Antiviral Research 85 (2010) 142–158

Contents lists available at ScienceDirect

Antiviral Research

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

Review

# Development of topical microbicides to prevent the sexual transmission of HIV

Robert W. Buckheit Jr.[a,*], Karen M. Watson[a], Kathleen M. Morrow[b], Anthony S. Ham[a]

[a] ImQuest BioSciences, Inc., 7340 Executive Way, Suite R, Frederick, MD 21704, USA
[b] The Miriam Hospital and The Warren Alpert Medical School of Brown University, One Hoppin Street, Providence, RI 02903, USA

ARTICLE INFO

*Article history:*
Received 2 September 2009
Accepted 16 October 2009

*Keywords:*
HIV transmission
Microbicide
Prevention
Formulation
Acceptability
Development algorithm

ABSTRACT

Women comprise almost 50% of the population of people living with HIV and the majority of these women contracted the virus through sexual transmission in monogamous relationships in the developing world. In these environments, where women are not empowered to protect themselves through the negotiation of condom use, effective means of preventing HIV transmission are urgently needed. In the absence of an approved and effective vaccine, microbicides have become the strategy of choice to provide women with the ability to prevent HIV transmission from their infected partners. Topical microbicides are agents specifically developed and formulated for use in either the vaginal or rectal environment that prevent infection by sexually transmitted infectious organisms, including pathogenic viruses, bacteria and fungi. Although a microbicidal product will have many of the same properties as other anti-infective agents and would be similarly developed through human clinical trials, microbicide development bears its own challenges related to formulation and delivery and the unique environment in which the product must act, as well as the requirement to develop a product that is acceptable to the user. Herein, perspectives based on preclinical and clinical microbicide development experience, which have led to an evolving microbicide development algorithm, will be discussed. This article forms part of a special issue of Antiviral Research marking the 25th anniversary of anti-retroviral drug discovery and development, *Vol 85, issue 1, 2010*.



**Contents**



* Corresponding author. Tel.: +1 301 696 0274; fax: +1 301 696 0381.
*E-mail address:* rbuckheit@imquest.com (R.W. Buckheit Jr.).

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doi:10.1016/j.antiviral.2009.10.013

## 1. Introduction

The latest UNAIDS report on the global AIDS epidemic has restated the global emergency status of the epidemic. Over 25 million people have died since the first case of AIDS was identified in 1981, and the number of people living with HIV worldwide numbered 33 million at the end of 2007. Almost 2.5 million people worldwide became newly infected with HIV and an estimated 2.1 million human deaths were attributed to AIDS in 2007 (UNAIDS/WHO, 2007). The rate of HIV infection and AIDS related deaths is projected to increase over the course of the next decade with rapid expansion in Asia, Africa, and Eastern Europe. The epidemic is not limited to underdeveloped and low to middle income countries, as the number of infected individuals living with HIV/AIDS has also risen and the rates of HIV infection have not declined in the United States and Western Europe (UNAIDS, 2004).

Nucleoside and non-nucleoside reverse transcriptase (RT) inhibitors and protease inhibitors have been effectively used for the past decade in highly active anti-retroviral therapies (HAART) to significantly reduce HIV virus load in infected individuals for prolonged periods of time (Fischl et al., 1987). The utilization of HAART has dramatically changed the therapeutic landscape of HIV treatment and the application of cocktails of anti-retroviral agents is now the standard of care for HIV patients (Bonfanti et al., 1999; Yeni et al., 2004). The dramatic reduction in viral load and clinical improvements achieved with HAART is a rigorous validation of the ability of anti-HIV drugs to contain and manage HIV disease, and demonstrates that a combination of three or more anti-HIV agents – even when directed against only two of the putative 10 viral targets – is superior to single or two drug chemotherapy. Thus, the prevailing belief is that the addition of new anti-HIV agents to HAART regimens will provide additional clinical benefits (Mocroft et al., 1998; Palella et al., 1998). Over the last several years, inhibitors of HIV integrase and HIV entry (CCR5 antagonist) have been added to the portfolio of approved drugs available to HIV-infected individuals and additional RT and protease inhibitors with greater potency continue to be developed. Despite its success, HAART suffers from the emergence of multi-drug-resistant virus strains, toxicity, difficult treatment regimens, and inadequate pharmacology, bioavailability and tissue distribution (Richman, 1996; Carpenter et al., 2000; Trabattoni et al., 2002). In the developing world, many of these therapeutic strategies are unavailable due to the prohibitively high cost of the drugs. In these areas, the absence of an effective vaccine and the lack of effective therapy, means that sub-Saharan Africa and Southeast Asia remain epicenters for the spread of HIV, especially among heterosexual women (Letvin, 2006). In these areas of extremely high HIV transmission rates, the opportunities to derail the AIDS pandemic rests on the processes of education and behavioral prevention and the development of effective prophylaxis, including specific HIV prevention strategies employing chemical agents to prevent the sexual transmission of HIV (Turpin, 2002; Lard-Whiteford et al., 2004).

Topical microbicides represent an important strategy with clear potential for preventing the transmission of HIV through sexual intercourse, the predominant mode of HIV transmission worldwide. The latest statistics indicate that the number of women with HIV infection and AIDS has been increasing steadily worldwide and according to the World Health Organization, women accounted for 50% of adults living with HIV at the end of 2007 (UNAIDS/WHO, 2007). Thus, the dynamics of the epidemic demand the development of safe, effective, and acceptable female-controlled chemical and physical barrier methods including topical microbicides, to reduce HIV transmission. The development of microbicidal agents has gained significant focus and momentum during the past few years due to the realization that suppression of HIV transmission in the developing world can have a great impact on the HIV pandemic. It has been estimated that a single microbicide with 60% effectiveness could prevent millions of new cases of HIV infection each year throughout the world (Watts and Zimmerman, 2002).

Topical microbicides consist of products that attack cellular or viral targets and prevent the infection of target cells or the replication of the virus, resulting in decreased virus transmission and acquisition of HIV. Microbicide strategies may or may not include those effective against sexually transmitted infections (STIs) that affect the acquisition or course of HIV infection and may or may not be contraceptive. A major challenge in the development of topical microbicides revolves around the actual biology of HIV infection in the vagina and/or rectum and full understanding of the actual molecular and cellular events which occur during transmission and infection. Infectious virus, supplied *via* the ejaculate, contains both cell-free and cell-associated virus (Gupta et al., 1997; Quayle et al., 1997; Coombs et al., 1998). Infectious virus can be recovered from mononuclear cells in seminal fluid, but endogenous antiviral factors in semen make quantification and recovery of infectious cell-free virus highly variable. Results from non-human primate models argue strongly for cell-free virus as the source of infection, and it has been shown that viral load correlates with transmission (Pilcher et al., 2004; Cohen and Pilcher, 2005). Once deposited in the vaginal or rectal vaults, the virus or virus infected cell(s) must penetrate the epithelium of the tissues in order to reach their target cells (monocytes, dendritic cells, and/or T-cells) in the sub-mucosa. In the case of the vagina and ectocervix, the squamous epithelium is keratinized and can be up to 50 cell layers thick. In the endocervix, the epithelia transitions to a single layer of columnar cells. Additional defenses may include the barrier properties of cervical mucus, antiviral factors secreted by the innate immune system, and protective factors from naturally occurring microflora such as *Lactobacilli sp.* (Miller and Shattock, 2003; Cole, 2006). The mechanism by which HIV evades these host defenses is unknown, but micro-trauma resulting in access to the sub-mucosa from intercourse and/or STI-induced lesions have been identified as potential routes of entry. Once access to susceptible cells in the sub-mucosa is obtained, a number of studies have suggested that infection potentially occurs in a two-stage process with local infection of these susceptible cells in the tissue followed by rapid dissemination from