Review

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Multipurpose prevention technologies: the future of HIV and STI protection

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Every day, more than 1 million people are newly infected with sexually transmitted infections (STIs) that can lead to morbidity, mortality, and an increased risk of human immunodeficiency virus (HIV) acquisition. Existing prevention and management strategies, including behavior change, condom promotion, and therapy have not reduced the global incidence and prevalence, pointing to the need for novel innovative strategies. This review summarizes important issues raised during a satellite session at the first HIV Research for Prevention (R4P) conference, held in Cape Town, on October 31, 2014. We explore key STIs that are challenging public health today, new biomedical prevention approaches including multipurpose prevention technologies (MPTs), and the scientific and regulatory hurdles that must be overcome to make combination prevention tools a reality.

Evolving epidemiology of STIs: approaching new technologies to prevent them

HIV, other STIs, and unintended pregnancy are global health crises that together affect hundreds of millions of women and men worldwide. These health concerns share a common means of exposure, which is important to recognize when planning for prevention and care services because there is great benefit to addressing them jointly through MPTs (Box 1).

MPTs are new, all-in-one tools being developed to protect against HIV, other STIs, and, in some cases, unintended pregnancy. Much of the work on MPTs to date has focused on unintended pregnancy and HIV, but there are important reasons for ensuring that other STIs are addressed as well (Box 2).

The prevalence of STIs represents a significant public health burden, and curable STIs are on the rise (Figure 1) [http://www.who.int/mediacentre/factsheets/fs110/en/]. In Asia, numbers of viral STIs such as herpes simplex virus 2 (HSV-2) and human papillomaviruses (HPV) continue to increase, and fear of these appears to be higher than fear of HIV acquisition [http://www.who.int/reproductivehealth/publications/rtis/stisestimates/en/]. Maternal and child health, mortality, and morbidity, as well as HIV prevalence, are also significant concerns in both Sub-Saharan Africa and South East Asia [http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2013/en/].

Infections with sexually transmitted pathogens other than HIV, as well as persistent reproductive tract infections, such as bacterial vaginosis, impose an enormous burden on morbidity and mortality in both resource-constrained and developed countries. They directly impact on quality of life, reproductive health, and child health, and augment the risk of acquiring and transmitting HIV [1] or alter the course of other infections. As examples, HIV-positive women and men are more likely to have oncogenic HPV types and develop cervical or anal intraepithelial neoplasias [2], have higher HIV plasma viral load with HSV-2 seropositivity [3], and decreased HIV-1 shedding in cervicovaginal lavages due to STI treatment [4].

Despite their common route of transmission, STIs are a diverse group of infections with multiple different causative agents. These can be differentiated into viral infections (e.g., HIV, HSV, HPV, or hepatitis B), bacterial infections (e.g., gonococcal, chlamydial, or syphilis) or protista infections (e.g., trichomoniasis). This is an important concept because the active agent necessary to control and prevent each infection may be very different based on the pathogen(s) involved [5]. The combination of indications may vary by prevalence of infections seen in differing geographic locations around the world. The next sections will review some of the STIs (other than HIV) that were discussed at the satellite session at HIVR4P, strategies to prevent them, and the potential to combine multiple active agents into one delivery method for broad protection not only against STIs but also against unintended pregnancy.

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Box 1. Qualities of ideal MPTs

- Represent the next generation of measures for STI control.
- Be customized for the infections in a targeted geographic area.
- Control various STIs.
- Control one or more STIs and reduce unintended pregnancies.
- Result in multi-faceted, positive outcomes.

HSV-2: major cofactor in the HIV epidemic

HSV continues to be a global health concern in its own right, but also in conjunction with HIV (Box 2) [6]. In developed countries, HSV-1 has emerged as the principal cause of genital disease, with a prevalence at 54% of HSV-1 cases in the USA, whereas HSV-2 predominates globally. Both HSV serotypes are lifelong, persistent infections. Notably, HSV-2 infection in Sub-Saharan Africa (~70% prevalence of HSV-2 cases) could increase HIV-1 acquisition and further spread [6–8]. Furthermore, HSV-2/HIV-1 co-infected individuals tend to have more severe herpetic lesions and increased HSV-2 shedding [9]. These findings, combined with the absence of any approved prophylactic drug and recent vaccine failures, highlight the importance of developing new HSV prevention strategies as a public health priority [10].

Tenofovir (TFV) and its prodrug tenofovir disoproxil fumarate (TDF), which function as reverse transcriptase inhibitors (RTI) after being converted by cellular kinases to TFV-diphosphate, are being evaluated for prevention of HIV. These drugs do not require viral kinases for phosphorylation and, surprisingly, recent studies suggest that TFV-DP may provide partial protection against HSV. TFV 1% gel (Table 1) reduced HSV-2 incidence by 51% in women applying the product before and after sex (BAT24 dosing) in the CAPRISA-004 pre-exposure prophylaxis (PrEP) trial [11]. A 30% reduction in HSV-2 was also observed in men and women using daily oral TFV-based PrEP in a secondary analysis [12]. Notably, TDF is 160-fold more active than TFV against HSV-2, and a 0.3% gel formulation of TDF provided significantly greater protection than 1% TFV gel against vaginal HSV-2 in mice [13,14]. The greater potency of TDF compared to TFV likely reflects the enhanced cellular uptake of the former. A polyurethane intravaginal ring (IVR) designed to deliver TDF recently completed a Phase I safety study (Table 1), and future studies should explore whether IVRs [containing either TDF or acyclovir (ACV)] distribute a sufficient quantity of drug to sites such as the external genital skin to protect against HSV acquisition.

Griffithsin (GRFT), a homodimeric lectin derived from red alga, has been previously reported to bind to gp120 (the HIV envelope glycoprotein that mediates virus interaction with cellular receptors and coreceptors) via *N*-linked mannose-rich glycosylation clusters and to have potent anti-HIV activity *in vitro* [15,16]. Recently, GRFT was shown to have modest inhibitory activity against HSV entry, but was highly potent when added to cultures post-entry and prevented cell-to-cell spread [17]. These *in vitro* findings translated to significant protection against genital herpes in mice treated with 0.1% GRFT gel (Table 1). Importantly, the drug retained activity when virus was added in seminal plasma [17]. The latter findings are distinct from results obtained with polyanion drugs, such as PRO 2000 and cellulose sulfate, which lost activity when the virus was added in seminal plasma, reflecting a competition between seminal proteins and the drug for the HSV envelope glycoproteins [18,19]. By contrast, the MZC gel or MZCL IVR (Table 1) combines carrageenan (CG) and zinc (in addition to MIV-150, an anti-HIV non-nucleoside RTI), and showed potent and durable synergistic anti-HSV-2 activity [20–22]. This MPT formulation retains antiviral activities when virus is added in seminal plasma [23].

Poly-[1,4-phenylene-(1-carboxy) methylene] (PPCM), another candidate microbicide that targets the viral envelope, is currently being evaluated for its anti-HSV and contraceptive activity, and is a potential candidate for MPT [24,25]. Thus, both GRFT and PPCM are candidate drugs for coformulation with TDF/TFV or dapivirine. These combinations would target HIV by two different mechanisms (entry and reverse transcription), and provide activity against HSV (GRFT and PPCM) and contraception (PPCM). However, currently these anti-HSV drugs have been only formulated as gels, and there are challenges to IVR formulation. In addition, the formulation of GRFT with CG (in IVR or nanofibers, Table 1) is being explored to target not only HIV and HSV but also HPV. Combining ACV with a RTI also holds promise, and it may be easier to coformulate ACV for IVR delivery (Table 1). An MPT to block HSV as well as HIV would provide both a direct and indirect means of HIV prevention and could have a major impact on the HIV epidemic.

HPV prevention strategies: learning from success and moving forward

Papillomaviruses, including the HPV types that are the central cause of cervical cancer, have a unique life cycle in that virion production only occurs in the stratified squamous epithelium of the skin or mucosal surfaces [26]. Presumably because infection of the basal cells of the tissue is necessary, they have also evolved a unique mechanism of infection. In HPV16 pseudovirion-based mouse and rhesus macaque cervicovaginal challenge models, mature virions in solution are unable to directly bind to any epithelial cells [27,28]. They must first attach to heparan sulfate proteoglycans (HSPGs) on the basement membrane that divides the epithelium from the dermis, at sites in which the integrity of the epithelium is compromised, such that the virions have direct access to its surface, and can enter

Box 2. STI key facts[a]

- >1 million people acquire a STI every day.
- >530 million people are infected with HSV-2, with an incidence rate of 20 million cases annually.
- >290 million women are infected with HPV.
- ~500 million people become ill with curable STIs every year.
- Some STIs can increase the risk of HIV acquisition or transmission.
- Some STIs can negatively impact upon the course of HIV infection.

[a]Modified from WHO Fact Sheet 110 [http://www.who.int/mediacentre/factsheets/fs110/en/].