Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2010: 2 (1) 141-149
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Microbicides for HIV: An Approach to reduce STDs

Harish K Chandrawanshi*, Urmila Pilaniya, Ankur Chaubey, Ashish Singhai, Neerja Gupta, Kavita Pilaniya

V.N.S. Institute of Pharmacy, Bhopal, MP, INDIA

Abstract

Humankind has been besieged throughout its evolution by microorganisms that pose a continual challenge to the survival of the species. The pandemic, the acquired immunodeficiency syndrome (AIDS), is due to a newly recognized microbe, the human immunodeficiency virus (HIV). As we prepare to enter the new millennium, it is appropriate to reflect on the origins of this epidemic, what has occurred over the past 18 years, what has been accomplished from a scientific and public health perspective, and what the prospects are for the future. With growing recognition of the potential value of microbicides for HIV prevention, the importance of the acceptability of this new technology has been widely acknowledged. We review the current body of microbicide acceptability research, characterize the limitations in assessment approaches, and suggest strategies for improvement. As acceptability is likely to be a key determinant in the use-effectiveness of microbicides, this includes exploring the effects that sexual partners, health care providers, and key opinion leaders have on the acceptability of microbicides among women and men, including youth and people living with HIV. According to the Joint United Nations Programme on HIV/AIDS, there are more than 40 million people living with HIV, and more than 15,000 new infections occur every day. One approach to curbing HIV is the development of topical microbicidal agents or microbicides. These are compounds designed to protect the body's mucosal surfaces from infection by sexually transmitted disease causing pathogens, including HIV. Several candidates are in preclinical stages; however, only a handful have been tested in humans for safety, and even fewer are ready for clinical efficacy trials.

Key words*:* HIV infection, HIV prevention, microbicides, contraception.

Introduction

An approach to curbing HIV is the development of topical microbicidal agents or microbicides. These are compounds designed to protect the body's mucosal surfaces from infection by sexually

transmitted disease causing pathogens, including HIV. Several candidates are in preclinical stages; however, only a handful have been tested in humans for safety, and even fewer are ready for clinical efficacy trials [1-3].

Microbicides are compounds that, when applied topically, protect the body's mucosal surfaces from infection by sexually transmitted disease-causing pathogens. The main target of these agents has been HIV, the etiologic agent of AIDS. Since the mucosal inflammation caused by these pathogens acts as a facilitating cofactor for HIV infection, some of the investigators had realized that targeting other sexually transmitted pathogens (STPs), such as herpes viruses, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, and organisms causing bacterial vaginosis, may be easier and will result in a reduction of HIV transmission [4].

Unprotected sexual intercourse is the most common mode of HIV-1 transmission worldwide [5-6]. Many biologic factors have been implicated in influencing rate of transmission from individual exposures, including virus strain and inoculum in semen or vaginal fluid, concomitant ulcerative anogenital infection, traumatic intercourse, menstrual cycle, and use of oral contraceptives [7].

In addition, genetic studies have shown that individuals with homozygous deletions of their chemokine receptor-5 (CCR5) alleles, the major HIV-1 co-receptor used by macrophage-tropic strains of virus (R5 viruses), are relatively protected from initial HIV-1 infection despite numerous exposures [8]. This fact points to the importance of CCR5 as a critical cofactor involved in sexual transmission of HIV-1 and also correlates with the finding that >90% of HIV-1 strains isolated from patients soon after primary infection are R5 viruses. The potent inhibitors of CCR5, such as aminooxy pentane (AOP)-RANTES (regulated upon activation, normal T cell expressed and secreted), may eventually prove useful in blocking sexual transmission of HIV-1 [9].

Condom use and behavioral interventions have only been partially successful in slowing the spread of HIV-1 infection. Thus, there is an urgent need for additional interventions to prevent new HIV-1 infections, including the development of female-controlled topical formulations of anti–HIV-1 compounds that could be used as a suppository, cream, or gel before sexual intercourse. Ideally, these topical microbicides should be inexpensive, easy to use, stable under low pH conditions, colorless, tasteless, and non-irritating to genital mucosal tissues and inactivate a variety of sexually transmitted microbes within genital secretions and/or block relevant HIV-1 receptors on initial target cells. To date, the spermicide nonoxynol-9 is the only compound that has been clinically tested for its ability to block sexual transmission of HIV-1, but results from this study were disappointing [10].

The need for contraceptive microbicides

The human population is steadily increasing. We currently are 6.4 billion, and statistical projections indicate we will be about 9 billion by the year 2050. Population, however, is growing fastest in countries and regions where resource needs are the greatest. By the year 2050, 86% of the global population will live in less developed countries. Although more developed nations will not increase their population significantly, the 49 least developed countries will triple their population sizes.

Accompanying high rates of population growth, poverty, malnutrition and infectious diseases are almost permanent features in many of these countries. Intricately intertwined, they compound health and social problems and interfere with their solutions. The acquired immune deficiency syndrome (AIDS) is the latest of these maladies, and it appears to thrive in the presence of overpopulation, poverty and other sexually transmitted diseases (STDs).

Since its beginning, the AIDS epidemic has expanded relentlessly. More than 30 million adults and children worldwide have died from AIDS, and about 40 million are currently infected with its causal agent, the human immunodeficiency virus (HIV). It is a reality that more than 95% of new infections (about 15 000 per day) occur in less developed countries. Sub-Saharan Africa remains by far the most affected region with 25.4 million people living with HIV at the end of 2004. Furthermore, women are increasingly and disproportionately affected. Globally, just under half of all people living with HIV are female, but in sub-Saharan Africa, a striking 76% of young people (aged 15–24 years) are women. It is clear that there is an urgent need for developing options that allow women to prevent or delay pregnancy and to protect themselves from STDs, especially AIDS. Although other preventative strategies are possible (e.g. behavioral changes and vaccines), development of microbicides, with and without contraceptive properties, has recently gathered momentum, owing to better science, increased funding and political pressure. For women willing to prevent pregnancy and STDs, dually active contraceptive microbicides offer convenience as well as additional safety and discretion. Single-molecule compounds also have toxicological, manufacturing and regulatory advantages.

Non-contraceptive microbicides are also desperately needed, as they fit the need of a large population of women, especially in developing countries, who want to protect themselves against sexually transmitted infections while remaining fertile. Because of the close interaction between microbicides with or without contraceptive activity and sperm, reproductive toxicity and teratogenicity studies are an essential part of the preclinical assessment of these compounds [11]. So far, however, none of the compounds in clinical testing have shown significant effects on fetal development or pregnancy outcome.

Pathophysiology

The pathophysiology of initial HIV-1 entry and potential of topical microbicides can appropriately be studied by the cell culture models that include Langerhans cells (LCs) and members of the dendritic cell family, because they exhibit the following characteristics:
(a) Location within mucosal epithelium at sites of HIV-1 exposure.
(b) Expression of CD4, capable of supporting HIV-1 infection.
(c) Ability to immigrate to paracortical T-cell rich areas of regional lymph nodes after contact with virus or other antigens.
(d) Ability to efficiently transmit HIV-1 to co-cultured $CD4^+$ T cells during the process of antigen-specific activation [12].

Potential mechanisms for HIV transmission across mucosal epithelium

Various mechanisms for HIV transmission across mucosal epithelium have been studied, some important of them are as follows-
(a) Direct infection of epithelial cells.
(b) Transcytosis through epithelial cells or specialized microfold cells.

(c) Epithelial transmigration of infected donor cells.
(d) Uptake by intraepithelial Langerhans cells.
(e) Circumvention of the epithelial barrier through physical breaches.

Successful transfer of the virus across epithelial barriers would result in viral uptake by migratory dendritic cells and subsequent dissemination to T cells in the lymphatic system or localized mucosal infection, leading to recruitment of additional susceptible cells [13].

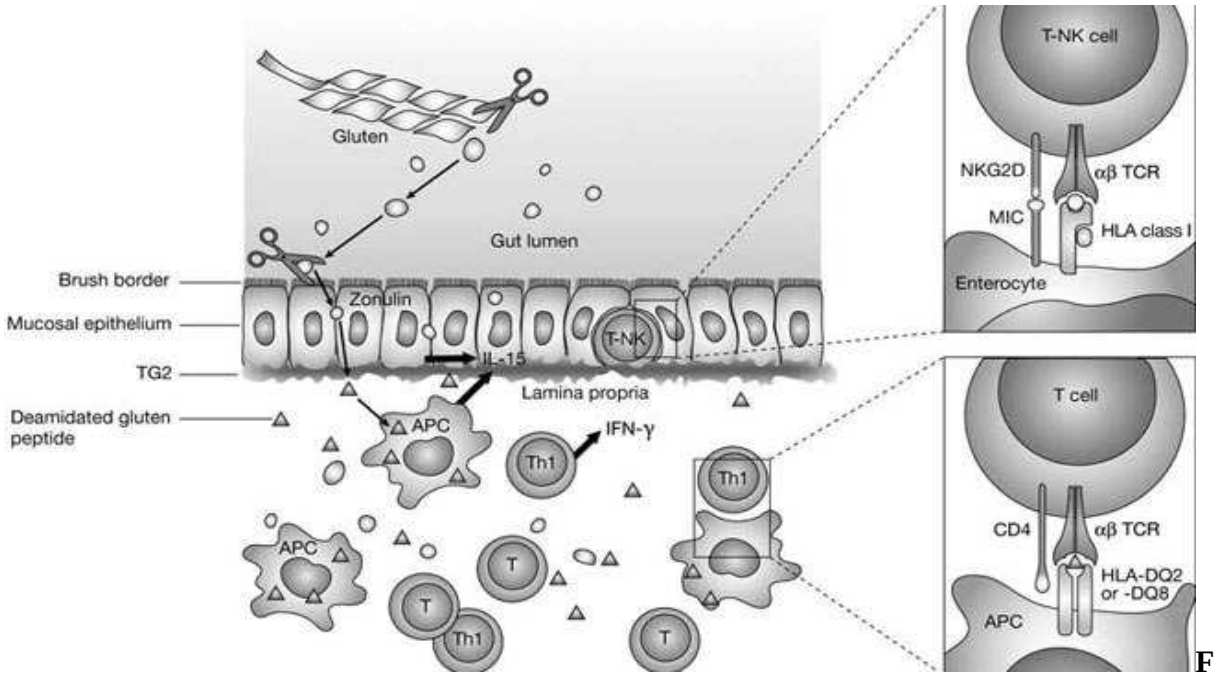


Fig.1. Mechanisms for HIV transmission across mucosal epithelium

Potential mechanisms of action for microbicide compounds

Microbicides that act as a lubricant coat the epithelial surface, which might reduce the risk of trauma and provide a physical barrier against viral infection. Prevention (or treatment) of other STDs (Sexually transmitted diseases) can reduce the risk of HIV transmission by reducing the risk of epithelial inflammation and ulceration. In the vagina, maintaining the normal flora, and therefore maintaining the vaginal pH at virucidal levels (pH less than 4.5), could also reduce the risk of transmission. Once the virus has crossed the epithelial barrier, the potential microbicidal strategies will be -

a) Targeting HIV uptake by dendritic cells.
b) Targeting HIV adsorption and fusion.
c) Targeting reverse transcriptase and integration into the host cell genome.

The various ways by which microbicides can act is illustrated in fig.2. They can be nonspecific, moderately specific or highly (exclusively) specific to HIV. The nonspecific and moderately specific agents are often active against a variety of sexually transmitted microorganisms (e.g. chlamydia and herpesvirus) and may have a contraceptive effect. The HIV-specific agents interact directly with one or several steps of the infection or replication cycle of HIV [14].

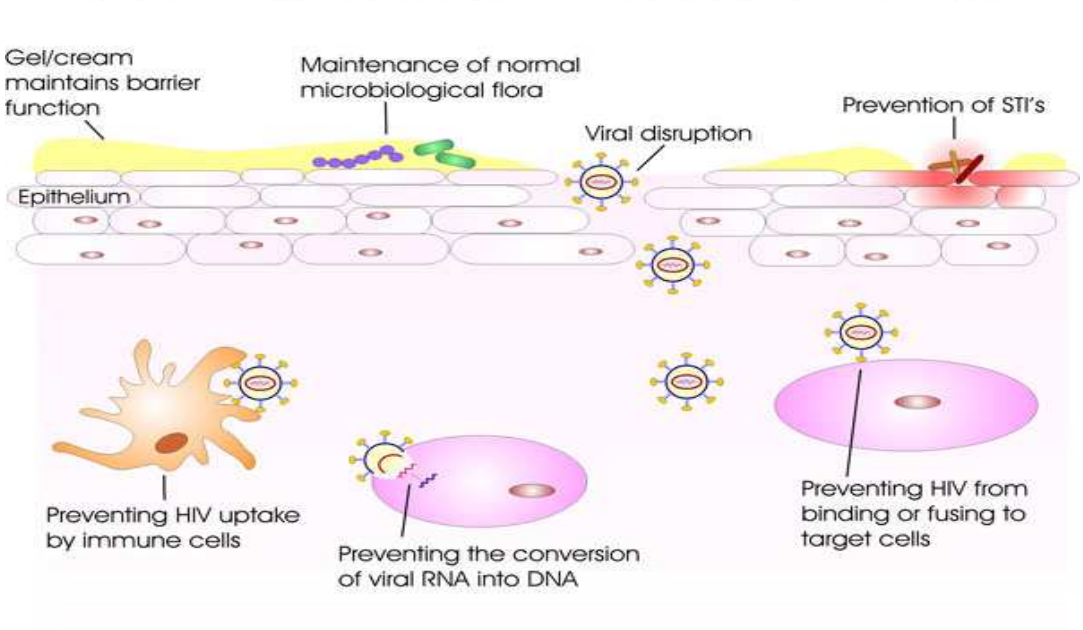


Fig.2. Potential mechanisms of action for microbicide compounds

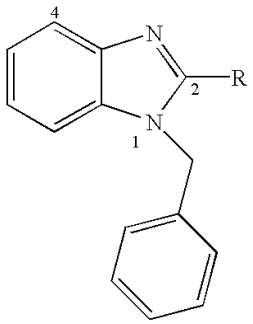
Highly active antiretroviral therapy (HAART) is a combination of at least three antiretroviral agents, two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or possible a third NRTI1. HIV PIs have contributed greatly to reductions in HIV associated morbidity and mortality over the last decade and remain a cornerstone of HAART [15].

One promising compound currently under development, cellulose acetate phthalate (CAP), is a component of enteric film coating for tablets and capsules and has been shown to inactivate HIV-1 and other sexually transmitted agents *in vitro*, inhibit *herpes simplex* type 2 infection *in vivo* in mice and block vaginal transmission of SIV(Simian immunodeficiency virus) in rhesus monkeys [16-17].

Examples of some Microbicides

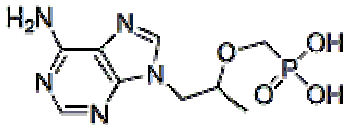
Various compounds could be considered to be vaginal microbicides, preventing heterosexual transmission of HIV (i.e. virucidal agents such as nonoxynol 9 and chlorhexidine) and antiviral agents interfering with either virus adsorption/fusion [polyanionic substances such as polysulfates (i.e. PVAS, PAVAS), polysulfonates, polycarboxylates, polyoxometalates and negatively charged albumins], or fusion/uncoating (bicyclams), or reverse transcription [dideoxynucleoside analogues, acyclic nucleoside phosphonates such as 9-(2-phosphonyl methoxyethyl)adenine (PMEA) and *9-(2*- phosphonyl methoxy propyl adenine) (PMPA), and non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as 4,5,1-jk][1,4] benzodiazepin-2 (1 H)-one and-thione(TIBO), 1-[(2-hydroxyethoxy)methyl]-6-(phenyl thio) thymine (HEPT), and alpha-APA (anilino phenyl acetamide) derivatives]. In particular, combination of two or more of these compounds seems to be an attractive approach to interrupt transmission of HIV at different stages of the infectious process [18].

Some herbal drugs can also be used for the formulation of microbicides for HIV for example Syzygium cumini (Syn. Eugenia cumini, Eugenia jambolana, jambul, black plum) is a tree of the family Myrtaceae distributed in Asia. The barks, leaves and seed extracts of Syzygium cumini have been reported to possess anti HIV activity [19].



1

4, [5, 1-jk] [1, 4] benzodiazepin-2 (1 h)-one (TIBO)



9-(2- phosphonyl methoxy propyl adenine) (PMPA)

HIV- Human immuno deficiency, HPV- human papillomavirus

Despite nonoxynol-9, there has been significant recent progress toward the development of safe and effective topical microbicides. Several different gel formulations, including PRO 2000, and BufferGel are currently undergoing testing in phase III clinical efficacy trials and about two dozen other products are in various phases of development [21].

In most cases, it is hoped that the gels will block the transmission of HIV, as well as other STDs, such as human papillomaviruses (HPVs) and herpes simplex viruses (HSVs). For example, carrageenan, the active ingredient in Carraguard, has been shown to block the replication of all three virus types in laboratory studies. Interestingly, carrageenan is already in use as a gelling agent in some over the counter personal lubricant products, such as Bioglide, Divine, and Oceanus Carrageenan brands (Table-1). Viva Gel is a particularly unique microbicide in that its active ingredient is a nanoscale dendrimer and 85-100% (highly) effective at stopping the transmission of both HIV and genital herpes in macaque monkeys. Viva Gel is also being evaluated for use in condoms by a leading manufacturer.

The phase III clinical trial for carrageenan-based Carraguard showed that it has no statistical effect on HIV infection. The researchers point out that the study at least proved that the gel is safe, with no side effects or increased risk, and provided valuable information about usage patterns in the test subjects [22].

Table 1. Microbicides available [20]

S.No.	Microbicide Name	Mechanism of action	Description	Potential STD/HIV protection
1	BufferGel (Carbomer 974P)	Vaginal defense/ acid buffer	Polymer gel reinforces vaginal acidity by acidifying the Ejaculate.	HIV, chlamydia, herpes, HPV
2	Carraguard (PC-515)	Attachment Inhibitor	Carrageenan (derived from seaweed) binds to block viruses from attaching to and Infecting healthy cells.	HIV, Herpes, HPV, gonorrhea
3	Cellulose sulfate	Attachment Inhibitor	Binds to viruses and bacteria, Prevent them from attaching to and infecting healthy cells.	HIV, gonorrhea, chlamydia,
4	PRO 2000 (Polynaphthalene sulfonate)	Entry and fusion Inhibitor	Binds to viruses and bacteria To prevent them from attaching to and infecting healthy cells.	HIV, gonorrhea, herpes
5	Savvy(C31G)	Surfactant	Detergent disrupts viral, bacterial, and cell membranes, including those of sperm.	HIV, chlamydia, herpes

Conclusion

The magnitude and devastating consequences of the AIDS epidemic as well as the long-term need for contraception, especially in less developed countries, warrant the development of dually active microbicidal contraceptives. Sharing an anatomical and functional context, the processes by which sperm capacitate and fertilize the oocyte and HIV infects genital mucosa offer the framework on which to develop dual inhibitory strategies. Essential to these strategies is the fact that these processes also share molecules and mechanisms that represent common targets for dual inhibition. Microbicide research and drug development has been built on the understanding of sexual transmission of HIV and progress in anti-HIV drug discovery from research focused on the systemic treatment of the disease [23]. Several drugs that are currently used or considered for use for systemic HIV treatment could probably also qualify for microbicidal research and drug development has been built on the understanding of sexual transmission of HIV and progress in anti-HIV drug discovery from research focused on the systemic treatment of the disease. Several drugs that are currently used or considered for use for systemic HIV treatment could probably also qualify for microbicidal action.

Even in the absence of a proven microbicide on the market, empirical evidence indicates that women and men from different socio-cultural backgrounds in both developed and resource-constrained countries are interested in using a microbicide. The desired effect of microbicides in reducing women's risk of infection clearly cannot be achieved without understanding and addressing the issues surrounding product acceptability and use. Most disease prevention and contraceptive methods take years after development to achieve widespread acceptance. In the

case of microbicides, physical barrier methods, and HIV vaccines, the years required for products to achieve widespread acceptability and use also will see millions of women and men becoming newly infected with HIV. With the acceleration in the development and testing of microbicides, any steps taken to reduce the time from the establishment of an efficacious microbicide to its widespread uptake and continued use will have an enormous public health benefit. Unlike the female condom, conducting microbicide acceptability studies in the early stages of clinical testing will optimize decisions about product characteristics, understanding impediments to use, and potentially useful promotional strategies. Failure to consider how microbicides are positioned within heterosexual and same-sex relationships may doom an efficacious product to become ineffective in practice. Building on the strengths and avoiding the weaknesses of the introduction of the female condom can better help to translate microbicides and other emerging disease and pregnancy prevention methods into effective public health interventions.

References

[1] RM Krause; Introduction to infectious diseases: stemming the tide, *New York, Academic Press*, **1998**, 1, 22.
[2] AS Fauci, *Science* **1988**, 239, 617-622.
[3] GF Doncel, *Hum Reprod Update* **2006,** 12, 103-117.
[4] GF Doncel; C Mauck vaginal microbicides: a novel approach to preventing sexual transmission of HIV. Curr HIV/AIDS Rep, **2004,** 1, 25–32.
[5] RA Royce; A Sena; W Cates; MS Cohen. *N. Engl. J. Med*, **1997**, 336, 1072-1078.
[6] JO Kahn; BD Walker, *N. Engl. J. Med.* **1998,** 339, 33-39.
[7] AS Fauci. *N. Engl. J. Med*, **1999,** 341, 1046-1050.
[8] M Samson; F Libert; BJ Doranz; J Rucker; C Liesnard; CM Farber; S Saragosti; C Lapoumeroulie; J Cognaux; C Forceille, *Nature*, **1996,** 382, 722-725.
[9] G Simmons; PRL Clapham Picard; RE Offord.; MM Rosenkilde; Schwartz, T.W., Buser, R., Wells, T.N.C., and Proudfoot, A.E, *Science*, **1997,** 276, 276-279.
[10] RE Roddy; L Zekeng; KA Ryan; U Tamoufe; SS Weir; EL Wong, *N. Engl. J. Med.* **1998,** 339:504-510.
[11] GF Doncel. *Hum Reprod Update*, **2006,** 12, 103-117.
[12] KH Manson; MS Wyand; C Miller; AR Neurath. *Antimicrob. Agents Chemother,* **2000,** 44, 3199-3202.
[13] RP Shattock JP Moore, *Nature Rev Microbiol*, **2003**, 1, 25-34.
[14] Jan Balzarini; Lut Van Damm, CMAJ, February 15, **2005**, 4, 172.
[15] SK Mastan; K Eswar Kumar; *Der Pharmacia Lettre;* **2009**, *1 (1),* 108-116
[16] T Gyotoku; L Aurelian; AR Neurath, *Antiviral Chem. Chemother*, **1999,** 10, 327-332.
[17] KH Manson; MS Wyand; C Millerand Neurath, *Antimicrob. Agents Chemother,* **2000,** 44, 3199-3202.
[18] R Pauwels; E De Clercq *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol*, **1996,** 11, 211-221.
[19] SK Mastan; G Chaitanya; T Bhavya Latha; A Srikanth; G Sumalatha; K Eswar Kumar, *Der Pharmacia Lettre;* **2009**, *1(1),* 143-149.
[20] www.global-campaign.org

[21] Trial Shows Anti-HIV Microbicide Is Safe, but does Not Prove it Effective, *Population Council*. **2008**, 02, 18.
[22] Experimental Microbicide Carraguard Does Not Provide Protection Against HIV, Study Finds, *kaisernetwork.org*. **2008**, 02, 20.
[23] Jan Balzarini; Lut Van Damme, *Lancet*, **2007**,369, 787–97.