363(27):2587–2599. Epub 2010/11/26. [PubMed: 21091279]
7. Baeten J, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367(5):399–410. Epub 2012 Jul 11. [PubMed: 22784037]
8. Centers for Disease Control and Prevention. CDC trial and another major study find PrEP can reduce risk of HIV infection among heterosexuals. 2011 Jul 13.
9. Van Damme, L.; Corneli, A.; Ahmed, K.; Agot, K.; Lombaard, J.; Kapiga, S., et al. Conference on Retroviruses and Opportunistic Infections. Seattle, WA: 2012. The FEM-PrEP Trial of Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) among African Women.
10. MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. 2011 Nov 25. Available at: http://www.mtnstopshiv.org/node/3909
11. Donnnel, D.; Baeten, J.; Hendrix, C., et al. Conference on Retroviruses and Opportunistic Infections. Seattle, WA: 2012. Tenofovir Disoproxil Fumarate drug levels indicate PrEP use is strongly correlated with HIV-1 protective effects: Kenya and Uganda.
12. Norris Turner A, De Kock AE, Meehan-Ritter A, et al. Many vaginal microbicide trial participants acknowledged they had misreported sensitive sexual behavior in face-to-face interviews. Journal of Clinical Epidemiology. 2009; 62(7):759–765. [PubMed: 19013762]
13. Mensch BS, Hewett PC, Abbott S, et al. Assessing the reporting of adherence and sexual activity in a simulated microbicide trial in South Africa: an interview mode experiment using a placebo gel. AIDS Behav. 2011; 15(2):407–421. Epub 2010/10/05. [PubMed: 20886278]
14. Thomsen S, Gallo M, Ombidi W, et al. Randomised controlled trial on whether advance knowledge of prostate-specific antigen testing improves participant reporting of unprotected sex. Sex Transm Infect. 2007; 83(5):419–420. [PubMed: 17135328]
15. Carraguard Phase II South Africa Study Team. Expanded safety and acceptability of the candidate vaginal microbicide Carraguard(R) in South Africa. Contraception. 2010; 82(6):563–571. Epub 2010/11/16. [PubMed: 21074021]
16. Greene E, Batona G, Hallad J, Johnson S, Neema S, Tolley EE. Acceptability and adherence of a candidate microbicide gel among high-risk women in Africa and India. Cult Health Sex. 2010; 12(7):739–754. Epub 2010/04/17. [PubMed: 20397080]
17. Coly A, Gorbach PM. Microbicide acceptability research: recent findings and evolution across phases of product development. Curr Opin HIV AIDS. 2008; 3(5):581–586. Epub 2009/04/18. [PubMed: 19373025]
18. Severy LJ, Tolley E, Woodsong C, Guest G. A framework for examining the sustained acceptability of microbicides. AIDS Behav. 2005; 9(1):121–131. Epub 2005/04/07. [PubMed: 15812619]
19. Minnis AM, Shiboski SC, Padian NS. Barrier contraceptive method acceptability and choice are not reliable indicators of use. Sex Transm Dis. 2003; 30(7):556–561. Epub 2003/07/03. [PubMed: 12838083]

20. Hendrix, C.; Minnis, A.; Guddera, V.; Riddler, S.; Salata, R.; Nakabiito, C., et al. Conference on Retroviruses and Opportunistic Infections. Boston, MA: 2011. MTN-001: A phase 2 cross-over study of daily oral and vaginal TFV in healthy, sexually active women results in significantly different product acceptability and vaginal tissue drug concentrations.

21. Beigi R, Noguchi L, Parsons T, Macio I, Kunjara Na Ayudhya R, Chen J, et al. Pharmacokinetics and placental transfer of single-dose tenofovir 1% vaginal gel in term pregnancy. J Infect Dis. 2011; 204(10):1527–1531. [PubMed: 21930612]

22. Donnell, D.; Baeten, J.; Hendrix, C.; Bumpus, N.; Bangsberg, D.; Haberer, J., et al. 19th Conference on Retroviruses and Opportunistic Infections. Seattle, WA: 2012. Tenofovir drug levels indicate PrEP use is strongly correlated with HIV-1 protective effects.

23. Gafos M, Mzimela M, Sukazi S, Pool R, Montgomery C, Elford J. Intravaginal insertion in KwaZulu-Natal: sexual practices and preferences in the context of microbicide gel use. Cult Health Sex. 2010; 12(8):929–942. Epub 2010/08/26. [PubMed: 20737330]

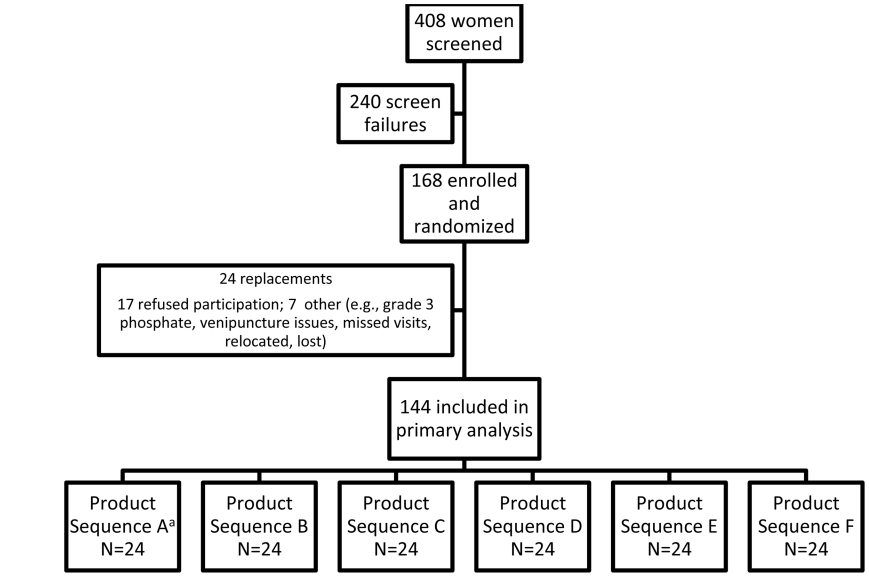
24. Montgomery CM, Gafos M, Lees S, Morar NS, Mweemba O, Ssali A, et al. Re-framing microbicide acceptability: findings from the MDP301 trial. Cult Health Sex. 2010; 12(6):649–662. Epub 2010/04/17. [PubMed: 20397079]

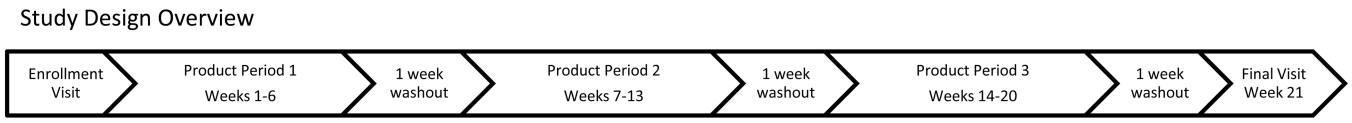
25. MacPhail C, Terris-Prestholt F, Kumaranayake L, Ngoako P, Watts C, Rees H. Managing men: women's dilemmas about overt and covert use of barrier methods for HIV prevention. Cult Health Sex. 2009; 11(5):485–497. Epub 2009/05/30. [PubMed: 19479490]

26. Baumgartner JN, Lugina H, Johnson L, Nyamhanga T. "Being faithful" in a sexual relationship: perceptions of Tanzanian adolescents in the context of HIV and pregnancy prevention. AIDS Care. 2010; 22(9):1153–1158. Epub 2010/09/09. [PubMed: 20824568]

27. Minnis AM, Steiner MJ, Gallo MF, Warner L, Hobbs MM, van der Straten A, et al. Biomarker validation of reports of recent sexual activity: results of a randomized controlled study in Zimbabwe. Am J Epidemiol. 2009; 170(7):918–924. Epub 2009/09/11. [PubMed: 19741042]

28. Rotheram-Borus MJ, Swendeman D, Chovnick G. The past, present, and future of HIV prevention: integrating behavioral, biomedical, and structural intervention strategies for the next generation of HIV prevention. Annu Rev Clin Psychol. 2009; 5:143–167. Epub 2009/03/31. [PubMed: 19327028]





[a]Product sequence refers to product regimen order (vaginal gel, oral tablets, and dual use yielded six unique sequences of products).

Figure 1.
MTN 001 – Phase 2 Adherence and Pharmacokinetic Study of Oral and Vaginal Preparations of Tenofovir

Table 1

Baseline characteristics of study participants in MTN 001, a Phase 2 cross-over study of daily vaginal and oral tenofovir

		Study sites[a]		
	Overall N=144 N (%)	**South Africa N=48 N (%)**	**Uganda N=24 N (%)**	**United States N=72 N (%)**
Sociodemographic background				
Mean age (std dev)	30.8 (7.1)	31.0 (6.8)	30.3 (5.5)	30.8 (7.8)
Married	57 (40)	19 (40)	23 (96)	15 (21)
Educational attainment				
Less than primary	9 (6)	2 (4)	7 (29)	0
Primary	44 (31)	26 (54)	14 (58)	4 (6)
Secondary	29 (20)	18 (38)	1 (4)	10 (14)
Attended college	62 (43)	2 (4)	2 (8)	58 (81)
Sexual behavior				
Mean no. sex partners in the past 3 months (std dev)[b]	1.4 (2.5)	1.0 (0.1)	2.6 (6.0)	1.2 (0.5)
Vaginal sex >3×/week in past 3 weeks	48 (33)	16 (33)	17 (71)	15 (21)
Male condom used during last sex act	68 (48)	29 (62)	5 (21)	34 (48)
Ever had anal sex	39 (27)	1 (2)	0	38 (53)

[a] Study sites included: South Africa (Umkomaas [N=36] and Botha's Hill [N=12]); Uganda (Kampala [N=24]); United States (Bronx [N=12], Pittsburgh [N=24], Cleveland [N=24], Birmingham [N=12]).

[b] Median is 1.0.

Table 2

Adherence to each product regimen: vaginal gel, oral tablets and dual use in MTN 001

	Overall	Vaginal	Oral	Dual
	N=851[a] %	N=285 %	N=282 %	N=284 %
Adherence: self-reported use				
% daily doses taken (mean, SD)[b]	94.0 (10.8)	94.4 (12.2)	93.9 (10.1)	93.8 (10.2)
>=90% doses taken	81	85	79	79
Frequency of use				
< once a week	<2	1	<1	<1
1–3 times a week	2	3	2	2
4–6 times a week	17	15	21	17
Once a day	79	81	77	80
Number of days product not used in past week (mean, SD)	0.4 (1.1)	0.4 (1.0)	0.4 (1.1)	0.4 (1.1)
Adherence: biomarker of use				
Serum tenofovir concentration consistent with daily product use (>40 ng/mL)[c]			N=138	N=140
All sites[c]		-	64	62
South Africa		-	44	39
Uganda		-	39	50
United States		-	84	81

[a] N=visits among 144 participants; maximum of 864 possible visits (adherence assessments) and 432 (acceptability assessments).

[b] p=0.8; mixed effects model adjusted for period and sequence and random effect of participant within sequence.

[c] Serum tenofovir concentrations reported for end-of-period p<0.01, Fisher's Exact test.

Table 3

Comparison of self-reported adherence and serum-level tenofovir concentration in two regimens with oral product dosing in MTN 001

	% adherent by self-report		Tenofovir concentration inconsistent with daily product use (<=40ng/mL)			
			Oral N=138		Dual N=140	
Self-reported adherence measures	**Oral**	**Dual**	**N**	**%**	**N**	**%**
100% of doses taken in past three weeks (all sites)	63.0	65.7	33	37.9	37	40.2
South Africa	71.1	76.1	19	59.4	21	60.0
Uganda	82.6	91.7	11	57.9	11	50.0
United States	51.4	50.0	3	8.3	5	14.3
Frequency of use in past three weeks: once a day	80.4	80.7	39	35.1	42	37.2
No. days product not used in past week: 0 or 1 vs. >1	92.8	93.5	47	36.7	49	37.7

Table 4

Method preferences and male partner involvement in product use in MTN 001

		Study sites		
	All sites N=144 N (%)	**South Africa N=48 N (%)**	**Uganda N=24 N (%)**	**United States N=72 N (%)**
Women's method preferences				
Vaginal gel	40 (28)	19 (40)	11 (46)	10 (14)
Oral tablets	81 (57)	18 (38)	11 (46)	52 (72)
Both liked equally	15 (10)	9 (19)	1 (4)	5 (7)
Neither liked	7 (5)	1 (2)	1 (4)	5 (7)
Partner knew participant used study product(s)				
Vaginal gel	121 (88)	40 (85)	14 (64)	67 (97)
Oral tablet	117 (87)	38 (84)	15 (68)	64 (96)
Dual (gel + tablet)	116 (85)	37 (80)	14 (58)	65 (97)
Among participants whose partners knew about study product use:				
Partner support for gel use				
Not supportive	18 (15)	10 (26)	3 (20)	5 (8)
Somewhat supportive	36 (30)	10 (26)	4 (27)	22 (34)
Very supportive	65 (55)	19 (49)	8 (53)	38 (58)
Partner support for tablet use				
Not supportive	15 (13)	9 (23)	4 (27)	2 (3)
Somewhat supportive	35 (29)	11 (28)	4 (27)	20 (31)
Very supportive	69 (58)	19 (49)	7 (47)	43 (66)

Table 5

Factors that influenced product adherence and acceptability: summary of qualitative interview data from MTN 001 (N=36)

Factors that facilitated use	
Product attributes	
Gel	Improved sexual intercourse due to increased lubrication Reduced vaginal dryness during sex
Tablets	Cultural and personal familiarity with pills Ease of use Discreetness of pill taking
Partner involvement	
Supported participant in managing side-effects	
Helped remind woman to use product(s)	
Openness regarding study participation negated need to conceal use	
Perceived health benefits of study products	
HIV negative status during trial perceived as evidence of product effectiveness	
Belief that only effective products would be used in a trial	
Products bestowed unanticipated benefits: cleansing, menstrual cramps stopped	
Study participation necessitated compliance and offered benefits	
Sense of personal responsibility to follow protocol	
Trust in "professional doctors" and staff	
Access to medical care and testing	
Use of behavioral triggers	
Pairing of product use with existing daily activity (teeth brushing, television show)	
Electronic reminder system (watch or telephone alarm)	
Factors that presented barriers to use	
Product attributes	
Gel	Consistency and leakiness External irritation Vaginal tightness Insertion and disposal of product applicators
Tablets	Side-effects (nausea, hunger, fatigue) Pill size
Pill-taking associated with illness; HIV infection, in particular	
Disruptions to usual routine	
Travel/sleeping away from home (did not have products; lack of privacy for use)	
Partner reactions to study and/or products	
Woman joined study without partner's knowledge	
Mis-information held by partner: gel "impregnated" with viruses	