

Microbicides: the end of the beginning, not the beginning of the end

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About 22.4 million people are living with HIV/AIDS in sub-Saharan Africa today (1), of which South Africa counts the largest population with 5.7 million people (2). Worldwide, HIV incidence has been steady since the beginning of the 1990s (1) with an epidemic expanding towards women. Indeed, 60% of the infected people in sub-Saharan Africa are women (1). In South Africa, Zambia and Zimbabwe, young women aged 15 to 24 are three to six times more likely to be infected than men (3). The development of a novel female-controlled prevention method against HIV transmission is a necessity. Vaginal microbicides, chemical agents used intravaginally with a goal to protect users against sexually transmitted infections (STIs) including HIV (4), adequately respond to the social context of the epidemic impacting vulnerable women of the developing world and underserved women in richer countries.

Critical issues

Microbicides indeed provide solutions to critical issues such as high risk for HIV infection within steady partnerships, difficulties in safe sex negotiations, stigmatisation, coercion and rape. First, women in steady partnerships can become infected through their male partner who is unfaithful. Second, women must convince their sexual partners to use a condom, to ensure safe sex practices and protect themselves from HIV infection. However, in many situations, a difficult psychological barrier linked to male entitlement threatens women's sexual and reproductive rights and health and ultimately prevents them from even asking their partner to wear a condom (5). Third, the fear of stigmatisation within the community that often views women's sexuality through the lens of reproductive health and birth hood can be extremely important (6). In that sense, women often have to explore the trade-off between the risk of being stigmatised within the community if a condom were to be used and the risk of becoming HIV infected if a condom were not to be used. Lastly, for many women, sexual encounters can come from coercion, economic transactions, or acts of rape: the negotiation of safe sex can sometimes be life threatening (7). In addition, a microbicide is likely to be highly acceptable. Above all, it realizes a paradigm shift in HIV prevention as it chooses the woman's perspective. In that sense, it fits particularly well into existing family planning policies and reproductive health infrastructures where women take a central participative role. Also, microbicides offer women control over their sexuality and therefore facilitate negotiating protection with their partners increasing

sexual confidence and autonomy. In contrast, the female condom, the only currently available female-controlled HIV prevention method, though highly effective, does not offer covert use and has shown substantial obstacles to its uptake in terms of cost, usability, and technology (8).

Evidence for effectiveness

After two decades of setbacks with the trials involving detergent and polyanionic formulations (9), recently two studies demonstrated a proof of concept for microbicides for the first time: the Pro 2000 trial showed a non-statistically significant 30% efficacy (10), and - most importantly - the CAPRISA 004 trial showed a 28-54% range of efficacies depending on user's adherence (11). About 77 other microbicide candidates are currently in the clinical or preclinical pipeline (12). Multiple challenges lie ahead in terms of clinical trials and product development among which the issue of the user's adherence (13). Indeed, as observed in the CAPRISA 004 trial (11), a microbicide will not be effective unless applied consistently and correctly by the user. In particular, biophysical properties and behavioural attributes of microbicide products are intrinsically linked. For example, how fast a microbicide gel spreads (or its texture), will impact the intended user's adherence. A thick gel may require several hours to spread effectively, thus lengthening the waiting time before protected intercourse (14). Longer waiting times may be less well adhered to, or better, depending on the context and the user. Conversely, a thin product could spread more rapidly with a shorter waiting period, but would likely be messy (14). The preference over this range of biophysically constrained options may differ by user or by specific situation. A recent study conducted in Northern California (15) showed that women had a wide range of preferences for gels of different thicknesses. Developing various formulations addressing all users' preferences may well increase adherence and thus efficacy.

Modelling cost-effectiveness

With now a demonstrated proof of concept, understanding the potential cost-effectiveness of vaginal microbicides within the currently existing set of HIV prevention interventions becomes crucial. As there is not yet a safe and effective microbicide available, the challenge is to evaluate the potential of the microbicide technology for a hypothetical intervention. Recent work (16) has looked at a potential 1-year intervention targeting a population of women in reproductive age in South Africa and estimated the incremental cost-effectiveness over a

year of microbicides when distributed in conjunction with condoms. The baseline scenario corresponded to the case where women and their partner only had access to condoms over a year; the incremental intervention, where women and their partner had access to condoms and a microbicide effective at 55%. The microbicide intervention was assumed to benefit from the already existing infrastructures used by condom interventions and not to face additional costs except the cost of the microbicides themselves. The hypothetical microbicide gel available to women was vaginal, anti-HIV, coitally-dependent and preventing only HIV transmission from man to woman. No effects on STIs prevention were assumed in the model. The authors looked at a hypothetical intervention in a fictive city of 1,000,000 inhabitants having the broad epidemiological characteristics similar to South Africa. The base case scenario assumed a microbicide effective at 55% (corresponding to the higher end of efficacy demonstrated in the CAPRISA 004 trial (11)), used 30% of the sex acts and a cost of US\$0.51 per use for the health facilities (corresponding to a dose price assessed for 1st generation microbicides (17)). It was found the intervention would prevent a substantial number of infections (1,908). It would save nearly US\$13 million for the public sector in South Africa (US\$6,712 per infection averted) as opposed to providing antiretroviral treatment otherwise. It would be among cost-effective HIV prevention interventions in sub-Saharan Africa (18).

Overall, HIV prevalence was found to be the main driver for the intervention's cost-effectiveness. In South Africa, the intervention would break even when the male prevalence dropped to 2.9% with all other things staying the same (16). For that country, the projections depended mostly on both the microbicide's price and effectiveness: the intervention would break even when effectiveness dropped to 11% or price increased to US\$2.50 (16). As a conclusion, a microbicide intervention would be very cost-effective in a country severely impacted by HIV such as South Africa. Meanwhile, further investigation showed that a similar microbicide intervention would not be cost-effective in a country with similar epidemiological characteristics as the United States, unless it targeted very specific segments of the population where the epidemic is concentrated (16).

Way forward

The latter study (16) provides insightful qualitative conclusions. Further investigations should include considering the microbicide's effect on the prevention of STIs such as Herpes Simplex Virus Type 2 (HSV-2) as well as considering a rectally-potent microbicide as HIV transmission upon anal intercourse can be as much as 30 times more effective as upon vaginal intercourse (18). Most importantly, on the implementation and cost side of things, substantial work must be done. It is essential to examine the full costing and cost-effectiveness for the health sector of alternative delivery mechanisms for microbicides especially an intervention where microbicides are considered as stand-alone products. In particular, the

tenofovir gel (11), as antiretroviral drug-based, contains a highly potent drug. It will require compliance to unique drug regulatory frameworks and the use of key delivery mechanisms certainly very different than distribution channels for condoms. The question of rapid availability and accessibility, such as over-the-counter dispensing without a health practitioner's prescription, is therefore raised. In that respect, it is crucial that both researchers and policy makers joint their effort. They must collaboratively work and define the necessary non-trivial implementation science framework including an economic evaluation of alternative means of microbicide distribution in order to yield the greatest impact on the HIV epidemic.

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