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How effective is effective enough? Opinions of potential end-users of microbicides from a rural South African community

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To assess the views of potential end-users of a microbicide in KwaZulu-Natal regarding the characteristics that would justify further development, three focus group discussions were conducted in 2009 with 23 local staff members working on a microbicide clinical trial, 20 former trial participants and 14 Community Advisory Board members not enrolled in the trial, in an area with high HIV incidence and low consistent condom use. All participants agreed on the need for additional HIV prevention options that are as effective as possible and can be used by women. The majority of respondents stated that even a highly acceptable HIV prevention option with protection as low as 30% would still be an important addition to condoms for women; that a partially protective microbicide would have to be introduced as part of the existing prevention messages in order to continue promoting condom use; that there should eventually be a choice between antiretroviral (ARV) and non-ARV-based microbicides and a choice of how and where to access microbicides. Respondents also felt it would be important to make plans for access to a microbicide that can offer protection, even if partial, rather than wait to find out if alternative microbicides are equally or more effective. Potential end-users in a high HIV prevalence area believe that a partially effective microbicide would be an important addition to the limited HIV prevention options for women. The significant challenges of introducing a partially protective HIV prevention option were recognised, but seen as ones worth facing, as well as an opportunity to lay the ground work for the introduction of more efficacious HIV prevention methods in the future.

Keywords: microbicides; access; HIV; women; South Africa

Introduction

Vaginal microbicides are experimental products being evaluated to find out if they reduce the risk of HIV infection in women during sexual intercourse. In February 2009 the HPTN035 phase IIb clinical trial reported that 0.5% PRO2000/5 microbicide showed a 30% reduction in vaginally acquired HIV infection compared with a placebo, but the result was not statistically significant (Abdool-Karim et al., 2011). PRO2000/5 is a naphthalene sulphonate polymer which disrupts the attachment and fusion steps in HIV infection of target cells. The larger phase III Microbicides Development Programme (MDP) 301 clinical trial (Nunn et al., 2009) was due to report on the effectiveness of 0.5% PRO2000/5 at the end of 2009. The World Health Organization (WHO) convened a consultation in London in May 2009 to prepare for access to 0.5% PRO2000/5 in anticipation of a significant result. At the meeting there was a debate regarding the level of effectiveness that PRO2000/5 would have to demonstrate to garner support from researchers, policy-makers and advocates for further investment and development. The threshold for development differed widely, ranging from 20 to 80%, among representatives from diverse constituencies. The report noted that it would be important to engage women at risk of HIV infection, as the ultimate beneficiaries of microbicides, in future discussions regarding acceptable minimal levels of effectiveness (WHO, 2010).

The potential for a reduction in condom use as a result of the availability of a partially protective microbicide was also discussed at the meeting, although there was no consensus as to the weight that should be placed on such concerns. Mathematical modelling suggests that in areas of high HIV incidence with low rates of consistent condom use, even an inconsistently used 40% effective microbicide would avert a substantial number of HIV infections (Vickerman et al., 2006). Modelling also suggests that in areas with 50% or less consistent condom use, condom use would have to reduce by a third or more for the net benefit of a 40% effective microbicide to be negated (Foss, Vickerman, Heise, & Watts, 2003).

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Disappointingly, MDP 301 established that 0.5% PRO2000/5 did not prevent HIV infection in women (McCormack et al., 2010). However, in July 2010 the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 trial demonstrated that an antiretroviral (ARV) based vaginal microbicide gel containing tenofovir, when used before and after sex, reduced the risk of HIV infection in women by 39% (95% CI: 6, 60) compared with a placebo (Abdool-Karim et al., 2010). Since this ground-breaking result, the picture has become less clear. In November 2011 the Microbicide Trials Network VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial discontinued daily dosing with tenofovir gel after an interim analysis revealed that there was no possibility of demonstrating benefit (MTN, 2011b). The Follow on Africa Consortium for Tenofovir Studies (FACTS) 001 trial is repeating the CAPRISA 004 trial design in broader populations in South Africa evaluating peri-coital use of tenofovir gel and is expected to report results in 2013 (FACTS, 2012). The only other on-going microbicide trials are the International Partnership for Microbicides and the Microbicide Trials Network trials evaluating the ARV dapivirine in a slow release vaginal ring (MTN, 2012).

The use of ARVs as oral pre-exposure prophylaxis has been assessed in five trials (Baeten et al., 2012; Grant et al., 2010; MTN, 2011a; Thigpen et al., 2012; Van Damme et al., 2012b). A range of effect sizes from no protection to 73% reduction in HIV incidence have been observed. Three of these trial populations were comparable to the CAPRISA 004 trial population (i.e., HIV-negative women in sub-Saharan Africa whose partners' HIV status was unknown). Although 49% reduction in HIV acquisition was seen in young females in Botswana using oral Truvada (Thigpen et al., 2012), no protection was observed with this drug in the FEM-PrEP study among women in South Africa, Kenya and Tanzania (Van Damme et al., 2012b). The reasons for the conflicting results for the same drug in women in similar epidemic settings are still being evaluated (Celum & Baeten, 2012), but cannot be explained by biology alone (Van Damme et al., 2012a).

Vaginal microbicides may still offer the best levels of protection for women who do not know the status of their partners. Pharmacological studies provide evidence that topical application of tenofovir 1% gel leads to higher levels of drug in the vagina, compared with oral administration (Schwartz et al., 2011). In the VOICE trial, the oral tenofovir arm has been discontinued (MTN, 2011a), while the study continues with the oral Truvada arm and the final trial report is expected in 2013 (MTN, 2011c). The question still remains about the minimum level of protection that a vaginal microbicide would have to demonstrate in order to be considered a viable HIV prevention option.

The Africa Centre for Health and Population Studies (http://www.africacentre.ac.za) was one of six research centres that participated in the MDP 301 clinical trial. The Centre is located in a predominantly rural area of the Umkhanyakude District in KwaZulu-Natal, South Africa (Tanser et al., 2007). HIV incidence in the area in 2003–2005 was 3.8 per 100 person years for women aged 15–49, peaking at 8.0 per 100 person years in women aged 25–29 (Bärnighausen et al., 2008). Current data on consistent condom use in the general population in the province is limited, but available evidence suggests that it is substantially below 50% (Chimbindi, McGrath, Herbst, San Tint, & Newell, 2010; Maharaj & Cleland, 2005; Ngubane et al., 2008).

In this study, conducted in July 2009 prior to the release of the MDP 301 trial results, potential end-users were asked about the level of effectiveness that PRO2000/5 would have to demonstrate in order to garner their support for further development in South Africa. We conducted focus group discussions (FGDs) with MDP staff members from the area, former MDP 301 trial participants, and members of the Africa Centre Community Advisory Board (CAB) who were not enrolled in the trial but serve an advisory function across all Africa Centre studies. Each of these groups was very familiar with the MDP 301 protocol and that the protocol was designed to detect a 35–40% reduction in HIV incidence. They had also been regularly updated during presentations by the MDP team on other developments in the field, such as the Cellulose Sulphate, SAVVY, Carraguard and HPTN035 microbicide trial results (Abdool-Karim et al., 2011; Feldblum et al., 2008; Horwood, 2007; Peterson et al., 2007; Skoler-Karpoff et al., 2008), the discontinuation of 2% PRO2000/5 (MDP, 2008), the start of the CAPRISA 004 tenofovir microbicide trial (Abdool-Karim et al., 2010) and results from the circumcision trials (Bailey et al., 2007). The way in which trial results are reported had also been explained to these groups in terms of understanding different levels of effectiveness.

This study contributes to the on-going debate regarding the access to partially effective microbicides and more broadly the partially effective HIV prevention methods, by reporting the views of potential end-users.

Methods

Three FGDs were conducted, one with 20 female and 3 male MDP staff members, one with 20 former MDP 301 trial participants and one with 8 female and

6 male CAB members. In total there were 48 women and 9 men involved in the FGDs. All participants provided written informed consent. The clinical trial was approved by the Medicines Control Council (N2/19/8/2) and the University of KwaZulu-Natal Biomedical Research Ethics Committee (T111/05).

The discussion was framed on the hypothetical assumption that 0.5% PRO2000/5 would demonstrate a partial protection at a statistically significant level in the MDP 301 trial. Within this context, FGD participants were asked to discuss the minimum level of protection they would want PRO2000/5 to demonstrate in order for it to be considered an HIV prevention option in South Africa. They were also asked to discuss whether they would still want PRO2000/5 to be available if ARV-based microbicides (used pericoitally in the same way as PRO2000/5) were found to offer twice as much protection as PRO2000/5 in the future. The groups were asked to indicate their position on the topics under discussion by standing on one side of the room or the other (Winch, Wagman, Malouin, & Mehl, 2000). Some people in each group were then asked to explain the reasons behind their choices, and opposing views were discussed. Notes of the proceedings were taken by two research assistants independently. Both sets of notes were transcribed in English. The FGD transcripts were systematically reviewed and manually coded by the first and second authors.

Results

Table 1 shows the results on the level of effectiveness that each group would want 0.5% PRO2000/5 to demonstrate in order to eventually be made available in their community. All participants agreed on the need for additional HIV prevention options that could be used by women. The majority of respondents in all FGDs stated that PRO2000/5 should be available at any level of effectiveness if the MDP 301 trial result is statistically significant, because it would give women who could not negotiate condoms a risk reduction option that they could use, it was highly acceptable to both women and men and it assisted in condom negotiation. Former trial participants stated that the gel had a positive impact on sexual pleasure and provided lubrication which made condom use more tolerable to both them and their partners. Forty-seven of the 57 respondents (82%) argued that in the light of the extensive HIV epidemic in the Umkhanyakude District, women who could not consistently use condoms needed a microbicide that could offer even 30% protection.

On the other hand, 10 respondents, that is, 3 staff members (2 females and 1 male), 4 trial participants and 3 CAB members (1 female and 2 males), did not think that PRO2000/5 should be available at 30% effectiveness. These respondents were concerned about how a 30% effective product would be explained and rolled out in the government services. The rest of the respondents acknowledged that it would be more difficult to explain microbicides in government services than in clinical trial settings, but argued that it was possible. The 10 respondents who did not think that PRO2000/5 should be available at 30% all felt that the attraction of a novel prevention option could negatively impact on condom use. They believed that the benefits of rolling out a microbicide that could halve the risk of infection outweighed the associated risks of reducing condom use, whereas they did not believe that the benefits of rolling out a microbicide that could only reduce the risk by a third outweighed the risks. In response, other respondents in each of the FGDs argued strongly that the people who use condoms consistently and continuously are the "converted few" who will keep using condoms. They said that PRO2000/5 will be attractive to those who do not use condoms or use them inconsistently. All respondents agreed that any additional prevention option that was not as efficacious as condoms would have to be introduced in combination with comprehensive educational programmes as an addition to the existing HIV prevention messages and, if done so correctly, could have a positive impact on condom use. The introduction of a partially protective microbicide as the fourth-level message for women (after abstinence, be faithful, use condoms) was viewed as equivalent to the introduction of circumcision, which is only partially effective, as the fourth-level message for men. However, the

Table 1. Proportion of respondents in each FGD who voted for 0.5% PRO2000 to be available at different levels of effectiveness.

	Staff		Participants	CAB		
Effect size (%)	Female ($n=20$)	Male ($n=3$)	Female ($n=20$)	Female ($n=8$)	Male ($n=6$)	Total ($n=57$)
50	20 (100%)	3 (100%)	20 (100%)	8 (100%)	6 (100%)	57 (100%)
40	18 (90%)	2 (67%)	20 (100%)	8 (100%)	6 (100%)	54 (95%)
30	18 (90%)	2 (67%)	16 (80%)	7 (88%)	4 (67%)	47 (82%)

additional challenge of a microbicide being coitally dependent was acknowledged.

Twenty-two of the 23 staff members, all of the participants and 12 of the 14 CAB members would be in favour of having access to both non-ARV- and ARV-based microbicides in the future, even if non-ARV-based products were less effective than the ARV-based ones. The preference for non-ARV-based microbicides was largely due to a desire for HIV prevention options that require minimal medical management and could therefore be easily available. The main reasons were (1) they would want the ability to choose between systemically and non-systemically absorbed microbicides (largely driven by their knowledge of side effects with therapeutic ARVs and their desire to avoid these side effects in HIV prevention options), (2) that an ARV-based microbicide may remain under more restricted access from health care providers than a non-ARV-based product, (3) that the need for HIV testing before dispensing ARV-based microbicides could be a barrier to access for some people, (4) that people needed multiple prevention options to choose from to meet their various preferences and (5) that they need additional options as soon as possible. Several respondents commented that implementing a partially protective microbicide within the next few years could pave the way for implementing more potent microbicides (ARV- and non-ARV based) at a later stage in terms of distribution messages and strategies.

Discussion

Three main issues emerged from these discussions. First, even a partially protective HIV prevention option that is highly acceptable would be an important addition to condoms for women and should be made available rather than waiting to find out if alternative microbicides are equally or more effective. This urgency is reflected by the very high proportions wanting a partially effective microbicide to be available across the three categories of potential end-users in this study, and the higher proportions of females voting for access at lower effectiveness levels compared to males. Second, any prevention option that is less efficacious than condoms would have to be introduced as part of the existing HIV prevention messages in order to avoid a reduction in condom use among people willing and able to use condoms. However, developing appropriate messages around partial effectiveness was seen as a challenge rather than a barrier to access. Third, the introduction of ARV-based microbicides would have to be an addition to, not a replacement for, a non-ARV-based microbicide, as eventually there should be a choice of how and where to access microbicides. These findings echo arguments recently used by researchers to call for continued development of non-ARV-based microbicides (Omar & Bergeron, 2011).

There are two notable limitations to this study. First, this study did not consider the cost effectiveness of microbicides (Williams, Abdool Karim, Karim, & Gouws, 2011), the challenges of evaluating new microbicide and oral PrEP candidates against partially protective available products, the broader public health impact of rolling out microbicides, or the many logistical challenges involved with implementation. These factors will need to be considered by researchers, policy-makers and advocates, but did not emerge in this discussion with potential end-users. Second, the respondents could all be considered to have a vested interest in microbicides as they had been engaged in the research agenda for a number of years. However, evidence regarding community perceptions of the acceptable minimal levels of protection has been limited to date despite an abundance of literature on microbicide acceptability (Hoffman, Cooper, Ramjee, Higgins, & Mantell, 2008; Mantell et al., 2005), and this study gives a voice to potential end-users and contributes to the important discussion about HIV prevention options.

In conclusion, potential end-users in an area with high HIV incidence view the introduction of a partially protective microbicide, in the context of a well-positioned and well-funded introductory programme, as an opportunity to expand the existing HIV prevention package. Potential end-users are aware of the significant challenges to introducing a partially protective HIV prevention option, but believe that they are challenges worth facing and provide an opportunity to lay the ground work for the introduction of more efficacious HIV prevention methods in the future. These views remain highly relevant to the recent progress in the field of microbicide research and HIV prevention research more generally.

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