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Disclosure of Microbicide Gel Use to Sexual Partners: Influence on Adherence in the CAPRISA 004 Trial

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Abstract

Young women in sub-Saharan Africa are disproportionately affected by HIV, making the development of women initiated and controlled methods of prevention, including microbicides, a priority. Adherence is pivotal to microbicide efficacy and partner related factors are known to impact adherence. An analysis of disclosure of gel use to sexual partners and adherence in CAPRISA 004 women was conducted to better understand this relationship. Partner disclosure was significantly associated with a modest 4.2 % increased adherence (71.0 vs. 66.8 %, $p = 0.03$). Most women rated the experience of disclosure as positive, despite 6.7 % of partners expressing a negative reaction. Participants who disclosed were more likely to reside with their regular partner (14.4 vs. 8.4 %; $p = 0.01$) and reported consistent condom use at baseline (32.9 vs. 20.9 %; $p < 0.01$). Partner disclosure needs to be better understood as a potential facilitator or barrier to microbicide adherence.

Keywords

Adherence; Partner disclosure; HIV prevention; Microbicides; Pre-exposure prophylaxis

Introduction

Young women between the ages of 15 and 24 years in sub-Saharan Africa bear a disproportionately high prevalence of HIV compared to their male counterparts [1]. The development of HIV prevention technologies designed for, and initiated by, women remains a priority [2], particularly for women at high risk of HIV acquisition who are unable to negotiate other safe sex practices with their sexual partners. Tenofovir gel, a microbicide, is one such women-initiated technology. Protocol 004 at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) assessed the efficacy of tenofovir gel applied vaginally in a coitally-related dosing regimen and found a 39 % reduction in HIV incidence in women assigned to tenofovir gel [3]. The trial also demonstrated a clear relationship between adherence and gel efficacy: low adherers (gel use \50 % of sex acts) had 28 % efficacy, intermediate adherers (gel use 50–80 % of sex acts) had 39 % efficacy and high adherers (gel use [80 % of sex acts) had 54 % efficacy [3]. Further, the effectiveness of the gel increased to 74 % in women with protective drug levels [4], highlighting the importance of adherence for microbicide effectiveness. The reasons for suboptimal adherence in microbicidetrials are not fully understood [5]. The increasing efficacy of an intervention as adherence increases demonstrates the importance of understanding the conditions and factors that impact upon a woman's ability to adhere to the prescribed dosing regimen. A better understanding of the behavioural and social determinants that enhance adherence is needed to develop interventions to improve adherence and thereby enhance the probability

of demonstrating efficacy [5]. Microbicide research has focused on factors influencing adherence, such as preferred dosage forms and regimens, stigma and male perception of microbicide use [5]. A keysocial determinant of adherence identified among women, is the inter-personal dynamic with their sexual partners, which critically shapes the women's ability to use microbicides correctly and consistently [6–10].

While the FemPreP trial [6] identified women's perception of their risk of HIV acquisition as a key factor impacting adherence, other predictors of poor adherence have been difficult to identify. During adherence counseling sessions, women who had not disclosed their participation in the CAPRISA 004 trial raised the issue that gel use prior to sex may lead to their partners inadvertently discovering their gel use [3]. The purpose of this study was to identify the role, if any, of male partner disclosure in influencing gel adherence in women participating in the CAPRISA 004 trial.

Methods

CAPRISA 004 was a double-blind, randomized, placebo-controlled trial, conducted from May 2007 to March 2010, at an urban and rural clinic in Kwazulu-Natal, South Africa. The purpose of the trial was to assess the effectiveness of tenofovir gel in preventing HIV and other sexually transmitted infections [3]. HIV uninfected, sexually active, non-pregnant women (n = 889) were recruited from clients utilizing primary health care clinics for family planning or sexually transmitted infection (STI) services [7, 8], or through community outreach. A coitally-linked dosing strategy also referred to as BAT24 (first dose of gel inserted up to 12 h before sex and the second as soon as possible after sex, but within 12 h; with no more than two does in 24 h) was prescribed [3].

A structured, standardized set of questions, addressing disclosure of study participation and gel use to the last sexual partner, was administered to women in the CAPRISA 004 trial at their study exit visit. In October 2009, approximately half-way during the trial, the questionnaire was amended to include additional questions on disclosure of gel use to the last sexual partner, experience of disclosure, reactions of the sexual partner to gel use and sexual partner reaction to disclosure.

The questionnaire was administered by trained study nurses and counselors. Training included interviewing techniques such as being non-judgmental verbally or through body language. The questionnaire was administered at the study exit visit in order to reduce socially desirable responses. Study exit visits for women who acquired HIV during follow-up was scheduled at least 90 days post-seroconversion, and for HIV uninfected participants, at the study close-out visit or at the last study visit for participants who were being terminated either voluntarily or for study related reasons.

Disclosure of study participation and gel use to sexual partners or anyone else, was not a study requirement but for those women who chose to disclose gel use, additional support was available from study staff.

Adherence was measured as previously described [3], with the primary adherence measure being defined as the proportion of sex acts covered by two returned empty applicators based

on the pre- and post-coital dosing regimen. The median of each woman's monthly adherence estimates was assigned as her overall gel adherence, assuming that every reported sex act used two doses of gel. Data were analysed using SAS® (SAS Institute Inc., Cary, NC, USA) Version 9.3. Data using the shorter first (pre-October 2009) version and the longer second (post-October 2009) version of the questionnaire were combined for this analysis. Duration of time on study was calculated from randomisation to estimated date of HIV infection, date of withdrawal or study close-out, whichever occurred first. Categorical data were analysed using Fisher's exact test. Normally distributed continuous data were analysed using Student's *t* test and continuous data that were not normally distributed were analysed using Wilcoxon's rank sums test.

Written informed consent was obtained and regulatory oversight was provided by the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC), the South African Medicines Control Council and FHI 360 Protection for Human Subjects Committee.

Results

A total of 846 (95 %) of the 889 women enrolled in CAPRISA 004 were included in this study. Of the 43 not included, three women did not complete the question on gel disclosure and 40 did not complete the questionnaire for various reasons including, but not limited to loss to follow-up, participant refusal or study staff omission. Of the 846 women included in the analysis, three did not have data on adherence. In total, 93 out of 846 (11.0 %) women completed the shorter first version of the questionnaire and 753 out of 846 (89.0 %) women completed the longer second version of the questionnaire.

A total of 569 (67.3 %) of the women who completed the study questionnaire reported that they had disclosed gel use to their last sexual partner. Women who disclosed gel use to their sexual partners were similar in age, marital status and monthly income when compared to the women who did not disclose gel use to their sexual partners (Table 1). Women who disclosed gel use to sexual partners were more likely to be residing with their regular partner (14.4 vs. 8.4 %; $p = 0.01$) and were more likely to report consistent condom use during sexual intercourse (32.9 vs. 20.9 %; $p < 0.01$) than women who did not disclose gel use to their sexual partners.

Gel adherence was moderately higher in women who had disclosed gel use to sexual partners (71.0 %) than in women who had not disclosed gel use (66.8 %) (RD 4.0 %, CI 0.37–7.85, $p = 0.03$). Adjusting for age, study site, treatment arm, condom use and living with a regular partner did not alter this association materially.

Among the 569 women who disclosed gel use, the HIV incidence rate was 6.4 per 100 women-years compared to 9.3 per 100 women-years in the 277 women (IRR = 0.69; $p = 0.08$) who did not disclose gel use (Table 2). Among the women who disclosed gel use to their sexual partners, their risk of HIV infection in the tenofovir gel arm was 33 % lower, while in women who did not disclose their gel use to the sexual partners, their HIV risk was 44 % lower in the tenofovir gel arm compared to the placebo gel arm (Table 3). Of the 514

women who reported on their sexual partner's reaction to gel use, 160 (28.1 %) said that their sexual partners liked the gel; 262 (46.1 %) reported that their sexual partner had no reaction to the gel; 100 (17.6 %) reported that they did not know what their sexual partner's reaction was, and 38 (6.7 %) reported that their sexual partners did not like the gel (Table 2). Reported condom use at the last sex act, assessed monthly during the study, was not associated with partner perception of gel use ($p = 0.16$).

Of the 515 women who disclosed gel use to their sexual partners, 296 (57.5 %) found talking to their partner about the gel easy, 152 (29.5 %) found this conversation with their partner difficult and 67 (13.0 %) women found the discussion about gel use neither difficult nor easy. Overall, 342 (66.4 %) women rated disclosure of gel use to their partner as a positive experience.

Discussion

We found a significant but modest relationship between disclosure and adherence. The association between partner disclosure and higher adherence is supported by prior research which found that disclosure to sexual partners of study product use was associated with more consistent self-reported adherence [9–13]. The unreliability of self-report of product use has been well described [6, 14]. With antiretroviral based microbicides the ability to measure drug levels has enabled the quantification of the extent of over-reporting of product use [6, 14, 15].

Even though partner disclosure was significantly associated with adherence, disclosure was not related to efficacy of 1 % tenofovir gel. This suggests that other contextual and partner-related factors are influential in the relationship between adherence and efficacy. provide valuable clues as to the utility of facilitating such disclosure, in future microbicide research or roll-out programmes. In this analysis the risk attributable to disclosure was 3.3 %, which was not statistically significant, but in terms of informing a decision to include disclosure as an adherence strategy in the rollout of the gel, this may remain important. Of note, the group that did not disclose gel use to sexual partners, are likely to be less able to negotiate condom use and probably have less stability in their relationships. Though the protective effect of disclosure on incident HIV infection is not significant, it is important to note that the gel appears to offer more protection to non-disclosing women, who may also be at increased risk of HIV due to difficulties in negotiating safer sexual practices and lack of stability in their sexual relationships. This speaks to the efficacy of the 1 % tenofovir gel. Women in CAPRISA 004 were more likely to disclose product use if they were living with a regular partner, and if they reported consistent condom use at baseline; this suggests that existing established supportive relationship dynamics facilitated both disclosure and adherence. It may be more difficult to promote disclosure in settings where the partner is not a long-term regular partner or where the women are not co-habiting with their regular male partners.

The CAPRISA 004 trial was designed with a coitally-linked dosing regimen (BAT24), after consultation with the specific study communities indicated that this strategy would yield the greatest adherence [3]. This was coupled with an extensive adherence support program in that same community to support women through problems encountered during actual use

[3]. Despite this adherence program and high gel acceptability, about 40 % of the women in this study had below 50 % gel adherence [3], [9–13]. In the CAPRISA 004 trial, women's overall adherence to the dosing regimen, was not affected by partners' lack of provide valuable clues as to the utility of facilitating such disclosure, in future microbicide research or roll-out programmes. In this analysis the risk attributable to disclosure was 3.3 %, which was not statistically significant, but in terms of informing a decision to include disclosure as an adherence strategy in the rollout of the gel, this may remain important. Of note, the group that did not disclose gel use to sexual partners, are likely to be less able to negotiate condom use and probably have less stability in their relationships. Though the protective effect of disclosure on incident HIV infection is not significant, it is important to note that the gel appears to offer more protection to non-disclosing women, who may also be at increased risk of HIV due to difficulties in negotiating safer sexual practices and lack of stability in their sexual relationships. This speaks to the efficacy of the 1 % tenofovir gel.

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Condom use throughout CAPRISA 004 was shown to be similar between the active and placebo arms [3]. In this analysis there was a significant difference at baseline in condom use between women who disclosed gel use and those who did not, with the former group reporting consistently higher condom use both before and during the study. During follow-up women who disclosed were also more likely to report condom use at last sex act (84.0 %) and consistent condom use in the last 4 weeks (43.5 %) prior to study exit, but both were not statistically significant. However, both the established and continued stable relationship dynamic at baseline and during study conduct, and the unreliability of self-reported condom use due to social desirability and deliberate misreport may also be responsible for this effect [16].

Potential limitations of this analysis include its exploratory nature and the limited generalizability due to the small sample size and that the study was conducted only in two sites in Kwazulu-Natal. Furthermore, the impact of the change in the adherence support program on disclosure cannot be assessed as disclosure was only assessed at study exit [3].

Disclosure to the last sexual partner at study exit also does not take into account partner changes and disclosure to all partners during the conduct of the study, neither is the timing of disclosure known. Information on permission from the women's male partners to join the study was not collected and cannot be evaluated as a factor facilitating both disclosure and adherence. Several variables, including condom usage, relied on participant self-report collected through interviewer-administered questionnaires, and are thus subject to recall and social desirability bias [3]. Male perception was only explored from the aspect of the women participants' self-report and other studies have shown that women may report male perception according to their own beliefs of what their partners' response might be [17]. Social harms information was not collected in sufficient detail to determine relatedness to disclosure of gel use separately from that of study participation, which would be of great interest in gauging the severity of negative male responses to disclosure. Strengths include the comprehensive adherence support measures offered at every visit, the neutral supportive stance of the staff irrespective of the woman's decision on whether to disclose or not, encouragement of reporting of social harms and referral for the same if required, and the collection of disclosure data at study exit to counteract socially desirable responses in reaction to the adherence program.

Conclusion

Partner disclosure was significantly associated with a modest improvement in adherence and should be considered for inclusion when designing adherence programs in microbicide research. Adherence is probably impacted by many other enhancing/facilitating contextual factors which need further elucidation through research.

Acknowledgments

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Table 1

Baseline demographic and sexual behavioral characteristics stratified by disclosure of gel use to sexual partner

	Disclosure of gel use (*n* = 569)	**Non-disclosure of geluse (*n* = 277)**	***p* value**
Sociodemographic characteristics			
Mean age in years (range)	23.9 (18–40)	23.6 (18–39)	0.38
Proportion of women who are rural (*n)*	68.7 % (391)	68.6 % (190)	1.00
Proportion with monthly income[R1000(n)	92.3 % (525)	91.0 % (252)	0.51
Proportion married (*n*)	5.8 % (33)	5.1 % (14)	0.75
Proportion with a stable partner (*n*)	92.4 % (526)	92.8 % (257)	1.00
Proportion living with a stable partner (*n*)	14.4 % (81)	8.4 % (257)	0.01
Sexual behavioral characteristics			
Mean age of sexual debut (SD)	17.3 (2.04)	17.5 (2.04)	0.20
Number of lifetime sexual partners % (*n*)			
1	33.9 % (193)	32.5 % (90)	0.58
2	26.7 % (152)	31.0 % (86)	
3–6	35.3 % (201)	32.1 % (89)	
7 or more	4.0 % (23)	4.3 % (12)	
New partner in past 30 days (*n*)	0.5 % (5)	2.2 % (6)	0.07
Median number of reported sex acts in last 7 days (IQR)	1 (0–3)	2 (0–3)	0.93
Mean number of sex acts per month (SD)	6 (4–10)	6 (4–12)	0.27
Condom use during last sex act (*n*)	58.1 % (331)	60.0 % (165)	0.65
Always use a condom during sex (*n*)	32.9 % (187)	20.9 % (58)	\0.01

SD standard deviation, *IQR* interquartile range

Table 2

HIV incidence rates in women who disclosed gel use to the sexual partners in the CAPRISA 004 trial

	Women who disclosed gel use	Women who did not disclose gel use	*p* value
Number of women	569	277	
Number of HIV infections	57	37	
Incidence rate	6.4 (4.8–8.3)	9.3 (6.5–12.8)	
IRR	0.69 (0.5–1.0)		0.08

	Women who disclosed gel use			Women who did not disclose		
	Tenofovir	Placebo	*p* value	Tenofovir	Placebo	*p* value
Number of women	305	264		114	163	
Number of HIV infections	25	32		11	26	
Incidence rate	5.2 (3.4–7.7)	7.8 (5.3–11.0)		6.43 (3.2–11.5)	11.48 (7.5–16.8)	
IRR	0.67 (0.4–1.2)		0.10	0.56 (0.25–1.17)		0.12

IRR incidence rate ratio

Table 3

Sexual partner's opinion of study gel and its effect on the women's gel adherence in the CAPRISA 004 trial

What did your partner think of the study gel?	n	Adherence	
		Median	IQR
He liked it	28.1 (160)	56.9	50.0–100.0
He did not like it	6.7 (38)	63.5	50.0–100.0
He had no reaction to it	46.1 (262)	66.7	50.0–100.0
I don't know	17.6 (100)	73.9	50.0–100.0
Other	1.1 (6)	67.0	52.3–97.2
Missing	0.5 (3)	100.0	46.7–100.0