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Adherence in the CAPRISA 004 Tenofovir Gel Microbicide Trial

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Abstract

High adherence is key to microbicide effectiveness. Here we provide a description of adherence interventions and the adherence rates achieved in the CAPRISA 004 Tenofovir Gel Trial. Adherence support for the before-and-after dosing strategy (BAT 24) was provided at enrolment and at each monthly study visit. This initially comprised individual counselling and was replaced midway by a structured theory-based adherence support program (ASP) based on motivational interviewing. The 889 women were followed for an average of 18 months and attended a total of 17031 monthly visits. On average women reported 5 sex acts and returned 5.9 empty applicators per month. The adherence rate based on applicator count in relation to all reported sex acts was 72.2% compared to the 82.0% self-reported adherence during the last sex act. Adherence support activities, which achieve levels of adherence similar to or better than those achieved by the CAPRISA 004 ASP, will be critical to the success of future microbicide trials.

Keywords

adherence; adherence support; adherence measures; Microbicides; clinical trial; HIV prevention

INTRODUCTION

Young women bear a disproportionate burden of HIV infection in sub-Saharan Africa with HIV infection rates about 3-6 fold higher than that observed in young men (1). Microbicides offer a promising female-controlled option for HIV prevention. While findings from phase III trials of Nonoxynol-9 (2), SAVVY (3, 4), Carraguard (5) and Cellulose Sulphate (6, 7) have been disappointing, tenofovir gel offers a promising female-controlled option as an effective microbicide for HIV prevention (8).

The effectiveness of a microbicide in a clinical trial is dependent on the efficacy of the product as well as the participants' willingness and ability to use the product as instructed (9). For example, the effectiveness of a 100% efficacious product, which is used only 50% of the time, can be expected to be only 50%. This will depend on, amongst other issues, the risk profile of the participant, study product dosing strategy and timing of product use.

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Under-utilization or inappropriate use of product, especially in relation to exposure to HIV, is a serious threat to a microbicide trial being able to demonstrate an accurate level of product efficacy. Indeed, low adherence has been identified as being responsible for the lack of effectiveness in the FEM-PrEP trial, a study of daily oral antiretroviral prophylaxis in women (10) and in the MTN 003 (VOICE) trial, a study of daily oral and vaginal antiretroviral prophylaxis in women (11).

Adherence is multidimensional, involving the interplay of, amongst others, participant behavior, adverse effect profiles, patient fatigue, and integration of therapy into the routine of daily living (12). In a clinical trial it is particularly challenging to achieve high adherence, due to participants being repeatedly informed that they may be allocated to placebo or active arms, and that the true efficacy of the study product is as yet unknown.

There is, at present, no reference standard for measuring adherence in microbicide trials. In 2008, the Institute of Medicine (13) recommended that ‘investigators should use multiple types of measures to triangulate adherence estimates’. The report further recommended that interventions to increase adherence should be ‘methodologically rigorous, socially and culturally relevant, [and] grounded in behavioral and social science theories’.

The CAPRISA 004 trial assessed the safety and effectiveness of tenofovir gel in preventing sexually transmitted HIV infection in women. Here we describe the study product adherence achieved, using three different measures of gel adherence, through adherence activities implemented in the CAPRISA 004 Tenofovir Gel Microbicide trial. Additionally, we describe the relationship between gel adherence and HIV effectiveness.

METHODS

Study design and study population

CAPRISA 004 was a phase IIb, two-arm, double-blind, randomized, controlled trial to assess the effectiveness of tenofovir gel. The trial was conducted from May 2007 to March 2010. A total of 889 HIV-uninfected women between 18 and 40 years were eligibly enrolled at two sites: the CAPRISA Vulindlela Clinic in a rural community about 150 km west of Durban in the KwaZulu-Natal midlands (rural site); and CAPRISA eThekweni Clinic in central Durban (urban site). Participants were followed for a mean of 18 months (8).

Tenofovir gel dosing regimen

The dosing and timing of tenofovir gel in the CAPRISA 004 trial was informed by a review of non-human primate studies (14), safety studies of topical tenofovir (15), and extensive consultation with potential study participants (16). The dosing strategy comprised three key concepts described as “**BAT24**”:

- Insert first gel up to 12 hours **B**efore sex
- Insert second gel as soon as possible, within 12 hours **A**fter sex
- Do not insert more than **T**wo gels in a **24** hour period

Interventions to support gel use

The design of the CAPRISA 004 trial drew upon the experiences and benefited from previous microbicide trials, particularly in relation to the importance of adherence support. During the CAPRISA 004 trial preparation phase, several structured meetings and discussions were held with the target population and selected study staff (including clinicians, nurses, counselors, and research assistants) to develop and modify the design of the adherence activities. Adherence activities were adapted to accommodate participants' literacy levels, cultural beliefs, attitudes and expectations. Support materials used to facilitate adherence activities are shown and described in Table 1.

During the trial the adherence activities were regularly reviewed and adapted as needed. The adherence activities initially comprised individual counselling and this was adapted midway (from October 2008 onwards), based on an Information-Motivation-Behavioral (IMB) skills model framework (17). Depending on when a woman was enrolled into the trial, the duration of exposure to the adapted adherence activities differ. This model encompasses provision of information, motivation and self-efficacy to support desired behavior change, and skills needed for the desired behavior (17). The IMB model has been studied in various populations in both prevention and treatment settings (18-23) and has been proposed to sustain adherence in microbicide trials (24). Table 2 summarizes the IMB model for the Adherence Support Program (ASP) in the CAPRISA 004 trial.

The IMB adaptation included the introduction of a motivational interviewing approach (25-27) to facilitate a participant-centered, collaborative discussion to explore and resolve any obstacles or ambivalence to adherence. During the motivational interviewing based sessions, a trained nurse encouraged each woman to discuss how she thought she could incorporate gel use into her routine activities. The impact of motivational interviewing based counseling on adherence and gel effectiveness have been previously described in detail (28).

Adherence support was provided at screening, enrollment, and monthly follow-up visits according to the following structure:

- 1. Screening module** - As part of the decision-making for trial participation, women were given basic information on the use of study gel, followed by an introduction to the applicator and study gel.
- 2. Enrollment module** - Once enrolled, women were provided with detailed instructions on how to use study gel while in the trial. The main goals of this module were to familiarize women with the mechanics of using the applicator, to communicate the timing and dosing message for gel use, and to freely engage nurses with questions that they may have with gel use in relation to sexual experience.
- 3. Booster module** - During monthly follow-up visits, women were provided with ongoing counseling to support gel use. These included customized support based on previous month's experience of gel use as well as goal setting.

The modules were administered through individualized sessions by trained nurses. Initially, measurement of gel use occurred by the same nurses who were also responsible for

adherence support. When the motivational interviewing approach was introduced, behavioral data were collected independently from the provision of adherence support.

ASP materials were modified during the trial based on the opinions of the staff administering the ASP and the women in the study. These opinions were systematically collected and collated through qualitative, structured debriefing and interactive sessions with the nurses administering the ASP. In total, 26 debriefing sessions, each lasting approximately two hours, were hosted by the ASP Coordinator during the trial to review strengths and weaknesses of the content, structure and delivery of the ASP. These sessions focused on staff opinions of the program, on their interactions with the women, as well as the opinions of the participants. Specifically, the knowledge, behavior and motivation for adherence to gel use was monitored and discussed. The ASP Coordinator provided ongoing advice and support to the staff based on feedback received during the debriefing sessions (Figure 1).

Adherence measurements

At each monthly follow-up visit, self-reported behavioral data on sexual frequency and gel use were collected using interviewer administered standardized questionnaires for the preceding 30 days, last 7 days and day of last sex act. Timing of self-reported gel and condom use relative to sex were collected for the last sex act only. From October 2007, about 4 months after study initiation, the participants were requested to return all their used and unused gel applicators from the preceding month at each follow-up visit. These were counted and reconciled against the number of applicators dispensed previously.

Three different measures of gel adherence are defined below:

1. **Returned used applicator adherence:** The number of returned used applicators was recorded at each monthly visit for each woman; an adherence score was calculated as the median number of applicators returned per study visit (excluding missed study visits). Applicators that were not returned to the pharmacy were regarded as not used for the purposes of the adherence analysis. Women returning more than a median of 9 applicators per month over the trial period were classified as high gel users, those returning a median of 5 to 9 applicators on average per month were regarded as intermediate gel users and those returning less than a median of 5 applicators per month were considered to be low gel users.
2. **Self-reported adherence:** Women were asked detailed questions about the last day they had sex, including whether the study gel was used up to 12 hours before and after the last sex act. If gel was used according to the prescribed dosing regimen, the woman was regarded as being adherent that month. If no study gel or only one study gel was used within the appropriate time period, or if a study visit was missed or data on the last sex act was not collected, the woman was classified as non-adherent for that month. An adherence score was calculated for each woman, representing the proportion of adherent sex acts over all sex acts. Women with an adherence score of 100% were considered to be high adherers, whilst those with a

score of 80% to 99% were intermediate adherers and those with a score of less than 80% were low adherers.

- 3. *Applicator-based adherence:*** This measure was regarded as the primary adherence measure and has been reported previously (8). It was calculated by dividing the number of reported sex acts per month by half the number of returned used applicators for that month. The median of each woman's monthly adherence estimates was assigned as her overall gel adherence score. The assumption was that two doses of gel were required for every reported sex act. Although this assumption may not always apply, adjusting for multiple sex acts within 24 hours made no substantive difference. Women who used two doses of gel in more than 80% 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 act were regarded as low adherers.

Statistical analysis

We analyzed the final dataset (datalock date 09 December 2011). The differences between the final dataset and the previously published data (8) are minor and do not impact the overall results. HIV incidence rates and incidence rate ratios (IRRs) between tenofovir gel and placebo gel were calculated for each adherence measurement, stratified and reported as low, intermediate, or high to assess the relationship between each adherence measurement and effectiveness of tenofovir gel for HIV prevention.

A Poisson distribution was assumed for confidence intervals (CIs) of incidence rate ratios (IRRs). Stratified analyses of gel effectiveness in each of the adherence levels (high, intermediate, low) was evaluated using a log-rank test, adjusted for site. Categories were defined post hoc and were not based on a specific theoretical framework. All p-values are two-sided and CIs are 95%. The descriptive and statistical analysis of data was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

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

RESULTS

Demographics

A total of 278 urban and 611 rural women were eligibly enrolled and followed-up for a total of 1341 women-years (mean=18 months), attended 17031 monthly visits with an overall study retention rate of 94.8% (8). There were no significant differences in the demographic characteristics and baseline sexual behavior of participants in the tenofovir gel arm (n=445) compared to the placebo gel arm (n=444) (8).

Returned used applicator adherence

During the trial, a total of 181,870 applicators were dispensed, of which 95.3% were returned to the study pharmacy. Of these, 93,597 (51.5%) applicators had been returned empty and were regarded as 'used'. Each month, women returned an average of 5.9 (median: 6.0, interquartile range (IQR): 4 – 7) used applicators.

Self-reported adherence

According to self-reports, 459 of 889 women reported using both the before and after gel dose every month for the last sex act. Of the 459 women, 209 women missed at least 1 monthly visit. The remaining 250 women did not miss any visits during the study and they were regarded as high adherers as per the self-reported adherence measures (Table 3). Average gel adherence based on the women's self-report of their last sex acts was 82.0% (IQR: 76.5 – 100). Most self-reported last sex acts (96.6%) involved correct gel use, with 1.6% reporting gel use after sex only and 1.8% reporting gel use before sex only.

The majority of last sex acts (69.2%) had gel use within 5 hours before sex and 3 hours after sex (Figure 2). Women who inserted gel within two hours before the sex act were more likely to insert gel within 2 hours after sex [OR 1.73 (95% CI 1.56 - 1.93), $p < 0.0001$] compared to those inserting gel more than two hours before the sex act.

Self-reported data collected for the last sex act indicated that women used both a condom and gel for 79.6% of sex acts, used a condom only for 2.3% of sex acts, and used gel only for 17.3% of last sex acts. No differences were noted in self-reported condom use between the study arms, but was higher at the urban than the rural site (90.9% vs 77.7%, $p < 0.001$).

Applicator-based adherence (primary adherence measure)

Data on the applicator-based adherence has been previously reported. In brief, a mean of 72.2% (IQR: 50 - 100) of reported sex acts were estimated to have had two gel doses (8).

Gel adherence and effectiveness

All three adherence measures demonstrate that women who were high adherers had the highest tenofovir gel effectiveness (Table 3). High gel adherence based on returned used applicators, self-reported adherence and applicator-based adherence produced anti-HIV effectiveness estimates of 54%, 64% and 55% respectively. Eighteen women were classified as high adherers, irrespective of the adherence measure used. Of these 0/10 in the tenofovir gel arm and 4/8 in the placebo gel arm acquired HIV ($p = 0.02$). Tenofovir gel reduced HIV infection by an estimated 79% in the group of women who had a high median applicator use (> 9) and a high primary adherence measure ($> 80\%$), with an HIV incidence rate of 3.9 per 100 person-years (95% CI 0.5 – 14.2) in the tenofovir gel arm and 19.0 per 100 person-years (95% CI 8.2 – 37.4) in the placebo gel arm. A total of 64 women were classified as low adherers, irrespective of the adherence measure used. Of these 2/26 in the tenofovir gel arm and 4/38 in the placebo gel arm acquired HIV, with respective HIV incidence rates of 6.2 per 100 person-years (95% CI: 0.7-22.2) and 8.3 per 100 person-years (95% CI: 2.3-21.3) ($p = 0.73$).

DISCUSSION

Adherence is a major challenge in microbicide trials and well-developed programs to enhance adherence are critical. Adherence ranging from 72.2% to 82.0%, depending on the measure used, was achieved in the CAPRISA 004 study using an IMB-based adherence support program. Women with high adherence had the highest levels of protection, with effectiveness against HIV ranging from 54% to 64%, depending on which of the three measurements of adherence was used.

Based on self-reports, high levels of adherence were achieved during the last sex act before each monthly clinic visits. The discrepancy between the self-reported adherence of 82.0% in the last sex act and the mean applicator-based adherence of 72.2% in the last month may reflect a “white coat” effect of higher adherence in the last sex act prior to a scheduled study visit compared to the rest of the month. Given that the CAPRISA 004 ASP, through the individualized sessions, repeatedly emphasized the importance of adherence, data obtained from self-report may also be subject to social desirability bias (29). Self-reported adherence has often been shown to be an overestimate of true adherence when compared to a more objective marker of adherence such as plasma drug levels. In the FEM-PrEP trial (10) self-reported adherence was 95%, however only 26% of women had detectable drug levels at the beginning of the infection window. Similarly in the VOICE trial (11) the overall adherence by self-report was 90%, however drug levels were detected in only 25-30 % of participant samples depending on the study arm. Another objective marker of adherence is the applicator dye test used in the Carraguard trial (5, 30), where self-reported adherence was 96% compared to 41% based on the dye stain. Self-reported adherence also has other limitations, including inadequate recall, misunderstanding of questions and recall for the last sex act may not be representative of the sexual behavior throughout the month (29).

While returned applicators are a more direct, objective measure of gel use in the previous month, this method is still dependent on participant behavior (31) and does not account for sexual frequency, possible gel dumping or that participants could forget to return applicators. To overcome some of these limitations, data from self-report were combined with the objective applicator count data to obtain a more accurate applicator-based adherence measurement (primary adherence measure) for the preceding 30 days. While this combined measure may have its own limitations, effectiveness in preventing HIV infection was consistently higher among women considered to be high adherers.

Achieving good adherence requires more than access to accurate information; it is an interplay of several factors including contextualizing of information, motivation and behavior change skills (24). Adherence may be influenced by multiple factors, such as unpredictable patterns of coital activity and risk-taking behavior (9), disclosure of product use (32) and fatigue with clinical trial requirements combined with using a product of uncertain benefit (33). The motivational interviewing approach of the CAPRISA 004 ASP was a novel application for the microbicide field to identify, address and support a woman's decision making and allow her to anticipate situations that could lead to non-adherence.

There were several challenges in implementing the CAPRISA 004 ASP activities. Women recruited for the CAPRISA 004 trial came from diverse settings, including local family planning clinics and sexually transmitted infection clinics, which required nurses to be flexible and they had to tailor their interviewing techniques for each population accordingly. For example, the ability of women with multiple concurrent partners to negotiate safe sex may vary between casual and stable partners. In addition, ongoing staff motivation was identified as a challenge, despite the trial staff being well-trained. This problem was compounded as the size of the trial cohort and diversity of the women's needs grew.

Ongoing monitoring of the ASP was essential to its continual improvement and refinement. Further, it ensured quality, reinforced key messages and enhanced the women's acceptance of the ASP. The interviews were conducted in a supportive environment and ultimately led to customized goals to help each woman overcome her particular challenges.

Although the ASP was derived from a generalized theoretical framework with broad applicability, it was customized for CAPRISA 004 and would need to be modified and tailored to suit other clinical trials and populations. Additionally, the feasibility of applying an intensive behavioral intervention outside of a trial context is questionable. For example, the monthly booster sessions would require high staffing levels and it is not known whether women would be willing to attend monthly sessions for routine HIV prevention. On the other hand, adherence to a known effective product may offer its own incentives and less intensive activities may prove as effective under those conditions.

CONCLUSION

The success of any microbicide trial investigating a new drug rests largely on the individual's willingness and ability to use the investigational product as instructed. Our experiences with a structured, theory-based approach to enhancing gel use in a microbicide trial was encouraging and laid a good foundation for future microbicide trials seeking to attain high adherence. This method to enhance adherence may have utility for other HIV prevention interventions that require sustained product use.

Acknowledgments

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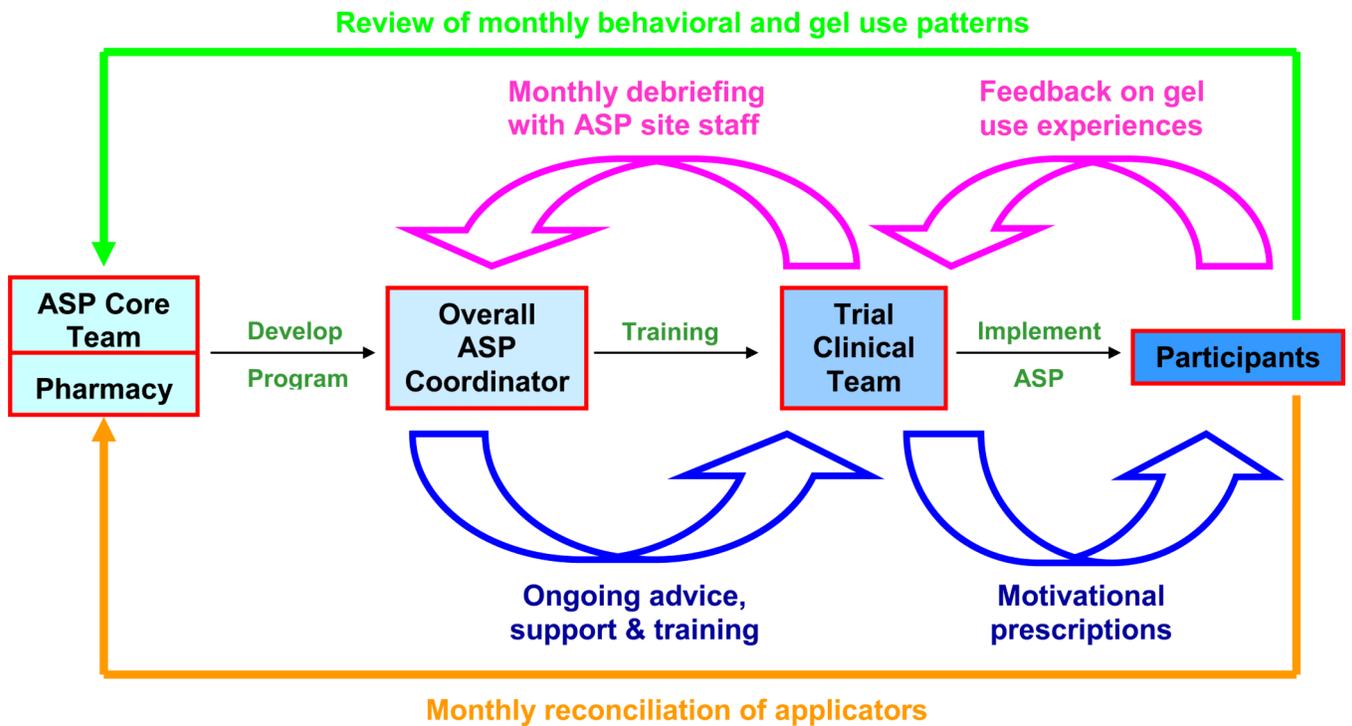


Figure 1. Inter-relationships created between the adherence support team, adherence support program coordinator, the clinical trial team and the study participants to monitor the delivery of the Adherence Support Program in the CAPRISA 004 trial

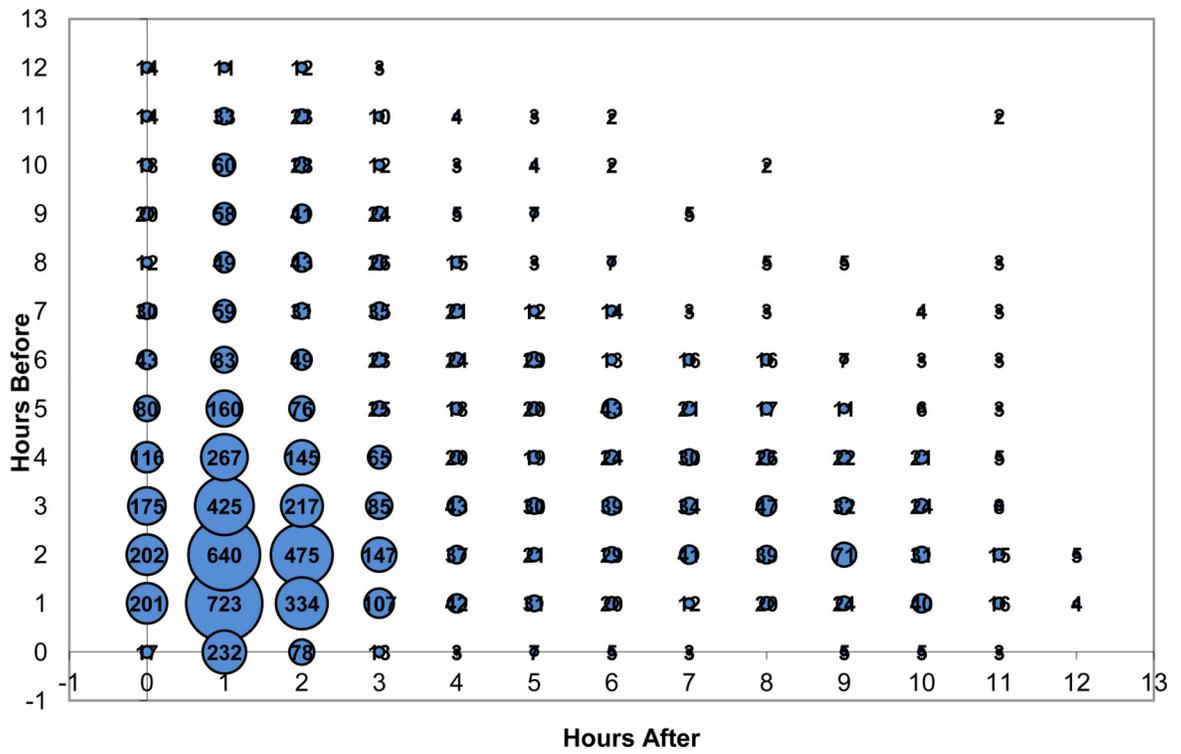


Figure 2.
Time of application of the before and after doses of study gel based on data collected at the last sex act before each month's study visit

Table 1

Tools used in the CAPRISA 004 adherence support program

ADHERENCE SUPPORT PROGRAM TOOLS	DESCRIPTION / APPLICATION
Sample applicators	Pre-filled and empty applicators used for demonstration purposes.
Sample of applicator box	Used for demonstration purposes.
Pelvic model	Assists the participant with learning about the female anatomy and to practice applicator insertion.
Flip charts	Contain information and pictures on the side facing the participant and notes for the nurse on the opposite side. It is available both in English and the local language (IsiZulu).
Clock face teaching aid*	A 24 hour clock face accompanied by nine picture disks depicting vignettes of daily life; used as an aid to map out the participants' day. Assists the participant in keeping track of the time of sex and gel insertion, supporting the incorporation of BAT24 into her daily life. A pocket size 24 hour clock face was also available to the participant for home use.
Patient information leaflet	Provides information on mechanics of gel use, as well as timing and dosing information with the clock face teaching aid.
Adherence support program checklist*	Assists in ensuring that all the appropriate information was given to the participant. Frequently asked questions or other concerns of the participant are also recorded here.
Zip-lock bags	Assists the participant with return of used applicators.
Diary	Used as a personal diary and may assist the participant record the time of sexual activity and gel use.
Flip file with tabs	Structured algorithms guide the nurse through the suitable support message, depending on the information obtained during the monthly behavioral assessment.
Adherence support program prescription**	Spells out steps, skills and/or messages to reinforce or support the necessary action to achieve the milestone for the month. Used by the participant as a summary or 'take home message' of the MI based discussion.

* Tools created specifically for the CAPRISA 004 trial

Table II

Summary of the content of the CAPRISA 004 Adherence Support Program (ASP) with reference to the 1MB Model.

INFORMATION	MOTIVATION	BEHAVIOURAL SKILLS	DESIRED BEHAVIOUR
<ul style="list-style-type: none"> • HIV/AIDS • Tenofovir and its mode of action • Microbicides • The female anatomy • Mechanics of gel use • Use of product in relation to coital activity • What to expect after inserting the gel • How to store the study gel 	<ul style="list-style-type: none"> ■ Participant's attitude: <ul style="list-style-type: none"> • Towards product use • Towards non-adherence & obstacles to adherence • Perception of HIV risk • Anticipated beliefs about benefits of product ■ Social support: <ul style="list-style-type: none"> • From study staff • From social network • Identifying need for disclosure of product use • Negotiation skills with partner ■ Assessing behavioral intention to adhere: <ul style="list-style-type: none"> • Through monthly measurement of product use ■ Perceived Vulnerability: <ul style="list-style-type: none"> • To adverse effects • To negative consequences of non-adherence • To positive outcomes of adherence ■ Availability of and/or access to suitable storage facilities 	<ul style="list-style-type: none"> ■ Ability to use product correctly: <ul style="list-style-type: none"> • Using the correct dose • Correct insertion of product • Keeping track of the time ■ Ecological Skills: <ul style="list-style-type: none"> • Incorporating regimen into social ecology of daily life • Proper storage of the product • Developing additional strategies for adherence in specific settings/situations, e.g. travel, parties, etc ■ Ability to seek out adherence support when needed ■ Self-reinforcement of adherence over time 	<ul style="list-style-type: none"> ■ Proper dosing ■ Proper insertion ■ Correct timing ■ Product stored adequately

HIV incidence and effectiveness of tenofovir gel in HIV prevention by adherence calculated for each of three different adherence measures in the CAPRISA 004 trial

Table III

Level of adherence	N (%)	HIV Incidence Rate (number of HIV endpoints)		IRR (95% CI)	Effectiveness	P-value
		Tenofovir	Placebo			
Returned used applicator adherence[†]						
High (>9 applicators)	158 (17.8)	8.1 (11)	17.9 (19)	0.46 (0.20; 1.01)	54%	0.04
Moderate (>5-9 applicators)	335 (37.7)	6.4 (16)	9.4 (25)	0.68 (0.34; 1.33)	32%	0.23
Low (0-5 applicators)	396 (44.5)	3.7 (11)	5.6 (16)	0.67 (0.28; 1.54)	33%	0.31
Self-reported adherence (last sex act)						
High (100%)	250 (28.1)	3.7 (7)	10.3 (18)	0.36 (0.13; 0.90)	64%	0.02
Moderate (80-100%)	374 (42.1)	4.5 (14)	6.1 (19)	0.73 (0.34; 1.53)	27%	0.37
Low (<80%)	265 (29.8)	9.6 (17)	13.0 (23)	0.74 (0.37; 1.44)	26%	0.34
Applicator based adherence [returned used applicators / (number of sex acts × 2)][#]						
High (>80%)	337 (38.0)	4.2 (11)	9.3 (25)	0.45 (0.20; 0.96)	55%	0.03
Moderate (50-80%)	180 (20.2)	6.3 (10)	10.2 (10)	0.61 (0.23; 1.64)	39%	0.28
Low (<50%)	367 (41.3)	6.2 (16)	8.6 (25)	0.72 (0.36; 1.41)	28%	0.31

IRR = incidence rate ratio; CI = confidence interval

[†] Adherence could not be calculated for one woman who did not return any applicators

[#] Adherence could not be calculated for the 5 women who reported no sex during their follow-up in the study

* The data on applicator based adherence that has been previously published (8), was based on a datalock on 09 April 2010. Here we provide an updated analysis based on the final dataset (datalock date 09 December 2011) where one participant, who was previously in the moderate category was re-categorized as a high adherer.