Advanced Drug Delivery Reviews 103 (2016) 33–56

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Microbicide vaginal rings: Technological challenges and clinical development☆

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ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 13 January 2016
Accepted 20 January 2016
Available online 30 January 2016

Keywords:
Vaginal rings
HIV microbicides
Antiretrovirals
HIV prevention
Controlled release
Adherence
Vaginal drug delivery

ABSTRACT

Vaginal rings (VRs) are flexible, torus-shaped, polymeric devices designed to sustain delivery of pharmaceutical drugs to the vagina for clinical benefit. Following first report in a 1970 patent application, several steroid-releasing VR products have since been marketed for use in hormone replacement therapy and contraception. Since 2002, there has been growing interest in the use of VR technology for delivery of drugs that can reduce the risk of sexual acquisition of human immunodeficiency virus type 1 (HIV-1), the causative agent of acquired immunodeficiency syndrome (AIDS). Although no vaginally-administered product has yet been approved for HIV reduction/prevention, extensive research efforts are continuing and a number of VR devices offering sustained release of so-called 'HIV microbicide' compounds are currently being evaluated in late-stage clinical studies. This review article provides an overview of the published scientific literature within this important field of research, focusing primarily on articles published within peer-reviewed journal publications. Many important aspects of microbicide-releasing VR technology are discussed, with a particular emphasis on the technological, manufacturing and clinical challenges that have emerged in recent years.

Contents

Abbreviations: ACV, acyclovir; AIDS, acquired immunodeficiency syndrome; API, active pharmaceutical ingredient; ARV, antiretroviral; AZT, zidovudine; Boc-LBA, Boc-lysinated betulonic acid; CG, carrageenan; DMPA, depot medroxyprogesterone acetate; DPV, dapivirine; DRV, darunavir; E2, estradiol; EE, ethinylestradiol; ETN, etonogestrel; EVA, ethylene vinyl acetate copolymer; FDA, U.S. Food and Drug Administration; GMP, good manufacturing practice; GRFT, griffithsin; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HRT, hormone replacement therapy; HSV, herpes simplex virus; HPEU, hydrophilic polyether urethane; HPMC, hydroxypropyl methylcellulose; HSV, herpes simplex virus; IgG, immunoglobulin G; IPM, International Partnership For Microbicides; IPA, isopropyl alcohol; IVIVC, in vitro–in vivo correlations; LNG, levonorgestrel; mAb, monoclonal antibody; MIV-150, Medivir-150; MIV-160, Medivir-160; MPT, multipurpose prevention technology; MTN, Microbicide Trials Network; MVC, maraviroc; N9, nonoxynol-9; NES, nestorone; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PCL, polycaprolactone; PD, pharmacodynamic; PDMS, polydimethylsiloxane; PEU, polyether urethane; PK, pharmacokinetic; PI, protease inhibitor; Pt, platinum; RTV, room-temperature vulcanizing; SE, silicone elastomer; SHIV, simian human immunodeficiency virus; SQV, saquinavir; STI, sexually transmitted infection; SVF, simulated vaginal fluid; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TPU, thermoplastic polyurethane; USP, United States Pharmacopeia; VR, vaginal ring; ZA, zinc acetate.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "HIV/AIDS_dasNeves_Sarmento_Sosnik".

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http://dx.doi.org/10.1016/j.addr.2016.01.015
0169-409X/

1. Introduction

In 1983, following two years of increasing number of reported cases in the United States (U.S.) of severe immune deficiency among gay men and infants receiving blood transfusions, scientists first identified the human immunodeficiency virus (HIV) as the retrovirus that causes acquired immune deficiency syndrome (AIDS). By 1987, three biomedical strategies were at the forefront of developments to treat or prevent HIV infection. In March 1987, the U.S. Food and Drug Administration (FDA) approved the first antiretroviral (ARV) drug, zidovudine (AZT), for treatment of HIV by reducing replication of the virus. In August 1987, the FDA sanctioned the first human testing of a candidate vaccine against HIV. Later the same year, the FDA declared HIV prevention as a new indication for male condoms.

Fast-forward three decades and, despite the tremendous advancements in our scientific knowledge and understanding, the HIV/AIDS pandemic remains one of the most serious global public health crises of our time. The latest (2014) global statistics for HIV/AIDS estimate 37 million people living with HIV, 2 million new infections annually, and 1.2 million deaths in 2014 from AIDS-related illnesses [1]. Sub-Saharan Africa remains the hardest hit region, accounting for more than 70% of people presently living with HIV/AIDS.

Development of a safe and effective HIV vaccine has proven very difficult. Ideally, an effective HIV vaccine should induce powerful and durable immunity capable of preventing infection in healthy individuals and/or reducing viral replication and viral load in infected individuals with the aim of slowing or halting disease transmission and progression. To date, more than 250 clinical trials of HIV vaccine candidates have been completed or are presently being conducted; only six of these candidates have reached late-stage clinical testing, and none have demonstrated significant efficacy [2].

With consistent and correct use, male latex condoms can reduce the risk of heterosexual transmission of HIV by more than 70% [3–5]. However, despite widespread and often aggressive promotion, condom use has not reached a sufficiently high level to impact rates of HIV acquisition in Sub-Saharan Africa. One reason lies with gender-power imbalances, resulting in women not always being able to negotiate condom use with male partners. For example, African men are more likely to refuse condom use when there are large differences in age between them and their female partners, if they are married, when they have multiple sexual partners, and where there is no communication about HIV/AIDS between them and their partners [6]. Female condoms, widely promoted as a female-controlled alternative to male condoms, have failed to gain acceptance, despite the introduction of new types [7–10].

On a more positive note, increased access to highly active antiretroviral therapy (HAART) means that an AIDS diagnosis is no longer a death sentence for millions of people. Today, 28 FDA-approved ARV drugs are available for treatment of HIV-1 infections [11]. These drugs are mainly classified into six distinct types based on their mechanism of action: nucleoside-analog reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, protease inhibitors (PIs), fusion inhibitors and co-receptor antagonists. As of March 2015, 15 million people living with HIV, including 11 million in Sub-Saharan Africa, were accessing life-saving HAART, up from 13.6 million in June 2014 and only 300,000 in 2002, exceeding the targets set as part of the Millennium Development Goals [1]. Meanwhile, the number of people newly infected with HIV has fallen by 35% since 2000 and global deaths due to AIDS have declined 42% since the peak in 2004. With this halting and reversing the spread of HIV/AIDS, and with continued effort and investment, the world is seemingly on track to end the AIDS pandemic by 2030 [1].

It is widely accepted that ARV treatment alone will not be able to curtail the HIV/AIDS pandemic. In the continued absence of an effective HIV vaccine, there is greater optimism about the clinical potential of HIV microbicides. HIV microbicides are pharmaceutical formulations administered vaginally (or rectally) to reduce sexual transmission of the virus. The concept of an HIV microbicide was first described in a 1990 commentary piece entitled 'HIV Prevention: The Need for Methods Women Can Use' [12]. Recognizing the limitations of behavior-modification strategies and use of condoms in reducing HIV infection rates, Stein strongly advocated research into new methods that women could use to prevent vaginal transmission of HIV. Of course, these 'topical virucides', as they were then called, would have to be acceptable to women in terms of convenience of use, safety and cost, as well as highly effective against the virus. A number of surfactant-type vaginal microbicides were tested in women during the 1990s (Fig. 1), including a compound called nonoxynol-9 (N9). Most of these studies not only failed to protect women against HIV infection, but some actually increased HIV infection rates compared with a placebo product. Surfactant-type microbicides were subsequently abandoned. Next, the focus switched to various polymer molecules (Fig. 1), whose negatively charged functional groups were shown in laboratory experiments to prevent the virus attaching to the immune cells. However, as with the surfactants, these polymer-based microbicides failed to provide protection in clinical studies, and once again, some increased the risk of infection.

The past five years has seen the microbicide field focus almost exclusively on more conventional small molecule ARV drugs, the same or similar drugs to those used since the 1980s for treating people already infected with HIV. A breakthrough came in 2010 when the first results emerged from the CAPRISA 004 trial [13]. For the first time, a vaginally-administered ARV gel product was shown to provide significant protection against HIV infection. A summary timeline describing key moments, and particularly major clinical activities, in the development of HIV microbicides is presented in Fig. 1.