Published in final edited form as:
AIDS Behav. 2014 May ; 18(5): 841–848. doi:10.1007/s10461-014-0752-9.

Impact of an Adherence Intervention on the Effectiveness of Tenofovir Gel in the CAPRISA 004 Trial

INTRODUCTION

It is widely recognised that high adherence to the prescribed dosing strategy is critical for assessing the effectiveness of investigational products being evaluated in microbicide and oral pre-exposure prophylaxis (PrEP) trials (1-6). While post-trial analyses can provide suggestions about the degree to which results may have been influenced by use and non-use of the study product (7-9), identifying effective strategies to promote study-product use during the trial are critical. Although many strategies to support adherence to study products have been tried (1, 10-13), there are limited data concerning the evaluation of effects of support strategies on product use.

The CAPRISA 004 trial, a phase IIb, double-blinded, randomized, placebo-controlled trial of tenofovir gel, demonstrated 39% effectiveness in reducing HIV infection in women using a coitally linked dosing strategy (2). Briefly, women (n=889) were instructed to insert one dose of gel up to 12 hours **B**efore sex (pre-coitally) followed by a second dose up to 12 hours **A**fter sex (post-coitally) with no more than **T**wo doses inserted in a **24** hour period, referred to as BAT 24. In the CAPRISA 004 trial, gel effectiveness was 54% among participants who used tenofovir gel as prescribed in more than 80% of their coital acts (referred to as high adherers), 28% among participants who used tenofovir gel as prescribed in <50% of their coital acts (referred to as low adherers) and 38% among participants who used tenofovir gel as prescribed in 50-80% of their coital acts (referred to as intermediate adherers) (2, 14).

The initial adherence support activities provided to participants during the CAPRISA 004 trial have been previously described in detail (14). Here, we describe the Adherence Support Program (ASP) that was introduced approximately midway during the implementation of the trial and evaluated for its impact on adherence and study outcomes. The ASP was developed specifically for this trial, based on the Information-Motivation-Behavioural Skills (IMB) model of adherence (15, 16) and incorporating a Motivational Interviewing (MI) approach (17, 18).

METHODOLOGY

The trial design, procedures, and conduct of CAPRISA 004 have been previously described (2). In summary, CAPRISA 004 assessed the safety and effectiveness of tenofovir gel in

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preventing HIV infection in women at high risk of acquiring HIV in KwaZulu-Natal. The trial was conducted between May 2007 and December 2009 in urban and rural CAPRISA Research Clinics. A total of 889 eligible women were enrolled and randomized to receive either tenofovir gel or placebo gel. During monthly study visits, HIV and pregnancy status were ascertained in the context of pre- and post-test counselling. Experiences in using gel, HIV risk behaviours, and clinical assessments of the safety of tenofovir gel were completed monthly. Vaginal aspirate samples, used to measure tenofovir levels in the genital tract, were collected at months 3, 12, 24 and study exit. The primary trial endpoint was incident HIV infection.

Initial Adherence Support Activities in CAPRISA 004

From trial initiation in May 2007 until September 2008 (pre-ASP), the focus of adherence support was didactic with emphasis on compliance to the BAT 24 dosing strategy, as described previously (14). Measurement of product use and adherence support were provided by dedicated adherence staff, whereas HIV risk reduction and contraceptive counselling and support were independently provided by a different set of staff. This pre-ASP support was initiated pre-enrolment, and continued through enrolment and monthly follow-up study visits. The focus of the pre-enrolment and enrolment sessions was on providing information about tenofovir use in the treatment of HIV, the safety of the gel formulation of tenofovir, the mechanics of correct applicator insertion, the trial dosing strategy (BAT 24), gel storage, the return of used and unused applicators, condom use to prevent HIV infection, the use of non-barrier fertility control methods to prevent pregnancy, not sharing trial product with others, and how to integrate gel use into everyday activities. During monthly follow-up visits, the adherence support staff administered a structured questionnaire that assessed gel use in the past month in relation to coital activity. The same staff member then provided information to trial participants that reinforced the BAT 24 dosing strategy (e.g., if a participant was experiencing difficulty with using the post-coital dose or was using more than two doses in 24 hours, she was provided with a standard adherence script to address that challenge, i.e. "*make sure you always use the before and after gel"*).

Team meetings were held with adherence support staff fortnightly to review experiences with trial participants and any challenges they were facing in relation to product adherence and returned applicators. Based on anecdotal concerns voiced by staff about adherence, an independent group, who had not previously been involved in trial conduct or any adherence support being provided to trial participants, were invited to evaluate the general adherence approach in the CAPRISA 004 trial.

Development of ASP

Following on-site observations of study procedures, as well as in-depth interviews and focus group discussions with trial staff, participants, and community members, the evaluation group recommended:

a. Provision of non-judgmental, individualized adherence support: For each individual participant, identify the facilitators of and barriers to consistent gel use, and then discuss specific strategies for addressing the participant's barriers to gel use.

b. b. Separation of adherence assessment from adherence support counselling: To minimize demand characteristics and maximize accuracy of self-reported adherence, the staff who administer the adherence outcome measure should be different from the staff who provide adherence support.

c. c. Facilitation of normative support for adherence and accurate reporting of it: Create a supportive environment in the waiting room by shifting group discussions towards an adherence-supporting discourse; i.e. situated activities and guided discussions reduce participant-to-participant influence supporting non-use of product or over-reporting of product use.

The key recommendation emanating from the review was that the adherence support activities needed to be more dynamic, supportive, and customized to individual participant needs. In response to this recommendation, the original adherence support activities were modified and an ASP was created based on the IMB skills model of health behaviour change and included the use of MI techniques (17, 18) to identify and address the barriers to adherence, specifically, the lack of information, motivation and behavioural skills, in a non-judgmental and supportive manner, and to develop a personalized plan of adherence with individualized, incremental goal setting. The steps comprising these brief adherence support counselling sessions have been previously reported (12) and are depicted in Figure 1.

An additional change that was made to the study protocol involved having different staff to provide adherence support counselling from those who assessed participants' product use; this was done to minimize socially desirable responses. Lastly, a supportive environment was created in the waiting room where staff and peers interacted with participants, providing information on a range of topics related to HIV risk reduction, and pro-actively monitoring and addressing myths and concerns about the gel.

Implementation of ASP

The ASP was implemented in October 2008. It replaced the previous adherence activities until trial completion in December 2009. While coital frequency and gel use in relation to coital activity were discussed, the focus of the counselling was on what the participant felt she needed in order to be able to use the gel consistently and correctly. Instead of being prescriptive the focus is on empowering and supporting the participant. For example, instead of instructing the participant when to use the gel in relation to sex, they are asked about their sex patterns, and then engaged in a discussion about how they think they can integrate gel use into their life. For those having difficulty consistently adhering to BAT-24, counselling and support were provided to assist participants with identifying barriers to product use and strategies for overcoming those barriers. Additionally, incremental goal setting occurred with these participants to help them achieve high rates of adherence over time. For those participants consistently adhering to gel use, positive reinforcement was provided to encourage continued adherence.

Measuring Adherence

Adherence was measured in multiple ways in CAPRISA 004 (14): 7- and 30-day recall of coital activity and product use, monthly return of used and unused applicators, detailed self-reports about the timing of product use in relation to coital frequency and types, and condom use on the day when the participant last had sex. In addition, tenofovir levels in the genital tract were measured at months 3, 12, 24 and study exit. We compared whether women with both pre-ASP and post-ASP drug level samples had any detectable tenofovir level at each of these time points. The primary adherence measure was the proportion of sex acts covered by two doses of microbicide gel, which was determined by monthly applicator count and self-reported coital frequency (2, 14). Since ASP may have had different effects on those with different rates of adherence at the introduction of ASP, we also calculated three strata of adherence; i.e. women who used two doses of gel in 80% or more of their last sex acts were regarded as "high adherers," those using two doses of gel in 50 to 79% of their last sex acts were regarded "intermediate adherers," and those using two doses of gel in less than 50% of their last sex acts were regarded as "low adherers." Monthly study visits where no sex was reported were not included in the calculation.

Statistical Analysis

All data analysis was undertaken using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). The primary adherence measure (2, 14) was used to compare adherence rates pre-ASP and post-ASP. Overall differences in median adherence pre- and post-ASP were evaluated with the Wilcoxon signed rank test. To better understand potential differences in changes in adherence, participants were classified as high adherers, intermediate adherers and low adherers based on their rates of adherence pre- and post-ASP implementation. A Chi-square test of symmetry was used to determine the impact of ASP on these different categories of adherers before and after the introduction of the ASP. A Chi-square test of agreement was used to compare detectability of genital tract tenofovir concentrations pre- and post-ASP. Since there are women who contributed time to both pre- and post-ASP periods, the comparison groups cannot be assumed independent; hence the overall impact of ASP on the effectiveness of tenofovir gel was assessed by comparing pre- and post-ASP HIV incidence rates using a time-dependent interaction term between study arm and ASP in a proportional hazards model. All p-values are two-sided, and 95% confidence intervals are provided, if indicated.

The CAPRISA 004 trial (NCT00441298) was reviewed and approved by the University of KwaZulu-Natal's Biomedical Research Ethics Committee (E111/06), FHI 360's Protection of Human Subjects Committee (#9946), and the South African Medicine Control Council (#20060835).

RESULTS

Trial population

Pre- and post-ASP characteristics of the cohort were similar (Table 1). Of the 889 women eligibly enrolled in CAPRISA 004, 774 participants contributed 486.1 women years of follow-up prior to implementation of the ASP (pre-ASP) and 828 contributed 854.7 women-

years of follow-up after the implementation of the ASP (post-ASP). A total of 669 women are included in both the pre- and post-ASP assessments.

Impact of ASP on adherence

Adherence in the tenofovir gel and placebo gel arms was similar (Figure 2). Overall median adherence pre- and post-ASP was 53.6% (IQR 50% - 100%) and 66.5% (IQR 50% - 100%) respectively ($p<0.01$).

Impact of ASP stratified by categories of adherence

The largest impact of ASP was the shifting of pre-ASP intermediate adherers into the post-ASP high adherer category (Table 2), thereby increasing the proportion of high adherers from 30.2% (pre-ASP) to 42.2% (post-ASP). Of the 143 women who were intermediate adherers before the implementation of ASP, 37.1% (53 women) moved into the high adherer category, while 41.3% (59 women) remained intermediate adherers. ASP had some impact on decreasing the proportion of low adherers (48.4% to 38.3%); of the 324 women who were low adherers prior to ASP, 13.6% (44 women) became high adherers while 20.1% (65 women) became intermediate adherers. However, majority of the pre-ASP low adherers (66.4%, n=215) remained low adherers post-ASP. Of those who were high adherers prior to ASP, 91.6% (185/202) remained high adherers after the implementation of ASP. A chi-square test for symmetry of paired proportions was significant ($p<0.001$).

Impact of ASP on detectable drug levels

Tenofovir concentrations in the genital tract were measured in 584 vaginal aspirate samples collected from 340 women in the tenofovir gel arm. When restricting it to data where women reported to have sex within 14 days prior to when the sample was collected, 64 women had paired tenofovir drug samples pre- and post-ASP. Tenofovir was detectable in 40.6% (26/64) of pre-ASP samples compared to 62.5% (40/64) of post-ASP samples ($p=0.0043$). Nineteen women (50.0%) who had undetectable tenofovir levels pre-ASP subsequently had detectable tenofovir levels post-ASP. The drug level analysis could not be stratified by categories of adherence as the sample size was too small.

Impact of ASP on effectiveness of tenofovir gel in preventing HIV

Data on the effectiveness of tenofovir gel pre- and post-ASP are presented in Table 3. Pre-ASP, HIV incidence was 7.4 per 100 women years in the tenofovir gel arm and 9.8 per 100 women years in the placebo gel arm (IRR: 0.76 (95% CI: 0.39 – 1.45, $p=0.37$)). Post-ASP, HIV incidence was 4.6 per 100 women years in the tenofovir gel arm and 8.6 per 100 women years in the placebo gel arm (IRR: 0.53 (95% CI: 0.29 - 0.94, $p=0.02$)). Following the implementation of the ASP, there was an increase in tenofovir gel effectiveness from 24% to 47% ($p=0.73$).

DISCUSSION

Gel adherence rose from a median of 53.6% prior to the intervention to a median of 66.5% following the implementation of the IMB / MI-based ASP, principally through intermediate level adherers becoming high adherers. In addition, detectable tenofovir concentrations in

the genital tract increased significantly. This in turn was associated with an increase in the effectiveness of tenofovir gel in preventing HIV infection.

Adherence has been the Achilles's heel in microbicides, as well as PrEP studies. In the Fem-PrEP trial for example, where women were asked to take a tablet every day, only 26% had detectable drug levels (7). Similarly, adherence was disappointingly low in the MTN 003 (Vaginal and Oral Interventions to Control the Epidemic – VOICE) trial, where women were randomized to daily Viread®, daily Truvada® and daily tenofovir gel. Tenofovir was detected systemically in 30%, 29%, and 25% respectively in these three groups (9). Of concern are the low levels of actual product use, despite high levels of self-reported use. Articulated simply, it is not possible to demonstrate the effectiveness of these tablets or gels if they are not being used by the women in the trials.

Until now, there has been little evidence of the effectiveness of each adherence strategy to help select one over the other for a microbicide or PrEP trial, in order to enhance the likelihood of trial success. Our data on the IMB / MI-based adherence strategy, which was developed for the CAPRISA 004 trial, provide new evidence demonstrating its ability to increase adherence in women advised to use a microbicide gel with coitus. However, this approach has had different effects on intermediate and low adherers. The ASP seems to have had little impact on low adherers; only a third improved their adherence. The low adherers are particularly important as they initially comprised almost half (48.4%) of the women in the CAPRISA 004 trial, highlighting the need to develop better adherence interventions focussing on this refractory group.

Adherence is influenced by multiple factors, including age, marital status, disclosure to partner and/or family members, risk-perception, as well as social and cultural factors (12, 19, 20). The IMB model, incorporating MI techniques, is able to address many of these challenges by providing a non-judgmental and supportive environment, enabling the women to discuss their barriers to adherence and to develop a personalized plan for their future adherence. The principles of MI that were utilized in the ASP have been previously applied to supporting antiretroviral treatment adherence and HIV risk reduction in infected individuals (15, 21-24). We have extended the utility of this approach by showing its potential value as an adherence strategy for microbicide trials. The separation of the adherence support activities from the measurement of adherence was an important aspect of the ASP. A similar approach was used successfully in the iPrEx study, which found that Truvada® tablets reduced the risk of HIV infection by 43.8% in men who have sex with men (4, 13).

The CAPRISA 004 ASP was specifically designed to address the combination of the information deficit, the participant's motivation and their ability and skills to effect behaviour change. Perception of risk has a major impact on motivation to use study product. In the FEM-PrEP trial 70% of the women reported that they did not perceive themselves to be at risk of infection (7), whereas the serodiscordant couples enrolled in Partners PrEP (3) were well aware of their risk for HIV acquisition, as they knew their partner's HIV positive status. An additional challenge in maintaining high levels of motivation is the concern about disclosing gel use to their male partners (25). While the impact of the ASP on these two

factors that undermine adherence remain to be assessed in future studies, a strength of this intervention is the support that it provides with regard to motivation and essential behavioral skills for gel use. In particular, ASP counsellors encouraged women experiencing difficulty with gel use to develop their individual practical solutions to improve their adherence. The pre-ASP adherence counselling, which is based on repeatedly instructing women participating in microbicide trials on what they should or must do fundamentally failed to take into account the women's motivation, or lack thereof, and did not adequately address the behaviour skills required to implement this HIV prevention intervention.

A significant shortcoming in this study is the lack of time matched controls in this before-and-after design. On the other hand, one of the strengths of this before-and-after design is that the same individuals are involved in both interventions. However, in the absence of a cross-over design, we are not able to eliminate bias emanating from the prior experience women may have had during the pre-ASP period.

The measure of adherence used is based on counting returned applicators and participant recall of sexual frequency; both of which have a subjective element. We therefore included the measurement of tenofovir drug levels, which provides a more objective marker of adherence. Additionally, HIV incidence and the calculation of effectiveness in preventing HIV were included in an attempt to reduce the impact of recall bias in this study's outcome measures.

While behavioural changes, such as reported sex acts (and in turn returned used applicators), partner changes and condom use may have contributed to the changes in the outcome measures over time, the impact on HIV incidence in the tenofovir arm was larger from pre- to post-ASP (7.4 to 4.6 per 100 women years) compared to the placebo arm (9.8 to 8.6 per 100 women years), indicating enhanced product effectiveness post-ASP.

The implementation of this intervention was dependent on the training of the ASP staff and on standardization of procedures. The ASP was resource intensive (both in training and monitoring of the program) and while it was possible to implement within a clinical trial setting, it may not be practical in real world programmatic scale-up. However, women who seek and initiate microbicides or PrEP use may already have high levels of motivation and the requisite skills to implement this type of HIV prevention option, and a shorter and simpler version of the ASP may be more appropriate in these settings.

In conclusion, the ASP developed for the CAPRISA 004 trial enhanced adherence and was associated with improved efficacy. While this approach may be useful in other microbicide trials, it needs to be strengthened to improve its impact on low adherers and simplified versions need to be developed for use in scale-up implementation of tenofovir gel.

Acknowledgments

We pay tribute to the women who participated in this trial; their dedication and commitment made this study possible. The CAPRISA 004 Tenofovir Gel trial is supported by the Centre for the AIDS Program of Research in South Africa (CAPRISA), the United States Agency for International Development (USAID), Family Health International (FHI) (cooperative agreement # GPO-A-00-05-00022-00, contract # 132119), and LIFElab, a biotechnology center of the South African Department of Science and Technology. Support from CONRAD for the product manufacturing and packaging as well as support from Gilead Sciences for the Tenofovir used in the

production of gel is gratefully acknowledged. We thank the US National Institutes for Health's Comprehensive International Program of Research on AIDS (CIPRA grant # AI51794) and the Columbia University-Southern African Fogarty AIDS International Training and Research Programme (AITRP grant # D43TW00231) for the research infrastructure and training that made this trial possible.

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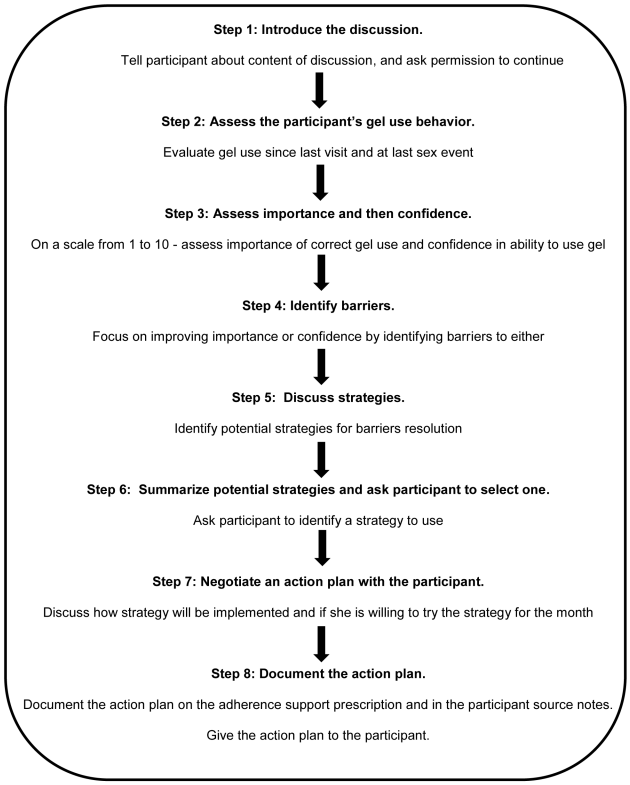

Figure 1.
Steps of the Adherence Support Program

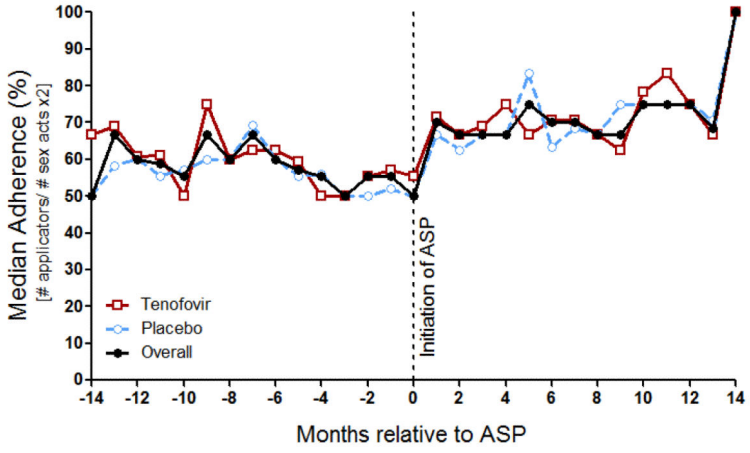

Figure 2.
Median adherence (# applicators / # sex acts x2) by trial month relative to ASP

Table I

Demographic and baseline sexual behaviour characteristics of participants pre- and post ASP

	All (N=889)	Pre-ASP Sub-set (N=774)	Post-ASP Sub-set (N=827)
Demographic characteristics			
Mean age (SD) (years)	23.8 (5.10)	23.9 (5.13)	24.0 (5.17)
Rural	68.7%	70.3%	69.5%
Monthly income < R1000	80.8%	82.3%	81.5%
Married	5.7%	5.8%	5.8%
Stable partner	92.5%	92.8%	92.5%
Baseline sexual behaviour			
Mean age sexual debut (SD)	17.4 (2.04)	17.4 (2.03)	17.4 (2.04)
Mean number sexual partners (lifetime) (SD)	3.3 (10.49)	3.4 (11.20)	3.1 (8.80)
Mean age of oldest partner (past 30 days) (SD)	27.4 (6.24)	27.5 (6.29)	27.5 (6.33)
Reported sex in the past 7 days	61.9%	62.0%	62.0%
Always use condom during sex	29.1%	29.7%	29.1%
New partner (past 30 days)	1.2%	1.3%	1.0%
Anal sex (past 30 days)	0.5%	0.5%	0.5%
HSV-2 prevalence	51.2%	52.2%	50.9%
Contraception			
Injectable	82.1%	81.8%	81.7%
Oral	15.5%	15.8%	15.7%
Tubal ligation	2.3%	2.3%	2.4%
Hysterectomy	0.1%	0.1%	0.1%

* 669 women represent those with data pre- and post- ASP.

Table II

Changes in adherence pre- and post-ASP using the frequency-based adherence measure

		Post-ASP % (N)			
	Level of adherence	**High Adherer (>80%)**	**Intermediate Adherer (50-80%)**	**Low Adherer (<50%)**	**Total**
Pre- ASP % (N)	**High Adherer (>80%)**	91.6 (185)	3.5 (7)	5.0 (10)	**30.2 (202)**
	Intermediate Adherer (50-80%)	37.1 (53)	41.3 (59)	21.7 (31)	**21.4 (143)**
	Low Adherer (>50%)	13.6 (44)	20.1 (65)	66.4 (215)	**48.4 (324)**
	Total	**42.2 (282)**	**19.6 (131)**	**38.3 (256)**	**100 (669)**

* The 669 women represent those with data pre- and post-ASP. The remaining 220 women not represented include: 71 contributed adherence data only to pre-ASP period, 145 contributed adherence data only post-ASP, and 4 women did not contribute any adherence data as they reported no sex or missed visits.

** Chi-square test for symmetry of paired proportions significant with $p<0.001$.

Table III

Impact of ASP on effectiveness of tenofovir gel

Period	# Women	# HIV infections	Women Years	Incidence rate per 100 women years (95% CI)	Incidence rate ratio (95% CI)	p-value
Pre- ASP						
Tenofovir	387	18	242.2	7.4 (4.4 – 11.7)	0.76 (0.39–1.45)	0.37
Placebo	387	24	243.9	9.8 (6.3 – 14.6)		
Post-ASP						
Tenofovir	417	20	438.3	4.6 (2.8 – 7.0)	0.53 (0.29–0.94)	0.02
Placebo	410	36	416.5	8.6 (6.1 – 12.0)		