Preference for gel over suppository as delivery vehicle for a rectal microbicide: results of a randomised, crossover acceptability trial among men who have sex with men

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ABSTRACT

Objective: To assess whether men who have sex with men (MSM) prefer a gel or a suppository as a delivery vehicle for a rectal microbicide.

Methods: 77 HIV-negative MSM with a recent history of inconsistent condom use during receptive anal intercourse (RAI) who acknowledged being at risk of contracting HIV were enrolled in a randomised, crossover acceptability trial. They compared 35 ml placebo gel with 8 g placebo rectal suppositories used on up to three RAI occasions each.

Results: Participants preferred the gel over the suppository (75% versus 25%, $p<0.001$) and so did their partners (71% versus 29%, $p<0.001$). The gel received more favourable ratings overall and on attributes such as colour, smell, consistency, feeling in rectum immediately after insertion and/or 30 minutes after insertion and application process. The gel resulted in less negative ratings in terms of participants being bothered by leakage, soiling, bloating, gassiness, stomach cramps, urge to have bowel movement, diarrhoea, pain or trauma. Participants liked the gel more in terms of feelings during anal sex, sexual satisfaction, partners' sexual satisfaction and liking the product when condoms were used and when condoms were not used.

Conclusions: In this sample taken from one of the populations most likely to benefit from rectal microbicide availability, gel had greater acceptability than a suppository as a potential microbicide vehicle.

Rectal microbicides are compounds under development that may decrease the risk of HIV transmission when applied inside the rectum before intercourse. Rectal microbicides need to be efficacious against HIV and, equally important, products that people are able and willing to use ("acceptability"). Initial acceptability studies were hypothetical (ie, potential users reported their likelihood of using a product described to them but which they did not use).[1 2] An exception was the pioneer rectal trial of Gross *et al*,[3] which highlighted the importance of acceptability in microbicide efficacy. Although progress in rectal microbicide development lags behind that made for vaginal microbicides,[4] several clinical trials testing the safety and acceptability of rectal microbicide candidates are underway.[5]

The rectal compartment is an open conduct with a large surface of mucosa that could be exposed to the virus.[6] Consequently, large volumes of a rectal topical microbicide have been assumed to be needed to provide coverage and maximise the product's effectiveness. In an earlier study[5] we explored what would be the largest acceptable volume of gel for men who practise receptive anal intercourse (RAI) and found that 35 ml was the upper limit, although smaller volumes were preferred.

Other than gels, suppositories offer another way to deliver a microbicidal agent intrarectally. Predicting that mucosal coverage would also be a concern with a suppository, we assumed that a suppository would have to be fairly large to accommodate enough active formula. Consequently, we designed a study to compare the relative acceptability of 35 ml of a gel formulation with that of a 8 g rectal suppository as delivery vehicles for a rectal microbicide to be used before RAI by men who have sex with men (MSM).

METHODS

The study design and procedures were approved by the Institutional Review Boards of both the New York State Psychiatric Institute and Fenway Community Health in Boston, Massachusetts, USA.

Recruitment and eligibility criteria

Participants were recruited[7] in Boston, Massachusetts, USA, between May 2005 and April 2007. Eligible men had to be 18 years of age or older, HIV negative by self-report, and aware that unprotected RAI with a partner of HIV-positive or unknown serostatus carries a risk of HIV transmission. Furthermore, they had to report having had unprotected RAI in the previous year and rate it as involving some risk of HIV transmission to themselves, have a male partner with whom they engaged in RAI at least once every 2 weeks, and be willing to abstain from RAI 3 days before the initial clinical examination and 3 days after finishing using the first product and before using the second one. Participants were excluded if they had had a genital or rectal herpes outbreak in the previous 6 months, diarrhoea or rectal bleeding within the past 2 months, a history of chronic gastrointestinal disorders, or large haemorrhoids or internal warts; further exclusion criteria were having been involved in a drug

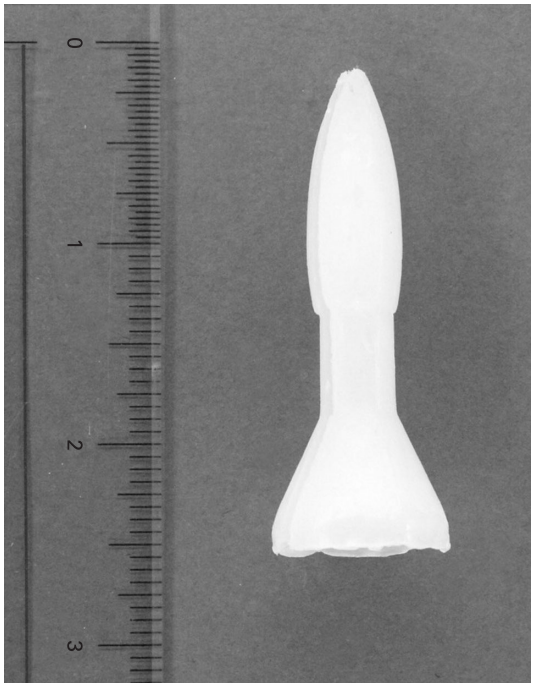

Figure 1 Caption to follow.

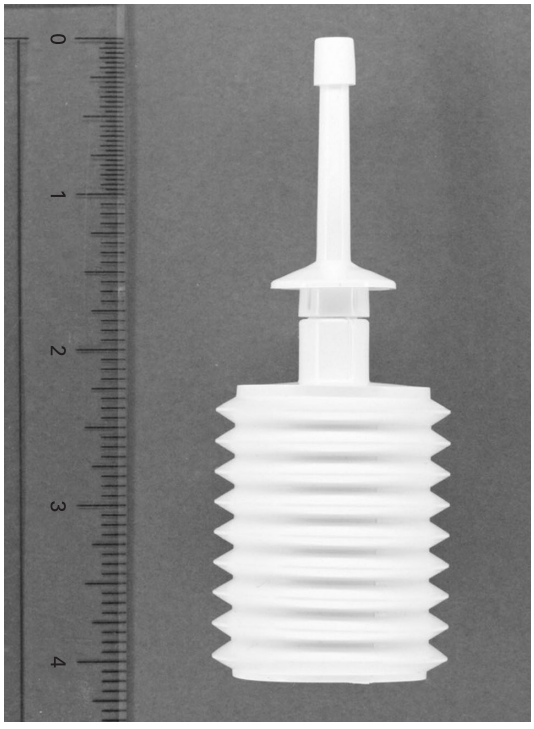

Figure 2 Caption to follow.

research protocol within the past year or having a current male partner also enrolled in the study.

Study products

Two placebo products were used: a gel manufactured by Cooper Surgical, Inc (Trumbull, Connecticut, USA) using deionised (purified) water, polyoxyethylene, methylparaben and sodium-carbomer, which is available on the market as a lubricant and sold as FemGlide or Slippery Stuff; and a suppository manufactured by JE Pierce Apothecary, Inc (Brookline, Massachusetts, USA) using two polyethylene glycol bases (PEG 1450 and PEG 300) with no other ingredients, which can be used as a vehicle for the delivery of rectal medications. The suppository, weighing approximately 8 g and measuring 2.5 inches (6 cm) in length (see fig 1) was dubbed "rectal rocket" by its manufacturer. Participants inserted 35 ml of the gel using an enema bottle (see fig 2) manufactured by Spruyt Hillen (The Netherlands). The suppository was inserted manually without any applicator.

Procedures

After completing the consent procedures and before being enrolled into the study (see fig 3), participants underwent a clinical examination. Participants completed a baseline quantitative assessment using a computer-administered self-interview (CASI) that included questions on demographic information and rectal microbicide intentions. After instruction on the proper use of both products, participants were sequentially randomly assigned to either group A (gel first, suppository second) or group B (suppository first, gel second) following the crossover design of the study. Participants were provided either with three filled gel applicators or four suppositories (one extra suppository was supplied in case there were problems during insertion) and were asked to insert the product up to 2 h before intercourse on three different intercourse occasions in the weeks that followed. For the suppositories, participants were asked to wait 30 minutes after insertion before having sex to allow the suppository to dissolve. Participants were reminded that the products were placebos that offered no protection against HIV/sexually transmitted diseases and were given condoms and lubricants. Participants were asked to call the research office within 24 h of product use to report on product acceptability for the specific sexual episode. Once the three occasions were completed, participants completed a mid-trial CASI acceptability assessment of the first product used. The second product was evaluated with identical procedures. Finally, once participants had had the chance to use and evaluate both products, they were asked to use a CASI to respond to a product preference measure and discuss any product recommendations.

Measures

Sexual behaviour

Respondents were asked to report their sexual behaviour during the previous 2 months, including the number of sexual partners and unprotected RAI occasions.

Rectal microbicide intentions

At baseline, we asked: "If a rectal microbicide were available that provided some protection against HIV, and it looked like the [gel/suppository] we showed you earlier, how likely would you be to use it every time you have receptive anal intercourse?" Answers could range from 1, extremely unlikely to 10, extremely likely. A slightly edited version of this question was asked after the participant had tried each study product one to three times.

Product acceptability

A summary measure of acceptability was completed once the participant had finished using each product. This measure included a general question ("Overall, how much did you like the gel/suppository?"), as well as specific questions on the level of like/dislike of the products' physical properties, application

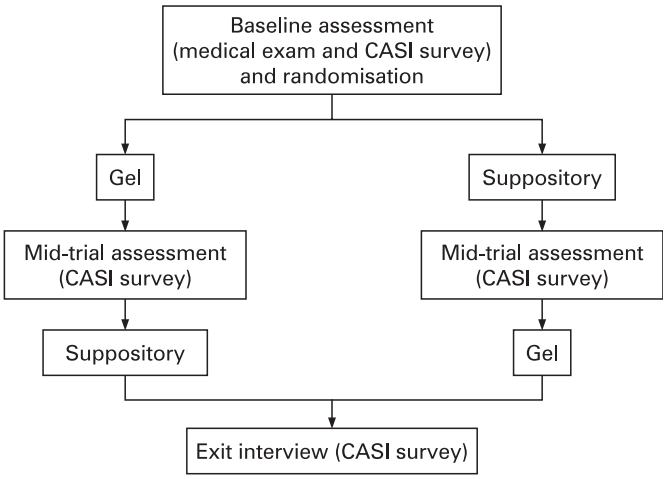

Figure 3 Study design and procedure.
CASI, computer-administered self-interview.

process and experiences using the product during sex. These questions were answered on a 10-point scale (1, disliked very much to 10, liked very much). We ascertained if any potential problems were experienced (eg, leakage, soiling of underwear or linens, bloating) and, for those experiencing them, how bothersome they were (1, not at all to 10, very much). Finally, participants were asked "How much would you be willing to spend on a gel/suppository per sexual occasion?" (0, less than condoms or nothing to 3, three times as much or more). Questions were worded identically (whenever possible) for both products to make comparison possible.

Product preference

Participants indicated which product they preferred ("Thinking about the gel and suppository, overall which product did you like the most?") and also reported which product they believed their partner liked the most.

Data analysis

Those who used and rated both products ("completers", n = 77) were compared with those who did not finish the trial ("attrited", n = 28) on all demographic variables using t tests and χ^2 tests. We restricted subsequent product comparisons to men who used both products. Binomial tests were used to determine whether one product was preferred by more participants than the other. Wilcoxon tests were used to evaluate whether the ratings for one product were significantly different from the ratings for the other product. We performed a post-hoc correction to decrease the type I error.

RESULTS

Sample description

We present the demographic characteristics of our sample (N = 77) in table 1. On average, participants were 41 years of age; the majority had completed a high school education or higher; two-thirds were employed, having a median income in the US$20 001–40 000 range; two-thirds identified as white or European American; and three quarters identified as gay.

Table 1 Sample description (N = 77)

	M 40.7, SD 9.97 (18–60)
Age in years (range)	**N (%)**
Education	
Less than a high school degree	6 (7.8)
High school degree	24 (31.2)
Some college	18 (23.4)
College degree	13 (16.9)
Post-baccalaureate education	16 (20.8)
Employed	48 (62.3)
Income (US$)	
10 000 or less	23 (29.8)
10 001 to 40 000	34(44.2)
40 001 to 80 000	12(15.6)
80 001 or more	5 (6.5)
Did not report	3 (3.9)
Race/ethnicity	
White/European American	50 (64.9)
Black/African American	20 (26.0)
Latino	4 (5.2)
Other	3 (3.9)
Identity/self-label	
Gay	58 (75.3)
Bisexual	19 (24.7)

Sexual behaviour in the 2 months before interview

At baseline, all but one of the participants reported having had at least one male sexual partner (M 4.40, SD 5.18) with whom they had engaged in RAI in the previous 2 months, slightly more than half (56.3%) of RAI occasions were unprotected. Eighty per cent (N = 62) of participants reported having insertive anal intercourse, on average on 5.78 occasions (SD 7.79), three-fifths (59.5%) of them unprotected.

Preference ratings for gel versus suppository

After using each product on up to three separate occasions, significantly more participants reported preferring the gel (N = 58; 75%) than those preferring the suppository (N = 19; 25%; binomial $p<0.001$). In addition, more participants believed their partners also preferred the gel (N = 55; 71%) than those who believed their partners preferred the suppository (N = 22; 29%; binomial $p<0.001$).

At baseline, participants' intention to use the gel in the future (M = 8.70) was statistically higher ($p<0.01$) than their intention to use the suppository (M = 6.99). After using the product, their intention to use the gel was still higher than the suppository, although the mean ratings for both products went down (ie, participants were less likely to intend to use the product after having used it).

Participants reported a higher overall acceptability of the gel over the suppository (see table 2). The gel was preferred for its physical properties and application process before RAI. The few participants experiencing problems were more bothered by the suppository. We detected a statistical difference between the gel and the suppository in terms of leaking (M = 3.38 versus 4.14), soiling (M = 2.82 versus 3.79), feeling bloated (M = 1.49 versus 2.92), having gas (M = 2.04 versus 3.62) or cramps (M = 1.30 versus 2.25), needing to have a bowel movement (M = 2.36 versus 4.95), diarrhoea (M = 1.36 versus 2.83) and pain or trauma (M = 1.16 versus 1.92). The gel was also preferred over the suppository in terms of experiences using the products during sexual intercourse (see table 2). In general, those participants who had not applied either product before sexual intercourse did not report feeling bothered by interrupting the sexual act to apply it. Partner's sexual satisfaction was also greater for the gel.

Table 2 Mean ratings of gel and suppository characteristics (N = 77)

Variable	Gel	Suppository	p Value
Overall, how much liked product	7.61	5.32	<0.001
Product properties			
Colour	8.08	6.65	<0.001
Smell	8.00	6.18	0.014
Consistency (thick or thin)	7.58	5.60	<0.001
Application process			
Process of applying	6.84	5.31	0.001
Ease of insertion	7.60	7.52	ns
Feeling in rectum after inserting	7.78	4.71	<0.001
Feeling in rectum 30 minutes later	7.55	5.97	<0.001
Ease of carrying around	6.39	6.55	ns
Experiences using product during sex			
Feeling during anal sex	7.91	5.95	<0.001
Sexual satisfaction using product	8.14	6.23	<0.001
Liked with condoms	7.76	6.14	0.001
Liked without condoms	8.31	6.78	0.004
Product improved sex*	1.30	0.86	<0.001
Penetration was easier†	1.04	0.74	0.001
Partner's sexual satisfaction	8.25	6.95	0.001
Overall, how much partner liked	7.56	6.08	0.001
Intentions to use product in the future			
Likely to use similar product	8.35	6.18	<0.001
Likely to use when no condoms	8.70	7.27	0.001
Would spend more than condoms	1.60	1.45	ns

*Response scale (0, worse; 1, no different; 2, better).
†Response scale (0, no; 1, penetration was somewhat easier; 2, penetration was much easier).

DISCUSSION

Our study was conducted with sexually active men who reported being HIV uninfected and engaged in unprotected RAI in circumstances that involved the risk of HIV transmission, ie, one of the populations most likely to benefit from efficacious and acceptable rectal microbicides. Having tried two different placebo formulations (gel and suppository) of a microbicide vehicle during RAI, men preferred the gel. Those who experienced problems reported feeling more bothered by suppository-related issues than gel-related issues. Participants did not appear to be too bothered by problems related to product administration; however, they expressed preference for a product that did not require waiting time before it became active and voiced a willingness to spend as much or slightly more for microbicides than what they spend on condoms. Men expressed greater intentionality to use a gel than a suppository after seeing both products but before trying them; this preference persisted after the trial. This seems to indicate that initial attitudes about the use of a product that an individual has had the chance to examine may be predictive of future intention to use such a product.

Whereas these findings offer promise to an emerging field in HIV prevention, several limitations must be noted. First, our sample consisted exclusively of men who have RAI; generalisations to women who engage in RAI are not warranted. Second, we did not account for men's previous history with gels or suppositories prior to baseline, which may confound our findings. In addition, at the time this study was designed, it was assumed that large volumes of gel (maybe up to 50 ml) would be necessary to confer mucosal coverage and protection. Current developments, including the likely utilisation of antiretroviral agents in microbicide trials, suggest smaller volumes of gel may be sufficient,[8] thus increasing the potential acceptability of rectal microbicidal gels in the future.

The overall preference for a gel as a rectal microbicide vehicle in this sample should not completely discount a suppository as an alternative mode of delivery. The suppository used for our study was relatively large, given our wish to make it somewhat comparable to the large volume of gel participants were using. Smaller suppositories or suppositories with different characteristics (eg, solubility, mode of application) may result in different acceptability ratings. Future research exploring the acceptability of different suppositories and other delivery vehicles should be conducted. For example, rectal douching before intercourse is a habitual behaviour among MSM,[9] and even some participants in this trial suggested that douching instructions be given as part of the microbicide use recommendations. A rectal douche that could deliver a microbicidal agent should also be considered. As biochemical progress is made by selecting an effective antiretroviral agent to serve as a rectal microbicide in clinical trials,[10] behavioural research on the acceptability and adherence of a potential microbicide delivery vehicle should continue if we are to understand what other practices or barriers to product use and adherence exist and may hamper the effectiveness of a microbicide.

Key messages

- A rectal microbicide formulated as a gel is likely to have greater acceptability among MSM than a suppository formulation
- A high volume of gel (35 ml) appears acceptable for intrarectal use before anal intercourse
- Partner's acceptability of a microbicide gel also appears to be high

Competing interests: None declared.

Ethics approval: Ethics approval was obtained.

Contributors: ACD was the principal investigator of the study and the researcher who took primary responsibility for reporting its results; CD was responsible for data analysis and interpretation; JAB contributed significantly to the writing of the paper and to the interpretation of results; BO'B was the project director of the study and contributed to the writing of the methods section of the manuscript; AV contributed to the implementation of assessment procedures and in the writing of the article; KM was the co-principal investigator of the study and also contributed to the editing of its final report.

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