ORIGINAL PAPER

Adherence to Rectal Gel Use Among Mainly Ethnic Minority Young Men Who have Sex with Men During A 3-Month Placebo Gel Trial: Implications for Microbicide Research

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Abstract   To study adherence to product use prior to a Phase I microbicide trial, we recruited young men who have sex with men (YMSM) with a history of unprotected receptive anal intercourse (RAI) and provided them with 40 rectal applicators containing a placebo gel to use prior to RAI during a 12-week period. Ninety-five YMSM completed the trial. Based on a Computer Assisted Self Interview, 83 participants had receptive anal intercourse (RAI) (Median 12 occasions) using gel on 82.4 % of occasions (SD 26.7; 0–100). Based on an interactive voice response system, 88 participants had RAI (Median 10 occasions) using gel on 87.9 % of occasions (SD 20.0; 20–100). By applicator counts the median gel use was 12. Participants showed high adherence to gel use. Those who did not use the product consistently (n = 40) adduced not having it with them (85 %), forgetting to use it (48 %), not wanting to use it (13 %), partner refusal (10 %) and gel messiness (10 %).

Resumen   Para estudiar la adherencia al uso del producto antes de realizar un ensayo Fase I de un microbicida, reclutamos hombres jóvenes que tienen sexo con hombres con una historia de sexo anal receptivo sin protección y les proveímos 40 aplicadores rectales que contenían un gel placebo para usar antes del sexo anal receptivo durante un período de 12 semanas. Noventa y cinco hombres completaron el ensayo. Basado en un Auto-Entrevista Asistida por Computadora, 83 participantes tuvieron sexo anal receptivo (Media = 12 ocasiones), usando el gel en 82.4 % de las ocasiones (SD 26.7; 0-100). Basado en un sistema telefónico interactivo, 88 participantes tuvieron sexo anal receptivo (Media = 10 ocasiones) usando el gel en 87.9 % de las ocasiones (SD 20.0; 20-100). Por el recuento de aplicadores, la media del número de veces de uso del gel fue 12. Los participantes demostraron alta adherencia al uso del gel. Los que no usaron el producto consistentemente (n = 40) citaron no tenerlo con ellos (85 %), olvidarse de usarlo (48 %), no querer usarlo (13 %), rechazo de la pareja (10 %) y que el gel ensuciaba (10 %).

Keywords   Rectal microbicide · Adherence · Young men who have sex with men · HIV prevention

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Introduction

Three decades of condom promotion have failed to eliminate sexual transmission of HIV. Alternatives to condoms are badly needed for those who cannot or will not use them consistently. Topical microbicides, under development since the early 1990s [1], could be an HIV prevention alternative to condom use. Typically, microbicides have been formulated as gels, foams, tablets or films that are administered in the vaginal or rectal lumen [2]. A Phase IIb study testing the efficacy of tenofovir-gel as a vaginal microbicide demonstrated a 39 % reduction in HIV acquisition among women [3]. Unfortunately, a subsequent Phase IIb trial [4] failed to replicate the results, mainly due to a lack of adherence to product use [5]. Therefore, studying factors influencing adherence is very important for successful product use and implementation.

Rectal microbicide (RM) development has not advanced as rapidly as vaginal microbicide development. Thus far, only Phase I safety and acceptability trials of RM have been completed [6–8]. The first Phase II RM trial to assess expanded safety and acceptability of rectally-applied tenofovir reduced-glycerin 1 % gel [9] is currently underway, and a Phase III trial is still in the planning stage. Prior studies have noted that a gel had more favorable ratings than a suppository as a microbicide delivery vehicle [10] and that 35 mL is the maximum volume of a rectal gel that MSM would find acceptable for use prior to intercourse [11]. Although these acceptability estimates help inform RM trials, there is scant information on the use of RM or RM surrogates in real life circumstances.

Our study focused on young men who have sex with men (YMSM), especially on those of ethnic-minority background, a population with high HIV prevalence and incidence [12, 13]. We targeted the subgroup for which RM are being developed: individuals who reported inconsistent condom use for receptive anal intercourse (RAI), the sexual behavior most likely to lead to HIV infection [14]. The initial stage of our study had two main aims: firstly, to determine the prevalence of sexually transmitted infections (STIs) and anal and rectal pathologies that might facilitate HIV infection (Stage 1A) and secondly, to determine the acceptability of and adherence to a placebo gel delivered rectally prior to RAI (Stage 1B). In this report, we present the adherence results for Stage 1B (additional results will be presented in other manuscripts currently in preparation). Our research question was, "How likely are YMSM with a history of condomless RAI to consistently apply a gel intrarectally prior to RAI?"

Methods

Product

Given that currently there is no RM of known efficacy, for our study we used hydroxyethylcellulose-based gel (HEC) manufactured by DPT Laboratories, Ltd. HEC is also known as the "universal placebo" because of its use as placebo in most gel microbicide trials.

Procedures

Recruitment

The study took place at three sites: the University of Pittsburgh in Pittsburgh, PA; Fenway Health in Boston, MA; and the University of Puerto Rico in San Juan, PR. Study candidates were recruited between December 2010 and June 2012 from clinics, bars, clubs, and other locations (e.g., the house and ball scene, social events organized by LGBTQ communities). Advertisements were placed in newspapers and at community-based organizations, and volunteers from previous research studies who authorized future contacts were invited to call. Recruiters also used social media (Facebook, Twitter), advertisements in Craigslist (an online advertisement site), postings in chat and dating sites for MSM, and smartphone applications.

Recruitment materials indicated that the investigators were looking for YMSM (ages 18–30 years) willing to undergo a complete physical exam, including an anorectal exam, be tested for HIV, and answer questions about their medical and sexual history. The eligibility screening script explained that the purpose of the study was to learn about the sexual health of YMSM and their feelings about inserting rectally a placebo gel resembling a to-be-developed microbicide gel prior to receptive anal sex.

Stage 1A: Screening

Participants underwent pre-eligibility screening by phone or in person to determine age, same sex behavior, and presumed negative HIV status. Those who passed pre-screening were invited to the clinic for in-person screening (Visit 1). Eligibility criteria included being sexually active (operationalized as at least one RAI episode in the prior month) and engaging in some potential risk behavior. So as to cast a wide net for the epidemiological objective of Stage 1A (i.e., prevalence of STIs and anal and rectal pathologies that may facilitate HIV infection), risk behavior was operationalized as at least one episode of condomless RAI in the prior 12 months, although we are

aware that not all condomless RAI involves HIV risk. After informed consent procedures, participants answered a medical history and received a physical exam including a digital rectal exam and anoscopy. Specimens were collected to test for HIV (oral rapid HIV test with confirmatory blood test if positive) and STIs (human papillomavirus (HPV), *Chlamydia trachomatis*, *Neisseria gonorrhea* (rectal/urethral), syphilis, herpes simplex virus 1 and 2 antibody, and both hepatitis B surface antigen and hepatitis C antibody). In addition, participants completed a Web-based computer assisted self-interview (CASI) that included, among other topics, questions on demographics and sexual practices in the prior 3 months. HIV counseling and condoms were provided.

Stage 1B: 3-Month Trial

Participants returned to the clinic within 28 days (Visit 2) and were informed of test results. From those who received medical clearance (as determined by negative HIV and STI tests, no known allergies to latex, parabens, or medications, and no other medical conditions that would make study participation unsafe) and who stated they did not currently engage or plan to engage in condomless RAI with HIV-infected partners, we selected those fulfilling the more stringent eligibility criterion of having had condomless RAI within the prior 3 months. This allowed us to focus on those with more recent potential risk and invite them to enroll in Stage 1B. After undergoing a new informed consent process and update of medical history, a video teleconference was held to train them on the use of a phone-based Interactive Voice Response System (IVRS) to report product use at least weekly during the following 3 months. Next, participants received 20 single use rectal applicators, measuring 13 mm when plunger is fully depressed, pre-filled with 4 mL of HEC gel and instructions to insert the entire content of one applicator rectally within 90 min prior to each RAI episode. Participants were also asked to place the used applicators (without washing them) into individual plastic bags with a zip enclosure labeled "Used Applicators" and to return the used and unused applicators at the next study visit. No tests were used to verify applicator use.

Six weeks after Visit 2, participants returned for the Mid-trial Follow-up Visit (Visit 3) at which the medical history was reviewed and updated; any reported adverse event was further explored; a physical exam including digital rectal exam and anoscopy was performed; samples were collected for STI and HIV testing if clinically indicated; used and unused applicators were collected, counted and recorded; and 20 new rectal applicators containing HEC were dispensed. HIV counseling and condoms were provided.

Six weeks after Visit 3, participants returned for the Final Follow-up Visit of Stage 1B (Visit 4). All procedures of Visit 3 were repeated but no rectal applicators were dispensed at this time. Additionally, participants completed a new Web-based CASI that included questions on adherence to product use.

Instruments

Demographics

Demographic information included age, education (1 = less than 8th grade, 2 = partial high school, 3 = high school graduate/or graduate equivalent as certified by General Education Development exams (GED), 4 = partial college, 5 = college graduate, 6 = partial graduate school, 7 = graduate school degree), annual income, work/student status (full or part time), race (White, Latino, African American mixed or other), and sexual identity ("Do you consider yourself… gay/homosexual, bisexual, straight/heterosexual, other").

Sexual Behavior and Gel Use

The sexual behavior assessment used at baseline was a modified version of the Sexual Practices Assessment Schedule [15] that was administered by Web-CASI. It covered the prior 3 months and included questions about number of male and female partners, type of partner (lover, one-night-stand, other), lubricant use, and number of sexual occasions for different acts. At the end of the 3-month trial, another CASI was administered with questions about sexual behavior during the prior 3 months, including number of occasions of RAI, condomless RAI, gel use prior to RAI, and reasons for lack of product use.

During the 3 months of the trial, sexual behavior was also assessed through IVRS: Participants were provided a toll-free phone number and an individual participant ID. They were asked to call every time they inserted the study gel and/or had RAI or, in the absence of either for 7 consecutive days, to call at least weekly to report that no gel use or RAI occurred. The system asked, among other things, number of RAI occasions since the prior call and number of occasions in which the gel was used. Participants could leave a recorded message explaining the reasons for not using the gel. Responses were entered by pressing keys or by speech. The system recorded date and time of call. Participants who did not call in 6 days received an automated follow-up call that prompted them to answer the questionnaire. If no response was received within 24 h, study coordinators were alerted via email to contact the participant to inquire about missed calls and adherence to the study product regimen.

Adherence to product use was also measured through the aggregate count of used and unused applicators returned to the clinic at Visits 3 and 4. If fewer than the 40 dispensed applicators were returned, this was noted, and participants were asked to report reasons for lack of return and whether the missing applicators had been used or not. However, only the returned applicator count was used for our primary adherence analysis.

Compensation

Participants in Stage 1 B received $50 for each of the three study visits. Additionally, to encourage use of the IVRS, participants received $1 for each call (up to one call per day) up to a maximum of $30 during the 12-week period regardless of their report of product use or lack of use; plus a $10 bonus at the end of each month if they called at least once per week. They also received $50 for completing a video teleconference interview and $1 per applicator returned at visits 2 and 3. The maximum a participant could make by completing all procedures was $300.

Data Analysis

Descriptive demographic data were calculated and the 3 study sites were compared using ANOVAs for continuous and Chi square tests for dichotomous variables. Baseline and 12-week follow-up sexual behaviors were compared using paired t tests for continuous variables (after log-transformation due to skewed distributions) and McNemar tests for dichotomous variables. Intraclass correlations were calculated to compare self-reported product use to actual returned and used applicators. We also examined whether sexual behavior outcomes reported in the IVRS data were congruent with follow-up CASI measurements, and we compared study drop-outs to those who completed each study stage to understand whether participants in these two groups differed on their demographic and sexual risk variables. We used t tests for continuous and Chi square tests for categorical variables for the above comparisons.

Results

Demographics and Retention

Two hundred twenty-eight MSM completed Stage 1A. The initial 124 who both fulfilled eligibility criteria for Stage 1B and were available for a 3-month trial were enrolled in Stage 1B. We compared those not enrolled in Stage 1B (N = 104) to those enrolled (N = 124) on demographics (age, education, income, race/ethnicity, employment status,

student status, sexual identity) and sexual behavior variables (number of male sex partners, frequency of condomless receptive anal sex, and frequency of condomless insertive anal sex), and found only one significant difference: those who enrolled in 1B had more education (M = 4.39, SD = 1.15) than those who did not (M = 4.11, SD = 0.98; t = −1.98, df = 226, p = .049). However, both scores correspond to having completed a partial college education on our 7-point scale. In sum, participants in the Stage 1B sample were very similar those in the larger original sample.

Of the 124 YMSM enrolled in Stage 1B (Boston N = 38, Pittsburgh N = 38, San Juan N = 48), one participant seroconverted before his last scheduled visit for Stage 1B, and 28 (23 %) did not complete the trial, either because they withdrew from the study or were lost to follow-up. Attrition was 32 % in Boston, 26 % in Pittsburgh, and 15 % in San Juan. Reasons for participant withdrawal included moving to another state, family problems, lack of time for study participation, or other reasons; others were lost to follow up despite repeated attempts to contact them. As before, we compared the 95 HIV-negative participants who completed 1B to the 29 participants who did not on demographics and sexual risk behavior. The only significant difference found was that those who completed 1B had more education (M = 4.55, SD = 1.13) than those who did not (M = 3.86, SD = 1.06; t = −2.90, df = 122, p = .004).

Table 1 presents the demographic characteristics of 95 participants who completed Stage 1B. On average, they were in their early 20s; had completed some college education; and were working, studying, or both. Most were racial/ethnic minorities and identified as gay. Not shown in Table 1: 41 out of 46 Latino-identified men in the study were recruited in San Juan, and these participants had lower average income than those in the other two sites (mean = $9,223, SD = 14,455, vs. $15,229, SD = 14,834 for Pittsburgh and $23,250, SD = 16,846 for Boston; F = 5.25, df = 2, p = .007). No African American participants identified as bisexual. Those identifying as bisexual were 46 % White, 46 % Latino, and 8 % "other ethnicity".

Sexual Behavior and Gel Use

CASI

According to eligibility criteria for Stage 1B, all participants had engaged in condomless RAI at least once; 69 % of participants believed their partner(s) to be HIV-negative. Table 2 shows the participants' reported sexual behavior with males in the 3 months prior to study enrollment and for the 3 months of the trial. The comparison between the

Table 1 Demographic characteristics of the STAGE 1B sample (N = 95)

	Mean	(SD)	Range
Demographics			
Age	23.2	(3.2)	18–30
Education[a]	4.6	(1.1)	2–7
Annual income	$15,260	(16,163)	$0–68,000

	N	(%)
Currently working full- or part-time[b]	60	(63)
Currently in school full- or part-time[b]	47	(50)
Race/ethnicity		
White/European American	34	(36)
Latino/Hispanic	46	(48)
Black/African American	9	(10)
Mixed/other	6	(6)
Sexual identity self-label		
Gay/homosexual	81	(86)
Bisexual	13	(14)

[a] Measured on a 7-point scale (4 = partial college)

[b] 23 participants were both working and in school

two time periods shows no significant changes in frequency of receptive anal sex or type of partner. Yet, men reported having fewer sexual partners and fewer occasions of condomless RAI during the trial. Table 2 also shows that, at baseline, 56 % of participants reported always using a lubricant for RAI, 40 % reported sometimes using one, and only 4 % reported never using a lubricant for RAI.

Of the 95 men who used CASI to report their behavior at follow up, 9 refused to answer the question regarding RAI and 3 reported no RAI. The remaining 83 men reported a median of 12 RAI occasions (range = 1–70), a median of 12 occasions of gel use (range = 0–40), and using the gel on 82.4 % of occasions (SD = 26.7; range = 0–100); 70 % of men typically applied gel immediately before RAI. Forty-six YMSM reported using the product in 100 % of the RAI occasions whereas 37 had RAI but did not use the gel consistently. Eight men reported having greater than 40 occasions of RAI; three of them used the product 40 times and were considered 100 % adherent; the remaining five used the product <40 times, so their adherence was calculated as number of product uses divided by number of occasions of RAI. The main reasons the product was not used among those who reported not using it every time they had receptive anal sex included: not having gel with them (85 %); forgetting to use it (48 %); partner refusal (10 %); gel messiness (10 %); and not liking the feeling of the gel internally (5 %). There were no reports of lack of use due to product leaking out (a common complaint among users of vaginal microbicides), bleeding, or burning or itching sensations.

Table 2 Sexual behavior with males during prior 3 months as reported by CASI (N = 95)

	Baseline Median; range	Follow up Median; range	t (df)	p
Number of male partners[a]	3; 1–70	2; 0–40	3.82 (92)	<.001
Frequency of receptive anal sex[a]	7; 1–95	12; 0–70	−1.90 (85)	ns
Frequency of unprotected receptive anal sex occasions[a]	3; 1–95	2; 0–60	2.96 (92)	.004

	N (%)	N (%)	χ^2	p[b]
Had a lover (emotionally involved in a committed relationship)	75 (79)[c]	64 (70)[d]	1.63	ns
Had a one-night stand	51 (54)	42 (46)	1.63	ns
Had other male partner (neither lover nor one-night stand)	54 (57)	44 (48)	2.07	ns
Had URAI[e] with partner of serodiscordant or unknown status	29 (31)	NA		
Used a commercial sexual lubricant during RAI[e]				
Never	4 (4)	NA		
Sometimes	38 (40)			
Always	53 (56)			

Some variables have missing data; percentages are of those with non-missing data

[a] Variables log-transformed prior to t tests due to skewed distributions

[b] McNemar test

[c] At baseline, 25 men reported having only a lover

[d] At follow up, 31 men reported having only a lover

[e] (U)RAI = (unprotected) receptive anal intercourse

IVRS

Of the 95 participants who completed the trial, 94 provided information about their sexual behavior and product use through IVRS. The one participant who did not provide information later reported not having sex during the 3-month period and not wanting to call "just to confirm my lack of ass." Eighty-eight participants had RAI (Median 10 occasions) using gel on 87.9 % of occasions (SD 20.0, range 20–100).

Applicator Counts

The 95 participants who completed the 3-month trial received 40 applicators each. Sixty-nine participants (73 %) returned all 40 applicators, and 24 (25 %) made only partial returns, ranging from 19 to 39 applicators (mean = 29.54, SD = 9.36). Two participants (2 %) did not return any applicators. Based on returned applicator counts, there was a median of 12 used applicators returned. If any applicators were not returned, participants were asked how many unreturned applicators were used versus unused. Approximately 2/3 of the unreturned applicators were reported as unused. The most frequent reason for lack of applicator return was forgetting to do so. In four cases, the applicators were discarded (by participant, grandmother, and Transportation Security Authority personnel). Only one participant and the partner of another participant expressed reservations about having to return used applicators.

Comparison Among Different Adherence Measurements

Overall, there was convergence among the different measures of product use. Estimates obtained retrospectively at 12-week CASI follow-up approximate those based on returned applicator counts. Seventy-nine men reporting on applicator use in CASI also returned applicators at both time points. Among those, 28 % of participants in CASI self-reported *more* gel use and 47 % self-reported *less* gel use than indicated by their returned applicator count. The intraclass correlation for those with all three measures of product use (CASI, IVRS, and used applicator counts) was .74. Of the 78 participants with data for all three measures, 4 reported exactly the same number of applicators used, 35 reported a discrepancy of between 1 and 5 applicators, and 16 reported a discrepancy of between 6 and 10 applicators, and 23 reported a discrepancy of between 11 and 37 applicators (see Fig. 1).
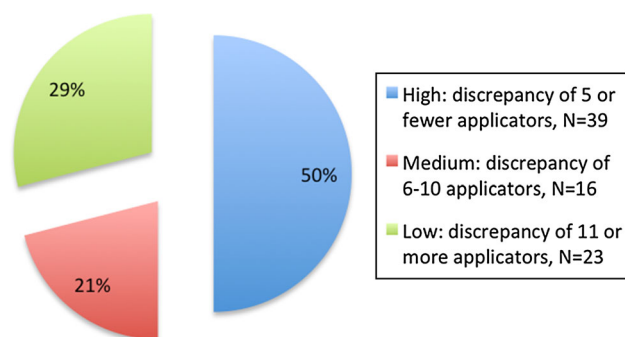

Fig. 1 Concordance of gel use measures

Legend:
- High: discrepancy of 5 or fewer applicators, N=39 (50%)
- Medium: discrepancy of 6-10 applicators, N=16 (21%)
- Low: discrepancy of 11 or more applicators, N=23 (29%)

Discussion

YMSM with a history of inconsistent condom use during RAI had the chance to use in real-life circumstances a gel resembling a future rectal microbicide delivered with a rectal applicator. The results show that, overall, participants completing the 3-month trial used the gel prior to RAI in 82 % of rectal occasions and that about half of the sample reported using the product on 100 % of RAI occasions.

These results are encouraging. Although self-reports may be subject to social desirability and produce inflated results, we observed convergence among results obtained with different methods. Among those who had multiple data sources, the concordance of different measures increases the credibility of the results. This is short of a desirable objective measure of adherence that could provide irrefutable proof of product use during the full length of the trial. However, given that such a gold standard does not exist and that even biomarkers (e.g., pharmacokinetic assays) have limitations, a combination of several indicators of adherence is our best choice for now. In future studies, adherence levels obtained from different measures could be discussed with participants themselves to gain further insights into reasons for potential discrepancies. This technique was implemented before [16] and will be used in an upcoming Phase II rectal microbicide study [17].

Our study population had been carefully selected to include individuals whose inconsistent condom use potentially exposed them to HIV. About a third of them acknowledged having had condomless RAI with a serodiscordant or unknown-status partner in the 3 months prior to enrollment, and this figure is likely to be an underestimate considering that most people tend to rationalize that what they do is not risky (e.g., assuming their partner is uninfected) [18]. Therefore, our participants were a sample of the intended users of rectal microbicides.

The report that these participants used a microbicide-like gel in four out of five RAI occasions is heartening, especially considering that they knew it was a placebo that offered no HIV protection. Interestingly, similar proportions of men who at baseline reported using lubricants always (56 %) and sometimes (40 %) also reported using the placebo gel always (55 %) and sometimes (44 %) during the trial. This may be expected, given that the gel did not include a microbicide. The fact that we did not observe a decrease in the proportions using gel is encouraging, since the procedure for applying the placebo gel is more involved than application of lubricants with the fingers in the context of sex. This result also points out the need to increase promotion and marketability of microbicides so as to increase the proportion of MSM who will use them at every RAI encounter.

In occasions when the gel was not used, the main reason by far was not having it available when needed. This may have been in part because the size of the applicator made it impractical to carry around. Improvements in product portability may significantly contribute to increased microbicide use. Product delivery without the need for an applicator would be desirable and needs to be further researched by teams that include manufacturers, social/behavioral scientists, and marketing experts.

The second most frequently cited reason for lack of product use was forgetfulness. In some cases individuals forgot to take the product with them when they were to have RAI outside their home; in others, they forgot to use it despite having the product available. Facilitating the development of routines around sexual behavior may help to counteract forgetfulness. Furthermore, improving motivation to use the product and partner negotiation skills may also aid adherence.

Interestingly, there were no complaints of gel leakage among our study participants. Leakage has been a consistent problem of vaginal microbicides [19]. It is likely that the anal sphincter tone makes retention of 4 mL of gel in the rectum more effective than vaginal retention.

The decrease in number of male partners and frequency of URAI occasions between baseline and follow up may be in part an artifact of the detailed baseline assessment that may have heightened awareness of risk behavior among participants. Although this was not a safer sex intervention, participants were exposed to information that may have also influenced their behavior.

Limitations of the Study

There are several factors that limit the generalizability of these study results. Participants were not randomly selected and are not necessarily representative of YMSM in the cities where the research was conducted. Participants were based in the continental USA and Puerto Rico, and therefore findings may not apply to YMSM in other countries, in particular resource-poor settings where there is high HIV incidence among YMSM (currently, a Phase II rectal microbicide trials is taking place Perú, South Africa and Thailand, in addition to the US) [17]. Also, age of the participants may make results not generalizable to older populations. Participants who volunteered for a rectal microbicide study may be particularly interested in this kind of product. By eligibility criteria, all participants acknowledged having URAI in the prior 3 months, and although condomless RAI is not per se a risk behavior unless partners are serodiscordant, lack of consistent condom use may have heightened participants' risk perception and willingness to try out and adhere to rectal microbicide use. We relied on participants' classification of applicators as used; although some investigators have used dye stain or ultraviolet light assays [20–23] to determine if returned applicators had been used, these methods are still in experimental phases and were not employed in our study. Finally, use of a gel with an active microbicide component may have resulted in different levels of adherence.

Within these limitations, our study makes an important contribution to the field. It provides evidence that those most at risk of HIV infection may use a microbicide-like gel prior to RAI with sufficient frequency that an efficacious microbicide may have an impact in controlling the HIV epidemic.

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