REPRODUCTIVE HEALTH matters

Multipurpose prevention technologies for reproductive and sexual health

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Abstract: *Global statistics on unplanned pregnancies, abortions and STIs show that unprotected sex is still widely practised. More needs to be done to provide women and men with a wider choice of convenient protective options. To address this need, international efforts are focusing on developing multipurpose prevention technologies (MPTs) that address two or more indications simultaneously. These technologies would have significant advantages over single-indication products. They include* inter alia *novel barrier devices, drugs administered either as oral tablets or vaginal/rectal gels, drugs used in combination with medical devices, and genetically engineered organisms which secrete antimicrobial substances. As an example of progress in the MPT field, this paper describes an on-demand contraceptive/antimicrobial vaginal gel, Amphora (previously known as Acidform), now in an advanced stage of development. Clinical trials are currently being planned to find out whether this product's promising antimicrobial profile translates into protective and preventive choices.* © 2014 Reproductive Health Matters

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Until recently, the development of products to prevent unintended pregnancy and methods to protect against sexually transmitted infections (STIs) have proceeded largely independently of each other. The obvious exception, of course, is the condom which, if used consistently and correctly, provides an effective physical barrier to sperm and can protect both men and women from many STIs.[1] Unfortunately, despite vigorous campaigns to promote condoms, they and other protective options are still not used anywhere near as widely as they might be. This is reflected in the global statistics: every year some 80 million women experience an unplanned pregnancy, 45 million of which end in an abortion; an estimated 500 million people acquire at least one of the four primary curable STIs (*Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis*, and syphilis); there are around 2 million new cases of HIV infection; and many millions are infected with the genital herpes virus, HSV-2.[2,3]

The rationale for multipurpose prevention technologies

Voluntary male circumcision, being rolled out in some countries, can be expected to make a significant impact on some of these figures; clinical trials have shown that the procedure can reduce the risk that a man will acquire HIV from a positive female partner by up to 75%, and also reduces his risk of other STIs.[4] Although there is no reliable evidence that male circumcision lessens women's HIV risk, circumcised men are less likely to infect their female partners with certain other STIs.[4] However, a great deal more needs to be done to provide people of all genders with appropriate protective choices, – if necessary without the active cooperation of their partners. User-friendly products that address two or more indications simultaneously would have significant advantages. The advancement of such products is now the focus of CAMI Health, secretariat to the Initiative for Multipurpose Prevention Technologies (MPTs), an international collaboration of product developers, researchers, funders, health care providers and others.[5] MPTs would offer greater convenience and cost efficiency than single-indication products, and users would be protected automatically against more than one indication even if they had obtained the product with respect to a single perceived risk. For example, a woman in a long-term relationship using an MPT for family planning purposes would

also be protected against STIs, the risk of which she may not recognise.

The diversity of MPTs

The variety of MPTs being developed will widen protective and preventive choices. CAMI Health's website provides an up-to-date listing of MPTs under development, their stages of development, and the organisations undertaking the work.[5] Some MPTs are based on single drugs or on drug-drug combinations. For example, the antiretroviral drug tenofovir, when used for pre-exposure prophylaxis (PrEP), reduces the risk of infection by both HIV and HSV-2 when administered as an oral tablet (oral PrEP), either on its own or combined, in Truvada tablets, with another antiretroviral, emtricitabine.[6–8] There are also promising indications that tenofovir administered as a vaginal gel (topical PrEP) reduces womens' risk of HIV and HSV-2, and confirmatory trials are underway.[9,10] Some examples of other MPTs under development are intravaginal rings which continuously release a contraceptive hormone and an antiretroviral drug over several weeks or months, cervical barriers and female condoms designed to deliver contraceptive and antimicrobial products, male condoms coated with anti-infective gels, and suppositories that deliver live lactobacilli genetically engineered to secrete an antimicrobial agent.[11–17] Given the great number of potential MPTs, the Initiative for Multipurpose Prevention Technologies has prioritised the following dosage forms as those that will best meet the needs of the most vulnerable women: on-demand MPTs, e.g. gels and physical barriers, intravaginal rings, and injectables.

The rationale for MPT vaccines in the sexual and reproductive health arena is the same as for the MPTs discussed above, but at present there is a lack of activity to develop these, with work being focused on single-indication vaccines. Anti-STI vaccines are already in use against HPV and hepatitis B, and several others are in the investigational phase (against HIV, HSV-2, *C. trachomatis* and *N. gonorrhoeae*), while research on contraceptive vaccines is proceeding.[18–22] It is not known how feasible it would be to combine some of these vaccines, although it is worth noting that in the childhood immunisation field there are vaccines which target as many as six pathogens.

Amphora: an example of progress

A good example of progress in the MPT field is an on-demand contraceptive/antimicrobial vaginal gel, Amphora (previously known as Acidform), now in an advanced stage of development. It inactivates sperm by virtue of its mild acidity and is strongly buffered against the alkalinity of the incoming semen.[23] A recently completed Phase 3 clinical trial involving over 3,300 women demonstrated that it is a safe and effective contraceptive, the six-month pregnancy rates for typical use being approximately 10%, as expected for a spermicidal contraceptive (Personal communication, M Rosenberg, CEO, Health Decisions Inc, Raleigh-Durham, NC, USA, 1 May 2014). Submission to the US Food and Drug Administration for marketing approval as a contraceptive is expected early in 2015. Amphora would offer the prospect of immediate, yet rapidly reversible, contraception. It does not contain surfactants or hormones and thus avoids their well-known side-effects, and circumvents the ongoing debate about hormones and a woman's risk of HIV infection.[24,25] The gel's bioadhesivity and viscosity are designed to minimize leakage of protective product from the vagina and to reduce messiness to the user. Amphora's activity against STI pathogens has yet to be demonstrated in clinical studies, although laboratory studies are very promising. The gel's antimicrobial properties are partly due to its acidic pH but, significantly, one of its ingredients, L-lactic acid, unlike other acids at the same pH, is a potent microbicide, whether in the absence or in the presence of cervicovaginal secretions and seminal plasma.[26,27]

Amphora is active against several STI pathogens, *in vitro* and in the mouse model. These include HSV-2, the leading cause of genital ulcers and an important co-factor for HIV infection, and *N. gonorrhoeae*, which is especially significant given that multi-drug-resistant gonococcus strains are now spreading globally.[28–31] Laboratory studies have also demonstrated that Amphora inhibits *C. trachomatis* (Personal communication, S Garg, Professor of Pharmaceutical Science, School of Pharmacy and Medical Sciences, University of South Australia, 30 September 2014) and the protozoal pathogen *Trichomonas vaginalis*, responsible for an estimated 160 million new infections annually.[32,33] Amphora also shows activity against many of the organisms associated with bacterial vaginosis, including *Gardnerella vaginalis*.[32,34] Importantly, it does not affect the beneficial lactobacilli which populate the healthy human vagina.[34]