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Women's preferences regarding the formulation of over-the-counter vaginal spermicides

There is an urgent need for safe, effective and acceptable vaginal barrier methods for the prevention of sexually transmitted diseases (STD), including HIV. As product acceptability ultimately determines use-effectiveness, developing microbicidal vaginal products requires insight into users' perspectives [1]. We sought to explore the characteristics of existing vaginal products that influence user preferences for various formulations.

A diverse group of study sites was included: Projet RETRO-CI (Abidjan, Côte d'Ivoire), Siriraj Family Health Research Centre (Bangkok, Thailand), University of Zimbabwe (Chitungwiza, Zimbabwe), University of Khon Kaen (northeastern Thailand), and Columbia University School of Public Health (New York City, New York, USA). Women were recruited via fliers and word of mouth or through health-care facilities (e.g., antenatal/maternal–child health clinics). Study participants used a vaginal contraceptive film containing 70 mg nonoxynol-9 (Apothecus Pharmaceutical Corp., Oyster Bay, New York, USA), a vaginal suppository (Ortho Conceptrol Vaginal Inserts, Ortho Pharmaceutical Corp., Raritan, New Jersey, USA) with 150 mg nonoxynol-9, and a vaginal gel in a pre-filled applicator (Ortho Conceptrol Gel, Ortho) containing 200 mg nonoxynol-9 (in our laboratory we found that only 100–120 mg was actually dispensed from the applicator).

A crossover study design ensured that every woman used each of the products for 4 weeks. Women were advised to use the products together with a male latex condom whenever possible. Prior to and following product use, women participated in focus group discussions and structured interviews to assess their knowledge, practices and preferences regarding each vaginal formulation. Women were asked to record each act of intercourse in a daily log book in which they also noted whether the study product/condoms were used. They returned every 2 weeks for an interview and pelvic and speculum examination. Women's experiences with product use, as well as any evidence of vulvar, cervical or vaginal abnormality were recorded.

Selected characteristics of the study populations are described in Table 1. When asked whether they were able to use the study products without their partner's knowledge, most women in this study (approximately 75%) reported that they preferred to inform their partners that they were using vaginal products, both in the context of the study and in the future. They preferred telling their partners at the outset, in case they or their partners subsequently experienced problems with a particular product. Some were particularly concerned about having to explain the presence of a product if her partner detected its use. Others said that their partners supported them in using vaginal products, especially if it was perceived to enhance sexual frequency or pleasure. There was no correlation between formulation preferences and the desire to hide product use from one's partner.

When asked why they might use vaginal products in the future, among the four sites that reported data for this question, women reported that the primary reason would be from infection alone (40%), protection from pregnancy alone (13%), or both (44%).

In most cases, women found the suppository to be the messiest and, therefore, least desirable of the formulations (it tended to melt at the tropical ambient temperatures of several of the study sites and consequently needed refrigeration to prevent melting prior to insertion). Film was the overall preferred formulation in three of the five sites and was liked by many of the

Table 1. Selected characteristics of study populations.

	Abidjan, Côte d'Ivoire (n = 31)	Bangkok, Thailand (n = 25)	Chitungwiza, Zimbabwe (n = 22)	Khon Kaen, Thailand (n = 36)	New York City, USA (n = 31)
Age (mean)	25	30	32	37	30
Married (%)	17	100	96	100	42
Coital frequency in the month preceding the study (mean)	4	5	18	5	8
Parity (mode)	2	1	4	3	1
Ever tried to convince partner to use condoms (%)	63	40	79	27	97
Always uses condoms with partner (%)	0	0	9	0	55

women's partners. The film was considered the most difficult to insert by many users; however, their confidence and ability to use this product increased substantially with experience and supportive counseling. Women in Khon Kaen, Bangkok, Chitungwiza, and Abidjan all stated that they especially liked the film, due to the fact that it left the vagina feeling 'tight' or 'fit'. Indeed, preferences were often related to their perceptions of 'wet' versus 'dry'

The gel was the most preferred formulation in New York and Abidjan, and was generally deemed the easiest to apply and had an advantage of not requiring a waiting time following insertion. It was also preferred by older women in the Khon Kaen site specifically because of its lubricant qualities. Many other women, however, complained of excessive lubrication following intercourse with the gel product.

We found that preferences after actual use did not correlate well with those expressed in hypothetical pre-use focus group discussions, especially in those sites where women had little prior experience with vaginal product use. Some participants were 'intrigued' by unfamiliar products and predicted that they would like them best. On the other hand, women's hypothetical preferences were often informed by what they were already familiar with. For example, in Khon Kaen, women thought that they would like the suppository because they were familiar with products of this kind for the treatment of vaginal yeast infections, whereas they had never previously seen a vaginal film or applicator. Following actual product use, however, other concerns such as messiness and the enhancement of sexual pleasure were more important in determining women's formulation preferences.

In three of the sites (Abidjan, Chitungwiza and Khon Kaen), women favoured some products because they enhanced sexual pleasure. In general, reports of their partners' reactions to various products largely agreed with the women's personal preferences.

There were often trade-offs regarding product characteristics. For example, some women liked the ease of insertion of the gel, but felt it was also too messy. Several of these women compensated for this by decreasing the volume of gel they applied. Some women reported that use of certain products resulted in increased frequency of intercourse; however, overall product preference was not a function of coital frequency. Despite specific drawbacks to each formulation, study participants expressed great interest in the products, and many stated that they would continue to use them, even their least preferred formulations, if they were available and approved for STD prevention.

Overall, we observed considerable variation in users' perspectives and formulation preferences both within and between sites. As with an earlier three-country study [2], film was the overall preferred formulation, although cultural norms affected specific preferences for relative 'dryness' of the formulations, and generational differences, even within the same site, influenced the degree of lubrication considered desirable. This suggests that, in the development of new vaginal microbicides, multiple products will be required to meet the needs of all users.

Because of the wide range of cultural norms governing desirable fertility levels, and given their differing personal expectations and needs, study participants expressed considerable interest in the possibility of using a vaginal microbicide that would be non-spermicidal. Although it could be argued that most women, at any given point in their lives, probably do not want to become pregnant, nearly every woman, at some point in her life, does want to conceive, preferably without putting herself at risk of infection. Ideally, contraceptive and non-contraceptive products should be pursued in research and development efforts.

In almost every site, at least some of the women reported that they and their partner enjoyed using the products because their use was felt to enhance sexual pleasure. Clearly, the 'trade-offs' of promoting a product for disease prevention versus increased sexual pleasure must be further explored.

Women in this study, many of whom were family planning clients or hospital employees, expressed little interest in covert methods. Women in partnerships characterized by higher levels of coercion or commerce, however, might have a greater need for products that could be used without a partner's knowledge. It is also possible that covert use would be more common outside the context of a research study. For this group of women, partner's perceptions of product characteristics and the dynamics of partner communication proved to be very important. It is therefore critical to explore more explicitly men's attitudes and beliefs regarding vaginal microbicide use in future studies.

Given the trade-offs that women and their partners face in using vaginal products we must also learn more about the dynamics of actual product use. Few people will adhere strictly to package instructions, especially when using products outside the context of a clinical study. For instance, if women are going to decrease the volume of vaginal applications because the product is otherwise too messy, we must know this in order to ensure that dosage is adequate under real use conditions. As with other user-controlled methods, product acceptability is a central determinant of use-effectiveness and, ultimately, the development and introduction of any new vaginal microbicide will need to take into more careful consideration the preferences of potential users.

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Distinct recognition of closely-related HIV-1 and HIV-2 cytotoxic T-cell epitopes presented by HLA-B*2703 and B*2705

HIV-1 infection is increasing in many countries where HIV-2 is endemic [1], so the potential interaction between the two strains, which differ at the nucleotide level by 40–60% [2], is important. HIV-2 infection is less aggressive than HIV-1 [1], and may protect against HIV-1 infection [3], but this theory is controversial [4,5].

HIV-specific cytotoxic T lymphocytes (CTL) recognizing conserved viral proteins could mediate cross-immunity. We described extensive cross-reactivity between HIV-1 and HIV-2 CTL epitopes from *gag*, *pol* and *nef* presented by HLA-B35 [6]. Cross-reactivity was also reported for an HLA-B★2705-restricted HIV-1 epitope [7]; however, most CTL epitopes are not cross-reactive (e.g., those presented by HLA-B8 in p17 [8], by HLA-B8 and B14 in gp41 [9], by HLA-Cw4 in gp120 [10], and by HLA-B53 in HIV-2 *gag* [11]). Amino-acid substitutions between HIV-1 and HIV-2 can prevent binding to the HLA molecule or interfere with T-cell receptor (TCR) recognition, and may also interfere with recognition of the index sequence. This process of TCR antagonism has been described for naturally occurring variants of HIV-1 [12,13], hepatitis B virus [14], Epstein–Barr virus [15], and *Plasmodium falciparum* [16]. Antagonism as a potential mechanism for vaccine failure has been described in a volunteer immunized with an HIV-1 envelope construct who became infected with HIV-1 and generated CD4+ CTL specific for the immunizing envelope sequence that were antagonized by the infecting virus [17]. Although only a few unrecognized sequence variants can act as antagonists, the high mutation rate of HIV makes this a potentially important mechanism of immune evasion *in vivo*. It could adversely affect cross-immunity in settings where dual infections with HIV-1 and HIV-2 or with different clades of HIV-1 can occur. Potential antagonism should therefore be investigated where there is no cross-reactive recognition between CTL epitopes from different virus strains.

We studied cross-reactivity and antagonism between the HIV-1 and HIV-2 sequences of an epitope from HIV *gag* 265–274, restricted by HLA-B27; both are presented equally well by the Caucasian subtype B★2705 and the African variant B★2703, which differ at a single position (P59) in the 'A' pocket of the peptide-binding cleft [18]. The HIV-1 sequence (KRWIILGLNK) differs by three amino acids from the HIV-2 sequence (RRWIQLGLQK).

CTL bulk cultures [19] were generated as described from HIV-infected Gambians with HLA-B★2703, typed by ARMS-PCR [20] or single-strand conformational polymorphism analysis [21]. CTL responses to HIV-2 *gag* from HIV-2-infected donors were mapped to the equivalent sequence of the known B★2705-restricted HIV-1 epitope [19], to which HIV-1-infected Gambians with B★2703 also responded [18].

Bulk CTL cultures generated from the HIV-2-infected donors did not recognize either HIV-1 *gag-vac*-infected targets or the HIV-1 epitope (Fig. 1a), or *vice versa*. CTL cultures established by direct stimulation with peptide and interleukin-7 (a more sensitive method of generating specific CTL [22]) yielded strong responses from HIV-1-infected Gambians with the HIV-1 peptide and with the HIV-2 peptide for HIV-2-infected donors, but not in anyone using the peptide from the other virus strain (not shown).