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Review

Combining prevention of HIV-1, other sexually transmitted infections and unintended pregnancies: Development of dual-protection technologies

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ABSTRACT

A significant number of women, especially in developing countries, need protection against more than one sexually transmitted infection (STIs), for instance HIV-1 and HSV-2, and family planning methods to prevent unwanted pregnancies. Dual protection technologies (DPTs; also known as multipurpose technologies) are designed to address two different indications with one product. Examples of DPTs are vaginal products capable of preventing transmission of HIV-1 in women while simultaneously providing contraceptive properties and a vaginal product capable of reducing HIV-1 transmission while preventing transmission of a second STI. DPTs can be categorized into three main approaches: 1) physical barriers, 2) chemical barriers, and 3) a combination of physical and chemical barriers. Examples of physical barriers are male and female condoms, diaphragms and cervical caps. Chemical barriers include use of a single drug with two mechanisms of action (viz., dual-activity compounds with microbicidal and contraceptive properties or activity against HIV-1 and a second STI pathogen such as HSV-2) or a combination of two drugs each targeted against separate mechanisms for achieving contraception and inhibition of HIV-1. Combinations of chemical and physical barriers are based on physical barriers such as a diaphragm along with a microbicide. Examples of each approach and current prototypes (such as vaginal gels and intravaginal rings) under development are described in this paper. Challenges facing development and regulatory approval of DPTs are also reviewed. This article forms part of a special supplement on a presentation covering DPTs, based on the symposium "Trends in Microbicide Formulations", held on 25 and 26 January 2010, Arlington, VA.

Contents

Abbreviations: STIs, sexually transmitted infections; HSV, herpes simplex virus; HPV, human papillomavirus; DPT, dual protection system; FC, female condom; LNG, levonorgestrel; CD, cyclodextrin; RTI, reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; TFV, tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor; IVR, intravaginal ring; EVAc, ethylene vinylacetate copolymer; PU, polyurethane; PK, pharmacokinetic; PD, pharmacodynamic; TDF, tenofovir disoproxil fumarate; IPA, isopropyl alcohol; ACV, acyclovir; NHP, nonhuman primates.

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1. Introduction

The risk of acquiringSTIsremains high throughout the world and efforts to reduce transmission of STIs, in particular HIV-1, are a high priority in the global public health agenda. UNAIDS/WHO recentlyreported 33.4 million people living with HIV-1 and 2.7 million new infectionsin 2008 (UNAIDS/WHO, 2009). There were 2.0 million deaths due to HIV/AIDS during that year. The number of those infected with HIV-1 in sub-Saharan Africa was 22.4 million, and the majority of them were women. The continuing rise in the population of people living with HIV-1 reflects the combined effects of continued high rates of new HIV-1 infections and the beneficial impact of antiretroviral therapy. Although important progress has been achieved in preventing new HIV-1 infections and in lowering the annual number of AIDS-related deaths, the number of people living with HIV-1 continues to increase. AIDS-related illnesses remain one of the leading causes of death globally and are projected to continue asa significant global cause of premature mortality in the coming decades (World Health Organization, 2008).

Regarding other STIs, the WHO estimates that 340 million new cases of syphilis, gonorrhea, chlamydia and trichomoniasis occurred throughout the world in 1999 in men and women aged 15-49 years (WHO, 2001). The largest number of new infections occurred in the region of South & Southeast Asia, followed by sub-Saharan Africa, Latin America and the Caribbean. Viral STIs are also a major health problem. The number of women infected with HPV, a main cause of cervical cancer, is about 20% of the population under 24 years of age (Glasier et al., 2006). HSV-2 is the commonest cause of genital ulcers and a highly prevalent infection in sexually-active people worldwide. Seroprevalence rates of HSV-2 range from 22% of sexually-active adults in the USA, to up to 60% in HIV-negative women in sub-Saharan Africa and men who have sex with men (MSM) in Latin America, and to more than 80% in people infected with HIV-1 (Celum et al., 2008).

Equally disappointing is the number of unwanted pregnancies in both the developed and developing world. This problem will only get worse as the world population continues to grow and is estimated to reach 9.1 billion by 2050 (Aitken et al., 2008). Annually there are over 75 million unwanted pregnancies (Glasier and Shields, 2006). Of these, 45 million pregnancies are terminated through abortions. Significant numbers of deaths are associated with unsafe abortions performed primarily in the developing world (Åhman and Shah, 2002; Ciment, 1999; Glasier et al., 2006). Contextual similarities make women at risk of unplanned pregnancies also at risk for STIs, including HIV-1. Family planning could therefore save hundreds of thousands of lives, not only by reducing maternal mortality but also by averting mother-to-child transmission of HIV-1 (Hladik and Hope, 2009).

The HIV-1 pandemic and the unabated prevalence of STIs and unintended pregnancies are intricately intertwined with poverty, malnutrition, poor education and gender inequality. A significant number of women, especially in developing countries, need protection against sexually transmitted diseases, in particular HIV/AIDS, and family planning methods to prevent unwanted pregnancies. There is an urgent need for the development of multipurpose (e.g., contraceptive and microbicidal) prevention technologies. This paper reviews their developmental strategies and prototypes.

This paper forms part of a group of seven reviews covering presentations from the Trends in Microbicide Formulations Workshop that was held on 25-26 January, 2010 in Arlington, Virginia, USA. The other articles discuss the prevention of mucosal transmission (Hladik and Doncel, 2010), preclinical evaluation of microbicides (Doncel and Clark, 2010), gels, tablets, and films (Garg et al., 2010), intravaginal rings (Malcolm et al., 2010), clinical evaluation of microbicides (Morrow and Hendrix, 2010), and novel approaches to microbicide delivery and safety assessment (Whaley et al., 2010).

2. Dual protection technologies

Given the cited transmission commonalitiesamong STIs and between HIV-1infection and fertilization/pregnancy (Doncel, 2006), there is a logic thread unifying the development of dual-protection technologies, which are aimed at preventing two STIs or an STI and unintended pregnancy (Berer, 2006; Brady, 2003; Bull and Shlay, 2005; Cates and Steiner, 2002; Chandran and Kabir, 2010; Baptista and Ramalho-Santos, 2009). In a more general sense, DPTsare also called "multipurpose technologies" (Young Holt et al., 2010).

The main strategies for combining multipurpose STI prevention and HIV-1 prevention and contraception are the development or improvement of physical barriers, chemical barriers, and physical/chemical barrier combinations. The first DPT approach is to use a physical barrier method normally associated with contraception, for instance male condoms, yet also capable of preventing HIV-1 transmission. The second approach is to develop improved chemical barriers such as coformulation of two or more microbicides with different targets. Related to this approach is the design of dual function drugs, i.e., drugs that potentially act against two distinct targets, displaying, for instance, both antiviral and contraceptive properties. The third approach to DPTs is the combination of a physical barrier with a chemical barrier. An example of this case is a drug-releasing barrier such as a female condom or diaphragm. Examples of these various approaches and current prototypes are discussed in greater detail in the following sections.

3. Improved physical barriers

Male condoms, typically used to reduce the incidence of pregnancy, also reduce the risk of HIV transmission (Cates, 2001; Pazoi et al., 2010). However, in terms of effectiveness, the male condom ranks behind other contraceptive methods (sterilization, hormonal methods, intrauterine devices) with better records of prevention. Additionally, like most devices and drugs, male condoms must be used correctly and consistently to provide adequate protection (Cates and Steiner, 2002). While "perfect use" has an annual failure rate of about 2%, failure rates under"typical use" rise up to 15% on average (Trussell, 2007). Regarding HIV-1 prevention, several cross-sectional studies have shown that male condoms confer about 60-96% protection for male-to-female transmission (Davis and Weller, 1999). Real-world experience demonstrates significant challenges to consistently ensuring protected sex among women, especially in the developing world (Gollub, 2006).

An alternative to the male condom is FC. Examples of the FC are shown in Fig. 1. Like the male condom, the FC is a physical barrier preventing semen from reaching the vagina or cervixthus providing a barrier to pregnancy and HIV-1transmission (Vijayakumar et al., 2006). Typical- and perfect-use contraceptive failure rates are slightly higher than those of the male condom (Trussell, 2007). For non-HIV STIs, a randomized controlled trial showed similar degree of protection to the male condom (French et al., 2003). Regarding HIV-1 prevention, mathematical models predict about 63-82% effectiveness (Mukandavire and Garira, 2007).

Diaphragms have similar contraceptive failure rates to male condoms (6 and 16% for perfect and typical use). Cross-sectional studies on *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections have demonstrated 60-70% protection conferred by the use of the device (Minnis and Padian, 2005). In the more recent MIRA trial (n = 5,045), the investigators evaluated the effectiveness of the Ortho All-Flex® Diaphragm, lubricant gel (Replens®) and condoms compared to condoms alone on the incidence of HIV-1, chlamydial and gonococcal infections in an open-label randomized controlled trial among women at risk of HIV-1/STI infections (Padian et al.,